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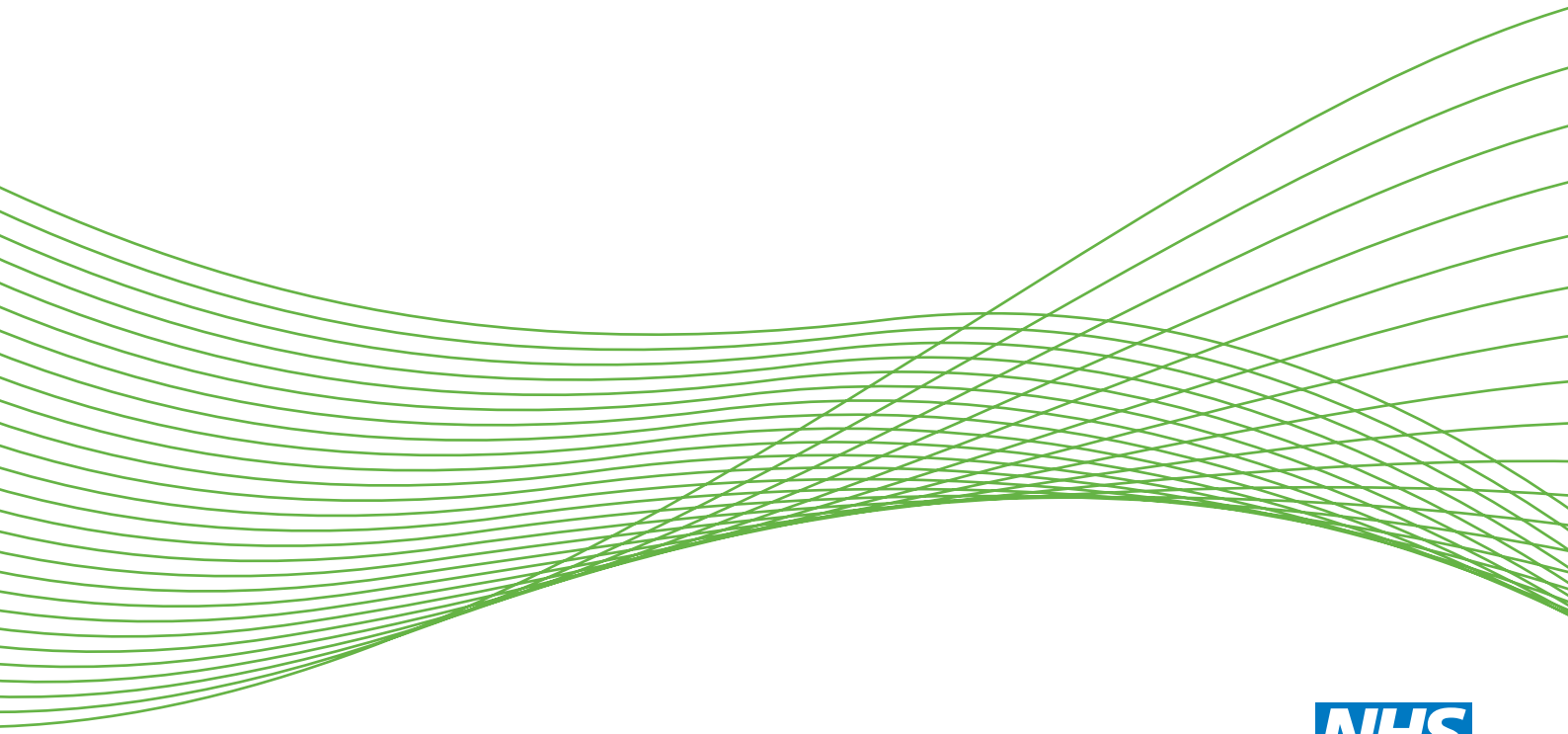

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Sue E Harnan,[1]* Paul Tappenden,[1] Munira Essat,[1] Tim Gomersall,[1] Jon Minton,[2] Ruth Wong,[1] Ian Pavord,[3] Mark Everard[4] and Rod Lawson[5]

[1]School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK
[2]Advanced Quantitative Methods Network (AQMEN), University of Glasgow, Glasgow, UK
[3]Nuffield Department of Medicine, University of Oxford, Oxford, UK
[4]School of Paediatrics and Child Health, University of Western Australia, Princess Margaret Hospital, WA, Australia
[5]Department of Respiratory Medicine, Royal Hallamshire Hospital, Sheffield, UK

*Corresponding author

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This report

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Abstract

Measurement of exhaled nitric oxide concentration in asthma: a systematic review and economic evaluation of NIOX MINO, NIOX VERO and NObreath

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[1]School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK
[2]Advanced Quantitative Methods Network (AQMEN), University of Glasgow, Glasgow, UK
[3]Nuffield Department of Medicine, University of Oxford, Oxford, UK
[4]School of Paediatrics and Child Health, University of Western Australia, Princess Margaret Hospital, WA, Australia
[5]Department of Respiratory Medicine, Royal Hallamshire Hospital, Sheffield, UK

*Corresponding author s.harnan@sheffield.ac.uk

Background: High fractions of exhaled nitric oxide (FeNO) in the breath of patients with symptoms of asthma are correlated with high levels of eosinophils and indicate that a patient is likely to respond to inhaled corticosteroids. This may have a role in the diagnosis and management of asthma.

Objective: To assess the diagnostic accuracy, clinical effectiveness and cost-effectiveness of the hand-held electrochemical devices NIOX MINO® (Aerocrine, Solna, Sweden), NIOX VERO® (Aerocrine) and NObreath® (Bedfont Scientific, Maidstone, UK) for the diagnosis and management of asthma.

Data sources: Systematic searches were carried out between March 2013 and April 2013 from database inception. Databases searched included MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, Science Citation Index Expanded and Conference Proceedings Citation Index – Science. Trial registers such as ClinicalTrials.gov and the *meta*Register of Controlled Trials were also searched in March 2013. All searches were updated in September 2013.

Review methods: A rapid review was conducted to assess the equivalence of hand-held and chemiluminescent FeNO monitors. Systematic reviews of diagnostic accuracy and management efficacy were conducted. A systematic review of economic analyses was also conducted and two de novo health economic models were developed. All three reviews were undertaken according to robust high-quality methodology.

Results: The rapid review (27 studies) found varying levels of agreement between monitors (Bland–Altman 95% limits of agreement up to ±10 parts per billion), with better agreement at lower FeNO values. Correlation was good (generally $r > 0.9$). The diagnostic accuracy review identified 22 studies in adults (all ages) and four in children. No studies used NObreath or NIOX VERO and seven used NIOX MINO. Estimates of diagnostic accuracy varied widely. FeNO used in combination with another test altered diagnostic accuracy only slightly. High levels of heterogeneity precluded meta-analysis. Limited observations included that FeNO may be more reliable and useful as a rule-in than as a rule-out test; lower cut-off values in children and in smokers may be appropriate; and FeNO may be less reliable in the elderly. The management review identified five randomised controlled trials in adults, one in pregnant asthmatics and

seven in children. Despite clinical heterogeneity, exacerbation rates were lower in all studies but not generally statistically significantly so. Effects on inhaled corticosteroid (ICS) use were inconsistent, possibly because of differences in management protocols, differential effectiveness in adults and children and differences in population severity. One UK diagnostic model and one management model were identified. Aerocrine also submitted diagnostic and management models. All had significant limitations including short time horizons and the selective use of efficacy evidence. The de novo diagnostic model suggested that the expected difference in quality-adjusted life-year (QALY) gains between diagnostic options is likely to be very small. Airway hyper-responsiveness by methacholine challenge test is expected to produce the greatest QALY gain but with an expected incremental cost-effectiveness ratio (ICER) compared with FeNO (NObreath) in combination with bronchodilator reversibility of £1.125M per QALY gained. All remaining options are expected to be dominated. The de novo management model indicates that the ICER of guidelines plus FeNO monitoring using NObreath compared with guidelines alone in children is expected to be approximately £45,200 per QALY gained. Within the adult subgroup, FeNO monitoring using NObreath compared with guidelines alone is expected to have an ICER of approximately £2100 per QALY gained. The results are particularly sensitive to assumptions regarding changes in ICS use over time, the number of nurse visits for FeNO monitoring and duration of effect.

Conclusions: Limitations of the evidence base impose considerable uncertainty on all analyses. Equivalence of devices was assumed but not assured. Evidence for diagnosis is difficult to interpret in the context of inserting FeNO monitoring into a diagnostic pathway. Evidence for management is also inconclusive, but largely consistent with FeNO monitoring resulting in fewer exacerbations, with a small or zero reduction in ICS use in adults and a possible increased ICS use in children or patients with more severe asthma. It is unclear which specific management protocol is likely to be most effective. The economic analysis indicates that FeNO monitoring could have value in diagnostic and management settings. The diagnostic model indicates that FeNO monitoring plus bronchodilator reversibility dominates many other diagnostic tests. FeNO-guided management has the potential to be cost-effective, although this is largely dependent on the duration of effect. The conclusions drawn from both models require strong technical value judgements with respect to several aspects of the decision problem in which little or no empirical evidence exists. There are many potential directions for further work, including investigations into which management protocol is best and long-term follow-up in both diagnosis and management studies.

Study registration: This study is registered as PROSPERO CRD42013004149.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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Glossary

Airway hyper-responsiveness Synonymous with bronchial hyper-responsiveness and an indicator of asthma. Usually assessed using a bronchial challenge test. In a bronchial challenge test an agent such as histamine or methacholine is inhaled. If these agents trigger bronchospasm at a significantly lower threshold than normal an individual is considered to have airway hyper-responsiveness.

Airway reversibility Airway obstruction that improves when a bronchodilator or corticosteroids are taken.

Antihistamine A drug that inhibits the action of histamine in the body and which may be effective in treating allergic asthma.

Area under the curve A measure of the diagnostic accuracy of a technology based on the geometric inspection of a receiver operating characteristic plot, which plots true-positive rate against false-positive rate. A technology with perfect diagnostic accuracy will have an area under the curve of 1, a technology that is no better than chance will have an area under the curve of 0.5 and a technology that miscategorises on every occasion will have an area under the curve of zero.

Atopy/atopic disorder A predisposition towards the development of some forms of allergic hypersensitivity. Atopy is considered to be a risk factor for asthma.

Attrition bias A statistical bias caused by systematic differences in rates of attrition in the control and intervention arms of a study. For example, the intervention may make some patients receiving it better but may cause others to experience severe side effects and be more likely to leave the study.

Bland–Altman plot Also known as a difference plot and used to estimate the level of agreement between two devices or assays used for measuring the same thing. Observations are paired and the mean of the paired observations is plotted against the difference in estimates between the two devices for the same observation.

Bronchoconstriction Constriction of the airways in the lungs as a result of the action of surrounding smooth muscle, airway inflammation or excessive production of mucus because of allergy or irritation from air friction, overcooling or drying of the airways. It is characterised by coughing, wheezing and shortness of breath.

Chemiluminescence A broad range of methods in which light is emitted as a result of a chemical reaction. Used to detect the presence and level of nitric oxide in exhaled breath.

Chronic obstructive pulmonary disease A lung disease in which airflow is persistently poor because of lung tissue damage and dysfunction of the small airways. Some treatment for chronic obstructive pulmonary disease is similar to that for asthma but, unlike asthma, chronic obstructive pulmonary disease is usually acquired rather than inherited and the prognosis and health-related quality of life are poorer.

Cut-off In a binary categorisation exercise, a value within a range of values used to categorise observations into one of two mutually exclusive groups. With respect to the fraction of exhaled nitric oxide devices considered in this assessment, the cut-off threshold is expressed as parts per billion of nitric oxide in exhaled breath; those with values above the threshold are considered ‘positive’ and those with values below the threshold are considered ‘negative’.

Detection bias Detection bias refers to systematic differences between groups in how outcomes are determined. This usually occurs as a result of preconceptions about treatment efficacy. As such, blinding (or masking) of outcome assessors may reduce the risk that knowledge of which intervention was received, rather than the intervention itself, affects outcome measurement. Blinding of outcome assessors can be especially important for assessment of subjective outcomes such as degree of postoperative pain. The outcome assessor can be the patient when outcomes are self-assessed.

Diagnostic accuracy The effectiveness of a diagnostic test in correctly categorising patients as either 'positive' or 'negative'. There are several ways that this can be expressed, for example the area under the curve or the sum of sensitivity and specificity.

Exacerbation A worsening of symptoms that may be acute or subacute. In the case of asthma, this can also be termed an 'asthma attack'. Symptoms include shortness of breath, wheezing, cough and chest tightness. Exacerbations also lead to decreases from baseline in lung function, such as forced expiratory volume in the first second.

Extended dominance The state when a strategy under study is both less effective and more costly than a linear combination of two other strategies with which it is mutually exclusive.

False negative An individual who has been incorrectly categorised as a member of the category 'negative' in a binary categorisation exercise when the only other possible classification is 'positive', for example someone who has asthma but who has been categorised as not having asthma.

False positive An individual who has been incorrectly categorised as a member of the category 'positive' in a binary categorisation exercise when the only other possible classification is 'negative', for example a patient incorrectly diagnosed with asthma.

Forced expiratory volume in the first second The volume of air expelled by a patient within the first second.

Fraction of exhaled nitric oxide The concentration of nitric oxide in exhaled breath, also known as fractional exhaled nitric oxide.

Index test A diagnostic test whose sensitivity and specificity are assessed by comparing its categorisations (positive, negative) with another diagnostic test, known as a reference standard, which is assumed to have perfect sensitivity and specificity. In this assessment the index test is the fraction of exhaled nitric oxide.

Inhaled corticosteroid responsiveness The degree to which the asthma condition improves in response to treatment with inhaled corticosteroids.

Juniper score A quality of life measure for patients with asthma.

Negative predictive value The probability that a patient who has been categorised as 'negative' really is negative.

Peak expiratory flow rate The maximum rate of expiration of breath, as measured by a peak flow metre. Considered a measure of lung function.

Pearson correlation A measure ranging between –1 and 1 indicating the degree and direction of linear dependence between two variables. Values close to zero indicate no/very low correlation and values close to 1 indicate very high correlation.

Performance bias A statistical bias caused by the control and treatment groups receiving different standards of care or being exposed to factors other than the interventions of interest.

Positive predictive value The probability that a patient who has been categorised as 'positive' really is positive.

Receiver operating characteristic plot A graph that plots the joint sensitivity and specificity of a diagnostic test at a range of cut-off thresholds.

Reference standard A diagnostic test used to estimate the sensitivity and specificity of another diagnostic test, known as an index test. The reference standard is assumed to have perfect sensitivity and specificity and so, when both tests categorise something differently, the index test categorisation is assumed to be incorrect (either a false negative or a false positive).

Reporting bias Reporting bias refers to systematic differences between reported and unreported findings. In any given study, analyses with statistically significant differences between intervention groups are more likely to be reported than analyses with non-significant differences. This is also known as outcome reporting bias or selective reporting bias. Reporting bias can also occur when results are reported in such a way that they cannot be included in a meta-analysis.

Selection bias Systematic differences in the baseline characteristics of the intervention and control groups. Randomisation should result in study groups with similar baseline characteristics but this can be subverted if there is a lack of allocation concealment (preventing foreknowledge of forthcoming allocations).

Sensitivity The proportion of 'positives' within a population undergoing diagnostic testing who are identified as such.

Simple dominance When a given treatment alternative is less effective and more expensive than its comparator.

Specificity The proportion of 'negatives' within a population undergoing diagnostic testing who are identified as such.

Spirometry Lung function tests based on the measurement of exhaled air under controlled conditions using a device called a spirometer.

Standardised mean difference A summary statistic showing the difference between two groups, calculated as the difference in mean outcomes between two groups divided by the standard deviation of scores for all study participants. This can be used to meta-analyse data for an outcome that has been measured using different metrics.

True negative An individual who has been correctly categorised as a member of the category 'negative' in a binary categorisation exercise when the only other possible classification is 'positive', for example someone who has been correctly identified as not asthmatic.

True positive An individual who has been correctly categorised as a member of the category 'positive' in a binary categorisation exercise when the only other possible classification is 'negative', for example someone who has been correctly diagnosed with asthma.

List of abbreviations

ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
AQLQ	Asthma Quality of Life Questionnaire
AQLQ-M	Asthma Quality of Life Questionnaire – Marks
ATS	American Thoracic Society
AUC	area under the curve
BTS	British Thoracic Society
CCRCT	Cochrane Central Register of Controlled Trials
CDSR	Cochrane Database of Systematic Reviews
CE	Conformité Européenne
CEAC	cost-effectiveness acceptability curve
COPD	chronic obstructive pulmonary disease
CPCI-S	Conference Proceedings Citation Index – Science
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstracts of Reviews of Effects
DSA	deterministic sensitivity analysis
EAG	External Assessment Group
EIB	exercise-induced bronchoconstriction
EQ-5D	European Quality of Life-5 Dimensions
FeNO	fractional exhaled nitric oxide [also known as fraction of exhaled nitric oxide and exhaled nitric oxide (ENO)]
FEV_1	forced expiratory volume in the first second
FEV_1%	percentage of predicted forced expiratory volume in the first second
FEV_1/FVC	forced expiry volume in the first second divided by forced vital capacity (Tiffeneau–Pinelli index)
FN	false negative
FP	false positive
FVC	forced vital capacity
GINA	Global Initiative for Asthma
GP	general practitioner
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICS	inhaled corticosteroid
IQR	interquartile range
LABA	long-acting beta2-agonist
LTRA	leukotriene receptor antagonist
mAQLQ	mini Asthma Quality of Life Questionnaire
MAUDE	Manufacturer and User Facility Device Experience
MCT	methacholine challenge test
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NPV	negative predictive value
OCS	oral corticosteroid
ONS	Office for National Statistics
PEF	peak expiratory flow
PEFR	peak expiratory flow rate
ppb	parts per billion
PPV	positive predictive value

PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies – second revision
RCT	randomised controlled trial
RDI	relative dose intensity
RR	relative risk
SABA	short-acting beta2-agonist
SCIE	Science Citation Index Expanded
SCM	specialist committee member
SD	standard deviation
SE	standard error
SF-12	Short Form questionnaire-12 items
SIGN	Scottish Intercollegiate Guidelines Network
TN	true negative
TP	true positive

Note

This monograph is based on the Technology Assessment Report produced for NICE. The full report contained a considerable number of data that were deemed academic-in-confidence. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of academic-in-confidence data removed and replaced by the statement 'academic-in-confidence information removed' is available on the NICE website: www.nice.org.uk. The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.

Plain English summary

High levels of nitric oxide in exhaled breath are thought to be a sign that a person might have asthma or that their asthma is poorly controlled. We aimed to assess the evidence relating to this and to estimate whether the cost of using NIOX MINO, NIOX VERO and/or NObreath to measure exhaled nitric oxide was worth the health benefits. We found that studies using exhaled nitric oxide to help diagnose asthma reported different results to one another but that, overall, exhaled nitric oxide was probably more able to indicate that a person does have asthma than to indicate that they do not. We also looked at studies that used exhaled nitric oxide levels to tailor treatment in people with asthma. These studies all reported fewer asthma attacks when exhaled nitric oxide was used, but this was not statistically significant in most studies. Most also reported less medication use, although some reported an increase in medication use. There were some differences between studies in adults and studies in children and between those with different severities of asthma. By making some assumptions about how long the benefits would last and how the test would be used in practice, it seems possible that using exhaled nitric oxide would be cost-effective in certain groups in both the management and the diagnosis of asthma. There is a lot of uncertainty over all of the conclusions drawn in the assessment, however, because not all of the evidence needed was available and some of the evidence used was not of the highest quality.

Scientific summary

Background

Asthma is a chronic disorder of the airways, caused primarily by inflammatory processes and bronchoconstriction. Symptoms of asthma include recurrent episodes of wheezing, breathlessness, chest tightness and coughing. The diagnosis of asthma is a clinical one, based on symptoms and clinical respiratory measurements. However, there is no definitive, objective diagnostic test and as such there is significant over- and underdiagnosis.

In 2011, an estimated 5.4 million people in the UK were receiving treatment for asthma. Deaths from asthma are generally rare, with 1041 in England and Wales in 2011.

The management of asthma aims to control symptoms, prevent exacerbations and achieve the best lung function, with minimal side effects. For both children and adults, asthma is monitored and managed in primary care by routine clinical review on at least an annual basis. Patients are managed in a stepwise manner, with escalation of medication until control is reached.

High fractional exhaled nitric oxide (FeNO) levels in a patient with symptoms suggestive of asthma may suggest that the patient has eosinophilic asthma that could be treated with inhaled corticosteroids (ICSs). In individuals already diagnosed with asthma, FeNO levels may indicate how well they are responding to ICS-based medication, whether medication is being adhered to and whether medication dosage should be increased or decreased (step up/step down).

Objectives

To assess the clinical effectiveness and cost-effectiveness of FeNO measurement for the diagnosis and management of asthma in adults and children using the hand-held monitors NIOX MINO® (Aerocrine, Solna, Sweden), NIOX VERO® (Aerocrine) and NObreath® (Bedfont Scientific, Maidstone, UK).

Methods

This report consists of two main parts: (1) an assessment of the clinical effectiveness of FeNO in the diagnosis and management of asthma and (2) an assessment of the cost-effectiveness of FeNO compared with standard care in the diagnosis and management of asthma.

Clinical evidence review

The following systematic reviews were conducted:

- *Rapid review of the equivalence of FeNO devices*. Aimed at establishing whether studies that used other FeNO measurement devices could inform this appraisal.
- *Systematic review of the diagnostic accuracy of FeNO measurement for asthma*. All levels of evidence were considered but, because of a lack of higher levels of evidence, diagnostic cohort studies informed this assessment. When available, three pairs of sensitivity and specificity estimates were selected: (1) the highest sum of sensitivity and specificity; (2) the highest sensitivity for rule-in scenarios; and (3) the highest specificity for rule-out scenarios. In rule-in scenarios, patients testing positive are assumed to have asthma and those testing negative go on to have further tests for asthma. In rule-out scenarios, those who test negative are assumed not to have asthma and those who test positive go on to have further tests for asthma.

- *Systematic review of the efficacy of FeNO-guided management of asthma*. Randomised controlled trial (RCT) evidence was included and lower levels of evidence included when RCT evidence was not available for pre-defined subgroups.

Databases searched included MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, Science Citation Index Expanded and Conference Proceedings Citation Index – Science. Trial registers such as ClinicalTrials.gov and the *meta*Register of Controlled Trials were also searched. Initial searches were undertaken between March 2013 and April 2013 and update searches for the diagnostic and management reviews were performed in September 2013. All reviews considered adults and children separately. Subgroups of interest included older adults, pregnant women and smokers. All three reviews were undertaken according to robust high-quality methodology.

Cost-effectiveness assessment

The cost-effectiveness assessment of FeNO included two components: a systematic review of existing economic analyses and the development of two de novo health economic models:

- *Systematic review and critical appraisal of existing economic evaluations*. This included published studies and evidence submitted by manufacturers.
- *Development of two de novo models*. Independent health economic models were developed to assess the incremental cost-effectiveness of FeNO compared with standard care in the diagnosis and management of asthma.

Results

Clinical effectiveness results

Rapid review of FeNO device equivalence

In total, 27 studies were included. Although there was often good correlation between FeNO measurement devices, equivalence of readings could not necessarily be assumed in all situations. The 95% limits of agreement were sometimes very wide (around $\pm$10 parts per billion) and equivalence was generally poorer between FeNO devices at higher FeNO levels. The direction of disagreement varied between studies and comparator devices.

Correlation between measurements across all devices was high. Consequently, sensitivities and specificities were assumed to be interchangeable, but it could not be assumed that the cut-off points used would be the same for each device; this is an important issue.

Test failure rates were generally low although there may be some problems with using the NIOX MINO device in younger children, with failure rates ranging from 5.5% to 27%.

Systematic review of the diagnostic accuracy of FeNO measurement for asthma

In total, 27 studies were included in the review, 23 in adults (all ages) and four in children. Studies that were similar to one another in terms of the position of the patients in the UK diagnostic pathway [Scottish Intercollegiate Guidelines Network (SIGN) guidelines] and the reference standards used were grouped together. No meta-analysis was conducted in any group as the clinical heterogeneity between studies was very high.

Estimates of cut-off points, sensitivity and specificity were not consistent within groups and ranged widely when used as a rule-in test and a rule-out test and when considering the highest sum of sensitivity and specificity. The large variation in estimates within groups may obscure any true underlying differences in the accuracy of FeNO between groups and compared with different reference standards. The evidence is

especially difficult to interpret in the context of inserting FeNO into the UK diagnostic pathway. The nearest equivalent to a pathway was reported in two studies in which FeNO was interpreted in conjunction with results from another test, resulting in a change in both sensitivity and specificity, but it was not clear whether clinical effectiveness and cost-effectiveness would also change. Some limited observations were made: 100% specificity was achieved more often than 100% sensitivity and ranges of specificity were generally smaller. This may indicate that FeNO has the highest potential for consistency and accuracy as a rule-in test. It was also concluded that FeNO cut-off points should probably be lower in children than in adults.

No cohort studies were found that provided evidence relating to pregnancy, the elderly and smokers/children with environmental tobacco exposure. Consequently, lower levels of evidence were consulted.

- smokers: accuracy seemed similar but FeNO was generally lower in smokers and children exposed to tobacco smoke
- the elderly: FeNO is unlikely to be a useful test in the diagnosis of asthma in the elderly
- pregnant women: pregnancy did not alter FeNO levels in asthmatics or non-asthmatics and FeNO distinguished between asthmatic and non-asthmatic pregnant and healthy women.

Systematic review of the efficacy of FeNO-guided management of asthma

Five adult population studies were included. High levels of heterogeneity in multiple study characteristics and outcome definitions prevented the External Assessment Group (EAG) from drawing any firm conclusions with regard to which step-up/step-down protocol or cut-off points offered the best efficacy. All studies reported fewer exacerbations in the FeNO arm, mostly driven by mild and moderate exacerbations, which was statistically significant in only one study. The effects on ICS use were heterogeneous, although it was not possible to conclude if this was because of differences in study populations or differences in management protocols. Pooled analysis showed less ICS use in the intervention arm, but the difference was not statistically significant. Health-related quality of life (HRQoL) was infrequently reported; two studies both showed no effect on the global Asthma Quality of Life Questionnaire (AQLQ) score, but one found a statistically significant difference in the symptoms score.

No study exceeded 12 months' follow-up; it is unclear if any observed effects would be maintained over longer time periods.

Seven studies in children were included. The severity of the patients' symptoms varied between studies. All studies except one reported a decrease in exacerbations in the intervention arm, but only one reported a statistically significant reduction. The effects on ICS use were heterogeneous with two studies showing a statistically significant increase in ICS use, two showing a non-significant increase, one showing no difference, one being difficult to interpret and one further study not reporting this outcome. HRQoL was reported in only one study; insufficient details were reported to draw conclusions.

A RCT of asthma management using FeNO in pregnant asthmatics was included. Statistically significant differences in all exacerbations, OCS use and ICS use were reported, favouring the intervention.

Non-RCT evidence indicated that FeNO was unlikely to be useful in elderly asthmatics. In smokers, the four non-RCT studies identified suggested that FeNO levels were lower in adult asthmatic smokers than in adult asthmatic non-smokers and that FeNO can no longer detect asthma control in those smokers treated with ICSs. The use of repeated measures and within-patient change from baseline may be worth further investigation.

Cost-effectiveness results

There is very limited available evidence concerning the cost-effectiveness of FeNO for the diagnosis and/or management of asthma. The systematic review identified one published UK model of FeNO testing in the diagnostic setting and one published UK model of FeNO testing in the management setting. Both models

were published within the same paper. Aerocrine also submitted a model of FeNO testing for diagnosis and a model of FeNO testing for management; these models were similar to, but not the same as, the published UK models. The existing economic diagnostic models indicate that NIOX MINO is likely to be cost saving compared with other tests routinely used in the diagnosis of asthma, but may be more expensive than standard diagnostic tests when used in conjunction with other tests. Neither diagnostic model captures the health consequences associated with correct or incorrect diagnostic outcomes; hence, these models do not provide any information regarding the economic trade-off between additional health gains resulting from the more accurate diagnosis of asthma and health losses associated with displacing existing services. The existing management models indicate that NIOX MINO produces more health gains at a lower cost than guidelines alone. The EAG critique of these management models highlighted several problems including the use of short time horizons, the selective use of efficacy evidence from different sources, the assumptions about the equivalence between sputum count monitoring and FeNO and invalid assumptions about the health losses associated with exacerbations. No economic evidence was submitted by the manufacturers for either NIOX VERO or NObreath.

The EAG developed two de novo models. The first model assesses the cost-effectiveness of FeNO testing using NIOX MINO, NIOX VERO and NObreath in addition to, or in place of, existing tests compared with other diagnostic options commonly used in the diagnosis of asthma. The second model assesses the cost-effectiveness of NIOX MINO, NIOX VERO and NObreath plus guidelines compared with guidelines alone for the management of asthma.

The EAG diagnostic model suggests that, across the diagnostic options included in the economic analysis, the expected difference in quality-adjusted life-year (QALY) gains is likely to be very small. Airway hyper-responsiveness [assessed using the methacholine challenge test (MCT)] is expected to produce the greatest QALY gain. The incremental cost-effectiveness ratio (ICER) of airway hyper-responsiveness (MCT) compared with FeNO (NObreath) plus bronchodilator reversibility is expected to be £1.125M per QALY gained. All remaining options are expected to be ruled out because of dominance. The results of the analysis are sensitive to assumptions about the time required to resolve misdiagnoses, assumptions about health losses associated with false-negative diagnoses, the costs of asthma management and the use of ‘rule-in’ and ‘rule-out’ diagnostic decision rules.

The EAG management model was evaluated across two subgroups: (1) children and (2) adults. Studies from the clinical effectiveness review were selected for the model, based on similarity to UK practice and patient populations. Sensitivity analyses were conducted using alternative studies to test the stability of the results in other populations and against different comparators. Within both the child and adult subgroup analyses, FeNO testing is expected to produce a small incremental QALY gain compared with guidelines alone. In both subgroups, NIOX MINO and NIOX VERO are expected to be dominated as their marginal per-test cost is higher than that for NObreath. Within the child subgroup, the ICER of guidelines plus FeNO monitoring using NObreath compared with guidelines alone is expected to be approximately £45,200 per QALY gained. Within the adult subgroup, FeNO monitoring using NObreath compared with guidelines alone is expected to cost approximately £2100 per QALY gained. A similarly favourable result was produced within a further analysis based on a subgroup of women who are pregnant. Importantly, these positive results are not held when alternative trials are used to inform the analysis. The results in the child and adult subgroups are particularly sensitive to assumptions about changes in ICS use over time, the number of nurse visits for FeNO monitoring and the duration over which FeNO monitoring impacts on exacerbations and ICS use.

Conclusions

Implications for service provision

There is considerable uncertainty associated with all analyses within this assessment. This is largely because of the limitations of the evidence base.

Studies using the devices that are the focus of this review were not available for all analyses and, in the absence of an alternative, equivalence has been assumed but is not assured.

The clinical evidence relating to the use of FeNO for the diagnosis of asthma is highly heterogeneous and difficult to interpret in the context of the insertion of FeNO into a diagnostic pathway.

Evidence for management is also inconclusive although consistent with FeNO resulting in fewer exacerbations, with a small or zero reduction in ICS use in adults and a possible increase in ICS use in children or patients with more severe asthma. It is unclear which specific management protocol is likely to be most effective. There was no evidence relating to whether these effects would be maintained over a longer time period.

The health economic analysis indicates that FeNO could have value in both the diagnostic setting and the management setting. In particular, the diagnostic model indicates that FeNO plus bronchodilator reversibility dominates many other diagnostic tests and may render airway hyper-responsiveness cost-ineffective. In the management setting, FeNO-guided management has the potential to appear cost-effective although this is largely dependent on the expected duration over which it continues to impact on medication decisions. The conclusions drawn from both models require strong technical value judgements with respect to several aspects of the decision problem in which little or no empirical evidence exists.

Suggested research priorities

Several research priorities were identified. The two key priorities, of equal importance, were:

1. What is the clinical utility of FeNO used in sequence with current guidelines for the diagnosis of asthma and/or ICS responsiveness compared with current guidelines alone, when a reference standard of long-term follow-up of diagnoses is used? What is the optimal placement for FeNO testing within the diagnostic pathway?
2. What is the most effective step-up/step-down protocol for the management of asthma using FeNO? Is it safe to step down treatment on the basis of low FeNO alone (e.g. in the presence of symptoms)?

Study registration

This study is registered as PROSPERO CRD42013004149.

Funding

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Chapter 1 Background

Condition and aetiology

Introduction

Asthma is a chronic disorder of the airways, caused primarily by inflammatory processes and constriction of the smooth muscle in airway walls (bronchoconstriction). It is characterised by airflow obstruction and increased responsiveness of the airways to various stimuli. Symptoms include recurrent episodes of wheezing, breathlessness, chest tightness and coughing. Typical asthma symptoms tend to be variable, intermittent and worse at night. Asthma is commonly triggered by viral respiratory infections, exercise or external factors such as smoke, a change in weather conditions and allergens, for instance pollen, mould and house dust mites.

Asthma usually develops in childhood but may start at any age. It runs in some families but many people with asthma have no other family members affected. In adults, asthma is more common in women than in men.[1] There is no cure for asthma, although people may experience long periods of remission. Poorly controlled asthma can have a significant impact on the quality of life of the affected individual and his or her family. However, there may be variation in an individual's perception of the symptoms and how he or she adapts to the condition over time. Clinical measures such as lung function may not correlate with an individual's quality of life scores, but if asthma is well controlled near-maximal scores on quality of life instruments can be achieved.

Classification of asthma

There are several ways of categorising different types of asthma, including:

- *Intrinsic and extrinsic asthma*. Asthma can be divided into extrinsic (external cause) and intrinsic (when no causative agent can be found) asthma. Extrinsic asthma is triggered by allergens and hence it is also termed 'allergic asthma'. In extrinsic asthma the immune system reacts to substances such as pollen and produces antibodies. Individuals with a predisposition to developing such allergies are said to be atopic and may develop any combination of the triad of hay fever, eczema and asthma. In the case of asthma, the allergic reaction is observed in bronchi and bronchioles, which results in the production of excess mucus that obstructs the air passages. Extrinsic asthma is commonly seen in children. About 90% of childhood asthma cases are caused by specific allergens. Individuals with a family history of atopy are at a higher risk of developing extrinsic asthma. In contrast, intrinsic asthma is a non-seasonal, non-allergic form of asthma, which usually first occurs at a later point in life than allergic asthma. Intrinsic asthma tends to be chronic and persistent rather than episodic. It is not related to specific allergens and may be provoked by the inhalation of chemicals such as cigarette smoke or cleaning agents, non-steroidal anti-inflammatory drugs, chest infections, emotion, exercise, cold air, food preservatives or various other non-specific irritants.
- *Eosinophilic and non-eosinophilic asthma (neutrophilic asthma)*. Asthma can also be categorised as eosinophilic or non-eosinophilic. There is some evidence that eosinophils may play an important proinflammatory role in the pathogenesis of asthma,[2,3] although there remains some uncertainty around this and other pathogenic mechanisms associated with asthma. Eosinophils are found in the airways of asthmatics but not healthy subjects and are believed to be related to exacerbations. It has also been noted that suppression of eosinophil infiltration is often associated with amelioration of symptoms[2] but that the relationship is not close. Poor inflammation control is most closely related to the risk of future exacerbations. The presence of eosinophils may be used to direct treatment as patients without eosinophilic inflammation are thought to be less responsive to inhaled corticosteroid (ICS) treatment.[4] High levels of eosinophils are correlated with high levels of fractional exhaled nitric oxide (FeNO) and it is thought that FeNO could be used as a biomarker of eosinophilic inflammation

and therefore of ICS responsiveness.[5,6] However, the presence of eosinophils is not always a marker of severity of disease; fatal asthma may be associated with neutrophilia rather than eosinophilia.[7] Targeting the type of inflammation may be a better guide to treatment than measures of disease severity alone. For instance, glucocorticosteroids are typically very effective in eosinophilic inflammation but less so if the inflammation is neutrophilic.

- *Eosinophilic and non-eosinophilic airway disease*. Eosinophilic inflammation occurs in both asthma and chronic obstructive pulmonary disease (COPD) and in both cases the appropriate treatment is ICSs.[6] There is a view held by some clinicians that, rather than a diagnosis of asthma, a diagnosis of responsiveness to ICSs [irrespective of diagnostic label (asthma or COPD)] may be a more helpful approach in terms of directing treatment, reducing costs and reducing exacerbations.[6] However, this form of classification has not yet been officially adopted in the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) guidelines[8] and this report will focus on the diagnosis of asthma as described in these guidelines.
- *Molecular approaches to classifying asthma phenotypes*. There is an increasing trend to characterise asthma by molecular and cellular factors to enable more targeted and personalised therapy. Such efforts are ongoing and specific phenotypes and the implications of these are not yet fully elucidated.[9]
- *Exercise-induced bronchoconstriction (EIB)*. Most patients with asthma will experience EIB but approximately 11% of the population without other forms of asthma also experience this. It is characterised by a reduction in the forced expiratory volume in the first second (FEV_1) of > 10% after exercise and can be treated pharmacologically with short-acting beta2-agonists (SABAs) or leukotriene receptor antagonists (LTRAs) and non-pharmacologically with a light warm-up before vigorous exercise for example. The exact mechanisms behind EIB are not fully understood but may include neural and biochemical mediators.[10]

Prevalence of asthma

It is estimated that 5.4 million people in the UK are receiving treatment for asthma. Of these, 1.1 million are children (one in 11) and 4.3 million are adults (one in 12) [see www.asthma.org.uk/asthma-facts-and-statistics (accessed 21 May 2015)]. The UK has one of the highest prevalence rates of asthma symptoms in children worldwide. In adults, occupational asthma, for instance because of allergens from animals, flour or grain, may affect up to 20% of the workforce exposed to the sensitiser. An analysis of routine UK databases undertaken by Anderson *et al.*[11] indicates that the prevalence of asthma in all age groups has risen substantially between 1955 and 2004 (*Figure 1*).

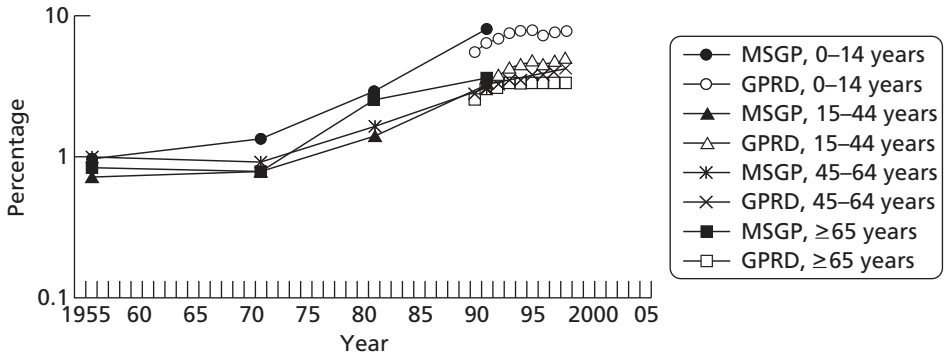


FIGURE 1 Patients consulting general practitioners for asthma per 100,000 population, England and Wales, 1955–88.[11] GPRD, General Practice Research Database; MSGP, Mortality Statistics in General Practice. Reproduced from *Thorax*, 50 years of asthma: UK trends from 1955 to 2004, Anderson H, Gupta R, Strachan D, Limb E, vol. 62, pp. 85–90, 2007, with permission from BMJ Publishing Group Ltd.

Estimates of the prevalence of doctor-diagnosed asthma by age and sex are presented in *Table 1*, taken from the Health Survey for England 2011.[12]

Based on data from the 2010 Health Survey for England,[12] the prevalence of lifetime doctor-diagnosed asthma was 16% among men and 17% among women and decreased with age for both sexes. At the time of the survey, approximately 9% of men and 10% of women were classed as currently having asthma as they had experienced symptoms of asthma or were controlling their symptoms with medication in the previous 12 months. The proportion of respondents with asthma in the last 12 months did not vary by age group in either sex. Of those individuals who had doctor-diagnosed asthma, 30% of men and

TABLE 1 Prevalence of doctor-diagnosed asthma by age and sex, 2010

	Age group (years)							
	16–24	25–34	35–44	45–54	55–64	65–74	75+	Total
Men (%)								
Ever								
Self-reported doctor-diagnosed asthma	25	20	16	12	13	13	9	16
Doctor-diagnosed asthma and in last 12 months								
Symptoms of asthma	6	7	7	4	5	5	4	5
No symptoms, asthma controlled with medications	4	3	3	3	3	5	4	3
Current asthma: with symptoms of asthma or taking medication	10	10	10	7	8	9	8	9
No symptoms and no medication for asthma	90	90	90	93	92	91	92	91
Women (%)								
Ever								
Self-reported doctor-diagnosed asthma	21	20	17	16	15	16	14	17
Doctor-diagnosed asthma and in last 12 months								
Symptoms of asthma	7	7	7	7	8	5	5	7
No symptoms, asthma controlled with medications	4	3	4	3	2	7	5	4
Current asthma: with symptoms of asthma or taking medication	10	10	11	10	10	12	10	10
No symptoms and no medication for asthma	90	90	89	90	90	88	90	90
Bases (unweighted)								
Men	378	493	642	624	642	518	402	3699
Women	476	695	820	874	722	566	563	4716
Bases (weighted)								
Men	644	701	754	720	608	429	318	4174
Women	610	686	760	730	630	470	441	4327

Source: Hall and Mindell.[12]

39% of women had experienced an asthma attack in the previous 12 months. Of these patients, 42% of men and 52% of women had experienced symptoms during the day in the last week, 22% of men and 29% of women reported that their symptoms had interfered with their usual activities in the last week and 19% of men and 28% of women reported difficulties with sleep in the last week.[12]

Any data on the prevalence of asthma are subject to the problems associated with diagnosing asthma. As there is no definitive, objective test, there is significant over- and underdiagnosis of the condition.

Asthma mortality

In England and Wales, deaths resulting from asthma are rare. In 2011, the Office for National Statistics (ONS) reported that there were 1041 reported deaths from asthma in England and Wales [see www.ons.gov.uk/ons/rel/vsob1/death-reg-sum-tables/2011–provisional-/deaths-summary-tables—2011.xls (accessed 21 May 2015)]. Approximately two-thirds (67.2%) of these were in women and almost 79% of all asthma deaths were in adults aged > 65 years (*Figure 2*).

As noted elsewhere,[13] audit and case–control studies[14–18] indicate that risk factors for death can be separated into four categories: (1) disease severity, (2) medical care factors both before and during the fatal episode, (3) health behaviour such as reduced concordance with prescribed medication, poor inhaler technique and reduced contact with primary care services and (4) adverse psychosocial factors. Shepherd *et al.*[13] suggest that, given this categorisation, a proportion of asthma-related deaths are preventable, especially in patients aged < 65 years.

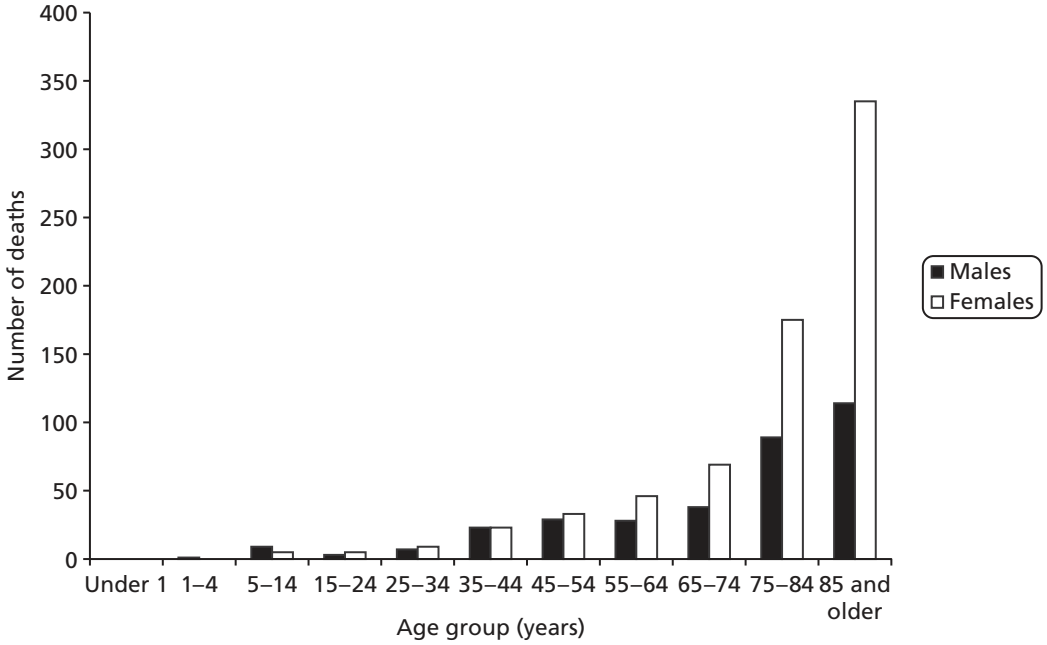


FIGURE 2 Registered deaths from asthma, England and Wales, 2011. Source: ONS [see www.ons.gov.uk/ons/rel/vsob1/death-reg-sum-tables/2011–provisional-/deaths-summary-tables—2011.xls (accessed 21 May 2015)].

Impact of the health problem

Impact of asthma on patients

The principal symptoms of asthma are wheezing attacks and episodic shortness of breath. An acute onset of symptoms is known as an exacerbation. Coughing, which worsens at night, may also be a symptom. Asthma exacerbations tend to vary considerably in terms of frequency and duration. Some people experience one or two per year lasting for a few hours, whereas others have exacerbations lasting for weeks or experience them more frequently. Exacerbations may be precipitated by a wide range of triggers, as described in *Classification of asthma*. Asthma is a major cause of impaired quality of life and may impact on a patient's work, recreational activities, physical activities and emotions. However, although patients' health-related quality of life (HRQoL) may be impacted on by poor asthma control and the incidence of exacerbations, it has been noted elsewhere that meeting clinical treatment goals may not result in noticeable changes in a patient's quality of life.[13]

In the long term, asthma may lead to permanent airflow obstruction and associated loss of quality of life, especially when it is persistent or poorly controlled.[19] Asthma also has a substantial impact on a patient's ability to work and study and has been estimated to result in at least 12.7 million lost working days per year.[12] Many patients will undergo regular monitoring and will be required to take medication for the rest of their life. There have been concerns that long-term ICS use may reduce growth rates in children, although evidence is conflicting and it appears that any reduction in growth may be transient, with patients eventually achieving a normal adult height.[20,21]

Burden on the NHS

Given the high prevalence of people with asthma, asthma treatment represents a significant cost to the NHS. The Health Survey for England 2010 estimated that direct health-care costs associated with asthma are £1B per year.[22] In addition, estimates from 2002 indicate that general practitioner (GP) prescriptions alone are worth approximately £600M per year.[22]

As asthma is an incurable condition, treatment, or at the least monitoring, is usually required for the remainder of the patient's lifetime. However, as the diagnosis of asthma is not definitive there is the potential for misdiagnoses to go undetected for many years or even an entire lifetime. Misdiagnosis can occur when a patient appears to respond to treatment but in fact has experienced a natural resolution of the symptoms of another underlying condition such as a cold, a respiratory infection or allergy. In these cases, patients will appear well controlled and a treating physician may simply assume that the treatment is working. The BTS/SIGN guidelines[8] recommend that patients who are well controlled should 'step down' their therapy dose. This could result in a patient being taken off treatment altogether and their diagnosis being reconsidered. However, clinical input to this review suggests that step down of doses does not always occur as treatment is relatively cheap per patient and physicians are cautious not to risk exacerbations. As such, there may be long-term unnecessary NHS expenditure associated with these misdiagnoses. Similarly, both overtreatment and undertreatment of patients who have been correctly diagnosed with asthma may be sources of substantial NHS expenditure. Undertreatment may increase costs to the NHS as poor control may lead to an increased rate of severe exacerbations, which require additional primary care management and acute hospital admissions. Overtreatment may increase costs to the NHS because a patient may be able to receive the same level of symptom control with less medication and so the condition could have been treated as effectively at a lower cost.

Guidelines for the diagnosis and management of asthma

Detailed guidelines on the diagnosis and management of asthma have been published and updated.[8] These guidelines are referred to as the BTS/SIGN guidelines throughout the remainder of this report.

Diagnosis of asthma

The diagnosis of asthma is a clinical one and there is no standardised definition of the condition. Central to all definitions in adults is the presence of symptoms (wheezing, breathlessness, chest tightness and cough) and of variable airflow obstruction measured through objective tests of lung function [such as peak expiratory flow rate (PEFR) and FEV_1 divided by forced vital capacity (FVC), known as the Tiffeneau–Pinelli index (FEV_1/FVC)] and percentage of predicted FEV_1 (FEV_1%; calculated as the percentage of the predicted FEV_1 for a person of the same height, sex and age without diagnosed asthma). Variability in PEFR and FEV_1, either spontaneously or in response to therapy, is a characteristic feature of asthma. The BTS/SIGN guidelines[8] indicate that the severity of asthma should be judged according to symptoms and the amount of medication required to control symptoms.

More recently, descriptions of asthma have included airway hyper-responsiveness and airway inflammation. It is unclear how these features relate to each other, how they are best measured and how they contribute to the clinical manifestations of asthma.

Figures 3 and *4* present the diagnostic pathways for children and adults, respectively, as they currently stand.[8]

Diagnosis in children is clinically based on recognising a characteristic pattern of episodic symptoms in the absence of an alternative explanation. Lung function tests are less useful because of variability and the inability of very young children to perform these tests reliably. According to the BTS/SIGN guidelines,[8] clinical features that increase the probability of asthma include:

- *More than one of the following symptoms: wheeze, cough, difficulty breathing, chest tightness, particularly if these symptoms:*
  - *are frequent and recurrent*
  - *are worse at night and in the early morning*
  - *occur in response to, or are worse after, exercise or other triggers, such as exposure to pets, cold or damp air, or with emotions or laughter*
  - *occur apart from colds*
- *Personal history of atopic disorder*
- *Family history of atopic disorder and/or asthma*
- *Widespread wheeze heard on auscultation*
- *History of improvement in symptoms or lung function in response to adequate therapy.*

Reproduced with permission from BTS/SIGN guidelines[8]

If asthma is suspected, an initial clinical assessment should be carried out to estimate the probability of asthma. According to the BTS/SIGN guidelines,[8] based on initial clinical assessment a child can be classified according to their risk of having asthma as:

- high probability, where an asthma diagnosis is likely
- low probability, where a diagnosis other than asthma is likely
- intermediate probability, where the likely diagnosis is uncertain.

For children identified as having a low probability of asthma, a more detailed investigation and specialist referral should be considered. For children with a high probability of asthma, a trial of treatment should be started immediately, with review at 6–8 weeks. When the response is good, the ICS dose should be reassessed every 6 months. Those with a poor response to treatment should undergo more detailed investigations.

There is insufficient evidence at first consultation to make a firm diagnosis of asthma in some children, particularly those aged < 4–5 years.[8] For those children who can perform spirometry and for whom airway obstruction is evident, change in forced expiratory flow volume or peak expiratory flow monitoring should be assessed in response to an inhaled bronchodilator and/or in response to a trial of treatment for a specified period.

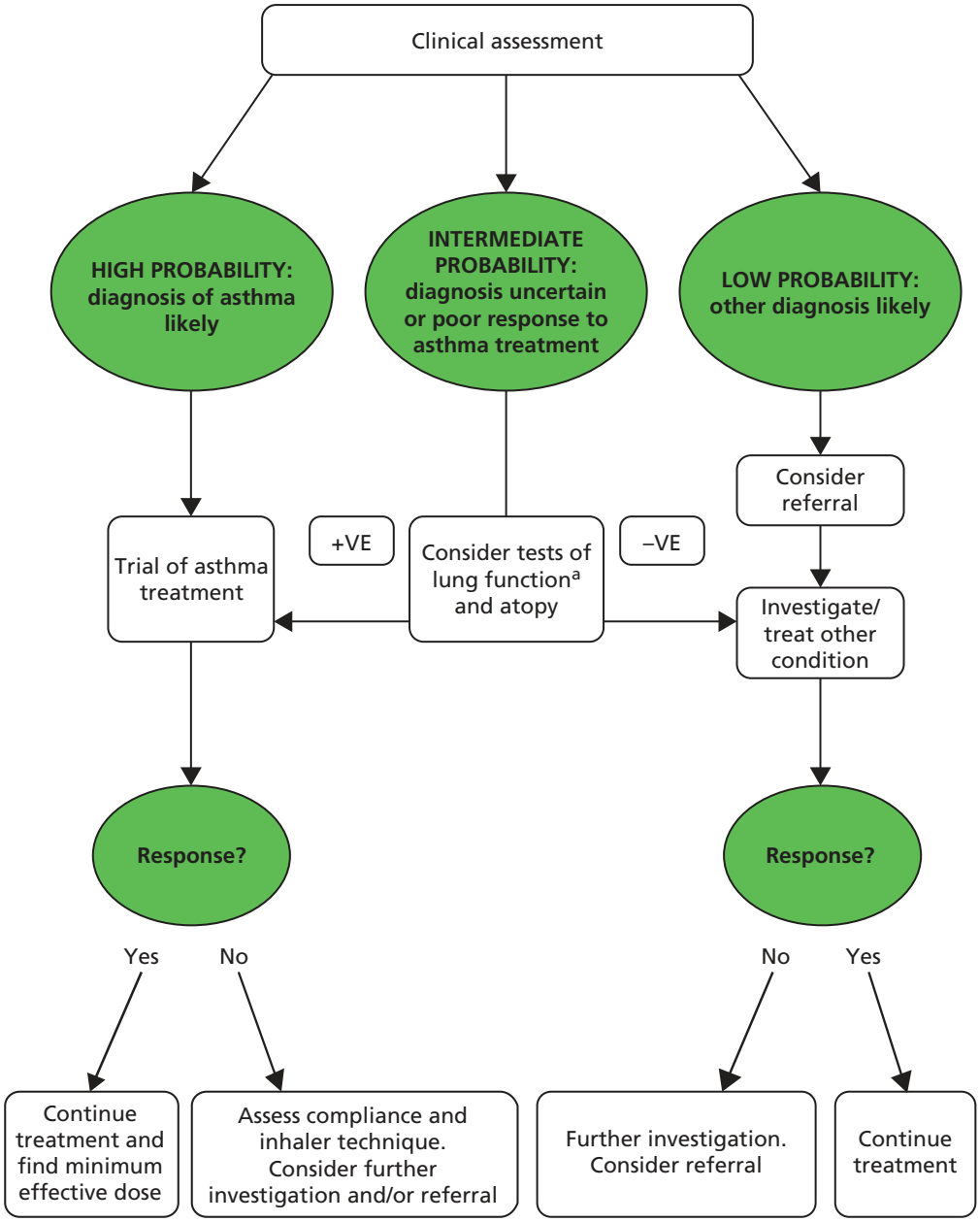


FIGURE 3 Diagnosis of asthma in children according to BTS/SIGN guidelines.[8] –ve, negative; +ve, positive. a, Lung function tests include spirometry before and after bronchodilator (test of airway reversibility) and possible exercise or methacholine challenge (tests of airway responsiveness). Most children over the age of 5 years can perform lung function tests. Reproduced with permission from BTS/SIGN. *British Guideline on the Management of Asthma: a National Clinical Guideline*. Edinburgh and London: BTS/SIGN; 2012.[8]

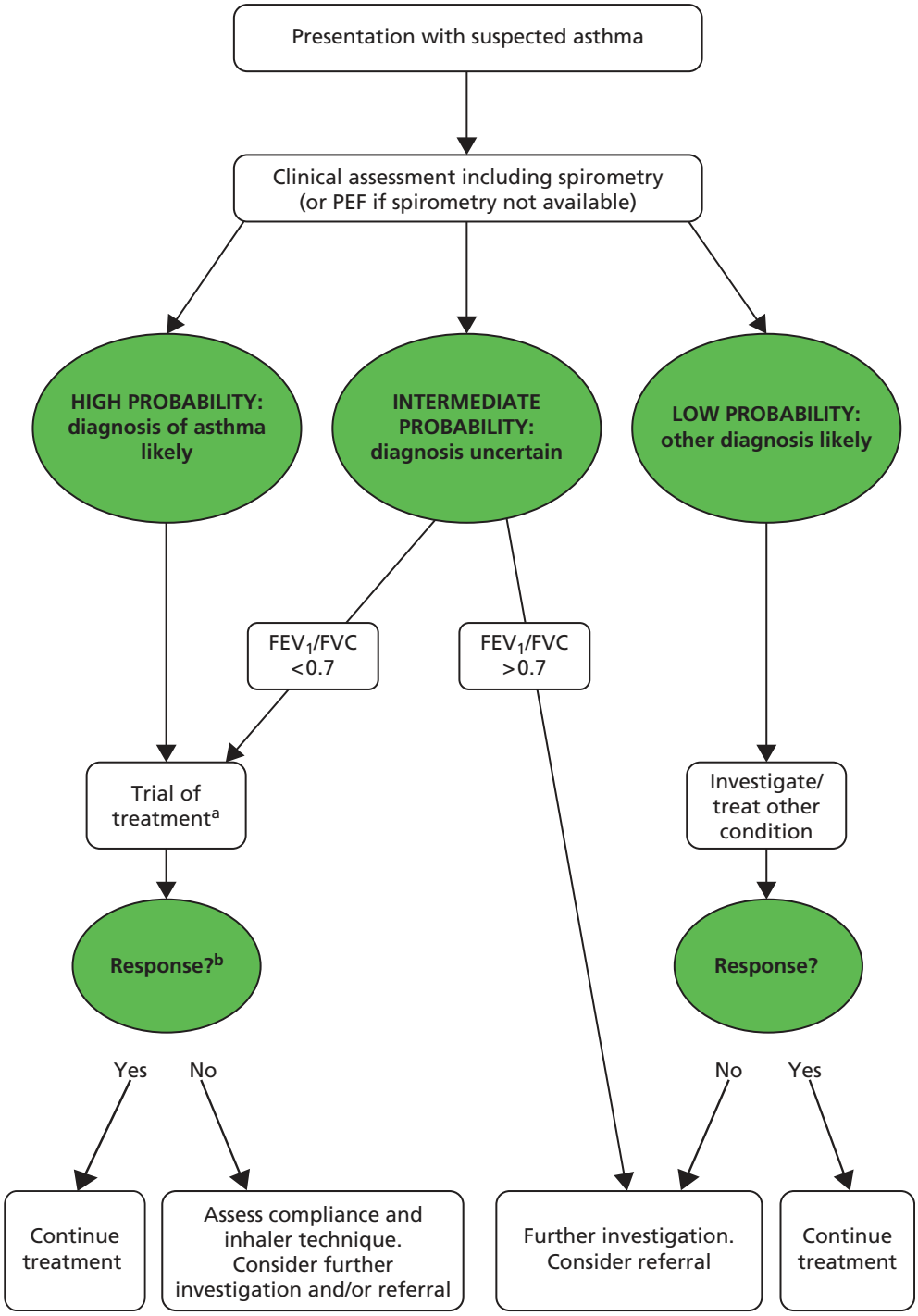


FIGURE 4 Diagnosis of asthma in adults according to BTS/SIGN guidelines.[8] PEF, peak expiratory flow. a, See section 2.5.1 of the BTS/SIGN guidelines; b, see table 6 of the BTS/SIGN guidelines. Reproduced with permission from BTS/SIGN. *British Guideline on the Management of Asthma: a National Clinical Guideline*. Edinburgh and London: BTS/SIGN; 2012.[8]

In children with an intermediate probability of asthma who can perform spirometry and who have no evidence of airway obstruction, tests for atopic status, assessment of bronchodilator reversibility and, if possible, assessment of bronchial hyper-responsiveness using methacholine, exercise or mannitol should be considered, although these last three would be performed in secondary care. In such cases specialist referral should always be considered.

Other investigations to support a diagnosis of, or alternatively rule out, asthma in children include tests of eosinophilic airway inflammation using induced sputum or exhaled nitric oxide concentrations, tests of atopy by skin prick test or blood eosinophilia and chest radiography or other imaging techniques to investigate other causes.

Diagnosis in adults is also based on clinical history and includes the recognition of a characteristic pattern of symptoms and signs and the absence of an alternative explanation for them. However, in contrast to the diagnostic pathway for children, in adults spirometry is performed at the first consultation to assess the presence and severity of airflow obstruction.

As in the diagnosis of children, adults are also classified as having a high, low or intermediate probability of asthma. Chest radiography and specialist referral may be considered in any patient presenting atypically or with additional symptoms or signs.

Monitoring and management of diagnosed asthma

Asthma management aims to control symptoms (including nocturnal symptoms and exercise-induced asthma), prevent exacerbations and achieve the best possible lung function, with minimal side effects of treatment. For both children and adults, asthma is monitored and managed in primary care by routine clinical review on at least an annual basis. These reviews include (but are not limited to) assessment of a patient's symptom score (using a validated questionnaire), exacerbations, oral corticosteroid (OCS) use, time off school or work, growth and inhaler technique; in adults, lung function is also assessed by spirometry of peak expiratory flow. Patients are managed in a stepwise manner, with escalation of medication until control is reached. This approach to pharmacological management for children and adults is represented in *Figures 5* and *6* respectively.[8] Treatment is started at the step most appropriate to the initial severity of the asthma, with the aim of achieving early control of symptoms and optimising respiratory function. Control is maintained by stepping up treatment as necessary and stepping down when control is good.

Monitoring asthma in children

The BTS/SIGN guidelines[8] on the management of asthma state that the monitoring of asthma in children should include the assessment and recording of:

- *symptom score, e.g. Children's Asthma Control Test, Asthma Control Questionnaire*
- *exacerbations, oral corticosteroid use and time off school/nursery due to asthma since last assessment*
- *inhaler technique*
- *adherence, which can be assessed by reviewing prescription refill frequency*
- *possession of and use of self management plan/personalised asthma action plan*
- *exposure to tobacco smoke*
- *growth (height and weight centile).*

Reproduced with permission from BTS/SIGN guidelines[8]

The guideline is indistinct with respect to the use of biomarkers such as FeNO in the monitoring of asthma. It states that 'a better understanding of the natural variability of biomarkers independent of asthma is required and studies are needed to establish whether subgroups of patients can be identified in which biomarker guided management is effective' (reproduced with permission from BTS/SIGN guidelines).[8]

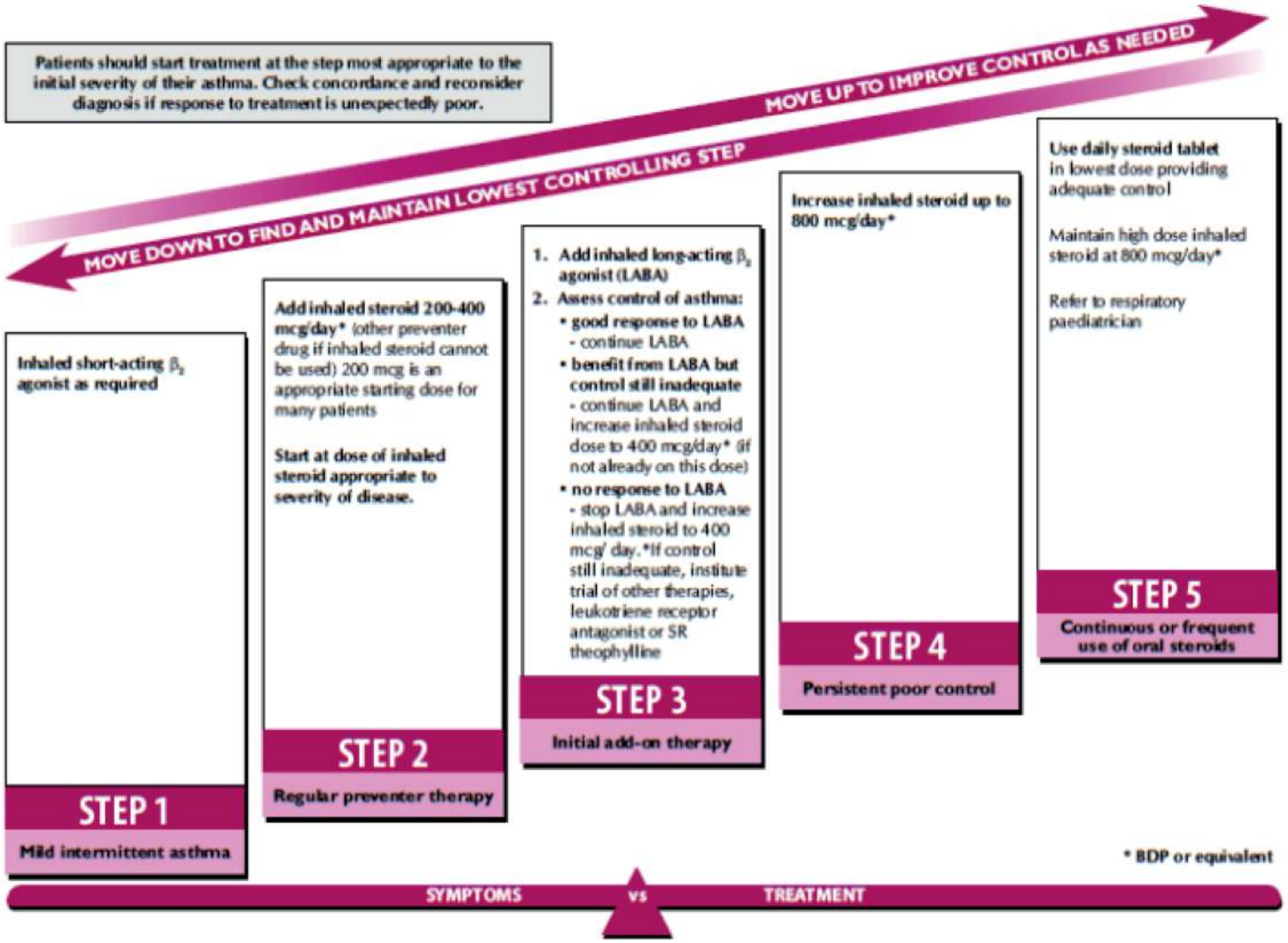


FIGURE 5 Management of asthma in children. BDP, beclomethasone dipropionate. Reproduced with permission from BTS/SIGN. *British Guideline on the Management of Asthma: a National Clinical Guideline*. Edinburgh and London: BTS/SIGN; 2012.[8]

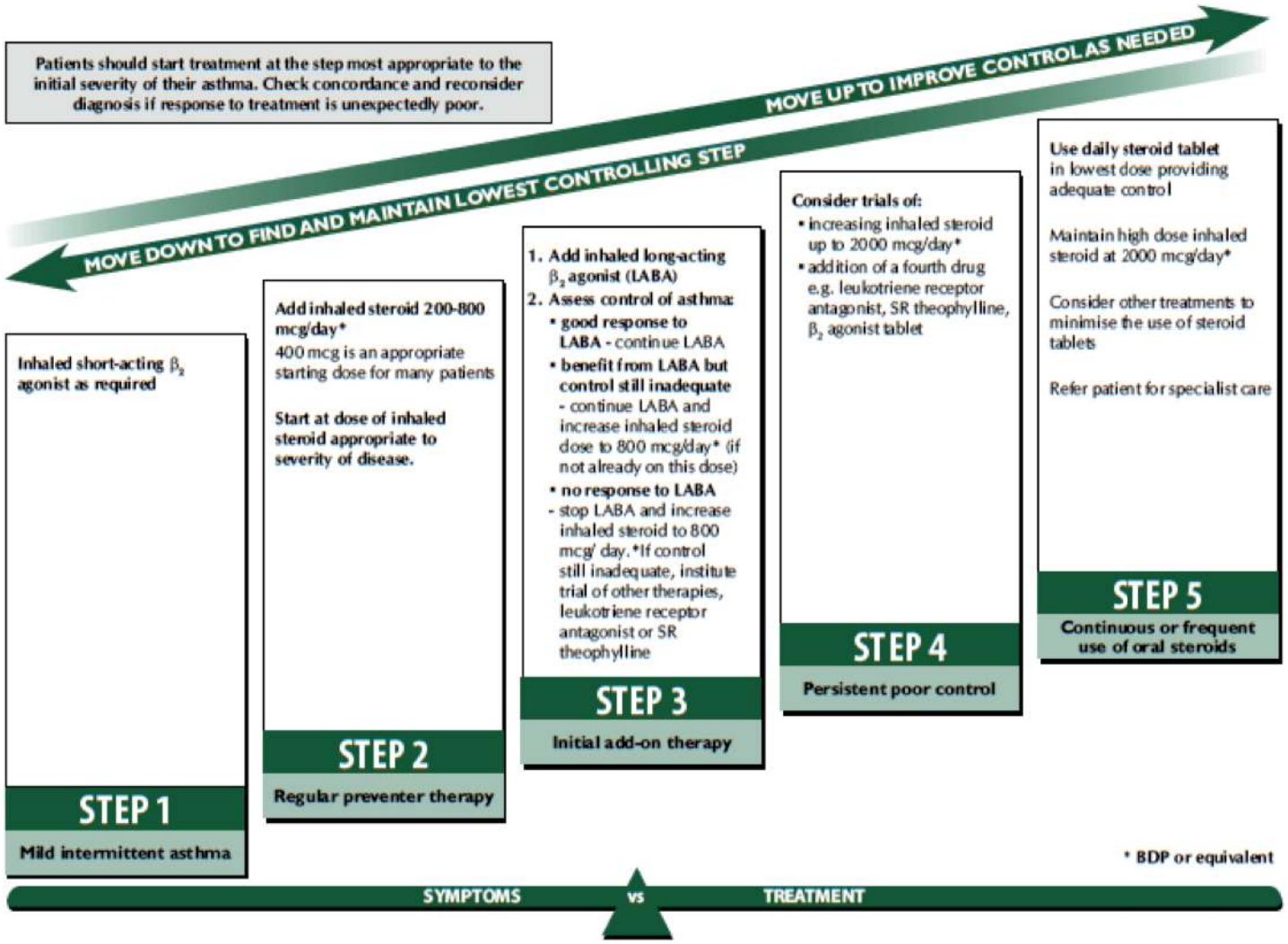


FIGURE 6 Management of asthma in adults. BDP, beclomethasone dipropionate. Reproduced with permission from BTS/SIGN. *British Guideline on the Management of Asthma: a National Clinical Guideline*. Edinburgh and London: BTS/SIGN; 2012.[8]

Monitoring asthma in adults

According to the BTS/SIGN guidelines,[8] symptom-based monitoring is adequate in the majority of adults with asthma. Those patients with poor lung function and a history of exacerbations in the previous year may be at a greater risk of future exacerbations for a given level of symptoms. For adults, the factors that should be assessed and recorded include:

- *symptomatic asthma control: best assessed using directive questions such as the . . . Asthma Control Questionnaire or Asthma Control Test*
- *lung function, assessed by spirometry or PEF [peak expiratory flow]*
- *exacerbations, oral corticosteroid use and time off work or school since last assessment*
- *inhaler technique*
- *adherence, which can be assessed by reviewing prescription refill frequency*
- *bronchodilator reliance, which can be assessed by prescription refill frequency*
- *possession of and use of self management plan/personal action plan.*

Reproduced with permission from BTS/SIGN guidelines[8]

Description of technologies under assessment

The potential role of FeNO devices in the diagnosis and management of asthma

Nitric oxide monitors measure FeNO. High FeNO levels in a patient with symptoms suggestive of asthma, such as coughing and wheezing, may suggest that the patient has eosinophilic asthma that could be treated with ICSs (see *Classification of asthma*). In individuals already diagnosed with asthma, changes in FeNO levels may indicate how well a patient is responding to ICS-based medication, whether medication is being adhered to and whether the dosage of medication should be increased or decreased (titrated or step-up/step-down adjustment). Consequently, FeNO monitors may have a role in the diagnosis, monitoring and management of patients with asthma.

However, current opinion is divided as to the utility of this measurement, in large part because of the potential for various factors to confound FeNO levels. Amongst these are age, sex, smoking status, exposure to environmental tobacco, pregnancy, height, measurement technique and atopic status and medication.[23,24] A further consideration is the observation that the dose–response plateaus within the therapeutic range of ICSs,[25,26] although doses up to 800 µg of beclomethasone dipropionate have been reported to be distinguishable from placebo.[27]

Current service provision

A number of FeNO devices have been developed. Some of these are hand-held portable devices (such as the devices that are the focus of this assessment) and others are stationary devices that measure FeNO through chemiluminescent techniques. Both types of FeNO monitor have been available for use in the NHS for a number of years. However, they are not available in all secondary care settings and their use in primary care is extremely rare. There are a number of possible reasons why FeNO devices have not had a more widespread diffusion into care, including the lack of clear guidance in the BTS/SIGN guidelines[8] on how they should be used, which itself is a consequence of contradictory research, and the previously prohibitive cost and operational requirements of large chemiluminescent devices.

A number of other diagnostic interventions are commonly used in the diagnosis of asthma in England and Wales, as described in *Diagnosis of asthma*. Some of these are performed in primary care, such as spirometry, reversibility testing and trials of treatment, whereas others are performed in secondary care, such as airway hyper-responsiveness [methacholine challenge test (MCT)] and sputum induction. As noted earlier, monitoring and management of asthma in diagnosed patients is guided by BTS/SIGN guidelines.[8]

Technologies under assessment

The three hand-held FeNO devices included in this assessment are NIOX MINO® (Aerocrine, Solna, Sweden), NIOX VERO® (Aerocrine) and NObreath® (Bedfont Scientific, Maidstone, UK).

NIOX MINO

The NIOX MINO device determines FeNO concentration in a breath sample. The device is small, hand-held and portable and it can be used by both adults and children. It requires a 10-second exhalation of breath by the patient at an exhalation pressure of 10–20 cmH_2O to maintain a fixed flow rate of 50 ± 5 ml/second. The last 3 seconds of the 10-second exhalation are analysed by a calibrated electrochemical sensor to give a definitive result in parts per billion (ppb). Clinical cut-off values can be applied to the FeNO values to categorise readings as low, intermediate or high, according to the reference ranges for ages < 12 years and ≥ 12 years, as detailed in the sponsor's submission (Aerocrine. *Clinical Guide to Interpretation of FeNO Values*. Sponsor's submission, 2013).

The NIOX MINO device is precalibrated and designed to ensure a service- and calibration-free system. It can be used as a stand-alone device or connected to a PC for monitoring with the NIOX MINO Data Management Program and for use with electronic medical record systems.

The device is Conformité Européenne (CE) marked and was launched in the UK in November 2004. According to information provided by the manufacturer,[28] there are currently 18 units available in primary care settings, including general practices and nurse outreach projects, and 197 units in 127 hospitals across the UK.[29] The manufacturer claims that NIOX MINO is indicated for use as follows:

- to diagnose the specific type of airway inflammation to guide treatment
- to predict the onset of asthma symptoms or loss of asthma control as a result of eosinophilic airway inflammation
- to monitor compliance to corticosteroid therapy and the effectiveness of treatment (frequency of exacerbations).

NIOX VERO

During the assessment, Aerocrine began launching a new FeNO device that is intended to replace the NIOX MINO device. The new device is called the NIOX VERO. This is a battery-powered device that features a longer operational life and extended test volume life than the NIOX MINO device.

NObreath

The NObreath device is a diagnostic monitoring device that measures FeNO. The reading is presented in ppb and is claimed to be directly related to the severity of inflammatory disease (e.g. asthma). NObreath requires 12 seconds of exhalation of breath in adults and 10 seconds in children. The device weighs approximately 400 g (including batteries). It has a battery life that lasts for up to 120 tests. The device is CE marked. The device does not have a set lifetime as sensor cells can, and should, be replaced every 2 years.

Anticipated costs associated with the intervention

The marginal per-test costs of each of the three technologies considered within this assessment depend on both fixed costs, such as the initial cost of the devices, and variable costs, such as the costs of consumables.

The NIOX MINO device has a unit cost of £2100 and has an effective unit lifetime of 3 years or 3000 tests (whichever comes first). The NIOX VERO device has a unit cost of £2310 and has an effective unit lifetime of 5 years or 5000 tests (whichever comes first). The NObreath device costs £1995 and has an unlimited unit lifetime. Maintenance for the NObreath device is provided free of charge by Bedfont Scientific.

Test kits for NIOX MINO are available in packs of 300 at a price of £1350, packs of 500 at a price of £2100 or packs of 1000 at a price of £3950. Test kits for NIOX VERO are available in packs of 300 at a price of £1500, packs of 500 at a price of £2200 or packs of 1000 at a price of £4200. Mouthpieces for NObreath are available in packs of 50, 100, 300 or 1000 at prices of £195, £365, £995 and £2995 respectively.

The NObreath device requires replacement of the sensor unit every 2 years at a cost of £295. Besides test kits, there are no other replacement costs for the NIOX MINO and NIOX VERO devices.

This information is summarised in *Table 2*.

TABLE 2 Cost of equipment and consumables for the NIOX MINO, NIOX VERO and NObreath devices

Item	NIOX MINO (£)	NIOX VERO (£)	NObreath (£)
Lifetime	3 years or 3000 tests	5 years or 5000 tests	Unlimited
Equipment cost	2100	2310	1995
Test kits – 100	NA	NA	365
Test kits – 300	1350	1500	995
Test kits – 500	2100	2200	NA
Test kits – 1000	3950	4200	2995
Sensor replacement	NA	NA	295
Maintenance	NA	NA	Provided free by Bedfont Scientific

NA, not applicable.

Chapter 2 Definition of the decision problem

Purpose of the decision to be made

The aim of the assessment was to assess the clinical effectiveness and cost-effectiveness of FeNO measurement in people with asthma. This was separated into two distinct questions:

1. What is the clinical effectiveness and cost-effectiveness of FeNO testing in the diagnosis of asthma in adults and children?
2. What is the clinical effectiveness and cost-effectiveness FeNO testing in the management and monitoring of asthma in adults and children?

The cut-off values used in diagnostic technologies affect their sensitivity and specificity and result in different proportions of patients being true positives (TPs), true negatives (TNs), false positives (FPs) and false negatives (FNs). The consequences of being TP, TN, FP and FN are different in terms of costs and health impacts; hence, the highest sum of sensitivity and specificity may not necessarily lead to optimal health outcomes. This is relevant to the use of FeNO in the diagnosis of asthma and also to its use in guiding asthma management.

Definition of the scope of the assessment

The scope of this assessment was informed by two scoping workshops attended by specialist committee members (SCMs), the External Assessment Group (EAG), the manufacturers, the National Institute for Health and Care Excellence (NICE) and patient stakeholders. The definition of the decision problem reflects the initial NICE scope[29] and the subsequent discussions in the second workshop.

Definition of the interventions

Two monitors were identified at the scoping stage for this appraisal: NIOX MINO, which is manufactured by Aerocrine, and NObreath, which is manufactured by Bedfont Scientific. During the latter stages of the assessment, Aerocrine alerted the EAG to a follow-up device to NIOX MINO, the NIOX VERO device. This device is also considered within this assessment although the evidence base is limited. All three interventions are evaluated in the context of the diagnosis and management of asthma.

Populations and relevant subgroups

Relevant population for the assessment of FeNO in the diagnosis of asthma

The population of interest is people with clinical characteristics suggestive of asthma. Relevant subgroups are:

- any patient aged ≥ 5 years presenting to primary care with symptoms of asthma
- people with clinical characteristics suggestive of asthma who are difficult to diagnose
- patients who may experience different outcomes from those of the main population under assessment with the use of FeNO, defined as smokers, the elderly and pregnant women.

Relevant population for the assessment of FeNO in the management of asthma

The population of interest is patients aged ≥ 5 years and diagnosed with asthma. There are two subgroups of particular interest:

- those with good asthma control who are being considered for a dose reduction
- those with uncontrolled asthma who are experiencing exacerbations or worsening of symptoms and who are being considered for a dose increase of ICSs or who are being checked for compliance with treatment.

Comparators

The relevant comparators are diagnosis or management according to the current UK guidelines, as described in *Chapter 3*. In the diagnostic setting, the relevant comparator consists of the current diagnostic pathway without the use of FeNO measurements; this is different for children and adults (see *Guidelines for the diagnosis and management of asthma*). In the management setting, the relevant comparator is management according to current guidelines without the use of FeNO.

Relevant outcomes for the assessment

The assessment includes consideration of the available evidence across a wide range of clinical and economic outcomes.

Clinical considerations

The intermediate measures for consideration include:

- diagnostic test accuracy
- test failure rate.

The clinical outcomes for consideration include:

- asthma control, which includes asthma symptoms
- exacerbation rates, which includes the frequency of exacerbations requiring unscheduled contact with health-care professionals, visits to accident and emergency departments or hospitalisations
- clinical complications associated with acute exacerbations
- levels of ICSs
- use of OCSs
- adverse effects of treatment (including bronchodilators and steroids)
- HRQoL
- mortality.

Cost considerations

- Costs of equipment, reagents and consumables.
- Maintenance and renewal of equipment.
- Costs associated with asthma medication.
- Cost associated with acute exacerbations.
- Cost of further investigations avoided.

Place of the intervention in the diagnostic/treatment pathways

During the scoping phase of this appraisal, workshop attendees considered that the interventions should be assessed when added to current practice. There are a number of potential places within the diagnostic/treatment pathways where FeNO may be of clinical use and each is likely to have different consequences for clinical effectiveness and cost-effectiveness.

Position of FeNO in the diagnostic pathway: children

During the scoping workshop it was agreed that FeNO is likely to be of most use in positions 1, 2 and 3 in *Figure 7*. This figure is based on the BTS/SIGN clinical guidelines,[8] with input from a clinician about how the tests are used in practice (Dr John White, York Teaching Hospital NHS Foundation Trust, 17 July 2013, personal communication). This equates to patients who are difficult to diagnose. Depending on whether FeNO is used as a direct replacement for a test or as a rule-in or rule-out test at these positions in the pathway, it may have the ability to prevent expensive secondary care visits if used in primary care. In secondary care it may have additional value alone or in conjunction with existing secondary care tests. FeNO could also be considered to replace the whole pathway or be inserted at other points along the pathway. *Tables 3–5* detail the actions and consequences associated with some different replacement and

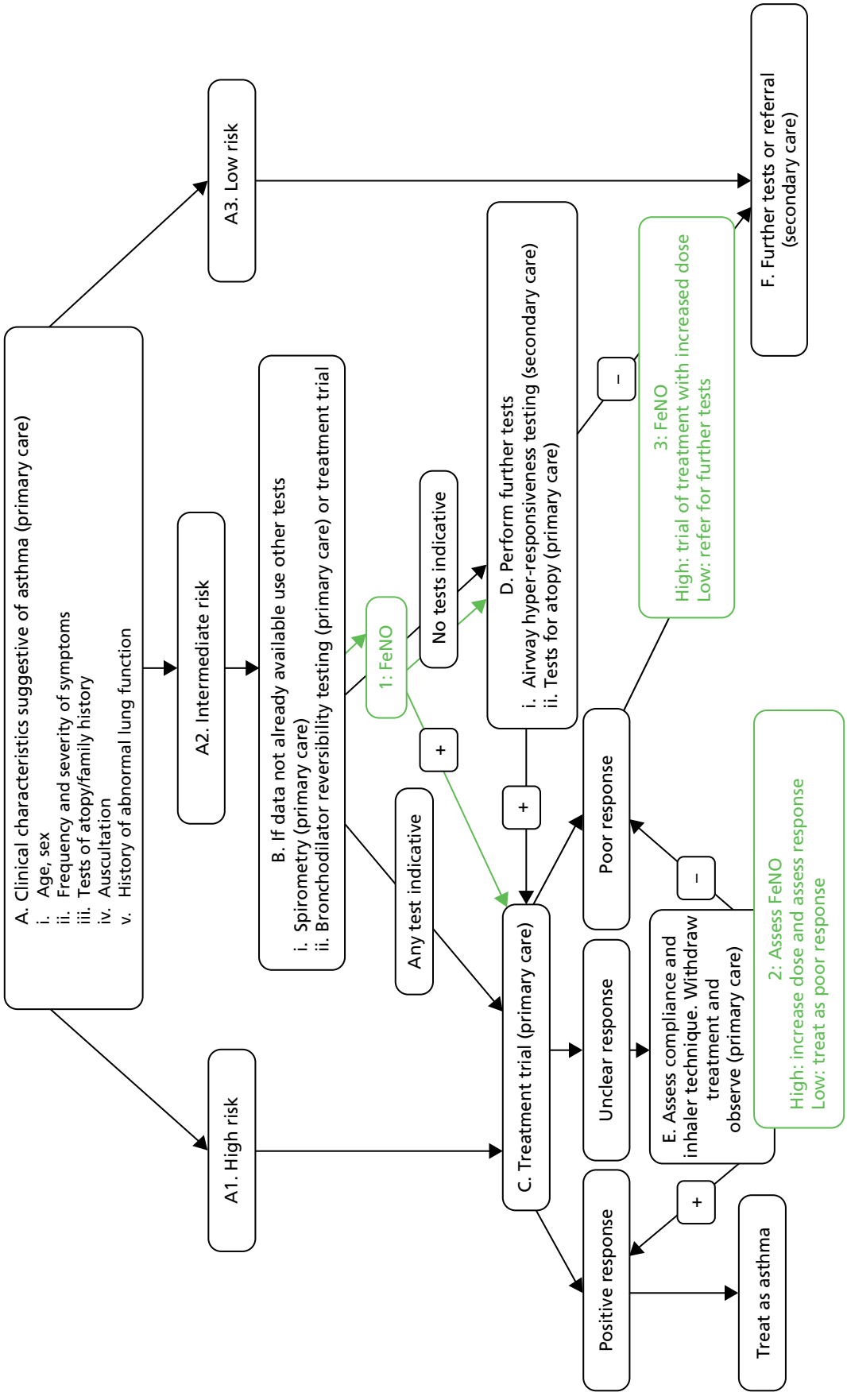


FIGURE 7 Potential positions for FeNO in the diagnostic pathway: children. Source: BTS/SIGN guidelines[8] with clinical input from Dr John White (17 July 2013, personal communication).

TABLE 3 Consequences of using FeNO as a direct replacement for the whole pathway or for airway hyper-responsiveness in patients indicated for this test within the pathway: adults and children

Replacement scenario	FeNO measurement	Action taken	Consequence 1	Consequence 2
TP	High FeNO measurement	Treat as asthma	Correct diagnosis of asthma reached	None
FP			Patient's misdiagnosis goes undetected until worsening of symptoms or routine review or continues lifelong	None
TN	Low FeNO measurement	Treat as not asthma	Further tests for other conditions	Correct diagnosis reached
FN				Further tests negative, re-enter asthma pathway or remain misdiagnosed until exacerbation or return to GP with ongoing symptoms

TABLE 4 Consequences of using FeNO as a rule-out test before airway hyper-responsiveness: adults and children

Rule-out scenario	FeNO measurement	Action taken	Consequence 1	Consequence 2
TP	High FeNO measurement	Treat as possibly asthma and undertake further confirmatory tests	Further tests confirm asthma diagnosis	Treat as asthma
FP			Further tests reject asthma diagnosis	Further tests for other conditions or diagnose as non-specific symptoms
TN	Low FeNO measurement	Treat as not asthma	Further tests for other conditions	Correct diagnosis reached
FN				Further tests negative, re-enter asthma pathway or remain misdiagnosed until exacerbation or return to GP with ongoing symptoms

TABLE 5 Consequences of using FeNO as a rule-in test before airway hyper-responsiveness: adults and children

Rule-in scenario	FeNO measurement	Action taken	Consequence 1	Consequence 2
TP	High FeNO measurement	Treat as asthma	Correct diagnosis of asthma reached	None
FP			Patient's misdiagnosis goes undetected until worsening of symptoms or routine review or continues lifelong	None
TN	Low FeNO measurement	Further tests for asthma	Tests for asthma negative	Further tests for other conditions or diagnose as non-specific symptoms
FN			Correct diagnosis of asthma reached	None

rule-in/rule-out scenarios. In rule-in scenarios, patients testing positive are assumed to have asthma and those testing negative go on to have further tests for asthma. In rule-out scenarios, those who test negative are assumed not to have asthma and those who test positive go on to have further tests for asthma.

Position of FeNO in the diagnostic pathway: adults

For the diagnostic pathway in adults, FeNO is thought to be of most use in positions 1 and 2 in *Figure 8*. This equates to patients who are difficult to diagnose. This figure is based on the BTS/SIGN clinical guidelines,[8] with input from a clinician about how the tests are used in practice (Dr John White, 17 July 2013, personal communication). This led to the understanding that, in nearly all or at least most cases, patients would undergo a trial of treatment or airway reversibility testing before being referred to secondary care, regardless of their FEV_1/FVC ratio. This is slightly different from our initial reading of the BTS/SIGN guidelines, in which only patients with a FEV_1/FVC ratio of < 0.7 would undergo these tests, with those with a FEV_1/FVC ratio of > 0.7 going on to secondary care for airway hyper-responsiveness testing. Our initial diagrammatic representation of the adult pathway can be viewed on the NICE website (www.nice.org.uk/guidance/dg12/documents/measurement-of-exhaled-nitric-oxide-concentration-in-asthma-niox-mino-and-nobreath-final-protocol2).

Depending on whether FeNO is used as a direct replacement for an existing test or as a rule-in or rule-out test at these positions in the pathway, it may have the ability to prevent expensive secondary care visits if used in primary care. In secondary care it may have additional value alone or in conjunction with existing secondary care tests. FeNO could also be considered to replace the whole pathway or be inserted at other points along the pathway.

Position of FeNO in the management pathway

The measurement of FeNO may be helpful in individuals diagnosed with asthma to facilitate titration of corticosteroid therapy, to check for compliance with medication and ultimately to lead to better asthma control. It is likely that management decisions would be based on a combination of the monitoring information collected at review and FeNO measurements. In these scenarios, high levels of FeNO could indicate that a patient's asthma is not fully treated and may be interpreted in combination with symptoms and medication use. A lack of control could be the result of worsening of the disease or it could be the result of failure to comply with medication. The latter could be ascertained through additional checks on the collection of prescriptions or the number of doses used, as measured by a dose-counter inhaler. Low levels of FeNO could indicate that asthma is well controlled and may be interpreted in combination with symptoms and medication use; this could guide a step down of medication and subsequent monitoring of control.

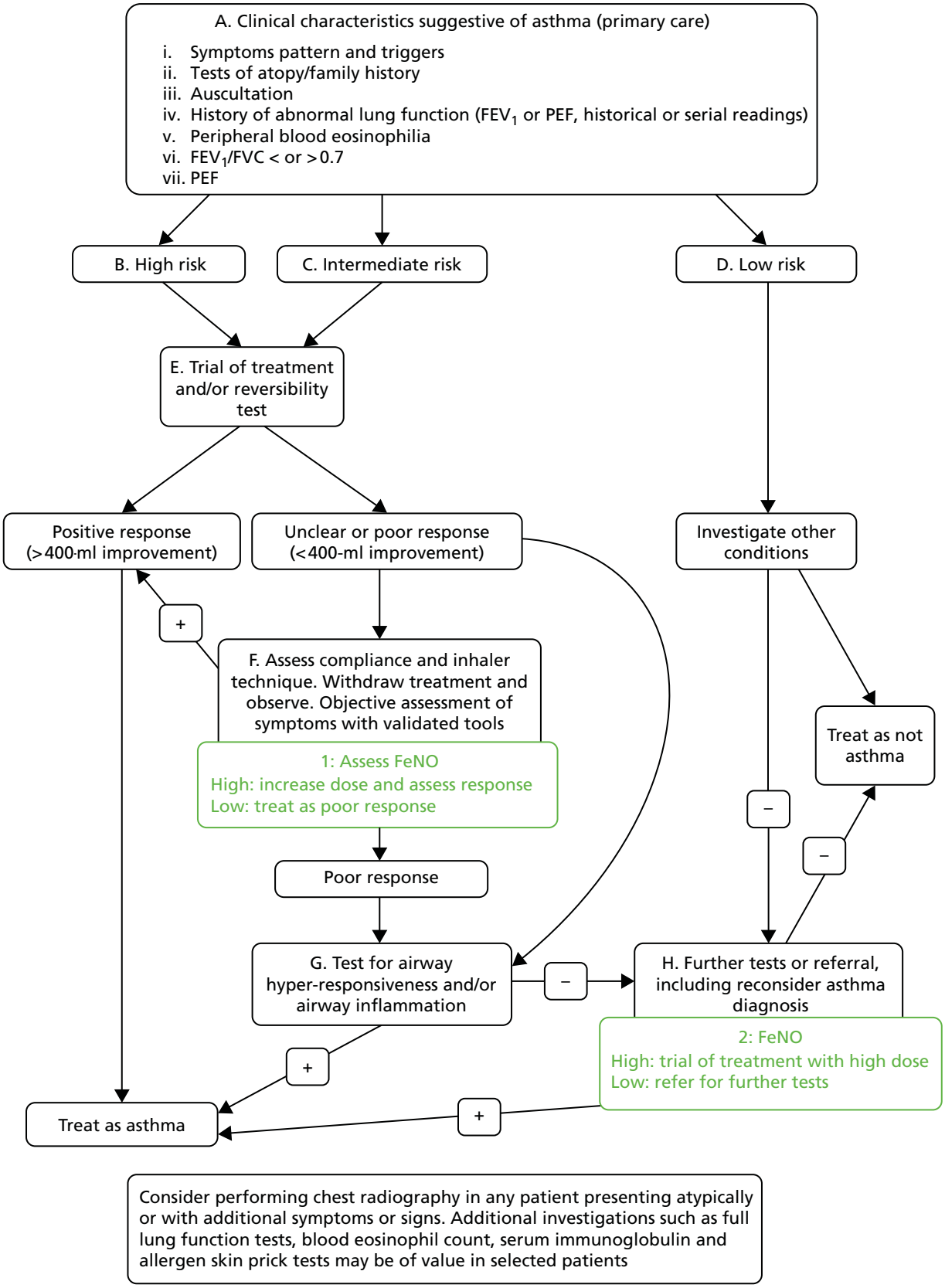


FIGURE 8 Potential positions for FeNO in the diagnostic pathway: adults. PEF, peak expiratory flow.
Source: BTS/SIGN guidelines[8] with clinical input from Dr John White (17 July 2013, personal communication).

Structure of the assessment report

The assessment report consists of two main parts: (1) an assessment of the clinical evidence relating to FeNO in the diagnosis and management of asthma and (2) an assessment of the cost-effectiveness of FeNO compared with standard care in the diagnosis and management of asthma.

Clinical evidence review

Two systematic reviews and one rapid review were conducted concurrently to identify clinical evidence relevant to the decision problem:

- *Rapid review of the equivalence of FeNO devices*. It was not clear at the outset if there would be sufficient primary research evidence relating to the three devices to inform the appraisal. As such, a review of the equivalence of these devices to other FeNO measurement devices was anticipated and appropriate searches were conducted. The review of equivalence was conducted in full when it became apparent that sufficient evidence was not available from the diagnostic accuracy review and management efficacy review. The equivalence review aimed to establish whether measurements from different FeNO measurement devices could be considered to be equivalent to one another and therefore whether studies that used other devices could helpfully inform this appraisal. This review was thought to be the least critical in terms of informing key model inputs and a rapid review using systematic methods was therefore conducted because of time and resource constraints. This represents a change to the published assessment protocol.[30] (www.nice.org.uk/guidance/dg12/documents/measurement-of-exhaled-nitric-oxide-concentration-in-asthma-niox-mino-and-nobreath-final-protocol2.)
- *Systematic review of the diagnostic accuracy of FeNO measurements for asthma*. The ideal study would recruit patients with symptoms of asthma, have a cohort design or randomise patients to diagnosis using FeNO or diagnosis using other methods and follow them to clinical outcomes. Such studies are known as end-to-end studies and demonstrate the ability of the test to improve patient outcomes. In the absence of such studies, diagnostic cohort studies represent the next best level of evidence, with modelling of clinical outcomes based on the numbers of patients classed as TP, TN, FP and FN. Below this are correlation studies. All levels of evidence were searched for in this review; lower levels of evidence were consulted when the higher levels of evidence were not identified. When available, three pairs of sensitivity and specificity values were selected: those that produced the highest sum of sensitivity and specificity; those that had the highest sensitivity for rule-in scenarios; and those that had the highest specificity for rule-out scenarios. In rule-in scenarios, patients testing positive are assumed to have asthma and those testing negative go on to have further tests for asthma. In rule-out scenarios, those who test negative are assumed not to have asthma and those who test positive go on to have further tests for asthma.
- *Systematic review of the efficacy of FeNO-guided management of asthma*. Existing systematic reviews of randomised controlled trial (RCT) evidence in adults[31] and children[32,33] meant that only RCT evidence was searched for in this review, with additional interrogation of the database for data on subgroups when RCT evidence was not found.

Cost-effectiveness assessment

The cost-effectiveness assessment of FeNO includes two components: a systematic review of existing economic analyses and the development of two de novo health economic models:

- *Systematic review of the cost-effectiveness of FeNO for the diagnosis and/or management of asthma*. A systematic review was undertaken to identify all existing economic analyses of FeNO testing for asthma; this includes published studies as well as evidence submitted by the manufacturers of NIOX MINO, NIOX VERO and NObreath. This included a critical appraisal of the available evidence and a summary of methodological problems and concerns relating to these analyses.
- *Development of two de novo models*. Independent health economic models were developed to assess the incremental cost-effectiveness of FeNO compared with standard care in the diagnosis and management of asthma.

Chapter 3 Clinical review

Methods

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

As described in *Chapter 2*, *Clinical evidence review*, two systematic reviews and one rapid review were conducted concurrently to identify clinical evidence relevant to the decision problem:

- rapid review of the equivalence of FeNO devices
- systematic review of the diagnostic accuracy of FeNO testing for asthma
- systematic review of the efficacy of FeNO-guided management of asthma.

The protocol is registered with PROSPERO (reference number CRD42013004149) and can be accessed at www.crd.york.ac.uk/NIHR_PROSPERO/.

Search methodology for the clinical reviews

Systematic searches were carried out between March 2013 and April 2013. Update searches were conducted in September 2013 for the diagnostic and management reviews. For the review of device equivalence and for both diagnostic and management reviews, the following databases were searched:

- MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (Ovid): 1948–present
- EMBASE (Ovid): 1974–present
- The Cochrane Library (Wiley Interscience):
    - Cochrane Database of Systematic Reviews (CDSR): 1996–present
    - Database of Abstracts of Reviews of Effects (DARE): 1995–present
    - Cochrane Central Register of Controlled Trials (CCRCT): 1898–present
    - Health Technology Assessment (HTA) database: 1995–present
    - NHS Economic Evaluation Database (NHS EED): 1995–present
- Science Citation Index Expanded (SCIE) (Web of Science): 1899–present
- Conference Proceedings Citation Index – Science (CPCI-S) (Web of Science): 1990–present.

The search strategies used in MEDLINE are provided in *Appendix 1*.

The following trial registers and websites were searched in March 2013 for all three reviews and again in September 2013 for the diagnostic and management reviews (search terms used are provided in *Appendix 1*):

- ClinicalTrials.gov (http://clinicaltrials.gov/)
- *meta*Register of Controlled Trials (www.controlled-trials.com/mrct/)
- US Food and Drug Administration Manufacturer and User Facility Device Experience (MAUDE) database (www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm)
- EuroScan International Network (http://euroscan.org.uk/).

Management review searches

Searches for the management review were developed following the identification of a 2009 Cochrane review.[31] Study design filters were not applied to the strategy in case lower levels of evidence were needed for the subgroups defined a priori in the protocol. The strategy (*Figure 9*) was made up of (1) free-text terms for NIOX MINO and NObreath (including manufacturer names), (2) subject heading and free-text terms for asthma (e.g. respiratory hypersensitivity, bronchoconstriction) and (3) subject heading and free-text terms for lower respiratory tract symptoms (e.g. coughing, wheezing, chest pain). Search strings (2) and (3) were combined with subject heading and free-text terms for exhaled nitric oxide and the results were added to the results for search string (1). Searches were limited to publications since 2009.

A summary of the search records retrieved from the searches is provided in *Table 6*.

Diagnostic review searches

Similar to the management review search strategy, the diagnostic search consisted of terms for NIOX MINO and NObreath, including manufacturer names, and subject heading and free-text terms for asthma and lower respiratory tract symptoms combined with terms for exhaled nitric oxide (see *Figure 9*). The strategy was combined with three filters: (1) a systematic reviews filter, (2) a RCT filter and (3) a diagnostic filter. No date limits were applied to the searches.

A summary of the search records retrieved from the searches is provided in *Table 7*.

Equivalence of devices review searches

The analytical validity study searches for NIOX MINO and NObreath were carried out using terms for NIOX MINO and NObreath and the manufacturer names without any application of filters and limits in the databases listed (*Figure 10*). The numbers of records retrieved by database are provided in *Table 7* (final column).

TABLE 6 Search records retrieved by database: management review

Database	Number of records
MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations	991
EMBASE	2269
CDSR	44
DARE	1
CCRCT	117
HTA database	8
SCIE	1387
CPCI-S	70
Total unique references	2747

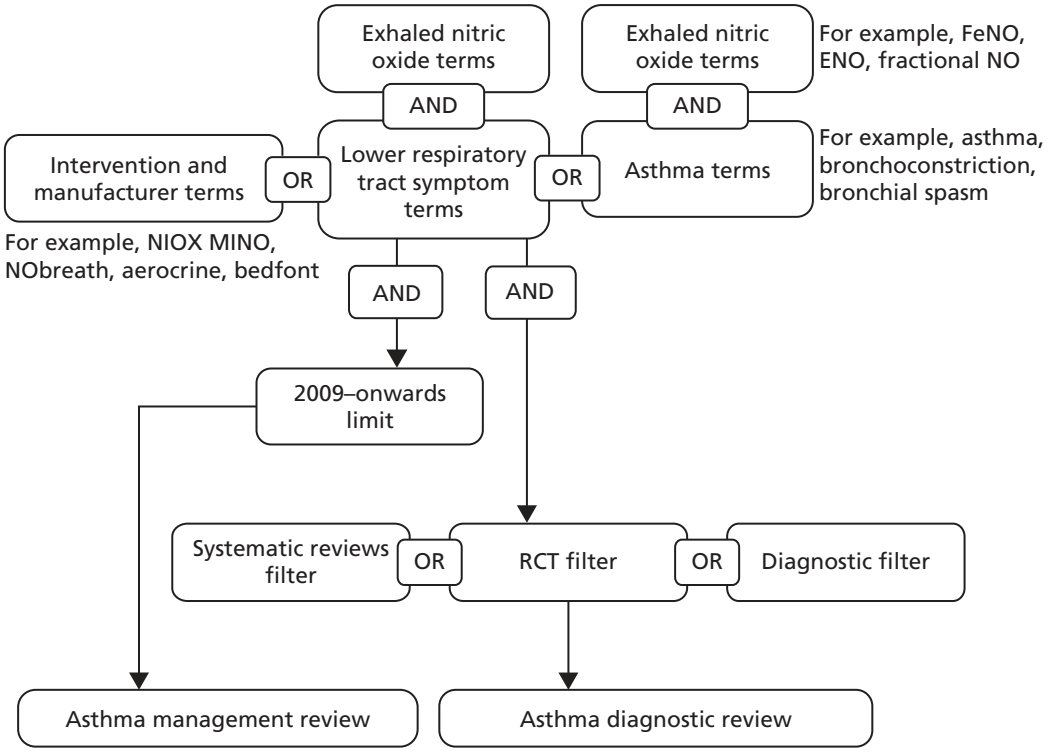


FIGURE 9 Management and diagnostic studies of FeNO devices.

TABLE 7 Search records retrieved by database: diagnostic review

Database	Search by study design			
	Systematic reviews	RCTs	Diagnostic studies	Equivalence review
MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations	26	958	377	97
EMBASE	114	1386	452	282
CDSR	44	–	–	0
DARE	1	–	–	0
CCRCT	–	509	–	10
HTA database	8	–	–	4
NHS EED	2	–	–	1
SCIE	76	637	284	92
CPCI-S	3	17	10	8
Total unique references	227	1635	680	309

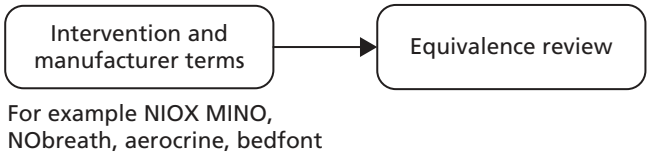


FIGURE 10 Equivalence studies of FeNO devices.

Additional search for NIOX VERO

Aerocrine's new device, NIOX VERO, was brought to the attention of the EAG in July 2013. An additional search was conducted on 13 August 2013 to check for any publications relating to this device that would have been missed by the original search. This search consisted of simply the term 'Niox Vero'. A summary of the search records retrieved from the searches is provided in *Table 8*.

Management and diagnostic review update searches: September 2013

In response to stakeholder comments received as part of the appraisal process, an update to the management and diagnostic reviews was undertaken in September 2013. *Table 9* summarises the search records retrieved. Searches were limited to papers published in 2013.

Reference management

All retrieved citations were downloaded into Reference Manager bibliographic software version 12 (Thomson ResearchSoft, San Francisco, CA, USA) and deduplicated to include only unique citations. The update searches were also deduplicated but not against the original searches.

Study selection

Retrieved citations were considered for inclusion in several stages. First, titles were considered and any studies obviously not relevant were excluded. Second, abstracts were consulted. At this stage, tags were applied to studies in Reference Manager to identify the device used, the age group of the participants and the study design. In instances in which it was obvious which review the study was likely to inform, this tag was also applied. In the third stage, articles tagged as the highest levels of evidence for each review were retrieved and the full texts were compared against the inclusion and exclusion criteria.

TABLE 8 Additional searches for NIOX VERO

Database	Number of records
MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations	0
EMBASE	0
CDSR	0
DARE	0
CCRCT	0
HTA database	0
NHS EED	0
SCIE	0
CPCI-S	0
ClinicalTrials.gov	0
*meta*Register of Controlled Trials	0
MAUDE database	0
EuroScan International Network	2

TABLE 9 Update of the management and diagnostic reviews: search records retrieved by database

Database	Number of records
MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations	206
EMBASE	341
CDSR	12
DARE	0
CCRCT	0
HTA database	0
SCIE	250
CPCI-S	8
Total	817
Total unique	464
Clinical trials.gov	9
*meta*Register of Controlled Trials	32
MAUDE database	0
EuroScan International Network	15

Once the full-text selection process was complete, a decision was made whether there were gaps in the evidence that would require lower levels of evidence to be consulted. This was the case for the diagnostic review, in which no end-to-end studies were identified; for the management review, in which only limited evidence was identified for NIOX MINO and no evidence was identified for NObreath; and for some of the subgroups of interest to the review. For the diagnostic review, studies including any device were included rather than just those using NIOX MINO, NIOX VERO or NObreath (see *Review of the diagnostic accuracy of FeNO testing for asthma*) and, for the management review, studies using any FeNO device were included (see *Review of the efficacy of FeNO-guided management of asthma*); the rapid review of the equivalence of devices was conducted in full (see *Review of the equivalence of devices*). To retrieve relevant titles from the database for the subgroups of interest to the review, the keyword search facility in Reference Manager was used to search for the following keywords:

- elderly asthmatics: elderly, old, older and elderly care
- smokers: smoke, smoking, smoking.adverse effects, smoking.epidemiology, smoking cessation, smoking cessation programme, smoking habit, smoking/ae [adverse drug reaction] and smoking: epidemiology
- pregnant women: pregnant, pregnancy, expectant, pregnancy complication/co [complication], pregnancy complication/si [side effect], pregnancy complications, pregnancy diabetes mellitus, pregnancy diabetes mellitus/dt [drug therapy], pregnancy outcome, pregnancy test and pregnant women.

These titles were then sifted by title, abstract and full text for inclusion in the review with relation to criteria for population, intervention and comparator. Criteria on study design and specific outcomes were relaxed and studies of the next best level of evidence that provided data evaluating the use of FeNO measurements in appropriate subgroups were included. The hierarchy of evidence used was as described in the NICE guidelines methods guide.[34]

Review of equivalence of devices

Table 10 describes the inclusion and exclusion criteria for this review.

Review of the diagnostic accuracy of FeNO testing for asthma

Table 11 describes the inclusion and exclusion criteria for this review and any differences from the published protocol (www.nice.org.uk/guidance/dg12/documents/measurement-of-exhaled-nitric-oxide-concentration-in-asthma-niox-mino-and-nobreath-final-protocol2). At full-text sift stage, some unforeseen questions about the scope were sent to SCM clinicians for clarification. This is documented in *Appendix 2*.

Review of the efficacy of FeNO-guided management of asthma

Table 12 describes the inclusion and exclusion criteria for this review and any differences from the published protocol (www.nice.org.uk/guidance/dg12/documents/measurement-of-exhaled-nitric-oxide-concentration-in-asthma-niox-mino-and-nobreath-final-protocol2).

Data extraction

A different standardised data extraction form was developed for each review following the guidelines given in the *Cochrane Handbook for Systematic Reviews of Interventions*[36] and the Centre for Reviews and Dissemination (CRD) *Guidance for Undertaking Reviews in Healthcare*;[37] these forms were piloted using two studies per review. Missing fields were added as appropriate and backfilled where necessary. *Appendix 3* lists the fields that were data extracted for each review. Data were extracted from the studies by one of three reviewers and checked by a second reviewer (SH, ME, TG), except for the rapid review of the equivalence of devices for which a sole reviewer (SH) extracted all relevant data. Any discrepancies were resolved by discussion, with involvement of a third reviewer when necessary. When appropriate, authors were contacted for missing or unclear data. Data from multiple publications of the same study were extracted and quality

TABLE 10 Inclusion and exclusion criteria for the review of equivalence of devices

Criterion	Inclusion	Exclusion	Change from protocol
Population	Studies conducted in humans only, regardless of asthmatic status or recruitment methods	Studies performed in vitro on gas samples unless no test evidence was found in humans	None
Primary device	NIOX MINO, NIOX VERO or NObreath operated in accordance with ATS 2005 guidelines:[35] • expiratory flow rate of 50 ml/second (0.05 l/second) • an exhalation time of ≥ 10 seconds for adults and ≥ 6 seconds for children		NIOX VERO added
Comparator	Other chemiluminescent devices operated in accordance with ATS 2005 guidelines:[35] • expiratory flow rate of 50 ml/second (0.05 l/second) • an exhalation time of ≥ 10 seconds for adults and ≥ 6 seconds for children If no studies at this flow rate and with this exhalation time were found, any flow rate or exhalation time was to be included		None
Outcomes	Studies of analytical validity were included if they reported the ability of the test to measure FeNO accurately, by any statistical method, compared with chemiluminescent devices	Studies of inter-rater reliability or intersubject repeatability were excluded	None
Study design	Any		None

ATS, American Thoracic Society.

TABLE 11 Inclusion and exclusion criteria for the review of diagnostic accuracy

Criterion	Inclusion	Exclusion	Change from protocol
Population	Primary population is patients presenting with clinical characteristics suggestive of asthma. The main relevant subgroups within this population are: • those presenting with clinical characteristics suggestive of asthma and who are difficult to diagnose • women during pregnancy • older people • smokers Studies were included if they recruited a wider population but reported a priori subgroup analyses for the populations of relevance to this review	• Children < 5 years old • Studies that recruited a wider population and did not report a priori subgroup analyses for the populations of relevance to this review • Animal models • Unselected specific populations (e.g. firefighters, obese people, athletes)	None
Intervention	Use of NIOX MINO or NObreath in the diagnosis of asthma, either with or without another test or tests. NIOX MINO and NObreath devices are set to record according to American Thoracic Society 2005 criteria:[35] • expiratory flow rate of 50 ml/second (0.05 l/second) • an exhalation time of ≥ 10 seconds for adults and ≥ 6 seconds for children If data were not available for the above interventions, studies were included if they reported the clinical validity of FeNO measured by any chemiluminescent device with appropriate measurement methods: • expiratory flow rate of 50 ml/second (0.05 l/second) • an exhalation time of ≥ 10 seconds for adults and ≥ 6 seconds for children • online measurement Studies that did not report any of these details were included and discussed in the narrative review. Studies using any cut-off value or combination of cut-off values were included	• Expiratory flow rate not 50 ml/second (0.05 l/second) • An exhalation time of < 10 seconds in adults and < 6 seconds in children • Offline measurements • Alveolar nitrogen oxide or nasal nitrogen oxide measurements	The protocol stated that studies using the following cut-off values would be included: • FeNO < 25 ppb (< 20 ppb in children) indicates that eosinophilic inflammation and responsiveness to corticosteroids are less likely • FeNO > 50 ppb (> 35 ppb in children) indicates that eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids are likely • FeNO values between 25 ppb and 50 ppb (20–35 ppb in children) should be interpreted cautiously and with reference to the clinical context However, no studies using these exact cut-off values were found and so all cut-off values were included Because no studies using NObreath or NIOX VERO were found, the contingency to include any chemiluminescent device was affected

continued

TABLE 11 Inclusion and exclusion criteria for the review of diagnostic accuracy (*continued*)

Criterion	Inclusion	Exclusion	Change from protocol
Comparator	Any combination or selection of tests and clinical characteristics described in the BTS/SIGN guidelines[8] for the diagnosis of asthma	Uses tests to diagnose asthma that are not included in the BTS/SIGN guidelines[8] or if the comparator includes the use of FeNO measurements	Studies using tests not in routine use in the UK but mentioned in the BTS/SIGN guidelines[8] were included in the review
Outcome	• End-to-end studies – include studies with relevant clinical outcomes (see *Table 12*) • Clinical validity studies – include studies which report data that allow the extraction of the numbers of patients who are TP, TN, FP and FN against the reference standard. Studies that report test failure rates were also included	Does not report useable diagnostic validity data (i.e. extraction of the numbers of patients who are TP, TN, FP and FN against the reference standard)	None
Study design	• End-to-end studies (which follow patients from diagnostic test to clinical outcomes) – if no evidence was found at this level, clinical validity studies (which compare the diagnosis of patients by the intervention with that by a reference standard) were included. These should be prospective cohort studies, cross-sectional studies or retrospective cohort studies. If studies of these designs were not located, other study designs were considered (e.g. case–control studies) • Both studies deriving cut-off values for diagnosis and studies validating existing cut-off values for diagnosis to be included • Abstracts with comparable data that do not exist in full published studies	• Preclinical and biological studies • Editorials and opinion pieces • Studies published only in languages other than English	Studies published as abstracts and not reporting sufficient methodological details to allow critical appraisal of study quality were *not* excluded
Setting	Primary care, secondary care, outpatient clinic or specialist clinic	Emergency care diagnosis of exacerbation	None

TABLE 12 Inclusion and exclusion criteria for the review of FeNO-guided management of asthma

Criterion	Inclusion	Exclusion	Change from protocol
Population	Patients diagnosed with asthma. The two subgroups of particular interest were: • those with good asthma control who are being considered for a dose reduction • those with uncontrolled asthma who are experiencing exacerbations or worsening of symptoms and who are being considered for a dose increase of ICSs or who are being checked for compliance to treatment In addition, further subgroups within each of these categories were included: • women during pregnancy • older people • smokers Studies were included if they recruited whole asthma populations or patients exclusively from any of the subgroups	• Children < 5 years old • Patients not diagnosed with asthma • Animal models • Unselected specific populations (e.g. firefighters, obese people, athletes)	None
Intervention	Use of NIOX MINO or NObreath in the diagnosis of asthma, either with or without another test. NIOX MINO and NObreath devices are set to record according to American Thoracic Society 2005 criteria:[35] • expiratory flow rate of 50 ml/second (0.05 l/second) • an exhalation time of ≥ 10 seconds for adults and ≥ 6 seconds for children If data were not available for the above interventions, studies were included if they reported the clinical validity of FeNO measured by any chemiluminescent device with appropriate measurement methods: • expiratory flow rate of 50 ml/second (0.05 l/second) • an exhalation time of ≥ 10 seconds for adults and ≥ 6 seconds for children • online measurement Studies that did not report any of these details were included and discussed in the narrative review Studies monitoring at intervals of > 2 weeks were included Any protocols and cut-off values for management decisions or compliance monitoring were included	Device that is not validated for measuring FeNO: • expiratory flow rate not 50 ml/second (0.05 l/second) • an exhalation time of < 10 seconds offline measurements Studies in which FeNO is measured on a more regular basis (i.e. not during routine annual review) were excluded	Studies that did not report any details about the device or measurement methods were included and discussed in the narrative review The protocol stated that 'only studies using FeNO measurements in: • routine annual monitoring • dose titration indicated during routine monitoring • assessment of compliance will be included in the review' However, no such studies were located and so studies monitoring at intervals of > 2 weeks were included

continued

TABLE 12 Inclusion and exclusion criteria for the review of FeNO-guided management of asthma (*continued*)

Criterion	Inclusion	Exclusion	Change from protocol
Comparator	• Studies comparing the interventions to any other management strategy that does not utilise FeNO measurements were included • Studies using management strategies that closely match all or part of UK practice as described in the BTS/SIGN guidelines[8] were included • When no studies that closely match UK practice were found, studies using other management strategies were included	Includes the use of FeNO measurements as part of the management strategy	None
Outcome	• Incidence of acute exacerbations, including those requiring unscheduled contact with health-care professionals, visits to accident and emergency departments or hospitalisations • Other measures (time-to-event data; numbers of patients experiencing an exacerbation) were considered only if insufficient data were available for the rate of exacerbations. Any definition of exacerbation was acceptable • Asthma control, which includes asthma symptoms, either reported individually or by use of a standardised patient outcome measure or symptom score • Clinical complications associated with acute exacerbations • Levels of ICSs • Use of OCSs • Adverse effects of treatments (including bronchodilators and steroids) • HRQoL • Mortality • Compliance	• Does not report data on FeNO-guided step-up step-down therapy • Measurement of alveolar nitrogen oxide or nasal nitrogen oxide	None
Study design	• RCTs • If insufficient RCT evidence is identified, other study designs will be included according to the hierarchy of evidence for efficacy trials • Abstracts with comparable data that do not exist in full published studies and with sufficient methodological details were included	• Preclinical and biological studies • Editorials and opinion pieces • Studies published only in languages other than English	Studies published as abstracts and not reporting sufficient methodological details to allow critical appraisal of study quality were *not* excluded
Setting	Primary care, secondary care, outpatient clinic or specialist clinic	Emergency care	None

assessed as a single study. In a change from the protocol, data were not extracted from existing systematic reviews, but directly from the primary research journal articles and conference abstracts.

Quality assessment

As it was a rapid review, quality assessment was not conducted for the review of the equivalence of devices.

Diagnostic cohort studies were assessed using the Quality Assessment of Diagnostic Accuracy Studies – second revision (QUADAS-2) tool.[38] The tool was adapted to the specifics of this appraisal and the scoring scheme can be found in *Appendix 4*. Because of the complexity of this assessment, items within QUADAS-2 that related to applicability were omitted and this was addressed in detail as follows:

(a) Are there concerns that the included patients do not match the review question? – addressed through the subcategorisation of studies according to patient characteristics.
(b) Are there concerns that the index test, its conduct or its interpretation differs from the review question? – addressed through a review of the equivalence of devices and through the selection of studies that recorded FeNO according to American Thoracic Society (ATS) guidelines.[35]
(c) Are there concerns that the target condition as defined by the reference standard does not match the review question? – addressed through the subcategorisation of studies according to the reference standard used.

Management RCT studies were assessed using domains listed in the Cochrane risk of bias tool.[36] The scoring scheme can also be found in *Appendix 4*.

Studies of lower quality were not formally quality assessed but were considered on their individual merits.

Quality assessment was conducted by one reviewer and checked by a second. A third reviewer was consulted in cases of disagreement.

Analysis and synthesis

A narrative synthesis was conducted for the rapid review of the equivalence of devices and no meta-analysis was planned or attempted.

A narrative synthesis was conducted for the review of diagnostic studies. A meta-analysis was planned if sufficient studies of acceptable clinical heterogeneity in terms of patient populations, devices, cut-off points and reference standards were available. A meta-regression to allow the use of multiple cut-off points in the modelling was planned, again if the necessary data were available with appropriate levels of heterogeneity between studies. However, data were not suitable for meta-analysis or meta-regression.

A narrative synthesis was conducted for the review of management studies. A meta-analysis was planned if enough studies of acceptable clinical heterogeneity in terms of patient populations, devices, cut-off points, interventions, comparators and outcomes were available. Clinical heterogeneity indicated that such an analysis was unlikely to produce meaningful results, but exploratory analyses and sensitivity analyses in relation to elements of study design were conducted in the review of adult studies, even though clinical heterogeneity was high. For rate outcomes, the generic inverse variance method was used in Review Manager version 5.3 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) to meta-analyse rate ratios. For continuous outcomes, a standardised mean difference analysis was conducted as metrics for ICS use were different.

In all cases, fixed effects were used first and random effects were applied if the I^2 statistic indicated that heterogeneity was moderate or high. This was judged to be the case at > 40%.

Results

A total of 4859 citations were retrieved and considered for inclusion in the review. After scrutiny of the titles and abstract, 4454 studies were excluded and the full texts of 405 citations were obtained and consulted. Of these, 338 were excluded (see *Appendix 5*), one additional study was retained for the subgroup reviews of management in pregnant women and 58 other studies (66 citations) were included in the review. The update search yielded 495 citations. These were not deduplicated against the original search. Of these, 489 were excluded and six studies (six citations) were included in the review. As such, in total, 65 studies (71 citations[39–109] plus two sponsors' submissions: Fukuhara A, Sato S, Saito J, Sato Y, Nikaido T, Inokoshi Y, *et al. Conversion equations of FeNO levels measured by two portable and a stationary analyzers*. Sponsor's submission, 2013. Unpublished abstract submitted by Bedfont, 2013. Hedlund A. *A Randomized, Multi-center Study to Determine the Agreement between the NIOX MINO® Nitric Oxide Monitoring System and the NIOX VERO@ Device Using the 10-Second Exhalation Mode*. Sponsor's submission received 18 July 2013) were included in the main equivalence, diagnostic and management reviews, including one study on the management of pregnant women with asthma.[102]

For the review of subgroups, a total of 162 citations were identified of which 14 studies (14 citations) were included.[110–123] A further three references[124–126] (two new studies and one update of a study already included in the main management review) were identified during the update search. *Appendices 5* (update search) and *6* (subgroup searches) summarise the process of identifying and selecting relevant literature. As such, a total of 17 studies (17 citations) were included in the subgroup reviews.

No end-to-end studies were identified within the review.

As previously described, a review of the equivalence between FeNO devices was undertaken, alongside a review of diagnostic validity (cohort study design) and a review of management (RCT study design), with data for subgroups of interest to the review taken from lower levels of evidence when necessary. This report considers each review separately in the following order:

- rapid review of the equivalence of devices [analytical validity; see *Equivalence of devices (analytical validity)*]
- systematic review of diagnostic studies (diagnostic validity; see *Diagnostic review*)
- systematic review of management studies (see *Management review*).

Equivalence of devices (analytical validity)

A total of 27 studies [30 citations[39–68] plus two sponsors' submissions (Fukuhara 2013 and Hedlund 2013)] comparing the intervention devices (NIOX MINO, NIOX VERO and NObreath) with other devices were included in the review. One additional study[127] was excluded as it compared NIOX MINO with another hand-held device (NoVario; FILT, Berlin, Germany) not in the scope of this appraisal. The studies have been categorised for presentation and discussion according to the devices compared and population age ranges as follows:

- NIOX MINO compared with the Niox chemiluminescent device (Aerocrine) in adults
- NIOX MINO compared with the Niox chemiluminescent device in children
- NIOX MINO compared with other stationary chemiluminescent devices in adults and/or children
- NIOX VERO compared with NIOX MINO
- NObreath compared with other stationary chemiluminescent devices in adults and/or children
- NIOX MINO compared with NObreath in adults and/or children
- area under the curve (AUC), cut-off points and correction equations
- test failure rates
- conclusions.

Three main comparisons were considered in this review:

- *Comparison of means* – comparison between reported mean FeNO values as measured by each device in the same cohort. This comparison may be confounded by natural within-patient variance between measurements by the two devices.
- *Correlation coefficients* – these show whether measurements by the two devices are correlated but not whether the actual values produced are the same (agreement). Highly correlated devices might produce slopes on a graph (plotting FeNO measurement against a known FeNO concentration) of the same gradient but at different heights, indicating that one device measures consistently higher or lower than another. Correlation coefficients can be confounded by the fact that comparison over wider ranges of values can lead to higher correlation values.[128]
- *Bland–Altman analysis* – produces a number of useful comparison statistics that assess agreement between devices rather than just correlation. Bland–Altman plots[128] plot the mean of two measurements by two devices (*x*-axis) against the difference between the measurements (*y*-axis). If the devices agreed perfectly across the whole range of measurements, all points would be at point zero on the *y*-axis across the range of measurements. However, if agreement is not perfect, the points will fall above and below zero. If there is a systematic bias in the results, such as one device consistently reading higher than the other, the mean of the points will be clustered either above or below zero on the *y*-axis and this will be evident both visually and by the mean difference value produced. If this deviation is consistent and can be relied on, readings between devices can be corrected by subtracting or adding the mean difference. However, if there is also variance in the difference between devices, points will be more scattered and there will be a wider 'limit of agreement', which is calculated as ± 2 standard deviations (SDs). If this limit of agreement is wide by clinical standards, it may be concluded that the devices are not clinically interchangeable, even if the mean difference is relatively small.

NIOX MINO compared with the Niox chemiluminescent device in adults

Eight studies compared NIOX MINO with the Niox chemiluminescent device (*Table 13*), of which five studies were carried out exclusively with adults[39–43] and three studies were undertaken with a mix of adults and other age groups.[44–46] When considering the mean values recorded in each study, differences between studies ranged from 0.3 to 9 ppb. NIOX MINO was found to give largely similar results to the Niox chemiluminescent device in five studies[39,41,43,45,46] but gave higher FeNO readings in two other studies.[42,44]

TABLE 13 Equivalence review: NIOX MINO compared with the Niox chemiluminescent device in adults, adolescents and adults or all ages

Author, year	Sponsored?	Population	Measurement according to guidelines 2005[35]?	*n*[a]	FeNO NIOX MINO (ppb)	FeNO chemiluminescence (ppb)	Comparison data	Correlation coefficient	Bland–Altman analysis (95% limits of agreement)	Interpretation
Adults: asthmatics or mixed including some asthmatics										
Grob 2008[40]	NR	AS	NR	1	Mean 32.5	Mean 26.9	NIOX MINO device A: no statistically significant difference NIOX MINO device B: 7.2 ppb greater ($p = 0.26$)	NIOX MINO device A: $r^2 = 0.73$, $p < 0.0001$; NIOX MINO device B: $r^2 = 0.74$, $p < 0.0001$		NIOX MINO device A: similar (NSD); NIOX MINO device B: trend to read higher (NSD)
Korn 2010[41]	NR	AS, COPD, HE	Yes	85	Median (95% CI) 16.3 (5.0 to 208.3)	Median (95% CI) 14.5 (0 to 196.6)	NIOX MINO 9% (SEM 3%) higher (range –32% to 38%)	Spearman: $r = 0.860$	2% (73% to –46%)	Similar, but wide upper and lower limits of BA plot
Menzies 2007[39]	Yes	AS	Yes	101	GM (95% CI) 26.6 (24.5 to 28.9)	GM (95% CI) 26.9 (24.8 to 29.6)	NR	Pearson: $r = 0.94$, $p < 0.001$; Spearman: lack of bias at either end of values	Log scale: –0.0 (0.2 to –0.2);[b] bigger differences at higher values[c,d]	Similar (SSNR)
Adults: non-asthmatics										
Chen 2007[42]	NR	AL	Yes	27	Mean 43.1	Mean 36.9	NIOX MINO 7.2 ppb higher (range 6.5–8.0 ppb), $p < 0.0001$	$r = 0.94$–0.99	NR	NIOX MINO reads higher (SS)
Adults: healthy participants										
Hemmingsson 2004[43]	Yes	HE	NR	19	NR	NR	0.5 (SD 3.8) ppb	NR	NR	Similar (SSNR)
Menzies 2007[39]	Yes	HE	Yes	50	GM (95% CI) 19.3 (17.6 to 21.1)	GM (95% CI) 17.7 (16.1 to 19.4)	NR	Pearson: $r = 0.96$, $p < 0.001$; Spearman: lack of bias at either end of values	Log scale: –0.0 (0.1 to –0.2);[b] bigger differences at higher values[c,d]	Similar (SSNR)

Author, year	Sponsored?	Population	Measurement according to guidelines 2005[35]?	*n*[a]	FeNO NIOX MINO (ppb)	FeNO chemiluminescence (ppb)	Comparison data	Correlation coefficient	Bland–Altman analysis (95% limits of agreement)	Interpretation
Adolescents and adults: asthmatics or mixed including some asthmatics										
Pizzimenti 2008[44]	No	AS, HE	Yes	32	Mean (95% CI) 47.1 (35.2 to 59.1)	Mean (95% CI) 36.9 (25.0 to 49.0)	NIOX MINO higher, $p<0.05$	$r=0.998$, $p<0.001$	NR	NIOX MINO reads higher (SS)
No age restrictions: asthmatics or mixed including some asthmatics										
Alving 2006[46]	Yes	AS, HE	Yes	71	Mean (SD) 27.5 (23.2), $n=62$	Mean (SD) 26.5 (24.2), $n=63$		$r=0.97$	1.5 (10.2 to –13.2) ppb; bigger differences at higher values[c]	Similar (SSNR); NIOX MINO slightly higher than Niox chemiluminescent device
Khalili 2007[45]	Yes	AS	Yes	110	NR	NR	NIOX MINO higher, –0.5 ppb ($p=0.21$)	Spearman: $r=0.98$, $p<0.0001$	0.5 (8.3 to –9.4) ppb; bigger differences at higher values[c]	Similar, but with wide range in BA analysis (NSD)

AL, allergy; AS, asthmatic; BA, Bland–Altman; CI, confidence interval; GM, geometric mean; HE, healthy; NR, not reported; NSD, not statistically significantly different; *r*, correlation coefficient; SE, standard error; SEM, standard error of the mean; SS; statistically significant; SSNR, statistical significance not reported.

a Number analysed.

b Estimated from graph.

c Visual interpretation of Bland–Altman plot.

d Values were logged; therefore, the apparently random distribution on the graph represents a multiplicative association between values in the direction of greater differences at higher values.

One further study[40] tested two NIOX MINO devices side by side and found that the mean FeNO recorded was higher for one device than for the Niox chemiluminescent device but similar for the other device and the Niox chemiluminescent device. Another study[45] tested three devices and found excellent correlation between them and no statistically significant difference between them. This may indicate that there is some variation between NIOX MINO devices themselves, which may account for some of the heterogeneity in estimates of equivalence with other devices in other studies. In summary:

- When the cohort mean FeNO value was < 30 ppb as measured by the Niox chemiluminescent device, studies showed small differences between the cohort means for devices,[39,40,46] whereas when the mean FeNO value was > 35 ppb as measured by the Niox chemiluminescent device, larger and statistically significant differences in cohort means were seen.[42,44]
- Correlation coefficients ranged from 0.73 to 0.998.
- Bland–Altman analyses were not reported in a consistent way, with some studies using proportions, some using absolute values and some using log values. It is not clear whether log transformation is appropriate as results varied across studies and were apparently conflicting on this point. When the relationship between devices was multiplicative, differences between devices became greater at higher values. Studies saw limits of agreement (when reported on the absolute scale) of around 10 ppb in both directions.[45,46] These large limits of agreement may be due to an assumption that the relationship is additive rather than multiplicative. The difference in percent reported by Korn *et al.*[41] is large, with limits of agreement of –46% to 73%, and it is assumed that a log transformation was performed. However, the log values reported by Menzies *et al.*[39] indicate tighter limits of agreement, but the Bland–Altman plot did not suggest a multiplicative relationship on the absolute scale. It is therefore unclear if the upper and lower limits of agreement between devices are of clinical importance and whether this is a multiplicative or an additive relationship. It seems likely that a range of 20 ppb could be important even at high FeNO values.

NIOX MINO compared with the Niox chemiluminescent device in children

Three studies compared NIOX MINO with the Niox chemiluminescent device in children (*Table 14*). All cohorts included children with asthma.

- One study[47] reported statistically significantly higher mean FeNO values with NIOX MINO whereas two studies[48,49] reported statistically significantly lower values. One of these studies[49] had low mean values (< 10 ppb).
- All studies reported good correlation between the devices.

Bland–Altman statistics were reported in two studies[48,49] and indicated that NIOX MINO gave lower readings in both cases, by 1.1 ppb (limits of agreement –4.4 to 6.7 ppb) and 3.9 ppb (limits of agreement –1.1 to 8.9 ppb) respectively.

NIOX MINO compared with other chemiluminescent devices in adults and children

Twelve studies compared NIOX MINO with chemiluminescent devices other than the Niox chemiluminescent device and were included in the review (*Table 15*). Six studies [reported across nine studies and one sponsor's submission (Fukuhara 2013)] were carried out in adults,[50–57,64] three were carried out in an unspecified age group[58–60] (two of which had potentially largely overlapping cohorts and will be considered as one study)[58,59] and three were carried out in children.[61–63] All studies included at least some asthmatic patients, except that by de Laurentiis *et al.*[57] Mean FeNO values varied across the studies (from 7 ppb in a healthy cohort of patients[52,53] to 64.3 ppb in an asthmatic cohort[54]). Devices studied in adults/unspecified age groups were the EndoNO (SERES, Aix en Provence, France), N-6008 (SIR, Madrid, Spain), NA623N (CHEST Inc., Tokyo, Japan), NOA 280i (Sievers, Boulder, CO, USA), CLD 88sp (ECO MEDICS, Dürnten, Switzerland), NOA (Sievers, Boulder, CO, USA) and LR2000 (Logan Research Ltd, Rochester, UK), whereas devices tested in children were the CLD 88 and CLD 77 (ECO MEDICS). Within subgroups no chemiluminescence device was tested in more than one study apart from LR2000, which was tested in one

TABLE 14 Equivalence review: NIOX MINO compared with the Niox chemiluminescent device in children

Author, year	Sponsored?	Population	Measurement according to ATS 2005 guidelines[35]?	*n*[a]	FeNO NIOX MINO (ppb)	FeNO chemiluminescence (ppb)	Comparison data	Correlation coefficient	Bland–Altman analysis (95% limits of agreement)	Interpretation
Children: asthmatics or mixed including some asthmatics										
Kalliola 2011[49]	No	AS and HE	Yes	40	GM 7.8	GM 9.9	NIOX MINO lower, $p = 0.002$	Pearson: $r = 0.972$, $p < 0.001$	1.1 (–4.4 to 6.7) ppb; no obvious difference at higher values[b]	NIOX MINO slightly lower (SS)
McGill 2006[48]	Yes	AS and others	Yes	34	NR	NR	NIOX MINO lower; greater difference at higher values ($p < 0.001$)	0.986 (95% CI 0.972 to 0.993)	3.9 (–1.1 to 8.9) ppb; mean difference greater with higher FeNO values[b]	NIOX MINO lower (SS)
Vahlkvist 2006[47]	Yes	AS with AL	Yes	11	Mean 30	Mean 26	NIOX MINO higher, $p = 0.004$	$r = 0.977$; unclear which method	Correlation independent of level	NIOX MINO higher (SS)

AL, allergy; AS, asthmatic; CI, confidence interval; GM, geometric mean; HE, healthy; NR, not reported; SS; statistically significant; *r*, correlation coefficient.
a Number analysed.
b visual interpretation of Bland–Altman plot.

TABLE 15 Equivalence review: NIOX MINO compared with other chemiluminescent devices in adults and children

Author, year	Sponsored?	Population	Comparator device	Measurement according to ATS 2005 guidelines[35]?	*n*[a]	FeNO NIOX MINO (ppb)	FeNO chemiluminescence (ppb)	Comparison data	Correlation coefficient	Bland–Altman analysis (95% limits of agreement)	Interpretation
Adults: asthma or mixed including some asthmatics											
Boot 2008[64]	No	AS, HE	CLD 88sp	Yes	37	HE: mean (range) 20.3 (8.0 to 39.0); HE smokers: mean (range) 12.2 (5 to 23); AS: mean (range) 63.8 (13 to 172)	HE: mean (range) 18 (7.4 to 35.5); HE smokers: mean (range) 11.1 (4.7 to 20.5); AS: mean (range) 60.8 (10.9 to 184.6)	Non-significant difference	$r = 0.975$, $p < 0.0001$	–10% (–36% to 28%); bigger differences at higher values[b,c]	Similar (NSD) but with wide range in BA analysis
Fortuna 2006,[52] Fortuna 2007[53]	NR	AS	N-6008	Yes	11	Mean (SD) 79 (55)	Mean (SD) 40 (30)	Mean (SD) 47 (30) ppb	$r = 0.9$	NR	NIOX MINO higher (SS NR)
Fukuhara 2011,[54] Fukuhara 2013 (sponsor's submission)	Yes	AS – treated	NA623N	NR	13	Treated AS: GM (95% CI) 50.0 (26.5 to 73.4)	Treated AS: GM (95% CI) 64.5 (33.4 to 95.6)	$p = 0.009$	NR	NR	NIOX MINO lower (SS)
Fukuhara 2011,[54] Fukuhara 2013 (sponsor's submission)	Yes	AS – untreated	NA623N	NR	14	Non-treated AS: GM (95% CI) 52.3 (28.8 to 75.7)	Non-treated AS: GM (95% CI) 64.3 (39.6 to 89.0)	$p = 0.0167$	NR	NR	NIOX MINO lower (SS)
Fukuhara 2011,[54] Fukuhara 2013 (sponsor's submission)	Yes	AS, HE	NA623N	NR	32	NR	NR	$p < 0.001$	NR	NR	NIOX MINO lower (SS)
Ozier 2010,[50] Ozier 2011[51]	Yes	AS	EndoNO	Yes	NIOX MINO: 78, Endo-NO: 89	Controlled AS: approx. 23;[d] uncontrolled AS: approx. 38[d]	Controlled AS: approx. 19;[d] uncontrolled AS: approx. 30[d]	9 ppb difference, $p < 0.0001$	Pearson, log-transformed data: $r = 0.96$, $p \leq 0.001$	Log scale: 0.12 (0.3 to –0.6);[d] no obvious difference at higher values[b]	NIOX MINO higher (SS)
Yoon 2011,[56] Kim 2012[55]	No	AS, HE	NOA 280i	Yes	100	Mean (SEM, 95% CI) 18.8 (0.9, 17.0 to 20.6)	Mean (SEM, 95% CI) 22.1 (1.2, 19.8 to 24.5)	14.5% (2.5%),[e] range –61.7% to 111.1%	Spearman: $r = 0.876$, $p < 0.001$	3.3 (–7.0 to 13.6) ppb; mean difference greater with higher FeNO values[b]	NIOX MINO lower (SS)

Author, year	Sponsored?	Population	Comparator device	Measurement according to ATS 2005 guidelines[35]?	*n*[a]	FeNO NIOX MINO (ppb)	FeNO chemiluminescence (ppb)	Comparison data	Correlation coefficient	Bland–Altman analysis (95% limits of agreement)	Interpretation
Adults: non-asthmatics											
de Laurentiis 2008[57]	Yes	COPD, HE	NOA	Yes	20	Mean (SD) 14.8 (5.7)	Mean (SD) 14.2 (5.9)	NR	$r = 0.96$, $p < 0.0001$	–0.4 (– 2.7 to 1.9) ppb; bigger differences at higher values[b]	Similar (SSNR)
Adults: healthy participants											
Fortuna 2006,[52] Fortuna 2007[53]	NR	HE	N-6008	Yes	28	Mean (SD) 20 (8)	Mean (SD) 7 (5)	Mean (SD) 13 (14) ppb	$r = 0.92$, $p = 0.001$[53]	NR	NIOX MINO higher (SSNR)
Fukuhara 2011,[54] Fukuhara 2013 (sponsor's submission)	Yes	HE	NA623N	NR	5	GM (95% CI) 23.4 (7.18 to 39.6)	GM (95% CI) 29.3 (7.77 to 50.8)	$p = 0.073$	NR	NR	NIOX MINO lower (trend, NSD)
Population unclear: mix including some asthmatics											
Logan Research Ltd 2009[60]	Yes	AS, HE	LR2000	NR	16	NR	NR	+13.1 ppb		NR	NIOX MINO higher (SSNR)
[f]Michils 2008[59]	NR	AS, HE	LR2000	Yes	102	NR	NR	Mean log difference 0.144; NIOX MINO average 39% higher	$r = 0.957$, $p < 0.001$; bigger differences at higher values[c,g]	NR	NIOX MINO higher (SSNR)
[f]Peche 2007[58]	NR	AS, HE, lung transplant patients	LR2000	Yes	118	NR	NR	NIOX MINO average 35% higher	NR highly correlated ($p < 0.001$)	NR	NIOX MINO higher (SSNR)
Children: mix including some asthmatics											
Chladkova 2008[63]	No	AS, AL Rh	CLD 88sp	Yes	82	> 12 years: GM (95% CI) 17.4 (7.05 to 43.4); < 12 years: GM (95% CI) 11.9 (6.87 to 21.9)	> 12 years: GM (95% CI) 19.6 (7.43 to 51.6); < 12 years: GM (95% CI) 9.59 (4.74 to 19.4)	> 12 years: CLD 88sp 11% higher; < 12 years: CLD 88sp 11% lower	NR	Median ratio: > 12 years: 1.11 (0.59 to 2.08), < 12 years: 0.89 (0.52 to 1.52); bigger difference at higher values[b]	> 12 years: NIOX MINO lower; < 12 years: NIOX MINO higher

continued

TABLE 15 Equivalence review: NIOX MINO compared with other chemiluminescent devices in adults and children (*continued*)

Author, year	Sponsored?	Population	Comparator device	Measurement according to ATS 2005 guidelines[35]?	*n*[a]	FeNO NIOX MINO (ppb)	FeNO chemiluminescence (ppb)	Comparison data	Correlation coefficient	Bland–Altman analysis (95% limits of agreement)	Interpretation
Park 2011[61]	NR	AS, HE	CLD 88	NR	188	Mean (SD) 30.8 (23.4)	Mean (SD) 42.8 (30.1)	NR	0.690 ($p < 0.001$)	NR	NIOX MINO lower (SSNR)
Schiller 2009[62]	NR	AS, HE	CLD 77	Yes	66	Three measurements: mean 23.7; first measurement: mean 23.6	Three measurements: mean 20.1; first measurement: mean 20.3	NR	0.98, $p < 0.001$	Ratio: 0.79 (0.44 to 1.42)	NIOX MINO higher (SSNR); larger difference at higher values (SSNR)

AL, allergy; AS, asthmatic; CI, confidence interval; GM, geometric mean; HE, healthy; NR, not reported; NSD, not statistically significantly different; *r*, correlation coefficient; Rh, rhinitis; SEM, standard error of the mean; SS; statistically significant; SSNR, statistical significance not reported.

a Number analysed.
b Visual interpretation of Bland–Altman plot.
c Values were logged; therefore, the apparently random distribution on the graph represents a multiplicative association between values in the direction of greater differences at higher values.
d Data estimated from graph.
e Mean relative difference (SEM).
f Likely that Peche *et al.*[58] and Michils *et al.*[59] include some of the same patients.
g Assumed from mean values.

comparatively large study ($n = 118$)[58,59] and one small study ($n = 16$) within the subgroup mixed including some asthmatics.[60] In summary:

- correlation coefficients (r) in adults/unspecified age groups ranged from 0.876 to 0.96, indicating a good level of correlation between devices.

However, comparison of mean FeNO levels between devices and Bland–Altman statistics within studies recruiting adult or mixed populations show a more variable picture:

- NIOX MINO appeared to give higher readings than the comparator device according to the mean FeNO values in two studies[50–53] and lower readings in a further two studies.[54–56] Devices appeared to be comparable in only two studies.[57,64] Absolute differences in mean FeNO values on the natural scale were not always reported, but when they were they ranged from 9 ppb[50,51] to 47 ppb,[52,53] which could represent a clinically meaningful difference.
- Bland–Altman statistics were reported in only four studies,[50,51,55–57,64] and were not reported consistently. Mean values were reported as relative values, log-transformed data and absolute data. Interpretation would suggest that mean differences were small, 0–5 ppb, but that limits of agreement were much larger, with ranges of around 10 ppb above and below the mean. The studies with the largest mean differences in absolute FeNO values did not report Bland–Altman statistics.

In children:

- Correlation coefficients (r) in children ranged from 0.69 to 0.98, indicating variable correlation. The study with the poorest correlation[61] also had higher mean FeNO levels and it would be tempting to suggest that the poorer correlation is the result of the greater variability at higher FeNO values. However, the study authors state that correlation improved at higher values. One study[63] noted that the direction of disagreement was different in children aged over and under 12 years.
- The back-transformed Bland–Altman statistics[63] and range of ratios reported[62] indicate a wide range of agreement and suggest that the devices are not interchangeable.

NIOX VERO compared with NIOX MINO

(Academic-in-confidence information has been removed.) The results are summarised in *Table 16*.

NObreath compared with chemiluminescent devices in adults and children

Four studies compared NObreath with chemiluminescent devices (*Table 17*).[54,60,65,66] All studies were carried out in adults or in an unspecified age group likely to be adults and all included some asthmatic patients and reported good correlation coefficients. Only one study compared NObreath with the Niox chemiluminescent device;[65] this study reported a small statistically significant difference between the devices [intervention arm: geometric mean 22.6 ppb (geometric standard error of the mean 1.075), control arm: geometric mean 24.6 ppb (geometric standard error of the mean 1.073 ppb); $p = 0.0002$] and a good level of agreement with Bland–Altman analysis. However, the cut-off points with the best combination of sensitivity and specificity derived in this study for each device differed by 10 ppb (25 ppb for NObreath, 15 ppb for Niox; see *Areas under the curve, cut-off points and correction equations*), indicating that even small differences in agreement may have potentially large effects on derived sensitivity and specificity.

The NObreath device was compared with three other chemiluminescent devices: NA623N, LR2500 and LR2000. Bland–Altman analysis was reported in only one study[66] and showed a mean difference of –3.95 ppb compared with the LR2500 device in a healthy cohort with low FeNO values, with wide limits of agreement (–10.98 to 4.08 ppb). Similarly, another study using a Logan device (LR2000) reported an absolute mean difference in FeNO measurements of –3.81 ppb.[60] Comparison with the NA623N device[54] showed small differences between mean FeNO values for the cohorts, with NObreath giving lower values in some cohorts.

TABLE 16 Equivalence review: NIOX VERO compared with NIOX MINO

(Academic-in-confidence information has been removed)	(Academic-in-confidence information has been removed)	(Academic-in-confidence information has been removed)	(Academic-in-confidence information has been removed)	(Academic-in-confidence information has been removed)	(Academic-in-confidence information has been removed)	(Academic-in-confidence information has been removed)	(Academic-in-confidence information has been removed)
(Academic-in-confidence information has been removed)	(Academic-in-confidence information has been removed)	(Academic-in-confidence information has been removed)	(Academic-in-confidence information has been removed)	(Academic-in-confidence information has been removed)	(Academic-in-confidence information has been removed)	(Academic-in-confidence information has been removed)	(Academic-in-confidence information has been removed)
(Academic-in-confidence information has been removed.)							

TABLE 17 Equivalence review: NObreath compared with chemiluminescent devices in adults and children

Author, year	Sponsored?	Population	Comparator device	Measurement according to ATS 2005 guidelines[35]?	*n*[a]	FeNO NObreath (ppb)	FeNO chemiluminescence (ppb)	Comparison data	Correlation coefficient	Bland–Altman analysis (95% limits of agreement)	Interpretation
Adults: asthmatics or mix including some asthmatics											
Fukuhara 2011,[54] Fukuhara 2013 (sponsor's submission)	Yes	AS – treated	NA623N	NR	13	Mean (95% CI) 55.6 (28.1 to 83.2)	Mean (95% CI) 64.5 (33.4 to 95.6)	$p = 0.015$	NR	NR	NObreath lower (SS)
Fukuhara 2011,[54] Fukuhara 2013 (sponsor's submission)	Yes	AS – untreated	NA623N	NR	14	Mean (95% CI) 66.8 (38.3 to 95.4)	Mean (95% CI) 64.3 (39.6 to 89.0)	$p = 0.413$	NR	NR	Similar (NSD)
Fukuhara 2011,[54] Fukuhara 2013 (sponsor's submission)	Yes	AS, HE	NA623N	NR	32	NR	NR	$p = 0.138$	$r = 0.969$, $p < 0.001$	NR	Similar (NSD)
Pisi 2010[65]	No	AS	Niox	Yes	154	GM (GSEM) 22.6 (1.075)	GM (GSEM) 24.6 (1.073)	$p = 0.0002$	Pearson: $r = 0.95$, $p < 0.001$; Spearman: $r = -0.088$, $p = 0.275$)	Log scale: +0.0 (0.5 to –0.5);[b] no obvious difference at higher values[c]	NObreath lower (SS) but small difference

continued

TABLE 17 Equivalence review: NObreath compared with chemiluminescent devices in adults and children (*continued*)

Author, year	Sponsored?	Population	Comparator device	Measurement according to ATS 2005 guidelines[35]?	*n*[a]	FeNO NObreath (ppb)	FeNO chemiluminescence (ppb)	Comparison data	Correlation coefficient	Bland–Altman analysis (95% limits of agreement)	Interpretation
Adults: healthy participants											
[d]Antus 2010[66]	Yes	HE	LR2500	Yes	18	GM (95% CI) 15.7 (11.7 to 21.9)	GM (95% CI) 13.0 (10.1 to 16.7)	$p = 0.299$	$r = 0.897$, $p < 0.001$	–3.95 (–10.98 to 4.08) ppb; plot suggestive of systematic bias[c]	Similar (NSD)
						GM (95% CI) 14.8 (10.4 to 21.3)	GM (95% CI) 13.5 (10.4 to 17.4)	$p = 0.351$	$r = 0.913$, $p < 0.001$		
						GM (95% CI) 16.4 (12.3 to 21.9)	GM (95% CI) 12.9 (9.9 to 16.6)	$p = 0.179$	$r = 0.938$, $p < 0.001$		
Fukuhara 2011,[54] Fukuhara 2013 (sponsor's submission)	Yes	HE	NA623N	NR	5	Mean (95% CI) 25.0 (7.87 to 42.1)	Mean (95% CI) 29.3 (7.77 to 50.8)	$p = 0.233$	NR	NR	NObreath lower (trend, NSD)
Population unclear: mix including some asthmatics											
Logan Research Ltd 2009[60]	Yes	AS, HE	LR2000	NR	16			NObreath compared with LR2000: –3.81 ppb			NObreath lower (SSNR)

AS, asthmatic; GM, geometric mean; GSEM, geometric standard error of the mean; HE, healthy; NR, not reported; NSD, not statistically significantly different; *r*, correlation coefficient; SS; statistically significant; SSNR, statistical significance not reported.

a Number analysed.

b Estimated from graph.

c Visual interpretation of Bland–Altman plot.

d FeNO measured at three time points.

NObreath compared with NIOX MINO in adults and children

Table 18 details the two studies that compared NObreath with NIOX MINO in adults.[54,66] Both studies found that in most analyses NIOX MINO provided lower mean FeNO values than NObreath. This contradicts the available evidence for comparisons between NIOX MINO and the Niox chemiluminescent device and NObreath and the Niox chemiluminescent device, for which NIOX MINO > Niox > NObreath. This would predict that NIOX MINO should provide higher readings than NObreath. However, it should be noted that there is only one study comparing NObreath with Niox[65] and the difference observed was small. The two direct comparisons between NObreath and NIOX MINO include small numbers of patients; only one includes asthmatic patients[54] and this study does not provide a Bland–Altman analysis to assess agreement. As such, it is unclear whether the two devices are interchangeable and, if not, in which direction the difference may be.

One study compared NIOX MINO and NObreath in children with asthma[67,68] and found that NIOX MINO measured statistically significantly higher than NObreath with a mean difference of 7.8 ppb (95% limits of agreement –11.5 to 27.52 ppb; $p < 0.001$) in Bland–Altman analysis.

Areas under the curve, cut-off points and correction equations

The mean FeNO values, correlations and Bland–Altman data for each of these trials have already been considered in the previous narrative synthesis; this section considers the impact that differences between devices can have on cut-off points and reports the attempts that researchers have made to provide correction equations for measurements between devices.

Six studies reported other comparative data between devices (*Table 19*). One study[39] demonstrated that the AUC and cut-off points derived to diagnose asthma using the Niox chemiluminescent device or NIOX MINO were very similar (this study used a case–control design and so data were not includable in the diagnostic review), supporting the conclusion that the Niox chemiluminescent device and NIOX MINO are roughly interchangeable. However, another study[44] reported a correction factor that should be used to convert NIOX MINO values to Niox values. Three[50,51,54,65] of the remaining four studies demonstrate how cut-off points derived using measurements from different devices can be very different, with 7 ppb, 9 ppb and 10 ppb differences. One of these studies[65] compared NObreath with the Niox chemiluminescent device directly and found a 10-ppb difference between cut-off points that provide the highest AUC (15 ppb and 25 ppb respectively) and very different sensitivity and specificity values at these cut-off points. Another study[54] compared NObreath with NIOX MINO and found a 7-ppb difference in derived cut-off points. In this case, the cut-off point for NObreath was higher at 36 ppb. Two studies[52–54] also reported correction equations between various devices, indicating that measurements from these devices are not directly interchangeable.

Test failure rates

Nine studies[39,45,46,48,49,63–65,67] were included in the review of test failure rates and are described in *Table 20*. The review intended to draw evidence from studies included in the review of equivalence of devices, the diagnostic accuracy review and the review of the efficacy of FeNO-guided management for asthma. However, all nine of the studies that provided some relevant information with respect to test failure rates came from the review of the equivalence of devices. Eight studies[39,45,46,48,49,63,64,67] examined NIOX MINO and two studies[65,67] used NObreath. The definition of a test failure was reasonably consistent across the body of literature. Boot *et al.*,[64] Kalliola *et al.*,[49] Kapande *et al.*,[67] Khalili *et al.*,[45] Pisi *et al.*[65] and Menzies *et al.*[39] all defined test failure rates in terms of the number of patients who could not perform acceptable measurements. However, McGill *et al.*[48] specified a test failure as the inability to provide a successful reading from six attempts; Chladkova *et al.*[63] defined a test failure as three unsuccessful attempts; and Alving *et al.*[46] defined a test failure as three invalid readings out of six or one failed single first attempt, depending on the device used.

TABLE 18 Equivalence review: NObreath compared with NIOX MINO in adults and children

Author, year	Sponsored?	Population	Measurement according to ATS 2005 guidelines[35]?	*n*[a]	FeNO NIOX MINO (ppb)	FeNO NObreath (ppb)	Comparison data	Correlation coefficient	Bland–Altman analysis (95% limits of agreement)	Interpretation
Adults: asthmatics or mix including some asthmatics										
Fukuhara 2011,[54] Fukuhara 2013 (sponsor's submission)	Yes	AS – treated	NR	13	Mean (95% CI) 50.0 (26.5 to 73.4)	Mean (95% CI) 55.6 (28.1 to 83.2)	$p=0.135$	NR	NR	NIOX MINO lower (trend, NSD)
Fukuhara 2011,[54] Fukuhara 2013 (sponsor's submission)	Yes	AS – untreated	NR	14	Mean (95% CI) 52.3 (28.8 to 75.7)	Mean (95% CI) 66.8 (38.3 to 95.4)	$p \leq 0.001$	NR	NR	NIOX MINO lower (SS)
Fukuhara 2011,[54] Fukuhara 2013 (sponsor's submission)	Yes	AS, HE	NR	32	NR	NR	$p<0.001$	$r=0.973$, $p<0.001$	NR	NIOX MINO lower (SS)
Adults: healthy participants										
[b]Antus 2010[66]	Yes	HE	Yes	18	GM (95% CI) 12.6 (9.3 to 17.1)	GM (95% CI) 14.9 (11.9 to 18.8)	$p=0.409$	$r=0.661$, $p=0.004$	4.36 (–7.38 to 16.1) ppb	NIOX MINO lower (SS in two analyses); correlation relatively poor
					GM (95% CI) 10.3 (7.8 to 13.4)	GM (95% CI) 16.1 (13.3 to 19.6)	$p=0.010$	$r=0.750$, $p<0.001$		
					GM (95% CI) 10.9 (8.4 to 14.2)	GM (95% CI) 16.3 (12.8 to 20.6)	$p=0.043$	$r=0.654$, $p=0.003$		
Fukuhara 2011,[54] Fukuhara 2013 (sponsor's submission)	Yes	HE	NR	5	Mean (95% CI) 23.4 (7.18 to 39.6)	Mean (95% CI) 25.0 (7.87 to 42.1)	$p=0.669$	NR	NR	Similar (NSD)
Children: asthmatics										
Kapande 2011,[68] 2012[67]	No	AS	Yes[c]	109	NR	NR	NR	Lin's CC (rho) = 0.65 with reduced major axis slope of 1.32 and intercept of 5.03	7.8 (–11.5 to 27.52) ppb; NIOX MINO higher	NIOX MINO higher (SS)

ACT, Asthma Control Test; AS, asthmatic; CC, concordance correlation; GM, geometric mean; HE, healthy; NR, not reported; NSD, not statistically significantly different; SS, statistically significant.

a Number analysed.

b FeNO measured at three time points.

c At least partially.

TABLE 19 Equivalence review: AUCs, sensitivity, specificity and cut-off points using different devices and correction equations derived to convert FeNO values between devices

Author, year	Population	Comparator device	AUC	Sensitivity, specificity and cut-off values	Correction equation
NIOX MINO vs. Niox: adults/adolescents – mix including some asthmatics					
Menzies 2007[39]	AS, HE	Niox	Niox: 0.654 (95% CI 0.565 to 0.744, $p = 0.002$); NIOX MINO: 0.619 (95% CI 0.527 to 0.711, $p = 0.018$) Pairwise comparison difference in AUC of 0.036 (95% CI –0.002 to 0.073, $p = 0.061$)	Sens 83.2%, spec 27%; Niox 13 ppb, NIOX MINO 12.5 ppb	NR
Pizzimenti 2008[44]	AS, HE	Niox	NR	NR	FeNO Niox = –1.656 (SE 0.61) + 0.808 (SE 0.009) × FeNO NIOX MINO Correction factor = approximately 0.81 to convert NIOX MINO values to Niox values
NIOX MINO vs. other chemiluminescent devices: adults – mix including some asthmatics					
Fortuna 2006,[52] Fortuna 2007[53]	AS, HE	N-6008	NR	NR	Correction factor = 3 For HE people: FeNO NIOX MINO = 10 + (1.5 × FeNO N6008)
Fukuhara 2011,[54] Fukuhara 2013 (sponsor's submission)	AS, HE	NObreath, NA623N	NR	NObreath: > 36 ppb; NIOX MINO: > 29 ppb	FeNO NA623N = FeNO NIOX MINO × 1.278 + 3.065; FeNO NA623N = FeNO NObreath × 0.953 + 5.779
Ozier 2010,[50] Ozier 2011[51]	AS	EndoNO	NR	To identify patients who will lose control: NIOX MINO: 40 ppb (sens 85.7%, spec 87.8%); EndoNO: 31 ppb (sens 80.0%, spec 91.1%)	NR
NObreath vs. Niox: adults, asthmatics					
Pisi 2010[65]	AS	Niox	To identify patients who have ACT ≥ 20 (uncontrolled asthma): NObreath: 0.607 (95% CI 0.525 to 0.684); Niox: 0.644 (95% CI 0.562 to 0.719) Pairwise comparisons of difference in AUC of 0.0369 (95% CI 0.004 to 0.0697, $p = 0.028$)	To identify patients who have ACT ≥ 20 (uncontrolled asthma): NObreath: 15 ppb (sens 84%, spec 42%); NIOX: 25 ppb (sens 53%, spec 69%)	NR

AS, asthmatic; CI, confidence interval; HE, healthy; NR, not reported; SE, standard error; sens, sensitivity; spec, specificity.

TABLE 20 Test failure rates

Author, year	Patient sample and no. of participants	Relevant device(s) used	Definition of test failure	Test failure rates
Alving 2006[46]	Asthmatic and healthy, all ages ($n = 75$)	NIOX MINO	Successful test defined as three valid readings out of six or one single first attempt	All: 92% (65/71) successful; children: 84% (31/37) successful; adults: 100% (34/34) successful
Boot 2008[64]	Asthmatic and healthy adults ($n = 50$)	NIOX MINO	Number of patients who could not perform acceptable measurement	0/50
Chladkov 2008[63]	Children with asthma ($n = 82$)	NIOX MINO	Number of patients who could not perform acceptable measurement within three attempts	2/36
Kalliola 2011[49]	Children referred because of asthma symptoms and healthy age-matched children (total $n = 55$)	NIOX MINO	Number of patients who could not perform acceptable measurement	15/55 (younger than successful measurement group, $p = 0.004$)
Kapande 2012[67]	Children (aged 4–14 years) with asthma ($n = 109$)	NIOX MINO, NObreath	Number of patients who could not perform acceptable measurement	NIOX MINO: 7/109; NObreath: 0/109
Khalili 2007[45]	Patients (all ages) with asthma ($n = 115$)	NIOX MINO	Number of patients who could not perform acceptable measurement	1/115; a few subjects needed to perform a test four to seven times
McGill 2006[48]	Children attending respiratory clinic aged > 5 years ($n = 55$)	NIOX MINO	Number of children unable to provide a single measurement in of six attempts	11/55 (therefore at least 66 failed tests out of 330 = 20% test failure rate)
Menzies 2007[39]	Patients known to have mild to moderate asthma ($n = 101$) and healthy volunteers ($n = 50$)	NIOX MINO	Number of patients who could not perform acceptable measurement	0
Pisi 2010[65]	Patients aged ≥ 14 years diagnosed with asthma according to GINA guidelines;[129] included only patients able to perform at least two acceptable measurements with both devices	NObreath	Number of patients who could not perform acceptable measurement	NObreath: 5/154; both (Niox and NObreath): 1; unapproved values: 2

GINA, Global Initiative for Asthma.

All studies included patients with confirmed asthma or symptoms suggestive of asthma; however, the criteria for establishing this diagnosis varied across the literature. For instance, Pisi *et al.*[65] included those who met the criteria for a diagnosis of asthma according to Global Initiative for Asthma (GINA) guidelines[129] whereas Menzies *et al.*[39] stated that they included those with mild to moderate persistent asthma, McGill *et al.*[48] included children attending a respiratory clinic and Kalliola *et al.*[49] included children who had been referred to a specialist clinic because of asthma-like symptoms. In terms of the age range of study samples, the studies by Kalliola *et al.*,[49] Kapande *et al.*,[67] Chladkova *et al.*[63] and McGill *et al.*[48] were all conducted with children whereas the study by Boot *et al.*[64] was conducted with adults. In addition, although Menzies *et al.*[39] did not report any cut-off ages for inclusion, the mean age of the study sample suggests that it was conducted with adults only. Alving *et al.*[46] included all ages and provided separate data for children and adults whereas Khalili *et al.*[45] included all ages and reported test failures for the whole study cohort. Pisi *et al.*[65] included adolescents and adults (the cut-off age for inclusion was ≥ 14 years of age).

NIOX MINO

Eight studies[39,45,46,48,49,63,64,67] reported test failure rates with NIOX MINO. The studies by Kalliola *et al.*,[49] Kapande *et al.*,[67] Chladkova *et al.*[63] and McGill *et al.*[48] were conducted with children whereas the studies by Boot *et al.*[64] and Menzies *et al.*[39] were conducted with adults only. Alving *et al.*[46] and Khalili *et al.*[45] included all age ranges; however, only Alving provided separate data for adults and children. Although the data sets were limited in both age cohorts, the test failure rates for NIOX MINO were consistently higher in the studies of children. In the adult-only studies of Boot *et al.*[64] and Menzies *et al.*,[39] no test failures were observed in cohorts of 50 and 151 participants, respectively, and, similarly, the adult cohort in Alving *et al.*[46] showed a test failure rate of 0% (0/34 participants). The overall test failure rate in adults is therefore likely to be close to 0%. However, data were unavailable on how many attempts were required on average to obtain a successful reading.

In the children's cohorts, however, there were test failures in each study. The rate ranged from two out of 36 (5.6%) in Chladkova *et al.*[63] to 27% (15/55 participants) in Kalliola *et al.*[49] Alving *et al.*[46] reported a failure rate of 16% (6/37 participants). McGill *et al.*[48] classified failures as those who were unable to provide a successful reading from six attempts. They reported 11 patients who fell into this category (20%). In terms of overall FeNO measurement attempts, there were at least 66 failed tests out of 330, that is, also a 20% test failure rate. It was also notable that, in the study with the highest incidence of failure,[49] the age of the children who failed was significantly lower than the age of those who successfully provided a measurement ($p = 0.004$). In Khalili *et al.*,[45] a failure rate of approximately 0.9% was observed (one failure out of 115 participants); however, as data were not presented separately for adults and children, the age of this participant was not clear.

NObreath

Only two studies[65,67] reported test failure rates with the NObreath device. In the study by Pisi *et al.*[65] of adolescents and adults there were five failures in a cohort of 154 patients (3.2%) and a single patient who failed with both NObreath and the Niox chemiluminescent device. Two patients were said to have provided 'unapproved values'; however, it was unclear whether this was with Niox chemiluminescence, NObreath or both. The study by Kapande *et al.*[67] of children only reported no test failures in a cohort of 109.

NIOX VERO

(Academic-in-confidence information has been removed.)

Based on the available data, FeNO test failure rates appeared to generally be low. Most studies reported test failure rates in terms of the number of patients who were unable to provide a satisfactory reading; however, the data also appeared to indicate that multiple readings would be needed for some patients. As this data were not quantified, and usually not reported at all, it is likely that the review underestimates the number of test failures. Moreover, variations in failure rates may be a result of individual differences in operator skills and techniques. Notably, the highest rate of test failure for both NIOX MINO and chemiluminescence was observed in the same study.[49]

There may also be important variations in test failure rates depending on age, particularly when using NIOX MINO. Three of the four NIOX MINO studies of adults reported failure rates of 0% whereas one study reported a withdrawal rate of 13.3%; however, it was unclear whether withdrawals could be treated as synonymous with test failures. By contrast, the failure rate in children's studies ranged from 5.5% to 27%. Indeed, in the study that reported the latter figure,[49] the children who failed the test were significantly younger than those who provided a successful reading. Although the study by Khalili *et al.*[45] included all age groups and reported a much lower failure rate (approximately 0.9%), the mean age of the study cohort (41.9 years, range 6–86 years) may indicate that few children took part. Hence, although the data are too limited to make any definitive conclusions, it seems likely that higher test failure rates may be encountered when using NIOX MINO with children. Finally, with respect to NObreath, the data were particularly sparse, although a low failure rate was apparent. Pisi *et al.*[65] reported six failures in a cohort of 154 adults and adolescents (3.9%) whereas Kapande *et al.*[67] saw no failures in a cohort of 109 children.

Discussion

It is worth noting that there were data available within some of these studies on which device was used first. However, because of time constraints, these data were not formally analysed. In some cases the order was random, in others the order was fixed and in yet others this information was not provided. We therefore cannot rule out the possibility that the order of device use may have confounded the results.

NIOX MINO

The comparability of NIOX MINO to chemiluminescent devices appears to be influenced by several factors. There may be some variability between NIOX MINO devices themselves,[40] although the extent of this is unclear and may be small.[45] There seems to be a generally consistent observation of poorer equivalence between FeNO devices at higher FeNO levels. There also appears to be a lack of comparability between other chemiluminescent devices themselves, as concluded by one study,[41] which leads to heterogeneity in estimates of the comparability of NIOX MINO to chemiluminescent devices. Comparability studies gave different estimates of equivalence between NIOX MINO and other devices and it is therefore unclear if equivalence can be assumed.

NIOX VERO

Only one study provided data on this device. (Academic-in-confidence information has been removed.)

NObreath

There are not enough data and too much apparently conflicting data on the comparability of NObreath to other devices to draw any specific conclusions about its comparability with other devices in asthma populations. However, based on the available evidence it would seem likely that any differences in absolute values between NObreath and other devices are relatively small, although derived cut-offs and maximum sensitivity and specificity may be quite different.

Test failure rates

Because of the small number of studies using NObreath and NIOX VERO, it is not possible to state definitively whether any FeNO measurement device has advantages over any other in terms of test failure rates. In all three studies of adults using NIOX MINO,[39,46,64] the test failure rate was 0%, whereas none of the studies using NIOX MINO in children reported a 0% test failure rate, with the lowest being 5.5%[63] and the highest 27%.[49] As such, there may be some problems with using NIOX MINO with children, although further research would be needed to confirm this pattern. Conversely, with regard to NObreath, the study in adults reported a 3.3% failure rate[65] whereas the study in children reported a 0% failure rate.[67] (Academic-in-confidence information has been removed.)

In summary, the overall test failure rate for FeNO measurement in adults was generally low across all devices and most patients appear to be able to provide FeNO readings, provided that they are permitted sufficient measurement attempts. There may be a higher test failure rate in children using NIOX MINO.

Conclusions

Overall, it cannot be concluded that any two devices are equivalent in all situations. Although there may be situations when they are similar, it appears to depend on the characteristics of the studies and cannot be generalised to all situations. Further research is required to identify what is driving the variability between studies and devices. However, as there is mostly a high degree of correlation between measurements across all devices, estimates of sensitivity and specificity are likely to be a reasonable indication of the potential diagnostic accuracy of using FeNO to guide diagnosis and management, but the derived cut-off points are not likely to be interchangeable between devices. As such, for the purpose of this assessment sensitivities and specificities will be assumed to be interchangeable but it cannot be assumed that the cut-off points that should be used to achieve them will be the same for each device, and there is still some doubt whether the same diagnostic accuracy would be achievable with all devices. The committee will need to consider this in their recommendations.

Diagnostic review

In the absence of an end-to-end study, the next best study design is a cohort study. The ideal cohort study would have recruited patients presenting to their GP with symptoms of asthma and would have assessed the standard UK diagnostic pathway[8] as well as this pathway with the addition of FeNO against a reference standard of long-term follow-up. No studies of this design were found. Instead, studies that compared FeNO with or without another test against a reference standard of any test or combination of tests in the UK guidelines (see *Figures 3* and *4*) were included. UK guideline tests include:

- Spirometry and lung function tests (mostly FEV_1%, FEV_1/FVC, PEFR).
- Airway reversibility: airway obstruction that shows reversibility when a bronchodilator is taken.
- ICS responsiveness: response to a trial of treatment with ICSs.
- Airway hyper-responsiveness to methacholine, histamine, exercise or mannitol.
- Tests for airway inflammation (FeNO or sputum eosinophil counts), although these are currently restricted to a few specialist centres. Studies that use sputum eosinophils within the reference standard are not considered to be similar to UK practice as this test is not widely available.

Twenty-three cohort studies [across 26 publications[54,69–79,82–91,93–96] and one sponsor's submission (Fukuhara 2013)] that reported the sensitivity and specificity of FeNO testing (alone or in combination with another test or tests) compared with the sensitivity and specificity of some or all of the tests within the UK diagnostic pathway were identified and included in the review. A further three studies[80,81,92] were identified from the update search. Four of these studies[70,77,87,95] included data for FeNO testing in conjunction with another test.

Studies were not similar enough to warrant a meta-analysis, with substantial heterogeneity in populations, cut-off values, devices used and reference standards. We decided to instead focus on key studies that most closely resembled UK practice and resifted the included studies to separate out these studies. We did not, however, want to exclude completely the other studies in case they might prove useful to the committee in their decision-making, especially as some were studies that the SCMs had indicated might be of use when consulted during the clarification of the inclusion and exclusion criteria (see *Appendix 2*).

This review is subdivided into a number of sections and to aid reading a summary is given here:

- Studies including adults, adults plus adolescents, all age groups and unspecified age groups.
    - Studies meeting the inclusion criteria – this section tabulates all included studies and assesses their relevance to the decision problem.
    - Studies relevant to the decision problem using only FeNO as the index test – this section provides an appraisal of study quality, a narrative synthesis and greater detail relating to these studies, along with estimates of sensitivity and specificity.

  - Studies using FeNO in conjunction with another test as the index test – this section provides a narrative synthesis and greater detail relating to these studies, along with estimates of sensitivity and specificity.

- Studies including children or children and adolescents.

  - Studies using only FeNO as the index test – because of the smaller number of studies relating to children, all studies are included without selection based on their relevance to the decision problem. This section provides a narrative synthesis and greater detail relating to these studies, along with estimates of sensitivity and specificity.
  - Studies using FeNO in conjunction with another test as the index test – this section provides greater detail relating to one study, along with estimates of sensitivity and specificity.

- Studies providing data on subgroups of interest to the review:

  - adult smokers
  - children exposed to tobacco smoke
  - pregnant women
  - the elderly.

More detailed descriptions of the study characteristics for studies that were judged to be less relevant, along with sensitivity and specificity data, are included in *Appendices 7* and *8* for reference.

Adults, adults plus adolescents, all age groups and unspecified age groups

Of the 26 studies included in the review, 22 (26 citations) were conducted in adults (13 studies, 16 citations[54,69–81,91]), adults plus adolescents (three studies, four citations[82–85]), all age groups (three studies, three citations[86–88]) or an unspecified age range (three studies, three citations[89,90,92]). *Table 21* summarises the characteristics of the studies and provides a brief description explaining their relevance to the decision problem (note: Schneider *et al.*[71,72] appears twice in this table as this study reported two differently defined populations). This table should be read alongside *Figure 8*, which ascribes a letter to positions that already exist in the current diagnostic pathway and a number to the positions where FeNO could be added to the pathway, as agreed during the scoping workshop.

Studies meeting the inclusion criteria

Of the 22 studies conducted in adults that met the inclusion criteria for the review:

- Nine studies[54,69–72,82–84,86,87,90] recruited patients with symptoms of asthma who were broadly equivalent to patients entering the UK pathway at position A (see *Figure 8*). Of these, six[69,71,72,82–84,86,87] were considered to be of most relevance to the decision problem, although the studies had not necessarily been conducted in the UK.
- Nine studies[73–77,81,85,88,89,91] recruited patients who could be considered 'difficult to diagnose' and are located at other points along the diagnostic pathway. These patients had already undergone some of the tests in the UK pathway and had tested negative for asthma thus far. One further study[71,72] reported a subset of difficult-to-diagnose patients from a larger cohort of patients at position A (see *Figure 8*). Of these, seven studies[73,74,76,77,81,85,88] were considered to be of most relevance to the decision problem, although the studies had not necessarily been conducted in the UK.
- One study[78] recruited patients with suspected EIB. This study was considered to be relevant to the decision problem, although it had not been conducted in the UK.
- One study[79] recruited army recruits, amongst whom a high proportion are thought to have lied about their asthmatic status. This study was not considered to be relevant to the decision problem and it had not been conducted in the UK.
- Two studies[80,92] did not describe the populations they included and their relevance to the decision problem is therefore unknown.

TABLE 21 Diagnostic review: key study characteristics of the diagnostic cohort studies

Author, year	Population	Age group	Device	Cut-off values (ppb)	Reference standard	Position of FeNO in the pathway	Relevance to decision problem
Position A							
Fortuna 2007[70]	Position A	Adults	N-6008	20	FEV_1, FEV_1/FVC, airway responsiveness, WBP, airway hyper-responsiveness (MCT)	No equivalent position in UK pathway	Not relevant – uses WBP and device of unknown equivalence
Fukuhara 2011,[54] Fukuhara 2013 (sponsor's submission)	Position A	Adults	NA623	40	At least two of the three criteria of induced sputum eosinophilia, airway hyper-responsiveness and reversibility. Exclusion of other lung diseases	No equivalent position in UK pathway (sputum eosinophilia)	Not relevant – reference standard not similar enough to common UK practice (sputum eosinophilia)
Schneider 2009[71,72]	Position A	Adults	NIOX MINO	12, 16, 20, 35, 46, 76	FEV_1, FEV_1/FVC, airway reversibility, airway hyper-responsiveness (MCT) in sequence similar to that in UK guidelines	FeNO replaces whole pathway (excluding trial of treatment)	Relevant
Schneider 2013[69]	Position A	Adults	NIOX MINO	9, 12,16, 20, 25, 35, 41, 42, 43, 44, 45, 46, 71	FEV_1, FEV_1/FVC, airway reversibility, hyper-responsiveness (MCT)	FeNO replaces whole pathway (excluding trial of treatment)	Relevant
Smith 2004[86]	Position A	All ages	NR	20	ATS 1987[130] symptoms plus one of airway reversibility, positive response to ICSs, airway hyper-responsiveness (MCT)	FeNO replaces whole pathway	Relevant although uses unknown device of unknown equivalence
Smith 2005[83]	Position A	Adults and adolescents	Niox	≥ 15, > 47, < 15	ATS 1987[130] symptoms plus one of airway reversibility, positive response to ICSs, airway hyper-responsiveness (MCT)	FeNO replaces whole pathway	Relevant
de La Barra 2011[84]				25, 40, 50, 70, 90, 110, 130, 150	Airway reversibility	FeNO replaces airway reversibility	Relevant

continued

TABLE 21 Diagnostic review: key study characteristics of the diagnostic cohort studies (*continued*)

Author, year	Population	Age group	Device	Cut-off values (ppb)	Reference standard	Position of FeNO in the pathway	Relevance to decision problem
Subset of position A							
Cordeiro 2011[87]	Position A with high prevalence of atopy	All ages	NIOX Flex (Aerocrine, Solna, Sweden)	27	Airway reversibility, airway hyper-responsiveness (histamine)	FeNO replaces whole pathway	Relevant although population not whole spectrum
			NIOX Flex, airway reversibility	FeNO 27 and/or > 12% and 200-ml improvement in FEV_1 with bronchodilator	Airway reversibility, airway hyper-responsiveness (histamine)	Combination replacing FEV_1/FVC and airway hyper-responsiveness	Relevant although population not whole spectrum
Heffler 2006[82]	Position A with rhinitis	Adults and adolescents	Niox	10, 15, 20, 25, 30, 34, 36, 40, 454, 50, 55, 60, 65, 75, 80, 85, 100	Airway hyper-responsiveness (MCT) or airway reversibility	FeNO replaces pathway (not including ICS responsiveness but including airway reversibility)	Relevant – rhinitis population generalisable to whole asthma population
Pizzimenti 2009[90]	Position A with chronic cough	Unclear age group	NIOX MINO	55	Airway hyper-responsiveness (MCT)	No equivalent position in UK practice	Not relevant – not equivalent to UK practice
Difficult to diagnose							
Bobolea 2012[88]	Position H	All ages	NIOX MINO	30	Adenosine challenge test	FeNO at position 2	Relevant
Katsoulis 2013[81]	Before position G (via negative bronchodilator response)	Adults	NIOX MINO	32	Hyper-responsiveness (MCT)	FeNO precedes MCT	Relevant
Mathew 2011[91]	Patients at E or F	Unclear age group	NR	NR	Airway hyper-responsiveness (MCT)	Equivalent to FeNO at position 1 or 2	Not relevant – device and cut-off values not reported and uses unknown device of unknown equivalence
Pedrosa 2010[85]	Before position G	Adults and adolescents	NIOX MINO	40	Airway hyper-responsiveness (MCT)	FeNO at position 1	Relevant

Author, year	Population	Age group	Device	Cut-off values (ppb)	Reference standard	Position of FeNO in the pathway	Relevance to decision problem
Schleich 2012[77]	Before position G	Adults	Niox	34	Airway hyper-responsiveness (MCT)	FeNO at positions 1 and 2 (in place of MCT)	Relevant
			Niox, FEV_1 101%	FeNO > 34 and $FEV_1 \leq 101\%$	Airway hyper-responsiveness (MCT)	Combination replaces FEV_1/FVC and airway hyper-responsiveness (MCT)	Relevant
Schneider 2009[71,72]	Position Bii	Adults	NIOX MINO	12, 46	Airway hyper-responsiveness (MCT)	NA	Not relevant – in the UK these patients are more likely to receive trial of treatment than MCT
Difficult to diagnose with chronic cough							
Hahn 2007[74]	Position F with chronic cough	Adults	NOA 280i	35, 38	ICS responsiveness	FeNO replaces trial of treatment (whole treatment pathway)	Relevant although diagnosis is of ICS responsiveness not asthma and uses device of unknown equivalence
Hsu 2013[73]	Position F with chronic cough	Adults	NOA 280i	30, 33.9	ICS responsiveness	FeNO replaces trial of treatment (whole treatment pathway)	Relevant although diagnosis is of ICS responsiveness not asthma and uses device of unknown equivalence
Prieto 2009[76]	Position F with chronic cough	Adults	Niox	20	ICS responsiveness	FeNO replaces trial of treatment	Relevant although diagnosis is of ICS responsiveness not asthma
Sato 2008,[75] Mathew 2011[91]	Position F with chronic cough	Adults	Chemiluminescence analyser (Kimoto; Osaka, Japan)	38.8	Cough with/without wheeze, sputum eosinophilia, airway reversibility, airway hyper-responsiveness (MCT)	No equivalent position in UK pathway (sputum eosinophilia)	Not relevant – reference standard not similar to common UK practice (sputum eosinophilia) and uses device of unknown equivalence

continued

TABLE 21 Diagnostic review: key study characteristics of the diagnostic cohort studies (*continued*)

Author, year	Population	Age group	Device	Cut-off values (ppb)	Reference standard	Position of FeNO in the pathway	Relevance to decision problem
Zhang 2011[89]	Position F with chronic cough	Unclear age group	NIOX MINO	31, 40	Sputum eosinophilia, pulmonary function test, airway hyper-responsiveness, 24-hour oesophageal pH monitoring, skin prick test and serum IgE	No equivalent position in UK practice	Not relevant – reference standard uses tests not used in UK standard practice
EIB							
El Halawani 2003[78]	Suspected EIB	Adults	NOA/Sievers 280A	12	Exercise challenge	NA	Relevant but unclear if patients similar to those who would be referred to exercise challenge test in the UK and uses device of unknown equivalence
Other							
Arora 2006[79]	Mix of undiagnosed and diagnosed[a]	Adults	Niox	6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 40, 46	Airway hyper-responsiveness (histamine)	Equivalent to MCT or later?	Not relevant – too different from UK population; reference standard would not be applied to all UK patients
Brannan 2013[92]	Unclear, referred for mannitol challenge in Australia	Unclear age group	HypAir (Medisoft, Leeds, UK) with 0.6-ppb correction to match Niox	47	Hyper-responsiveness – mannitol challenge	Unclear if comparable as population unknown	Unclear
Chancafe-Morgan 2013[80]	Unclear, referred for bronchial hyper-responsiveness testing in Spain	Adults	NR	35	Hyper-responsiveness (MCT)	Unclear if comparable as population unknown	Unclear

IgE, immunoglobulin E; NA, not applicable; NR, not reported; WBP, whole-body plethysmography.
a Army recruits, some of whom are thought to have lied about their existing asthma diagnosis.

Reasons for considering a study not relevant to the decision problem are given in *Table 21*. A total of 14 studies[69,71–74,76–78,81–88] were considered relevant and a further two[80,92] were considered to be of unknown relevance and are considered in greater detail in the following section. Full study details and results for the six studies[54,70,75,79,89–91] considered not relevant are provided in *Appendices 7* and *8*.

Studies relevant to the decision problem using only FeNO as the index test

From the initial 22 studies conducted in adults, adults plus adolescents, all age groups and unspecified age groups, 14 studies were considered to be of most or of some relevance to the decision problem. These studies are Schneider *et al.*,[69] Schneider *et al.*,[71,72] Schleich *et al.*,[77] Prieto *et al.*,[76] El Halawani *et al.*,[78] Hsu *et al.*,[73] Hahn *et al.*,[74] Pedrosa *et al.*,[85] Heffler *et al.*,[82] Smith *et al.*[83] (de la Barra *et al.*[84] reports additional analyses to Smith *et al.*[83]) Smith *et al.*,[86] Bobolea *et al.*,[88] Cordeiro *et al.*[87] and Katsoulis *et al.*[81] Two further studies[80,92] had unclear relevance to the decision problem and are also considered.

Table 22 groups the 14 studies considered to be of relevance to the decision problem according to the position on the pathway and the reference standard and tabulates the study and patient characteristics. *Appendix 9* provides more detail about the specifics of the reference standards used and *Appendix 10* provides more detail about the patient inclusion and exclusion criteria. There are several main sources of heterogeneity amongst these studies that preclude meta-analysis of the results. These include: the age groups recruited; the spectrum of patients in terms of their position in the pathway and other restrictions in recruitment such as having rhinitis or chronic cough; the device used to measure FeNO; the reference standards used; and the cut-offs reported.

For each study we have selected and presented in tables three sets of sensitivity and specificity estimates. These are:

- The highest sum of sensitivity and specificity as reported by the authors of the study.
- The highest sensitivity – in this scenario a negative test result rules out a diagnosis of asthma (see *Tables 3–5* for details). This was selected as the cut-off that provided the highest sensitivity. When 100% sensitivity was reported for more than one cut-off, the cut-off that maintained the highest specificity was selected. It should be noted that some studies did not report 100% sensitivity, although this may have been achievable at lower cut-off points. When the cut-off with the highest sensitivity was not also the cut-off with the highest positive predictive value (PPV), this latter cut-off was also presented.
- The highest specificity – in this scenario a positive test result rules in a diagnosis of asthma (see *Tables 3–5* for details). Selected as for the highest sensitivity but for specificity. When the cut-off with the highest specificity was not also the cut-off with the highest negative predictive value (NPV), this latter cut-off was also presented.

It should be noted that superior sets of sensitivity and specificity values may in fact have been achieved but selection was limited to the range of cut-off points reported within studies.

Quality assessment of studies relevant to the decision problem Sixteen studies (18 citations[69,71–74,76–78,80–88,92]) exploring FeNO measurement for the diagnosis of asthma in adults were assessed for quality according to QUADAS-2 criteria for diagnostic accuracy studies.[38] Although based on the same data as the study by Smith *et al.*,[83] the study by de la Barra *et al.*[84] was assessed separately as the analysis was different.

TABLE 22 Diagnostic review: study and patient characteristics of the 14 studies considered of relevance to the decision problem

Author, year	Study design, funding	Country, setting, recruitment dates	Population	Device	Reference standard	*n* analysed/*N* recruited (%), reasons for withdrawals	Mean (SD) age (years)	Sex male, *n/N* (%)	Severity, mean (SD) FEV_1%	Mean (SD) FeNO (ppb)	Smokers, *n/N* (%)	Atopic, *n/N* (%)
Position A vs. whole pathway												
Schneider 2009[71,72]	Prospective, consecutive cohort study Funding: GOVERNMENT	Germany Primary care – 14 GPs across 10 practices February 2006–June 2007	Adults Position A	NIOX MINO	FEV_1, FEV_1/FVC, airway reversibility, airway hyper-responsiveness (MCT)	160/160 (100)	43.9	72/160 (45)	Asthmatics (*n* = 75) 100 (12.2); COPD (*n* = 25) 67.8 (18.5); overlap (*n* = 8) 68.8 (18.4); no OAD (*n* = 52) 107.4 (12.8)	Asthmatics (*n* = 75) 42.6 (47.9); COPD (*n* = 25) 16.2 (11.1); overlap (*n* = 8) 20.4 (18.6); no OAD (*n* = 52) 24.7 (16.0)	Current and ex-smokers 86/160 (54)	NR
Schneider 2013[69]	Prospective, consecutive cohort study Funding NR: authors report no conflicts	Germany Private practice run by five pneumologists June 2010–October 2011	Adults, position A	NIOX MINO	FEV_1, FEV_1/FVC, airway reversibility, hyper-responsiveness (MCT)	393/400 (98) Lack of data: *n* = 7	Asthma: 40.5 (15.4); COPD: 60.8 (17.0); no OAD 44.6 (16.5)	158/393 (40.2)	Asthmatics 101.3 (17.0); COPD 74.1 (12.3); no OAD 107.7 (16.3)	Asthmatics 42.4 (46.4); COPD 16.6 (6.8); no OAD 22.0 (16.5)	Current smoker 39/393 (9.9); ex-smoker 139/393 (35.4)	NR
Smith 2004[86]	Prospective, consecutive cohort study Funding: mix of industry and non-industry but not device manufacturer	New Zealand Secondary care, one centre Dates NR	All patients	NR	Airway reversibility, positive response to ICSs, airway hyper-responsiveness (MCT)	44/51 (86) Withdrew: *n* = 7; withdrew consent (time): *n* = 4; technical difficulties *n* = 3	Asthmatics (*n* = 17) 41.6 (range 9–72); non-asthmatics (*n* = 30) 31.8 (range 9–64)	20 (42.6)	Asthmatics (*n* = 17) 90.5 (18.4); non-asthmatics (*n* = 30) 110.0 (13.5)	Asthmatics (*n* = 17) 52 (34.0); non-asthmatics (*n* = 30) 15.7 (12.9)	Ex-smokers 5/47 (10.6)	NR
Smith 2005[83]	Prospective, consecutive cohort study Funding: mix of industry and non-industry but not device manufacturer	New Zealand Secondary care, one centre Dates NR	Adults and adolescents Position A	Niox	Airway reversibility, positive response to ICSs, airway hyper-responsiveness (MCT)	52/60 (87) Withdrew: *n* = 8; withdrew consent: *n* = 3; respiratory tract infection *n* = 1; acute rhinitis *n* = 1, LTFU *n* = 3	40.5 (range 14–71)	20/52 (38.5)	97.8 (14.2)	Range 6.3–242.0[84]	Current smoker 3/52 (5.8); ex-smoker 10/52 (19.2)	40/52 (77)[84]

Author, year	Study design, funding	Country, setting, recruitment dates	Population	Device	Reference standard	*n* analysed/*N* recruited (%), reasons for withdrawals	Mean (SD) age (years)	Sex male, *n/N* (%)	Severity, mean (SD) FEV_1%	Mean (SD) FeNO (ppb)	Smokers, *n/N* (%)	Atopic, *n/N* (%)
Position A vs. airway reversibility												
de La Barra 2011[84]	Prospective, consecutive cohort study Funding: Aerocrine and lottery grants New Zealand	New Zealand Secondary care, one centre Dates NR	Adults and adolescents Position A	Niox	Airway reversibility	52/60 (87) Withdrew: *n* = 8; withdrew consent: *n* = 3; respiratory tract infection: *n* = 1; acute rhinitis: *n* = 1; LTFU: *n* = 3	40.5 (range 14–71)[83]	20 (38.5)[83]	97.8 (14.2)[83]	Range 6.3–242.0	Current smokers 3/52 (5.8); ex-smokers 10/52 (19.2)	40/52 (77)
Subset of Position A vs. airway reversibility or airway hyper-responsiveness												
Cordeiro 2011[87]	Retrospective (analysis of prospective database) Funding NR, authors reported no conflicts	Netherlands Secondary care January 2007–September 2007	All ages with high prevalence of atopy Position A	NIOX Flex	Airway reversibility, airway hyper-responsiveness (histamine)	114/114 (100)	Median (range): asthmatics (*n* = 42) 39 (7–83); non-asthmatics (*n* = 72): 38 (7–87)	43/114 (37.7)	FEV_1/FVC%, median (range): asthmatics 70 (42–95); non-asthmatics 77 (69–95)	Median (range): asthmatics (*n* = 42) 44 (6–290); non-asthmatics (*n* = 72) 17 (5–45)	11/114 (9.6)	81/114 (71.1)
Heffler 2006[82]	Prospective, consecutive cohort study Funding: government/non-industry	Italy Allergy and immunity clinic Dates NR	Adults and adolescents with rhinitis Position A	Niox	Airway hyper-responsiveness (MCT) or airway reversibility	48/48 (100)	40.08 (SD NR)	21 (43.75)	89.2 (95% CI 80.1 to 98.4)	59.7 (95% CI 50.2 to 89)	0	35/38 (92.1)
Difficult to diagnose vs. airway hyper-responsiveness												
Bobolea 2012[88]	Prospective, consecutive cohort study Funding: NR	Spain Assuming secondary care Dates NR	All ages Position H	NIOX MINO	Adenosine challenge test	30/30 (100)	37.3 (range 13–69)	13/30 (43.3)	NR	NR	NR	NR
Katsoulis 2013[81]	Assume prospective cohort Funding NR	Greece Army general hospital and local general hospital Dates NR	Adults Position G	NIOX MINO	Airway hyper-responsiveness (MCT)	112	Median (IQR) 25 (22 to 37)	95/112 (84.8)	Median (IQR) 89 (83 to 99)	Median (IQR) 20.5 (12 to 34)	NR Recent ex-smokers excluded	51/112 (45.5)

continued

TABLE 22 Diagnostic review: study and patient characteristics of the 14 studies considered of relevance to the decision problem (*continued*)

Author, year	Study design, funding	Country, setting, recruitment dates	Population	Device	Reference standard	*n* analysed/*N* recruited (%), reasons for withdrawals	Mean (SD) age (years)	Sex male, *n*/*N* (%)	Severity, mean (SD) FEV_1%	Mean (SD) FeNO (ppb)	Smokers, *n*/*N* (%)	Atopic, *n*/*N* (%)
Pedrosa 2010[85]	Prospective, consecutive cohort study Funding: NR, authors report no conflicts	Spain Secondary care Dates NR	Adults and adolescents Position G	NIOX MINO	Airway hyper-responsiveness (MCT)	114/115 (99) Withdrawal *n* = 1, reason NR	34 (13)	72/115 (62.6)	(*n* = 115) 104.29 (14.95)	(*n* = 115) 34	Current smokers 17/115 (14.8); ex-smokers 11/115 (9.6)	100/115 (87)
Schleich 2012[77]	Prospective cohort study Funding: non-industry	Belgium Secondary care March 2009–December 2009	Adults with chronic cough Position G	Niox	Airway hyper-responsiveness (MCT)	174/237 (73) *n* = 63 did not meet inclusion criteria	41 (16)	72/174 (41)	97 (13)	Median (range) 17 (4–271)	59/174 (33.9)	84/174 (48)
Suspected EIB vs. exercise challenge test												
El Halawani 2003[78]	Prospective, consecutive cohort study Funding: NR	USA Naval medical centre Dates NR	Adults Suspected EIB	NOA/ Sievers 280A	Exercise challenge	49/50 (98) Inability to complete spirometry *n* = 1	27.9 (SD NR)	35 (71.4)	NR	EIB group (*n* = 7) 41; non-EIB group (*n* = 42) 25.6	0	0
Position H with chronic cough vs. ICS responsiveness												
Hahn 2007[74]	Retrospective cohort study Funding: NR, authors reported no conflicts	Mayo Clinic, Rochester, MN, USA Secondary care December 2004–November 2005	Adults with chronic cough Position H	NOA 280i	ICS responsiveness	64/64 (100)	Pooled weighted mean 46.8 (NR)	26/64 (40.6)	ICS unresponsive group 98; ICS responsive group 94	ICS unresponsive group 26.0 ± 16.5; ICS responsive group 51.25 ± 20.1	Current smokers 0/64 (0); ex-smokers 10/64 (15.6)	NR
Hsu 2013[73]	Retrospective cohort study Funding: NR	Taiwan Asthma and cough-specific clinic June 2007–May 2008	Adults with chronic cough Position H	NOA 280i	ICS responsiveness	81/114 (71) *n* = 33 (26 lost after first visit, 7 stopped coughing after 1–2 weeks of treatment for UACS and GORD)	49 (14)	33/81 (40.7)	91.8 (15.3)	Mean rank FeNO by Kruskal–Wallis test: 47	0/81 (0)	NR

Author, year	Study design, funding	Country, setting, recruitment dates	Population	Device	Reference standard	*n* analysed/*N* recruited (%), reasons for withdrawals	Mean (SD) age (years)	Sex male, *n/N* (%)	Severity, mean (SD) FEV_1%	Mean (SD) FeNO (ppb)	Smokers, *n/N* (%)	Atopic, *n/N* (%)
Prieto 2009[76]	Prospective cohort study, unclear if consecutive Funding: none	Spain Allergy or respiratory clinics Dates NR	Adults with chronic cough Position H	Niox	ICS responsiveness	43/43 (100)	48 (95% CI 43 to 52)	18/43 (41.9)	113.2 (95% CI 108.0 to 118.3)	GM (95% CI): responders 23.2 (17.5 to 30.7); non-responders 18.6 (14.7 to 24.0)	0/43 (0)	43/43 (100)
Unclear population vs. airway hyper-responsiveness												
Brannan 2013[92]	Retrospective cohort study Funding NR	Australia Pulmonary function laboratory (secondary care) Dates NR	Unclear, referred for mannitol challenge in Australia	HypAir with 0.6-ppb correction to match Niox	Mannitol challenge	401	NR	NR	NR	NR	NR	NR
Chancafe-Morgan 2013[80]	Prospective, consecutive cohort study Funding NR	Spain Pulmonary function laboratory (secondary care) Dates NR	Unclear, referred for bronchial hyper-responsiveness testing in Spain	NR	Hyper-responsiveness (MCT)	30	44.2 (16.7)	10/30 (33)	NR	33.6 (18.7)	NR	NR

CI, confidence interval; GM, geometric mean; GORD, gastro-oesophageal reflux disease; IQR, interquartile range; LTFU, lost to follow-up; NR, not reported; OAD, obstructive airway disease; UACS, upper airway cough syndrome.

The overall study quality was variable, with the study by Smith *et al.*[83] scoring well on all of the domains and thus being at least risk of bias. The studies at highest risk appeared to be those by Hsu *et al.*[73] and Cordeiro *et al.*,[87] neither of which provided sufficient information on the nature of blinding for the index and reference standard tests. There were also some issues in terms of patient flow in both studies. In the study by Cordeiro *et al.*,[87] patients did not all receive the same reference test (MCT was provided only if asthma was suspected from other tests). Similarly, in the study by Hsu *et al.*,[73] the reference standard was allocated based on an algorithm rather than on an a priori set of tests (*Figure 11*). The studies by Katsoulis *et al.*[81] and Brannan *et al.*[92] were poorly reported and at unknown risk of bias. The risk of bias from the conduct of the index test scored worst overall, with only one study scoring positively for this domain. Studies scored poorly for risk of bias from the conduct of the reference standard, with 12 having a score of 'unclear' for this domain.

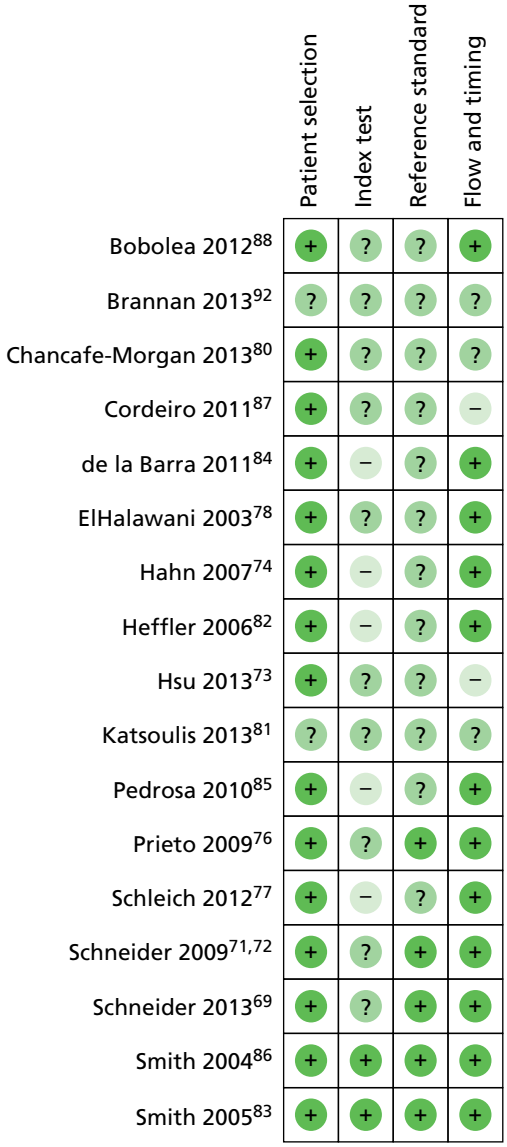


FIGURE 11 Risk of bias summary: review authors' judgements about each risk of bias item for each included study. Dark green circles with + sign, low risk of bias; light green circles with – sign, high risk of bias; medium green circles with ?, unclear risk of bias.

Risk of bias from patient selection As far as we could ascertain, patient selection did not appear to be a source of bias in the body of literature. All studies avoided a case–control design and recruited appropriately (i.e. those patients presenting with clinical signs of asthma or a subset thereof or patients at a definable point in the UK pathway). However, it was unclear in seven cases[73,74,76,77,81,87,92] whether a consecutive sample was recruited.

Risk of bias from the conduct of the index test The conduct of the index test was a potentially important source of bias, with only the study by Smith *et al.*[83] being free from bias in this domain as a whole. There were two component questions for this domain, one relating to blinding and one to whether the study was a derivation study or a validation study. Ten studies were unclear whether the index test was interpreted blind to the reference standard.[71,73,74,77,80–82,85,88,92] The studies by de la Barra *et al.*[84] and Cordeiro *et al.*[87] were not explicit with regard to the blinding of the reference standard results; however, as the index test was performed before the reference standard, it would not have been possible for the investigator to be aware of the reference results at the time of the index test unless interpretation was not performed at the time of the test. This would seem unlikely as FeNO measurement carried out according to standardised protocols is objective and interpretation is not required.

Several further studies were at potential risk of bias in that they were derivation studies that fitted cut-off points to the data post hoc and were thus likely to overestimate accuracy.[69,74,76–78,82,84,85,87]

Risk of bias from the conduct of the reference standard The reference standard and its interpretation was a further source of bias among much of the literature, with only the study by Prieto *et al.*,[76] the two studies by Schneider *et al.*[69,71] and the study by Smith *et al.*[83] being free of bias. It was not possible to ascertain in any of the remaining literature whether the operator conducting the reference standard had been blinded to the results of the index test.

Risk of bias from patient flow and timing of the study For the most part there was little concern about the patient flow and study timing. However, at least two studies did not provide an identical reference standard for all patients. In the study by Cordeiro *et al.*[87] patients received MCT only if asthma was suspected based on other tests, whereas in the study by Hsu *et al.*[73] reference standard provision was algorithm based, with some patients not receiving ICS treatment. It was not necessarily clear in all other studies whether patients received all reference standard tests or a sequence. In other respects, the patient flow and study timing were satisfactory. Dropout rates were low and, when dropouts occurred, these were adequately accounted for in the study reports.

Summary The corpus of included literature was of variable quality, with the study by Smith *et al.*[83] being at the least risk of bias and the two Schneider studies[69,71] also performing well. The conduct of the index test was identified as a potentially serious source of bias among the literature, with few studies providing adequate information on how blinding to the reference test results was achieved. Most studies were derivation studies and, in fitting cut-off points to the data post hoc, are likely to overestimate the accuracy of FeNO as a diagnostic test. In terms of the conduct of the reference standard, few studies provided satisfactory information on how operators were blinded to the results of the index test. However, it is important to stress that this may reflect lack of clarity in the study reports rather than in the conduct of the reference test itself. The likelihood of unblinding biasing the results is therefore unclear.

Studies recruiting patients at Position A

Position A is the start of the UK pathway. Patients will have undergone no other tests. The reference standard used in studies that recruit patients at this position will determine whether the results relate to a scenario in which FeNO is replacing the whole pathway or a scenario in which it is replacing just one test within the pathway. When replacing just one test it could be used as a rule-in scenario; patients testing positive would go on to be treated as asthmatic and patients testing negative would go on to have further tests for asthma. When a rule-out scenario is used, patients testing positive would go on to have further tests and patients testing negative would go on to be treated as not asthmatic.

Position A compared with the whole pathway

Population: Four studies[69,71,72,83,86] recruited patients with symptoms of asthma who had not undergone any other tests. These studies are unlikely to have recruited the full spectrum of patients at this point in the pathway because of common exclusions such as those who had experienced a respiratory infection in the last month and those taking ICSs (see *Appendix 10*). As in many cases a GP may provide a patient with ICSs before confirmation of asthma; these exclusions may result in a patient spectrum that does not reflect UK practice.

Of the four studies, those by Schneider *et al.*[69,71,72] recruited adults, that by Smith *et al.*[83] recruited adults and adolescents and that by Smith *et al.*[86] recruited patients of any age. The largest study was that by Schneider *et al.*[69] with 393 participants and the smallest was that by Smith *et al.*[86] with 44 participants. Mean age and FEV_1% and FeNO values were not always reported for the whole cohort, making it difficult to compare across studies. All studies recruited more females than males, with the proportion of males ranging from 38.5% to 45%. Schneider *et al.*[69,71,72] and Smith *et al.*[83] recruited a mix of smokers, ex-smokers and non-smokers whereas Smith *et al.*[86] did not recruit any smokers, although this was not listed as an exclusion criteria and may be a result of the small sample size. Only Smith *et al.*[83] reported how many participants were atopic, with a high prevalence of 77%; the other three studies did not list atopy as an exclusion criterion, making it likely they included a proportion of atopic patients. The study by Schneider *et al.*[69] excluded pregnant women.

Intervention: The two Schneider studies[69,71,72] both used NIOX MINO. The study by Smith *et al.*[83] used the Niox chemiluminescent device and that by Smith *et al.*[86] did not report the device used.

Reference standard: The reference standard for both studies by Schneider *et al.*[69,71,72] was airway reversibility or airway hyper-responsiveness (depending on spirometric test results), whereas in both studies by Smith *et al.*[83,86] the reference standard also incorporated ICS responsiveness. Although these reference standards do differ, bronchodilator reversibility and ICS responsiveness appear to be used interchangeably in the UK pathway and so both reference standards are equivalent to the whole pathway. However, it is likely that these reference standards may differentially influence estimates of FeNO diagnostic accuracy as FeNO would be expected to correlate better with ICS responsiveness than airway reversibility testing with a bronchodilator.

Study design and setting: All studies were prospective, consecutive cohort studies and none of the studies was funded by the manufacturers of a FeNO device. Both studies by Schneider *et al.*[69,71,72] were conducted in Germany in primary care or private practice whereas both studies by Smith *et al.*[83,86] were conducted in New Zealand in secondary care.

Estimates of diagnostic accuracy: Table 23 details the estimates of sensitivity and specificity for these studies. The results do not appear to be similar between studies. The cut-off for the highest sum of sensitivity and specificity varied from 20 ppb to 47 ppb and this did not appear to be dependent on any variable. The studies by Schneider *et al.*[69,71,72] and Smith *et al.*[83] all reported higher specificity values than sensitivity values, whereas the study by Smith *et al.*[86] reported the opposite. This study recruited a mixed population of adults and children and also did not report the device used to measure FeNO. Sensitivities varied greatly across studies, ranging from 32% to 88%. Specificities were more consistent across studies, ranging from 75% to 93%.

Rule-out cut-off points varied from 9 ppb to 16 ppb with sensitivities between 69% and 96%, specificities between 13% and 53%, PPVs between 29.4% and 56.5% and NPVs between 37.1% and 83.8%. Rule-in cut-off points varied from 47 ppb to 76 ppb, with specificities between 92% and 100%, sensitivities between 13% and 55.6%, PPV between 79.5% and 100% and NPV between 56.7% and 65.7%. The two studies by Schneider *et al.*[69,71,72] reported very similar rule-in (71 ppb and 76 ppb respectively) and rule-out (9 ppb and 12 ppb respectively) cut-off points, but the cut-off providing the highest sum of sensitivity and specificity was not similar between these two studies (25 ppb and 46 ppb respectively). Smith *et al.*[83] reported a similar rule-out cut-off point (15 ppb) to these studies but a quite different rule-out cut-off point (47 ppb). Only Schneider *et al.*[71,72] reported a 100% PPV that would reliably rule patients in, with no studies reporting a 100% NPV.

Position A compared with airway reversibility De la Barra *et al.*[84] performed a secondary analysis of the data from Smith *et al.*[83] against a reference standard of airway reversibility only. This is equivalent to replacing airway reversibility with FeNO, or placing FeNO before airway reversibility as a rule-in test or rule-out test, with patients going on to receive this and further tests as appropriate. The cut-off point with the best sum of sensitivity and specificity (41.7 ppb) seemed fairly similar to that reported in Smith *et al.*[83] (47 ppb). The rule-out cut-off point was somewhat higher at 25ppb, compared with 15 ppb in Smith *et al.*,[83] and the rule-in cut-off point was higher at 110 ppb (or 90 ppb if selecting the cut-off with the highest NPV) compared with 47 ppb respectively. Sensitivity and specificity values were also different (see *Table 23*).

Subset of patients at Position A compared with airway reversibility or airway hyper-responsiveness *Population:* These studies recruited patients who may represent a narrower selection of the full spectrum of patients who present with symptoms of asthma than described in the previous studies. Heffler *et al.*[82] recruited 48 adults and adolescents with rhinitis and symptoms of asthma whereas Cordeiro *et al.*[87] recruited 114 patients with a 'high prevalence of atopy'. However, it would appear that these two studies are in fact reasonably comparable to the studies that recruited a full spectrum of patients at position A. The prevalence of atopy in the study by Heffler *et al.*[82] was higher than that in the study by Cordeiro *et al.*,[87] at 92% compared with 71%. The study by Smith *et al.*[83] was the only study to report the prevalence of atopy among the studies that recruited the fuller spectrum of patients at position A and this study reported a similar prevalence of 77%. Similar to the previous studies, Heffler *et al.*[82] did not recruit any smokers whereas 9.6% of the participants in the study by Cordeiro *et al.*[87] were smokers. Mean age, severity and FeNO values were not reported in a way that allowed comparison between studies.

Intervention: Heffler *et al.*[82] used the Niox chemiluminescent device and Cordeiro *et al.*[87] used NIOX Flex.

Reference standard: Both studies used a combination of airway reversibility and airway hyper-responsiveness as the reference standard, which is equivalent to the whole UK pathway.

Study design and study setting: The study by Heffler *et al.*[82] was a prospective consecutive cohort study conducted in Italy in an allergy and immunity clinic. The study by Cordeiro *et al.*[87] was a retrospective analysis of a prospective database conducted in the Netherlands in secondary care. Neither study was funded by the manufacturers of the FeNO devices.

TABLE 23 Diagnostic review: diagnostic accuracy of FeNO tests in adults, adults and adolescents and all ages[a]

Author, year	Population	Device	*n*	Reference standard	Highest sum of sensitivity and specificity				
					Cut-off (ppb)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Position A vs. whole pathway									
Schneider 2009[71,72]	Adults Position A	NIOX MINO	160	FEV_1, FEV_1/FVC, airway reversibility, airway hyper-responsiveness (MCT)	46	32	93	77.3	59.5
Schneider 2013[69]	Adults Position A	NIOX MINO	393	FEV_1, FEV_1/FVC, airway reversibility, hyper-responsiveness (MCT)	25	49	75	56.0	69.5
Smith 2004[86]	All patients	NR	44	Airway reversibility, positive response to ICSs, airway hyper-responsiveness (MCT)	20	88	79	70	91.7
Smith 2005[83]	Adults and adolescents Position A	Niox	52	Airway reversibility, positive response to ICSs, airway hyper-responsiveness (MCT)	47	55.6	92	88.2	65.7
Position A vs. airway reversibility									
de la Barra 2011[84]	Adults and adolescents Position A	Niox	52	Airway reversibility	41.7	NR	NR		
Subset of Position A vs. airway reversibility or airway hyper-responsiveness									
Cordeiro 2011[87]	All ages with high prevalence of atopy Position A	NIOX Flex	114	Airway reversibility, airway hyper-responsiveness (histamine)	27	78	92	84.6	88
		NIOX Flex, airway reversibility		Airway reversibility, airway hyper-responsiveness (histamine)	27	87	90		
Heffler 2006[82]	Adults and adolescents with rhinitis Position A	Niox	48	Airway hyper-responsiveness (MCT) or airway reversibility	36	77.8	60	53.8	81.8
Difficult to diagnose vs. airway hyper-responsiveness									
Bobolea 2012[88]	All ages Position H	NIOX MINO	30	Adenosine challenge test	30[b]	100	29.2	26	100
Katsoulis 2013[81]	Adults Position G	NIOX MINO	112	Hyper-responsiveness (MCT)	32	47	85	70.1[c]	68.1[c]
	Atopics		51		26	55	85	NR	NR
Pedrosa 2010[85]	Adults and adolescents Position G	NIOX MINO	114	Airway hyper-responsiveness (MCT)	40	74.3	72.5	54.1	86.3
Schleich 2012[77]	Adults with chronic cough Position G	Niox	174	Airway hyper-responsiveness (MCT)	34	35	95	87.8	62.4
		Niox, FEV_1 ≤ 101%		Airway hyper-responsiveness (MCT)	34	24.4	98.9		
Suspected EIB vs. exercise challenge test									
El Halawani 2003[78]	Adults Suspected EIB	NOA/ Sievers 280A	49	Exercise challenge	12[b]	100	31	19.4	100

Rule out					Rule in				
Cut-off (ppb)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Cut-off (ppb)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
12	85	24	49.6	64.5	76	13	100	100	56.7
16	69	53	56.5	66.2					
9	96	13	41.6	83.8	71	18	97	79.5	64.6
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
15	81.5	48	29.4	37.1	As highest sum				
25	83.3	57.5	37.0	92	110	25	95	60	80.9
					90	41.7	92.5	62.5	84.1
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
25	100	46.7	52.9	100	100	27.8	100	100	69.8
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
10[d]	81	39	49.9[c]	73.2[c]	30[d]	49	82	67.1[c]	68.2[c]
10[d]	90	10%	NR	NR	30[d]	48	85	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

continued

TABLE 23 Diagnostic review: diagnostic accuracy of FeNO tests in adults, adults and adolescents and all ages[a] (*continued*)

Author, year	Population	Device	*n*	Reference standard	Highest sum of sensitivity and specificity				
					Cut-off (ppb)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Position H with chronic cough vs. ICS responsiveness									
Hahn 2007[74]	Adults with chronic cough Position H	NOA 280i	64	ICS responsiveness	38	90	85	89.5	84.6
Hsu 2013[73]	Adults with chronic cough Position H	NOA 280i	81	ICS responsiveness	33.9	94.7	76.3	80	94
Prieto 2009[76]	Adults with chronic cough Position H	Niox	43	ICS responsiveness	20	53	63	52.6	62.5
Unclear position in the pathway vs. airway hyper-responsiveness									
Brannan 2013[92]	Unclear	HypAir	401	Mannitol challenge	47	30.2[c]	96.3[c]	65.7[c]	85.5[c]
Chancafe-Morgan 2013[80]	Unclear	NR	30	Airway hyper-responsiveness (MCT)	35	75	83.3	75	83.3

NR, not reported.
a A table of all results reported by these studies is given in *Appendix 11*.
b Unclear if this is the best sum of sensitivity and specificity.
c Calculated by reviewer.
d Only reported cut-offs for 10–30 ppb.

Rule out					Rule in				
Cut-off (ppb)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Cut-off (ppb)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Estimates of diagnostic accuracy: Table 23 details the estimates of sensitivity and specificity for these studies. In Heffler *et al.*,[82] the sensitivity and specificity for the highest sum of sensitivity and specificity do not seem noticeably different from the values in studies recruiting the fuller spectrum of patients with symptoms of asthma (77.8% and 60% respectively), although the rule-in scenario achieved 100% for specificity and the rule-out scenario achieved 100% for sensitivity, which was not achieved by the studies with a full spectrum of patients at position A. This study also reported higher values for the paired sensitivity and specificity in the rule-in and rule-out scenarios than the studies with a fuller spectrum of patients at position A. In the study by Cordeiro *et al.*,[87] sensitivity and specificity were 78% and 92%, which has a similar sum to the highest pair of sensitivity and specificity values reported for studies recruiting the full spectrum of patients, reported by Smith 2004[86] at 88% and 79% respectively, but with the balance between sensitivity and specificity inverted.

Studies recruiting patients who are difficult to diagnose of relevance to the decision problem

The most appropriate reference standard in the difficult-to-diagnose population in relation to UK guidelines varies according to where in the pathway the group is recruited from, in other words, which tests they have already undergone and which test they would get next. As previously described, when a rule-in scenario is used, patients testing positive would go on to be treated as asthmatic and patients testing negative would go on to have further tests for asthma. When a rule-out scenario is used, patients testing positive would go on to have further tests and patients testing negative would go on to be treated as not asthmatic.

Population

Four studies recruited patients who fall into the difficult-to-diagnose category and were of relevance to the decision problem, but none recruited the same spectrum of patients at exactly the same point in the pathway (see *Appendix 10* for more details of study inclusion criteria). Schleich *et al.*[77] recruited adults with chronic cough who had a negative test for airway reversibility and normal spirometry (position G in the UK pathway). Pedrosa *et al.*[85] and Katsoulis *et al.*[81] also recruited patients at position G but in the study by Pedrosa *et al.*[85] this was not restricted to those with chronic cough and included adolescents as well as adults. Bobolea *et al.*[88] recruited a somewhat different spectrum of patients who were of all ages and who had a negative test for airway reversibility, normal spirometry and a negative MCT. Mean ages were between 34 and 41 years and FEV_1% when reported was similar at 97% and 104%; however, FeNO values were not reported in a way that allowed comparison between studies. The studies by Schleich *et al.*,[77] Katsoulis *et al.*[81] and Pedrosa *et al.*[85] recruited smokers and atopic patients, although the prevalence of atopy was higher in the study by Pedrosa *et al.*[85] at 87%, compared with 48% and 45.5% in the studies by Schleich *et al.*[77] and Katsoulis *et al.*[81] respectively.

Intervention

The studies by Katsoulis *et al.*,[81] Pedrosa *et al.*[85] and Bobolea *et al.*[88] used NIOX MINO, whereas the study by Schleich *et al.*[77] used the Niox chemiluminescent device.

Reference standard

All four studies[77,81,85,88] used airway hyper-responsiveness as the reference standard, which was appropriate to the UK pathway for the patients selected. The studies by Katsoulis *et al.*,[81] Schleich *et al.*[77] and Pedrosa *et al.*[85] used MCT whereas Bobolea *et al.*[88] used an adenosine challenge test as patients had already had a negative MCT test.

Estimates of diagnostic accuracy

Table 23 details the estimates of sensitivity and specificity for these studies. Katsoulis *et al.*,[81] Schleich *et al.*[77] and Pedrosa *et al.*[85] reported quite similar cut-offs for the highest sum of sensitivity and specificity at 32, 34 and 40 ppb respectively. The paired estimates of sensitivity and specificity were similar in Katsoulis *et al.*[81] and Schleich *et al.*,[77] with sensitivities of 47% and 35% and specificities of 85% and 95% respectively. Pedrosa *et al.*[85] reported a sensitivity of 74.3% and a specificity of 72.5%. There is no one obvious characteristic of the studies that correlates with the differences in results. Bobolea *et al.*[88] reported 100% sensitivity but only 29.2% specificity, indicating that FeNO measurement in this position would be most likely to be useful as a rule-out test. No data were available for other cut-off points.

In comparison to studies that recruited patients at position A in the pathway, patient populations are perhaps somewhat younger. Other patient spectrum characteristics look comparable. The range of estimates of sensitivity and specificity also look largely comparable. A sensitivity of 100% was achieved by Bobolea *et al.*,[88] although it is not clear if this was for the highest sum of sensitivity and specificity or if the cut-off was selected so that FeNO could perform as a rule-out test with high sensitivity.

Studies recruiting patients with chronic cough at position H

Population The studies by Prieto *et al.*,[76] Hsu *et al.*[73] and Hahn *et al.*[74] all recruited adults with chronic cough who were negative for some other causes of cough (see *Appendix 10* for more details on the inclusion and exclusion criteria). Prieto *et al.*[76] recruited patients with a FEV_1 of at least 80% predicted with chronic cough and no signs of other lung disease. Hsu *et al.*[73] recruited patients who were negative for upper airway cough syndrome and gastro-oesophageal reflux disease (GORD) and who had no obvious chest radiograph abnormalities. Hahn *et al.*[74] recruited patients with normal chest radiographs. All three patient groups appear to be equivalent to patients at position H in the UK pathway, who were classed as being at low risk for asthma, who have undergone tests for other conditions and for whom an asthma diagnosis is being reconsidered. All three studies recruited no current smokers and only the study by Prieto *et al.*[76] reported the prevalence of atopy and this was 100%. Cohorts were perhaps somewhat older than in other studies, with all averaging in the mid- to high 40s.

Intervention The device used was the NOA 280i in Hsu *et al.*[73] and Hahn *et al.*[74] and the Niox chemiluminescent device in Prieto *et al.*[76]

Reference standard The reference standard was ICS responsiveness, which would be the next test in UK practice for some or all of these patients.

Estimates of diagnostic accuracy *Table 23* details the estimates of sensitivity and specificity for these studies. In the study by Prieto *et al.*,[76] sensitivity and specificity were poor at 53% and 63%, respectively, although the studies by Hsu *et al.*[73] and Hahn *et al.*[74] both report high sensitivities (94.7% and 90% respectively) and fairly high specificities (76.3% and 85% respectively), indicating that FeNO could be a useful rule-out test. It is not clear why the estimates reported by Prieto *et al.*[76] differ from those reported by the other two similar studies, but it may be the result of differences in patient selection. Although the device used by Prieto *et al.*[76] was Niox, it is not thought that this would alter estimates of diagnostic accuracy, rather the cut-off points derived.

Other studies of some interest to the assessment

Table 23 details the estimates of sensitivity and specificity for other studies of some interest to the assessment. The study by El Halawani *et al.*[78] recruited adults with suspected EIB. As in the study by Arora *et al.*,[79] which was not considered relevant to the review because of the reference standard used, this group of patients was made up of army recruits. It is not clear what previous tests these patients had undergone, if any. None of the patients was a smoker or atopic. The reference standard was an exercise challenge test, which will identify only patients with EIB rather than other forms of asthma. The device used (NOA/Sievers 280A) is of unknown equivalence to NIOX MINO and NObreath. The study reports 100% sensitivity and 31% specificity, indicating that this test could be used as a rule-out test.

The studies by Brannan *et al.*[92] and Chancafe-Morgan *et al.*[80] both used airway hyper-responsiveness (MCT or mannitol challenge) as the reference standard but it is not clear if the patient spectrum matches UK practice for patients being referred for such testing. The next most similar studies are those by Schleich *et al.*,[77] Pedrosa *et al.*[85] and Katsoulis *et al.*,[81] all of which use MCT challenge testing as the reference standard, in patients with asthma symptoms. In the study by Chancafe-Morgan *et al.*,[80] the cut-off point was comparable to that in the other studies at 35 ppb, whereas in the study by Brannan *et al.*[92] the cut-off point was higher than in any of the other studies at 47 ppb (next highest 40 ppb[85]), which may reflect the use of a device known to read higher than the Niox chemiluminescent device (despite a correction of

0.6 ppb). Brannan *et al.*,[92] Katsoulis *et al.*[81] and Schleich *et al.*[77] all report sensitivities and specificities in similar ranges, with low sensitivity but high specificity, whereas Chancafe-Morgan *et al.*[80] and Pedrosa *et al.*[85] report a more even split between sensitivity and specificity (sensitivities of 75% and 74.3% and specificities of 83.3% and 72.5% respectively).

Diagnostic accuracy meta-analysis From *Table 22* it can be seen that only two sets of two studies are similar enough to each other to warrant meta-analysis:

- Schneider *et al.*[71,72] and Schneider *et al.*[69] – two studies conducted by the same research group with populations recruited in 2006–7 and 2010–11 respectively
- Hsu *et al.*[73] and Hahn *et al.*[74] – these studies recruited in 2009–10 and 2004–5, respectively, and were conducted in China and the USA respectively.

However, the value of such a meta-analysis is limited given that these studies are no more or less relevant to the decision problem than any of the other studies found.

Studies using FeNO in conjunction with another test as the index test

From the initial 22 studies conducted in adults, adults plus adolescents, all age groups and unspecified age groups, two[77,87] reported diagnostic accuracy data for FeNO in conjunction with another test as the index test. One further sudy[70] did not report actual data but did state that the addition of certain tests (see next paragraph) did not increase accuracy.

The study characteristics of the studies by Schleich *et al.*,[77] Cordeiro *et al.*[87] and Fortuna *et al.*[70] are presented in *Tables 21* and *22* and the diagnostic accuracies in the studies by Schleich *et al.*[77] and Cordeiro *et al.*[87] are presented in *Table 23*. Neither the study by Schleich *et al.*[77] nor that by Cordeiro *et al.*[87] reported a change in the optimum cut-off for FeNO when using it in conjunction with another test, but sensitivities and specificities did change. The study by Fortuna *et al.*[70] was not judged to be of high relevance to the decision problem as it used sputum eosinophilia as part of the reference standard. This test is not widely available in the UK and so this study has low generalisability. The study reported that the addition of sputum eosinophilia to FeNO measurements increased specificity from 64% to 76%; sensitivity was not reported for the two tests together. The authors also stated that the addition of lung function tests and bronchodilator tests did not increase accuracy, but actual data were not provided.

Cordeiro *et al.*[87] used FeNO with a cut-off of 27 ppb in conjunction with airway reversibility in a population of patients at position A in the UK pathway. If patients were positive by either test they were considered to have tested positive. Compared with using FeNO at a cut-off of 27 ppb alone, sensitivity increased from 78% to 87% whereas specificity decreased from 92% to 90%. However, it should be noted that the reference standard for this study was airway reversibility or airway hyper-responsiveness to histamine. As such, the study results are at high risk of incorporation bias as the reference standard incorporates some of the same results as the index test. This is likely to overestimate the actual diagnostic accuracy of this combination of tests.[131]

Schleich *et al.*[77] used FeNO with a cut-off of 34 ppb in conjunction with a FEV_1% predicted of $\leq 101\%$ in a population of patients with chronic cough and at position E (difficult to diagnose) in the diagnostic pathway. Patients were required to have both a FeNO > 34 ppb and an FEV_1% predicted $\leq 101\%$ to be judged positive by this combination of tests. This resulted in an increase in specificity from 95% to 98.9%, but a decrease in sensitivity from 35% to 24.4%. In this case the reference standard was airway hyper-responsiveness to MCT and so incorporation bias was avoided.

Conclusions In both cases the improvements in diagnostic accuracy are modest (or negative when considering the sum of sensitivity and specificity) and necessitate the usual trade-off between sensitivity and specificity. As both studies are derivation studies rather than validation studies (in which the cut-off points are pre-set), it is possible that the gains seen are an overestimate of increases in diagnostic accuracy.

However, it would seem that using a combination of tests may have additional benefit to using FeNO on its own, and these studies equate more accurately to adding FeNO into the pathway than studies that do not use FeNO in conjunction with other tests.

Studies including children or children and adolescents

Studies using only FeNO as the index test

Four studies that recruited children (plus adolescents and/or young adults) and compared FeNO- guided diagnosis to non-FeNO-guided diagnosis were identified.[93–96] All of the studies were based in secondary care and each study was undertaken in a different country: Finland,[93] Switzerland,[94] Israel[95] and Korea.[96] Funding sources were reported only in the studies by Linkosalo *et al.*[93] and Woo *et al.*:[96] these were the Tampere Tuberculosis Foundation/Medical Research Fund of Tampere University Hospital and the National Research Foundation of Korea respectively. The study by Sivan *et al.*[95] declared that there were no conflicts of interest in the research.

Quality assessment The four studies exploring FeNO measurement for the diagnosis of asthma in children were assessed for quality according to QUADAS-2 criteria for diagnostic accuracy studies.[38] The overall quality was variable, with no one study being free from potential bias in all domains and no single domain being free from bias in all studies. The Woo *et al.* study[96] appeared to be at the lowest risk of bias whereas the studies by Ramser *et al.*[94] and Linkosalo *et al.*[93] displayed the highest risk of bias (*Figure 12*).

Risk of bias from patient selection The studies by Sivan *et al.*[95] and Woo *et al.*[96] both appeared to be free of bias in terms of patient selection. Both studies enrolled consecutive samples, avoided a case–control design and recruited appropriately (i.e. those patients presenting with clinical signs of asthma). However, there were potential sources of bias in the studies by Linkosalo *et al.*[93] and Ramser *et al.*[94] in that neither study explicitly clarified whether it had enrolled patients consecutively.

Risk of bias from the conduct of the index test There was potential bias in the conduct of the index test throughout the corpus of literature. All four studies[93–96] were derivation studies; hence, in fitting the cut-off points to the data post hoc they are likely to provide liberal estimates of diagnostic accuracy. There was an additional source of possible bias in the Ramser *et al.* study[94] in that it was not clear whether the index test was interpreted blind to the results of the reference standard.

Risk of bias from the conduct of the reference standard The studies by Sivan *et al.*[95] and Woo *et al.*[96] both appeared to provide a satisfactory reference standard in that both adhered to all or part of the UK guidelines and clearly stated that the results were interpreted by a blinded investigator. Neither the study by Linkosalo *et al.*[93] nor that by Ramser *et al.*[94] provided sufficient information to confirm whether the result was interpreted blind to the index test results.

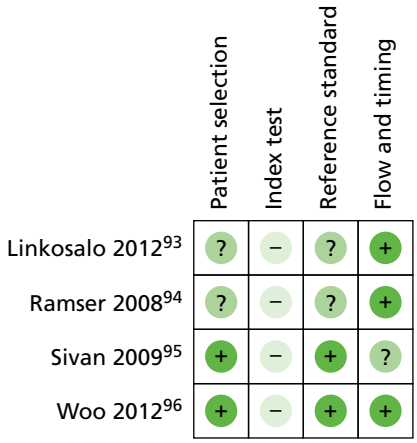


FIGURE 12 Risk of bias summary: review authors' judgements about each risk of bias item for each included study. Dark green circles with + sign, low risk of bias; light green circles with – sign, high risk of bias; medium green circles with ?, unclear risk of bias.

Risk of bias from patient flow and timing of the study The patient flow and test timing appeared to be broadly satisfactory. The studies by Linkosalo *et al.*,[93] Ramser *et al.*[94] and Woo *et al.*[96] each conducted tests consecutively, provided the same reference standard to all patients and included all enrolled patients in the final analysis. The one study that did display a potential source of bias in this domain was that by Sivan *et al.*[95] These investigators provided a list of criteria that may have been used to confirm a diagnosis of asthma, but it was not clear precisely which of these tests in which combination(s) were given to which patients.

Summary The small body of research was of variable quality, with the study by Woo *et al.*[96] displaying the least risk of bias and that by Ramser *et al.*[94] being at the highest risk of bias. The most important source of potential bias in this literature is concerned with the conduct and interpretation of the index test. All studies fitted FeNO cut-off points to the data post hoc and are thus likely to overestimate diagnostic accuracy. In addition, the study by Ramser *et al.*[94] did not provide sufficient information to judge whether the index test results had been interpreted blind to the reference standard. Study flow and timing was the least likely domain to contain sources of bias in that only the study by Sivan *et al.*[95] did not provide sufficient clarity on whether all patients received the same reference standard.

All studies included in the review of diagnostic accuracy of FeNO in children

Study design and timeline of studies Study characteristics and timelines are provided in *Tables 24* and *25*. All four studies had a prospective cohort design and, with the exception of the study by Linkosalo *et al.*[93] (when the relevant information was not reported), they each enrolled consecutive patients. The timing of diagnostic procedures among the studies also appeared broadly comparable. Linkosalo *et al.*[93] performed FeNO measurement before an exercise challenge test, after which spirometric testing was used at 4, 10 and 15 minutes. Final spirometry occurred at 20 minutes, after salbutamol inhalation. Ramser *et al.*[94] likewise performed FeNO measurement before pulmonary function assessment and spirometric testing. In addition, patients who did not react to the exercise testing were provided with an additional MCT at 1 hour. Sivan *et al.*[95] also assessed FeNO first and followed up with spirometry and sputum induction 1–2 hours later, although sputum induction did not contribute to the diagnosis of asthma, which was based on assessment by a certified paediatric pulmonologist after at least 18 months' follow-up and treatment. Finally, Woo *et al.*[96] asked all participants to fill in an ISAAC (International Study of Asthma and Allergies in Childhood) questionnaire[132] and undergo clinical assessment. FeNO measurements were then taken, followed by spirometry and a MCT.

Population The study populations were broadly similar in terms of their position on the diagnostic pathway and all recruited children and adolescents, although upper and lower age cut-offs varied a little, with the most inclusive being those in the study by Sivan *et al.*[95] at 5–18 years and Linkosalo *et al.*[93] at 6–19 years and the least inclusive being those in the study by Ramser *et al.*[94] at 6–16 years. There were some further differences in the inclusion criteria. Linkosalo *et al.*[93] included only children and adolescents with confirmed atopy whereas Ramser *et al.*[94] and Woo *et al.*[96] included a mix of atopic and non-atopic patients. Sivan *et al.*[95] did not report the number of patients with atopy but did not specifically include on this basis and the study is therefore likely to have included a mix of atopic and non-atopic patients. All studies recruited patients at position A in the UK pathway; Linkosalo *et al.*[93] recruited patients who had been referred to an allergist with asthma-like symptoms (position A); Ramser *et al.*[94] included children in position A who had been referred to an outpatient clinic for diagnostic assessment of possible reactive airway disease; Woo *et al.*[96] included children presenting with non-specific respiratory symptoms suggestive of asthma and who had not been receiving controller medications for at least 3 months prior to FeNO testing (position A); and Sivan *et al.*[95] also recruited from position A – in this case those with non-specific respiratory symptoms suggestive of asthma for at least 3 months. This study also excluded patients with any other conditions that may have interfered with FeNO testing or sputum eosinophil count, especially unresolved respiratory tract infection or underlying systemic or inflammatory disease.

TABLE 24 Diagnostic review: study and patient characteristics in studies recruiting children and adolescents

Author, year	Study details	Age group	Inclusion/exclusion criteria	No. analysed/ no. recruited	Age (years), sex	FEV_1% predicted	FeNO (ppb)	Atopic, *n*/*N* (%)
Linkosalo 2012[93]	Setting: paediatric allergist, Finland Funding: non-industry Design: prospective cohort study, unclear if consecutive	Children and adolescents	Children and adolescents aged 6–19 years; those with confirmed atopy referred to an allergist with asthma-like symptoms	30/30	Mean age (range): EIB +ve: 10.7 (8–19); EIB –ve: 9.6 (6–13) Code for population: children and adolescents Male, *n* (%): 20 (66.7)	Mean ± SE: EIB +ve: 97 ± 2; EIB –ve: 96 ± 3 ($p = 0.723$)	Mean ± SE: EIB +ve: 31.3 (SD 4.1); EIB –ve: 15.6 (SD 3.6)	30/30 (100)
Ramser 2008[94]	Setting: secondary care, Switzerland Funding: NR Design: prospective, consecutive cohort study	Children and adolescents	Children aged 6–16 years referred to an outpatient clinic for diagnostic work on possible reactive airway disease. SABAs must have been withheld on the day of testing and long-acting beta2-agonists withheld for at least 24 hours before testing	169/169	Mean age: NR Code for population: young children Male, *n*/*N* (%): 96/169 (57)	Mean (SD): atopic ($n = 104$): 97 (12); non-atopic ($n = 57$): 102 (13)	Mean (SD): atopic ($n = 104$): 35 (36); non-atopic ($n = 57$): 13 (16)	104/169 (61.5)

continued

TABLE 24 Diagnostic review: study and patient characteristics in studies recruiting children and adolescents (*continued*)

Author, year	Study details	Age group	Inclusion/exclusion criteria	No. analysed/ no. recruited	Age (years), sex	FEV_1% predicted	FeNO (ppb)	Atopic, *n*/*N* (%)
Sivan 2009[95]	Setting: secondary care, outpatient clinic, Israel Funding: authors declared no conflict of interests Design: prospective, consecutive patients	Children and adolescents	Children and adolescents Inclusion criteria: (1) non-specific respiratory symptoms suggestive of asthma for ≥ 3 months' duration, including cough, wheezing, and shortness of breath with or without trials of treatment with bronchodilators and ICSs; (2) children were co-operative and successfully completed all three tests; (3) follow-up at clinic for at least 1 year Exclusion criteria: patients with other conditions that could affect FeNO or sputum eosinophil count, including subjects with symptoms of unresolved respiratory tract infection, with systemic clinical manifestations of atopy such as anaphylaxis, angioedema, food allergy or urticaria or with an underlying systemic or inflammatory disease	150/156 ($n = 6$ unable to produce sputum)	Mean age (range): steroid-naive asthmatics ($n = 69$): 12.6 (5–18); asthma treated with ICSs ($n = 37$): 12.3 (6–18); non-asthmatics ($n = 44$): 12.0 (7–18) Code for population: children and adolescents Male, *n*/*N* (%): steroid-naive asthmatics: 40/69 (58); asthma treated with ICSs: 19/37 (51); non-asthmatics: 24/44 (55)	Mean (SD): steroid-nave asthmatics: 79.3 (44.4); asthma treated with ICSs: 75.0 (16.0); non-asthmatics: 86.1 (17.1)	Mean (SD): steroid-naive asthmatics: 69 (17); asthma treated with ICSs: 36 (57); non-asthmatics: 12.6 (9)	NR

Author, year	Study details	Age group	Inclusion/exclusion criteria	No. analysed/ no. recruited	Age (years), sex	FEV_1% predicted	FeNO (ppb)	Atopic, *n*/*N* (%)
Woo 2012[96]	Setting: secondary care (outpatient clinic), Korea Funding: non-industry Design: prospective, consecutive cohort study	Children and adolescents	Children and adolescents aged 8–16 years Inclusion criteria: children presenting with non-specific respiratory symptoms suggestive of asthma, including cough, wheezing, and shortness of breath. All included patients did not receive inhaled SABAs in the 8 hours before the measurements and were also not receiving a regular treatment with controller medications for ≥ 3 months before evaluation of FeNO and lung function	245/245	Mean (SD) age: 11.7 ± 2.2 Non-atopic asthmatic (*n* = 38): 11.6 (2.7); non-atopic non-asthmatic (*n* = 18): 11.4 (2.0); atopic asthmatic: 11.7 (2.4) (*n* = 129); atopic non-asthmatic (*n* = 60): 12.6 (2.6) Code for population: children and adolescents Male, *n*/*N* (%): non-atopic asthmatic 20/38 (52.6); non-atopic non-asthmatic 9/18 (50.0); atopic asthmatic 92/129 (71.3); atopic non-asthmatic 42/60 (70.0)	Mean (SD): 87.6 (11.6)	GM (95% CI): asthmatic: 23.4 (20.9 to 26.2); non-asthmatic: 12.6 (10.9 to 14.5)	189/245 (77)

+ve, positive; –ve, negative; CI, confidence interval; GM, geometric mean; NR, not reported; SE, standard error.

TABLE 25 Diagnostic review: description of interventions in studies recruiting children and adolescents

Author, year	Population	Age group	Device	Cut-off values (ppb)	Reference standard	Details of reference standard	Position of FeNO in the pathway	Relevance to decision problem
Linkosalo 2012[93]	Position A with confirmed atopy	Children and adolescents	NOA 280i (chemiluminescence)	10, 20, 30, 40, 50	Airway hyper-responsiveness to exercise	EIB – free-running test with goal of 80% maximum heart rate according to age. Spirometry 4, 10 and 15 minutes after exercise and after salbutamol inhalation given 20 minutes after exercise. EIB positive if maximal decrease in $FEV_1 \geq 12\%$	FeNO at position 1	Relevant
Ramser 2008[94]	Position A	Children and adolescents	CLD 77 AM (chemiluminescence)	10, 20, 30, 40, 50	Airway hyper-responsiveness (MCT or exercise)	Spirometry, body pleythysmography and MTC challenge according to ATS/ERS guidelines.[35] EIB was defined by decrease in FEV_1 by $\geq 15\%$ of baseline. MCT challenge was carried out using a panel of incremental dosages of MCT and a dose of 1.8 mg was defined as the threshold of PD20 to differentiate normal airway hyper-responsiveness from BHR	FeNO replaces whole pathway	Not relevant – uses reference standard not used in the UK
Sivan 2009[95]	Position A	Children and adolescents	CLD 88 (chemiluminescence)	15, 18, 19, 25, >20 or <15	Exacerbation history, airway reversibility, airway hyper-responsiveness	Patient's history of two or more clinical exacerbations of wheezing documented by a physician, dyspnoea or cough relieved by bronchodilators, documented variability in $FEV_1 \geq 15\%$ in response to bronchodilators at any time during the follow-up period (reversibility), documented variability in $FEV_1 \geq 15\%$ over time with or without controller medications (ICSs or montelukast). Results of provocation tests were included when available. Children in whom asthma did not manifest within 18 months of follow-up were considered as not having asthma	FeNO replaces whole pathway	Relevant – uses long-term follow-up
Woo 2012[96]	Position A	Children and adolescents	NIOX MINO	5, 10, 15, 20, 25, 30, 34, 40, 45, 50 (optimum at 22)	Airway reversibility, airway hyper-responsiveness (MCT)	Relevant symptom history and reversible airflow obstruction ($\geq 12\%$ improvement in FEV_1 in response to inhaled beta2-agonist) and/or airway hyper-responsiveness	FeNO replaces whole pathway	Relevant

BHR, bronchial hyper-responsiveness; ERS, European Respiratory Society; NR, not reported; PD20, dose of methacholine needed to cause a 20% fall from baseline in FEV_1.

Sample size ranged from 30[93] to 245[96] and the mean age (often reported for subgroups rather than whole cohorts) ranged from 9.6[93] to 12.6 years,[95] although mean age was not provided by Ramser *et al.*[94] Unlike adult studies in which male participants were in the minority, there was a preponderance towards male participants in all four studies, with the lowest percentage being observed in the Sivan *et al.*[95] study (55.3%).

Interventions Three of the four studies measured FeNO via chemiluminescence, although each used a different device: Linkosalo *et al.*[93] used the NOA280i; Ramser *et al.*[94] used the CLD 77 AM; and Sivan *et al.*[95] used the CLD 88. Woo *et al.*[96] was the only study to use NIOX MINO for FeNO evaluation. In terms of FeNO cut-off points, Linkosalo *et al.*[93] and Ramser *et al.*[94] both used the same prespecified cut-off points of 10, 20, 30, 40 and 50 ppb. Sivan *et al.*[95] used cut-offs of 15, 18, 19, 25 and > 20/< 15 ppb. Woo *et al.*[96] reported a large number of cut-off values, ranging from 5 ppb to 50 ppb.

Reference standard None of the studies fully replicated the UK guidelines. Linkosalo *et al*.[93] used an exercise challenge test (free-running test) with spirometric tests before and after exercise and after salbutamol inhalation. Sivan *et al.*[95] based the diagnosis of asthma on a history of two or more exacerbations, evidence of airway reversibility in response to ICSs or bronchodilators or airway hyper-responsiveness at any time during a period of 18 months' follow-up. Woo *et al.*[96] performed a battery of tests similar to those in the UK treatment pathway (spirometry, MCT and atopy assessment), with FeNO being measured before these other tests. Ramser *et al.*[94] reported results against a reference standard of MCT or exercise challenge testing.

Summary The study of greatest relevance for this assessment is that by Woo *et al*.,[96] which recruited patients in position A on the pathway and used the NIOX MINO device compared with a reference standard that roughly equates to UK practice. In this study FeNO replaces the whole pathway prior to ICS use.

The three remaining studies were of varying relevance to the UK context:

- Sivan *et al.*[95] used an ECO MEDICS CLD 88 device in patients at position A in the pathway compared with a reference standard similar to UK practice. In this study FeNO replaces the whole pathway prior to ICS use.
- The study by Ramser *et al.*,[94] used an Eco Physics CLD 77 AM device for patients in position A on the pathway with a reference standard of airway hyper-responsiveness to exercise or methacholine. As MCT is a very good test for asthma, this study can be seen as similar to testing FeNO against the whole UK diagnostic pathway.
- Linkosalo *et al.*,[93] used a Sievers NOA280i chemiluminescence device for patients at position A on the pathway with a reference standard of an exercise challenge test. In the UK this test is reserved for those with symptoms of EIB.

No studies in children were identified that incorporated ICS responsiveness in the reference standard.

Estimates of diagnostic accuracy The sensitivity and specificity values for each of the studies are presented in *Appendix 12*.

Table 26 also displays three sets of sensitivity and specificity values for each of the studies. These are:

- The highest sum of sensitivity and specificity as reported by the authors of the studies.
- The highest sensitivity – in this scenario a negative test result rules out a diagnosis. This was selected as the cut-off that provided the highest sensitivity. When 100% sensitivity was reported for more than one cut-off, the cut-off that maintained the highest specificity was selected. When the cut-off with the highest sensitivity was not also the cut-off with the highest PPV, this latter cut-off was also presented.
- The highest specificity – in this scenario a positive test result rules in a diagnosis of asthma. Selected as for the highest sensitivity but for specificity. When the cut-off with the highest specificity was not also the cut-off with the highest NPV, this latter cut-off was also presented.

TABLE 26 Diagnostic review: diagnostic accuracy of FeNO tests in children and adolescents

Author, year	Population	Device	Reference standard	No. analysed	Highest sum of sensitivity and specificity				
					Cut-off (ppb)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Position A vs. whole pathway									
Linkosalo 2012[93]	Position A with confirmed atopy	NOA280i (chemiluminescence)	Airway hyper-responsiveness to exercise	30	20	72	83	86.7	66.7
Ramser 2008[94]	Position A	CLD 77 AM (chemiluminescence)	Airway hyper-responsiveness (MCT or exercise)	169	20	49	76	74	51
Sivan 2009[95]	Position A	CLD 88 (chemiluminescence)	Exacerbation history, airway reversibility, airway hyper-responsiveness	150	19	86	89	92.2	79.6
					> 20 or < 15	89	88	93.5	82.1
Woo 2012[96]	Position A	NIOX MINO	Airway reversibility, airway hyper-responsiveness (MCT)	245	21	56.9	87.2	90.5	50.0

Rule out					Rule in				
Cut-off (ppb)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Cut-off (ppb)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
10	89	33	66.7	66.7	30	50	92	90	55
10	76	36	63	51	50	20	93	80	45
20	49	76	74	51					
15	90	70	82.7	81.6	As highest sum				
5	94	14.1	70.0	50	41	23.4	100.0	100	37.9

It should be noted that superior sets of sensitivity and specificity values may have in fact been achieved but selection was limited to the range of cut-off points reported within studies.

There was a high degree of agreement as to the cut-off point that produces the highest sum of sensitivity and specificity, despite the heterogeneity in devices and reference standards, with values between 19 and 21 ppb (see *Table 26*). However, estimates of sensitivity at these cut-off points were not similar across studies, ranging from 49% to 86%; specificity was more similar between studies, ranging from 76% to 89%. Rule-out cut-off points were not similar and varied from 5 to 20 ppb; rule-in cut-off points similarly ranged from 30 to 50 ppb. For ruling out, the highest sensitivity was reported by Woo *et al.*,[96] at 100%, with a paired specificity of 14.1%, PPV of 70% and NPV of 50%. Sensitivities ranged from 76% to 94%. For ruling in, the highest specificity was also reported by Woo *et al.*[96] at 100%, with a paired sensitivity of 23.4%, PPV of 100% and NPV of 37.9%. Specificities varied less than sensitivities, from 89% to 100%. It should be noted that superior rule-in and rule-out sets of sensitivity and specificity may in fact have been achieved but selection was limited to the range of cut-off points reported within the studies.

No meta-analysis was performed on these data because of heterogeneity in FeNO measurement devices and reference standards.

Studies using FeNO in conjunction with another test as the index test

One study recruiting children reported estimates of diagnostic accuracy for FeNO in conjunction with another test.[95] This study was described in more detail in the previous section but in summary recruited children at position A in the pathway and used FeNO in conjunction with sputum eosinophilia against a reference standard of evidence of airway reversibility in response to ICSs or bronchodilators or airway hyper-responsiveness at any time during 18 months' follow-up. Sputum eosinophilia is not a test in widespread use in the UK and the combination of it and FeNO as a diagnostic test is of low relevance to the UK pathway. The results showed that improvements in diagnostic accuracy were very small: sensitivity increased from 86% to 87% and specificity remained the same at 89%.

Studies providing data on subgroups of interest to the review

Adult smokers

Results are presented in *Table 27*. Malinovschi *et al.*[110] and Katsoulis *et al.*[81] investigated the effects of smoking on the usefulness of FeNO in diagnosing asthma. The study by Malinovschi *et al.*[110] was not included in the main diagnostic review as the method of recruitment was unusual.

Study design and setting Both studies were prospective cohort studies, with the study by Malinovschi *et al.*[110] conducted in Denmark and that by Katsoulis *et al.*[81] conducted in Greece in an army hospital.

Population Neither study recruited an ideal spectrum of patients. Both recruited patients on the basis of the presence of symptoms of asthma as reported in a questionnaire rather than through presentation to a GP. In the study by Malinovschi *et al.*[110] the questionnaire was mailed to the general population whereas in the study by Katsoulis *et al.*[81] the reason for patients filling in the questionnaire is not clear but may be for the purpose of army recruitment (army general hospital).

Intervention Both studies used NIOX MINO to measure FeNO values.

Reference standard In the study by Malinovschi *et al.*,[110] to be diagnosed with asthma patients had to exhibit symptoms and test positive by one of MCT; airway reversibility to bronchodilator use; daily use of steroids or SABAs; or asthma symptoms during but not outside the pollen season supported by allergic rhinitis. As the cohort was recruited from a random sample of the population with asthma symptoms and did not exclude existing asthmatics, the reference standard in part depends on a previous diagnosis of asthma in that a patient already prescribed steroids or SABAs is automatically classed as asthmatic. In practice, this reference standard may therefore include patients who have been wrongly diagnosed in primary care. In the study by Katsoulis *et al.*[81] the reference standard was MCT.

Estimates of diagnostic accuracy In both studies,[81,110] cohorts of smokers alone had lower cut-off values than mixed cohorts (11 ppb compared with 32 ppb[81] and 17 ppb compared with 20 ppb[110]) but the difference was small in one study.[110] Differences in cut-off values were not as apparent for rule-in and rule-out scenarios between these two subgroups. Malinovschi *et al.*[110] also reported data for never smokers and ex-smokers. Surprisingly, ex-smokers had a higher derived cut-off (22 ppb) than all other subgroups, but this difference did not hold true in rule-in and rule-out scenarios.

Children exposed to tobacco smoke

We were unable to identify any studies that evaluated the diagnostic accuracy of FeNO testing in children exposed to tobacco smoke. However, evidence from the review on the use of FeNO measurements in the management of asthmatic children exposed to tobacco smoke may provide some insight (albeit limited) on how environmental tobacco smoke may impact on mean FeNO values and therefore FeNO cut-off points. Mahut *et al.*[111] and Hanson *et al.*[112] both reported that FeNO levels were not statistically significantly different between those exposed and those not exposed to tobacco smoke whereas de la Riva-Velasco[113] reported that FeNO values were lower in ICS-treated children who were exposed to tobacco smoke. Similarly, evidence from a diagnostic cohort study[110] (see the previous section) that investigated the effects of smoking on the usefulness of FeNO in diagnosing asthma in adults and adolescents (rather than children) suggested that FeNO could differentiate asthmatic subjects from non-asthmatic subjects with asthma-like symptoms equally well in both never and current smokers. However, the FeNO cut-off levels were lower in current and ex-smokers.

The findings from the above studies suggest that it may be necessary to consider a child's exposure status when interpreting the results of FeNO testing for the diagnosis of asthma, as FeNO levels may be lower in children exposed to tobacco smoke.

Pregnant women

Although no studies were identified that evaluated the diagnostic accuracy of FeNO testing in pregnant women, a cross-sectional study by Tamasi *et al.*,[114] conducted in Hungary, compared FeNO levels in pregnant and non-pregnant asthmatic and healthy women. A total of 102 women were recruited from an outpatient clinic, of whom 35 were healthy non-pregnant women, 27 were healthy pregnant women, 20 were asthmatic non-pregnant women and 20 were asthmatic pregnant women. The exclusion criteria were as follows: current smokers or > 5 pack-years of smoking history, other chronic diseases (e.g. chronic rhinitis, hypertension), acute infection within 3 weeks of measurement or a body mass index > 30 kg/m^2. Asthma was diagnosed using the GINA guidelines[129] and all asthmatic patients had persistent disease. All asthmatic patients were receiving ICSs. In addition, 14 patients were on long-acting beta2-agonists (LABAs) and seven patients received additional LTRA therapy. Mean age ranged from 27 years for non-pregnant healthy women to 31 years for non-pregnant asthmatic women. FeNO was measured using the NIOX MINO device.

The authors found no significant difference in median FeNO levels between healthy pregnant subjects [16 ppb, interquartile range (IQR) 9–35 ppb] and healthy non-pregnant subjects (16, IQR 8–31 ppb). Similarly, no significant difference was observed in the level of asthma control between pregnant and non-pregnant asthmatic subjects and there was no significant difference in the total Asthma Control Test (ACT) scores (20.78 ± 2.96 vs. 19.17 ± 3.1 respectively; $p = 0.17$). In contrast, FeNO levels in pregnant asthmatic women were significantly higher than those in pregnant healthy women (28 ppb, IQR 10–56 ppb vs. 16 ppb, 9–35 ppb respectively; $p < 0.05$). Similarly, the FeNO levels in non-pregnant asthmatic women were significantly higher than those in non-pregnant healthy women (38 ppb, IQR 9–54 ppb vs. 16 ppb, 8–31 ppb respectively; $p < 0.0001$). In addition, the authors reported that there was no significant difference between the two groups of asthmatic women: the mean FeNO value (estimated from a graph in the published paper) for pregnant asthmatic women was 29 ppb and that for non-pregnant asthmatic women was 32 ppb.

TABLE 27 Diagnostic review: diagnostic accuracy in adult and adolescent smokers, non-smokers and ex-smokers in studies recruiting all ages

Author, year	Device	Reference standard	Population	No. analysed	Highest sum of sensitivity and specificity				
					Cut-off (ppb)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Katsoulis 2013[81]	NIOX MINO	Airway hyper-responsiveness (MCT)	All (excluded recent ex-smokers)	112	32	47	85	70.1	68.1
			Smokers	NR	11	85	50	NR	NR
Malinovschi 2012[110]	NIOX MINO	Symptoms plus one of airway reversibility, airway hyper-responsiveness (MCT), prescribed steroids or SABAs, symptoms in pollen season plus allergic rhinitis	All	282	20	52.08	82.8	61	77
			Smokers	112	17	56.3	82.5	56.3	82.5
			Never smokers	108	15	77.8	63.5	60.3	80.0
			Ex-smokers	62	22	62.2	86.1	66.7	84.1

NR, not reported.

Rule out					Rule in				
Cut-off (ppb)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Cut-off (ppb)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
10	81	39	49.9	73.2	30	49	82	67.1	68.2
10	84	55	NR	NR	30	12	95	NR	NR
10	87.5	33.3	40.4	83.8	50	15.6	96.8	71.4	69.0
7	90.6	15.0	29.9	80.0	50	9	98	60	72.9
10	78	48	37.3	84.4	35	16	96	62.5	74.0
10	91	27	47.1	81.0	50	20	95	75	62.5
10	95	16	33.3	87.5	35	37	98	87.5	77.8

Overall, the study authors concluded that pregnancy itself does not alter FeNO levels either in healthy patients or in asthmatic patients and that FeNO levels in pregnant asthmatic patients correlate with asthma control levels.

The elderly

No diagnostic studies that used FeNO to diagnose asthma in the elderly were identified; however, one study[115] that examined FeNO levels and eosinophilic airway inflammation in elderly subjects with airflow obstruction was identified. In asthma diagnosis, the main use of FeNO testing is to identify patients with eosinophilic airway inflammation who are likely to respond to ICSs, as a surrogate for other methods of ascertaining eosinophilic inflammation such as sputum counts. As such, this study should provide some evidence on whether FeNO still acts as a surrogate marker for eosinophilic inflammation in the elderly. This observational case–control study was conducted in Australia and was reported in abstract form only and thus provides limited data. The study recruited 65 elderly patients with or without fixed airflow obstruction and 32 healthy control subjects. The setting from which the patients were recruited is unclear and the majority of patients (86%) with air flow obstruction were on ICS treatment.

The authors found that participants with eosinophilic airway inflammation (sputum eosinophil count > 3%) had similar FeNO levels to those with non-eosinophilic inflammation (16.1 ppb vs.19.1 ppb respectively; $p = 0.762$). Those with a diagnosis of asthma had similar FeNO levels to those with COPD. There was no correlation between FeNO level and sputum eosinophils or any clinical markers. The authors concluded that FeNO was not a surrogate marker for eosinophilic airway inflammation in older people and showed no relationship with clinical outcomes.

Management review

This section is broken down into a number of subsections by population age and subgroup. Briefly, these are:

- FeNO-guided management in adults:
    - quality assessment
    - study details
    - estimates of efficacy.
- FeNO-guided management in children:
    - quality assessment
    - study details
    - estimates of efficacy.
- FeNO-guided management in subgroups defined in the scope:
    - pregnant women
    - the elderly
    - adult smokers
    - children exposed to tobacco smoke.

Adults

Four studies that recruited adults and compared FeNO-guided management with non-FeNO-guided management were included in the review.[97–100] One additional study[101] was identified from the update search. The study by Shaw *et al.*[98] was based in the UK, that by Smith *et al.*[97] was based in New Zealand, that by Syk *et al.*[99] was based in Sweden, that by Calhoun *et al.*[100] was based in the USA and that by Honkoop *et al.*[101] was based in the Netherlands. The studies by Smith *et al.*,[97] Syk *et al.*,[99] Calhoun *et al.*[100] and Honkoop *et al.*[101] were at least partly supported by Aerocrine and the study by Syk *et al.*[99] was submitted as part of Aerocrine's sponsor submission. An additional study by Powell *et al.*[102] was conducted in adult pregnant women and is discussed separately as this group was defined a priori as a distinct group.

Quality assessment

The quality of the five adult management studies was assessed according to criteria proposed in the *Cochrane Handbook for Systematic Reviews of Interventions*[36] and *Systematic Reviews – CRD's Guidance for Undertaking Reviews in Healthcare*.[37] The studies by Powell *et al.*[102] and Shaw *et al.*[98] appeared to be the highest-quality articles, with each containing only one potential source of bias (industry sponsorship and uncertain outcome assessor blinding respectively) (*Figure 13*). The study at highest risk of bias was the unpublished study by Syk *et al.*;[99] this was because of the lack of participant/personnel blinding, incomplete outcome data and selective reporting. In addition, Calhoun *et al.*[100] was largely at unclear or high risk, making this study a potential source of bias. The study by Honkoop *et al.*[101] was published as an abstract and some methodological data were available from the published protocol. However, it is unclear if the execution of the study was per protocol and so quality assessment items were scored as unclear.

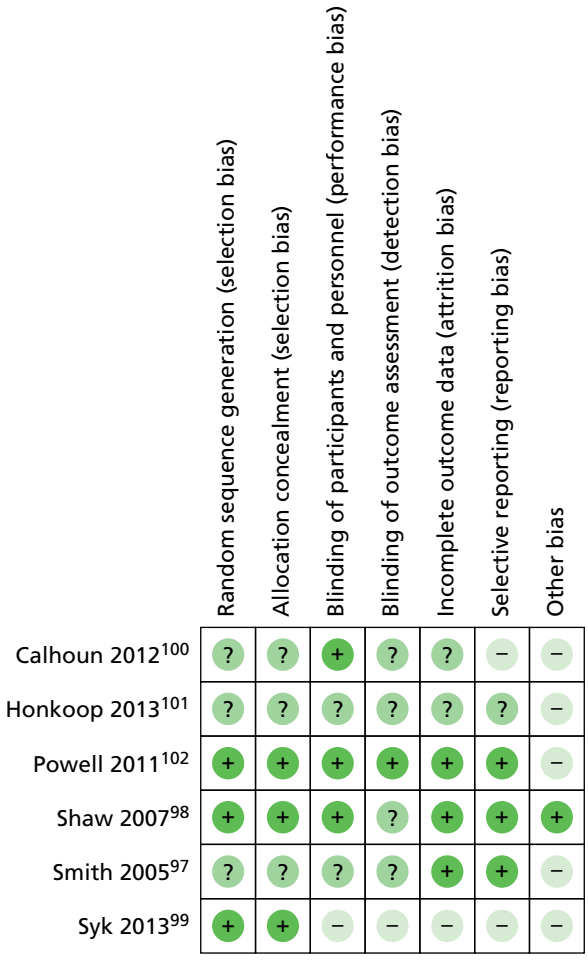


FIGURE 13 Methodological quality summary: review authors' judgements about each methodological quality item for all included studies. Dark green circles with + sign, low risk of bias; light green circles with – sign, high risk of bias; medium green circles with ?, unclear risk of bias.

Risk of selection bias All of the included studies were described as randomised and two of the five studies provided satisfactory information on both random sequence generation and allocation concealment. In the study by Shaw *et al.*,[98] allocation was performed by an independent individual; Syk *et al.*[99] drew lots from sealed envelopes. There may have been adequate randomisation procedures in the remaining three studies[97,100,101] but this could not be confirmed on the basis of the reports.

Risk of performance bias The study at highest risk from lack of blinding was that by Syk *et al.*,[99] which was described as an open-label study. The study by Smith *et al.*[97] was rated as 'unclear' on this item as the study was single blind (participants only). As many of the outcomes were patient reported, patient blinding may have been the most important source of bias to avoid, although the blinding of other study personnel who were deciding whether to step patients up or down may also have been important. The study by Honkoop *et al.*[101] was also scored as 'unclear'. The remaining two studies[98,100] were double-blind and therefore at low risk of performance bias.

Risk of detection bias The poor reporting of outcome assessment blinding in the studies means that unblinded outcome assessment may be a potentially important source of bias throughout this body of literature. However, as outcome assessment blinding often goes unreported in journal articles, it was unclear whether any potential bias was the result of reporting practices or methodological shortcomings in the conduct of the studies themselves.

Risk of attrition bias The studies by Shaw *et al.*[98] and Smith *et al.*[97] appeared to be at low risk of attrition bias. Dropout rates from these studies were low, adequately reported and corrected for in the statistical analyses. In addition, Smith *et al.*[97] performed analysis by intention to treat and extrapolated missing data. There was a potentially high risk of bias in the Syk *et al.* study[99] in that patients were missing and not corrected for in multiple analyses. However, Syk *et al.*[99] did consistently report the number of patients included in each analysis and so the attrition rate was transparent. There were two possible sources of bias in the Calhoun *et al.* study:[100] it was unclear how missing data were corrected for and there were more dropouts in the intervention arm. If these patients were dropping out because of unsatisfactory outcomes (which was not clear from the report), this could skew the results in favour of FeNO. Finally, the study by Honkoop *et al.*[101] was scored as 'unclear' for this item.

Risk of reporting bias Two of the five studies appeared to have provided data on all of the prespecified outcomes.[97,98] However, there was some evidence of selective reporting in Calhoun *et al.*[100] and Syk *et al.*[99] Calhoun *et al.*[100] failed to report oral prednisone levels, although this had been specified as an outcome in the study protocol, and Syk *et al.*[99] did not report the number of severe exacerbations. Syk *et al.*[99] also used medians rather than means in several of the outcomes, precluding these from meta-analysis. However, these data were supplied by the manufacturer (Aerocrine) on request. Finally, the study by Honkoop *et al.*[101] was scored as 'unclear' for this item.

Risk of other bias There were a number of further potential sources of bias in the studies. Smith *et al.*[97] reported receipt of commercial sponsorship whereas Syk *et al.*,[99] Calhoun *et al.*[100] and Honkoop *et al.*[101] reported at least partial commercial funding. Three studies[97,99,100] also conducted a run-in period before randomisation. It is unclear whether this may have introduced bias to the results in the studies by Smith *et al.*[97] and Syk *et al.*[99] In the study by Calhoun *et al.*[100] patients were excluded if their asthma did not remain controlled when administered two puffs twice a day of beclomethasone HFA (40 µg/puff). This is likely to have influenced the spectrum of patients recruited to this trial towards those with less severe asthma. However, this is likely to affect external validity rather than internal validity as both arms are subject to the same run-in period. No further sources of bias were identified in the remaining studies.

Summary The quality of the sampled literature was variable, with the study by Shaw *et al.*[98] being at the lowest risk of bias. The only potential source of bias that we identified in this study pertained to the failure to explicitly state the blinding of outcome assessors. However, it was unclear whether this was an actual methodological flaw or merely inadequate reporting, and at least some of the outcomes were patient reported (patients were blinded). Among the remaining literature, the most important potential source of bias was selective reporting in the Calhoun *et al.*[100] and Syk *et al.*[99] studies, both of which failed to report some prespecified outcomes. The study at highest overall risk of bias was the open-label Syk *et al.*[99] investigation. In addition to lack of blinding, and the aforementioned selective reporting, this study may have been subject to attrition bias. In the absence of information on why data were missing from this study, it is difficult to ascertain how this may have biased the results and in what direction. However, there may be debate about the impact of blinding as a source of bias in these studies. For example, patients could use knowledge of their FeNO readings to guide their self-management, which may capture real-world clinical benefits that would not be observable in double-blind studies.

Study details

Unlike other reviews of FeNO for asthma management, in this review our primary analysis of studies that assess the efficacy of guiding treatment by FeNO measurement in adults considers the study in pregnant women[102] separately, as this subgroup of patients was defined a priori as a separate group. This study is described and discussed later. This current section considers the other five studies in adults.

Study design and timeline of studies *Table 28* provides details of study design and the timelines of the studies. All five studies were RCTs. The studies by Smith *et al.*[97] and Shaw *et al.*[98] were both single blind whereas that by Syk *et al.*[99] was an open-label study. The study by Calhoun *et al.*[100] was described as 'multiply blinded', although it is not entirely clear who was blinded. The study by Honkoop *et al.*[101] did not report blinding. No two studies followed the same timeline exactly. Smith *et al.*,[97] Syk *et al.*[99] and Calhoun *et al.*[100] had a run-in period pre randomisation in which LABAs were reduced or withdrawn and/or doses of ICSs were standardised. Post randomisation, all studies except that by Honkoop *et al.*[101] had an initial period of time in which visits were more frequent. In the study by Calhoun *et al.*,[100] visits were made every 2 weeks for the first 6 weeks post randomisation and then were 6-weekly after that. In Shaw *et al.*[98] initial visits were monthly for 4 months and then every 2 months up to 12 months. In the study by Smith *et al.*,[97] treatment consisted of two phases: a optimisation phase of 3–12 months and a titration phase of a further 12 months. Patients were randomised before both phases and both phases managed patients according to protocols that either did or did not incorporate FeNO measurements. However, data on exacerbations were reported only for the titration phase and it was these data that were incorporated into the analysis. In the study by Syk *et al.*[99] participants had an initial visit 2–4 weeks after the initial titration visit, followed by every 2 months up to 4 months and then every 4 months up to 12 months. All studies titrated doses for at least 12 months except that by Calhoun *et al.*[100] in which doses were titrated for 9 months only. Calhoun *et al.*[100] included a third intervention arm that was not relevant to this review in which the ICS dose was controlled by matching ICS use on a puff-by-puff basis to the rescue use of albuterol in response to the occurrence of symptoms.

Population *Table 29* provides details of patient characteristics across studies. All studies were of a moderate size, with numbers analysed ranging from 94[97] to 611.[101] All patients were recruited from primary care, except in the study by Calhoun *et al.*,[100] in which it was not clear whether patients were recruited from primary or secondary care settings. All had either a doctor's diagnosis of asthma or asthma diagnosed according to guidelines. In the study by Calhoun *et al.*,[100] the doctor's diagnosis was confirmed with either a positive MCT or demonstration of airway reversibility. Inclusion and exclusion criteria varied across studies but, when compatible data are reported, study populations seem broadly similar in terms of age (mean ranged from around 34.5[100] to 45[97] years), FEV_1% (mean ranged from 81.4% to 87.7%) and FeNO values (range of geometric means 18.88–29.0 ppb). It is difficult to determine the comparability of study populations in terms of severity at baseline as different scales for severity and different metrics for medication use have been used. Inclusion and exclusion criteria suggest that at least three studies[97,99,100] recruited populations with mild to moderate asthma. Smith *et al.*[97] excluded those with four or more severe exacerbations in the previous 12 months and those ever

TABLE 28 Adult management review: study design and timelines

Author, year	Study design	Timeline of study
Calhoun 2012[100]	RCT – multiply blinded, multicentre study	Visit 1 (week 0): consent and start of run-in period of 2 weeks – two puffs b.i.d. of beclomethasone HFA (40 µg/puff). If asthma acceptably controlled at this level, enrolled in trial. Visits 2 and 3 (weeks 2–8): pre-randomisation period – patients given two pairs of inhalers to facilitate blinding, one with beclomethasone (2 × 40 µg b.i.d.) and a placebo counterpart and one with albuterol and a placebo counterpart (taken together on demand). Visit 4 (week 8): randomisation to group 1 or group 2. Visits 5–12 (titration): 2, 4, 6, 12, 18, 24, 30 and 36 weeks post randomisation – dose adjustments made at time of clinic visits, monitoring of secondary outcomes
Honkoop 2013[101]	RCT – cluster design	From protocol: Visit 1: introduction session run by practice nurses; randomisation by GP cluster with stratification on postcode; baseline measurement of IPQ, MARS, BMQ, ICQ, FACCT, SF-36, AQLQ, TTO, ASUI, EQ-5D and CostQ, all at home. Visit 2 (titration): GP measures ACQ, FEV_1 and FeNO and titrated dose according to algorithm. Visit 3 (titration): 3 months – GP measures ACQ, FEV_1 and FeNO; patients measure AQLQ, EQ-5D and CostQ at home. Visit 4 (titration): 6 months – GP measures ACQ, FEV_1 and FeNO; patients measure IPQ, MARS, BMQ, ICQ, FACCT, SF-36, AQLA, TTO, ASUI, EQ-5D and CostQ, all at home. Visit 5 (titration): 9 months – as visit 3. Visit 6 (titration): 12 months – as visit 4
Shaw 2007[98]	RCT – single blind, parallel group	Titration at each visit Visit 0: randomisation – FeNO, FEV_1, FVC, PC_{20}, induced sputum analysis, skin prick test, Juniper score. Visit 1: 2 weeks after visit 0 – FEV_1, FeNO, Juniper score. Visits 2–5: monthly visits to 4 months – FEV_1, FeNO, Juniper score. Visit 6: at 6 months – FEV_1, FeNO, Juniper score, PC_{20}, sputum analysis. Visits 7 and 8: at 8 and 10 months respectively – FEV_1, FeNO, Juniper score. Visit 9: 12 months – FEV_1, FeNO, Juniper score, PC_{20}, sputum analysis
Smith 2005[97]	RCT – single blind, single centre, placebo controlled	Visit 1: enrolment, start of 2-week run-in period in which LABA withdrawn, reinstated at fixed dose if not tolerated. Visit 2 (week 2): FeNO and spirometry; patients begin 4 weeks of 750 µg/day fluticasone or 500 µg/day if previous dose < 200 µg/day. Visit 3 (week 6): randomisation and start of phase 1 Titration phase 1 (3–12 months after randomisation): visits every 4 weeks, FeNO and spirometry, dose adjustment to optimal dose by downwards titration until FeNO ≥ 15 ppb (equivalent to 35 ppb at 50-ml flow rate) or uncontrolled, then uptitrated until controlled/≤ 15 ppb. This dose deemed the 'optimal dose' Titration phase 2 (12 months after completion of phase 1): visits every 2 months, upwards adjustments when control lost/FeNO > 15 ppb, downwards adjustment if controlled/FeNO ≤ 15 ppb for two consecutive visits, but not below optimal dose. Treatment orders assigned by blinded investigator. Compliance assessed by inhaler weight
Syk 2013[99]	RCT – open label, parallel group, multicentre	Visit 1: eligibility and consent – capillary blood for IgE confirmation, LABA withdrawn, ICSs continued (salbutamol inhaler with dose counter). Visit 2 (titration): 2–4 weeks later – FeNO, spirometry, reversibility, Juniper mini-AQLQ, generic quality of life, Juniper six-item ACQ, questionnaire on allergen exposure, venous blood for IgE analysis. ICSs and LTRAs altered according to (a) FeNO levels and six fixed treatment steps in FeNO group and (b) usual care (patient report, SABA use, physical examination, pulmonary function tests) in the control group, with FeNO measured but not revealed to treatment decision-maker or patient. Visit 3 (titration): 2 months – ACQ, FeNO and treatment altered. Visit 4 (titration): 4 months – mini-AQLQ, ACQ, FeNO and treatment altered. Visit 5 (titration): 8 months – as visit 3. Visit 6 (titration): 12 months – identical to visit 2. Outcomes recorded at visits 2–6

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; ASUI, Asthma Symptoms Utility Index; b.i.d., twice a day; BMQ, Beliefs about Medicines Questionnaire; CostQ, cost questionnaires; EQ-5D, European Quality of Life-5 Dimensions; FACCT, Foundation for Accountability; ICQ, undefined in source document; IgE, immunoglobulin E; IPQ, Illness Perception Questionnaire; MARS, Medication Adherence Report Scale; PC_{20}, provocative concentration that causes a positive reaction; SF-36, Short Form questionnaire-36 items; TTO, time-trade-off.

TABLE 29 Adult management review: study and population characteristics

Author, year	Study details	Inclusion/exclusion criteria	No. analysed/ no. recruited	Age (years), sex, *n*/*N* (%)	Spirometry, mean (SD)	Severity, mean (SD)	FeNO (ppb)	Smokers, atopic	Medication use
Calhoun 2012[100]	Setting: care level NR, USA Funding: mixed;[a] equipment from Aerocrine	Patients with mild to moderate, well-controlled persistent asthma with compliance rates ≥ 75% who could tolerate treatment of two puffs b.i.d. of beclomethasone HFA (40 µg/puff) during the 2-week run-in period	363 recruited to trial WBR: 21; I: 115/115;[b] C: 114/114[c] Other study arm (not included in review): 113/113	Adults (assumed from mean age) Mean (SD) age: I: 34.8 (11.3); C: 34.2 (11.9) Male 75/229 (32.8)	FEV_1%: I: 86.3 (10.4); C: 87.7 (12.1)	ACQ: I: 0.79 (0.54); C: 0.72 (0.50) AQLQ: I: 6.16 (0.77); C: 6.27 (0.76) ASUI: I: 0.88 (0.12); C: 0.90 (0.10)	FeNO, GM (SD): I: 18.88 (0.66); C: 21.38 (0.62)	Smokers NR Atopic: 196/229 (85.6%)	Albuterol rescue use, median (IQR): I: 0.07 (0 to 0.43); C: 0.04 (0 to 0.29)
Honkoop 2013[101]	Setting: Netherlands Funding: mixed[a]	From protocol: age 18–50 years; doctor's diagnosis of asthma; patients who need ICSs as controller medication (steps 2–4 GINA guidelines[112]); ICSs for ≥ 3 months in the previous year; written informed consent; no exacerbation of asthma within 1 month before entry. Exclusions: daily or alternate day OCS therapy for at least 1 month before entering into the study; inability to understand written and oral Dutch instructions; active diseases likely to interfere with the purpose of the study, such as end-stage disease or inability to visit GP	611 randomised Other data NR	43 Male: 32%	NR	NR	NR	NR	NR
Shaw 2007[98]	Setting: recruited from primary care UK Funding: Asthma UK grant; speakers' fees but not from Aerocrine	Included: patients with GP diagnosis of asthma who received one or more prescriptions for antiasthma medication in the last 12 months; current non-smokers with a past smoking history of < 10 pack-years. Excluded: those poorly compliant; those with a severe asthma exacerbation (needing prednisolone) in the last 4 weeks	118 (ITT LOCF)/119 WBR: 1; I: 58; C: 60	Adults > 18 years Mean age NR Male 54/118 (46)	FEV_1%: I: 81.4 (20.9); C: 84.9 (20.1) FEV_1/FVC: I: 71 (10.7); C: 72 (9.9)	Juniper score: I: 1.32 (0.65); C: 1.26 (0.75)	Log FeNO, GM (68% CI): I: 29.2 (14.0 to 61.0); C: 31.2 (13.3 to 73.1)	Ex-smokers: I: 22%; C: 25% Atopic: 78/118 (66.1%)	Mean (SD) daily dose of ICS: I: 697 (708) µg; C: 652 (533) µg

continued

TABLE 29 Adult management review: study and population characteristics (*continued*)

Author, year	Study details	Inclusion/exclusion criteria	No. analysed/ no. recruited	Age (years), sex, *n*/*N* (%)	Spirometry, mean (SD)	Severity, mean (SD)	FeNO (ppb)	Smokers, atopic	Medication use
Smith 2005[97]	Setting: primary care, New Zealand Funding: mixed;[a] equipment from Aerocrine	Included: chronic asthma[130] managed in primary care; regular ICSs for ≥ 6 months, no dose change in previous 6 weeks. If could not tolerate removal of LABA during run-in allowed to participate if could tolerate a fixed dose. Excluded: four or more courses of oral prednisone in previous 12 months, admission to hospital for asthma in previous 6 months, ever admitted to IC unit for asthma, smokers (current or ex) with history of > 10 pack-years	94/110 WBR: 13; I: 46/48; C: 48/49	Adolescents and adults 12–75 years Mean age (range): 44.8 (12–73) Male 41/110 (37.3)	FEV_1%, mean (95% CI): I: 86.4 (80.6 to 92.2); C: 83.1 (76.5 to 89.7)	Symptom score,[d] mean (95% CI): I: 0.6 (0.4 to 0.8); C: 0.8 (0.6 to 1.1)	FeNO 250 ml/second,[e] GM (95% CI): I: 7.8 (6.6 to 9.3); C: 6.4 (5.5 to 7.5)	Smokers NR Atopic NR	Bronchodilator use, mean per day previous 7 days (95% CI): I: 0.5 (0.2 to 0.8); C: 0.6 (0.3 to 0.8) ICS NR
Syk 2013[99]	Setting: primary care, Sweden Funding: mixed;[a] some from Aerocrine	Doctor's diagnosis of asthma and ICS treatment for ≥ 6 months; IgE sensitisation to at least one major airborne perennial allergen (dog, cat or mite); non-smoker for ≥ 1 year and with smoking history of < 10 pack-years. Patients all had mild to moderate asthma	165/187 WBR: 6; I: 87/93; C: 78/88	Adults (18–64 years) Mean (SD) age 41 (12.4) Male 94/181 (51.9)	FEV_1%, mean (SD): I: 84.3 (14.1); C: 83.7 (12.5) FEV_1/FVC, mean (SD): I: 0.78 (0.08); C: 0.79 (0.08)	NR	FeNO, GM (95% CI): I: 22.0 (19.3 to 25.2); C: 21.6 (18.7 to 25.0)	Smokers: 0/165 (0%) Atopic: 165/165 (100%)	Median (IQR) budesonide-equivalent ICS dose (μg/day): 400 (400 to 800) LABA before study entry: 54/180 (30.0%)

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; ASUI, Asthma Symptoms Utility Index; b.i.d., twice a day; C, control group; CI, confidence interval; GM, geometric mean; I, intervention group; IC, intensive care; IgE, immunoglobulin E; ITT, intention to treat; LOCF, last observation carried forward; NR, not reported; WBR, withdrew before randomisation.

a Mix of industry and non-industry funding, e.g. research council grants.

b 37 withdrew, imputation method NR.

c 13 withdrew, imputation method NR.

d Daily score, previous 7 days. Asthma symptoms were scored for each 24-hour period as follows: 0 – no symptoms, 1 – symptoms for one short period, 2 – symptoms for two or more short periods, 3 – symptoms most of the time that did not affect normal daily activities, 4 – symptoms most of the time that did affect normal daily activities, 5 – symptoms so severe as to disrupt daily activities.

e FeNO measured at 250 ml/second gives lower values than FeNO measured at 50 ml/second.

admitted to intensive care for asthma, whereas Syk *et al.*[99] and Calhoun *et al.*[100] stated that all patients were mild to moderate asthmatics. Smith *et al.*[97] and Syk *et al.*[99] also required patients to have been receiving ICS treatment for > 6 months and Calhoun *et al.*[100] recruited only patients who were well controlled when prescribed two puffs twice a day of beclomethasone HFA (40 µg/puff) and who were ≥ 75% compliant with medication during the 2-week run-in period. Shaw *et al.*[98] on the other hand may have recruited patients with a wider spectrum of severity. Patients were required only to have had one prescription for asthma medication in the previous 12 months, making it possible that patients with comparatively less severe or less well-documented asthma were included, but excluded only those with severe exacerbations in the previous 4 weeks, making it possible that severe asthmatics were included. Honkoop *et al.*[101] included patients with a broad spectrum of severity and excluded only very mild asthmatics. Unlike other studies, that by Honkoop *et al.*[101] had an upper age limit of 50 years.

The study by Smith *et al.*[97] included smokers (current or ex) with a history of < 10 pack-years whereas the studies by Shaw *et al.*,[98] Syk *et al.*[99] and Calhoun *et al.*[100] all excluded current smokers but included ex-smokers with a past smoking history of < 10 pack-years. Smith *et al.*,[97] Shaw *et al.*[98] and Calhoun *et al.*[100] all included a mix of atopic and non-atopic patients whereas Syk *et al.*[99] included only atopic patients. Honkoop *et al.*[101] included atopic patients and smokers. It is unclear whether studies in atopic patients will over- or underestimate efficacy or have no impact at all, although clinical input to the assessment suggested that it would be expected to increase estimates of efficacy as atopy is correlated with ICS responsiveness.

Overall, patient populations recruited by Honkoop *et al.*,[101] Smith *et al.*[97] and Shaw *et al.*[98] are likely to be the most representative of the general asthma population in the UK as these studies included atopic and non-atopic patients. Honkoop *et al.*[101] included smokers and a broad spectrum of patients from mild to severe, Smith *et al.*[97] included some smokers and Shaw *et al.*[98] included a potentially broader spectrum of patients than Smith *et al.*[97] Calhoun *et al.*[100] also recruited a mix of atopic and non-atopic asthmatics, but the run-in requirements for treatment tolerance and compliance may mean that generalisation to a wider population is difficult. However, were the application of FeNO management to be limited in the UK to certain populations (e.g. only atopic patients, only stable patients, only mild to moderate patients), data from Calhoun *et al.*[100] or Syk *et al.*[99] may be more appropriate.

Interventions *Table 30* provides details of the interventions used in each study. Syk *et al.*[99] and Honkoop *et al.*[101] used NIOX MINO. It is not possible to determine whether the other studies used the same devices as this information is not clearly reported.[97,98,100] Smith *et al.*[97] used an unusual flow rate but justified their conversion to 35 ppb equivalent at 50 ml/second. None of the studies used the same protocol or cut-off points for the management of asthma with FeNO. Syk *et al.*[99] and Calhoun *et al.*[100] used FeNO only to guide management, Smith *et al.*[97] used FeNO only, with a safety measure based on symptoms, bronchodilator use and spirometry, and Shaw *et al.*[98] used FeNO in addition to the Juniper score, which gauges control through symptoms. The study by Honkoop *et al.*[101] was similar to that by Shaw *et al.*[98] in that it used FeNO in conjunction with symptoms, spirometry and medication use [all captured in the Asthma Control Questionnaire (ACQ)]. Doses and medications used also varied from study to study, with Smith *et al.*[97] and Calhoun *et al.*[100] titrating only ICSs, Shaw *et al.*[98] titrating ICSs, LTRAs and bronchodilators and Syk *et al.*[99] titrating ICSs and LTRAs. Honkoop *et al.*[101] controlled multiple treatment doses rather than just ICSs. There were some differences between the doses and combinations of treatments indicated and the study allowed for a step-down in treatment on the basis of low FeNO in the presence of moderate symptoms (when FeNO was low for > 3 months) but not in the presence of a high ACQ score. This is in contrast to Shaw *et al.*[98] and Smith *et al.*[97] which did not allow step-down if moderate symptoms were present,[98] or did not allow the dose to fall below the optimum derived in the first titration phase,[97] thus placing a limit on how far ICS could be decreased. The number of cut-off points also varied. Smith *et al.*[97] used only one cut-off of 35 ppb (equivalent). Honkoop *et al.*,[101] Shaw *et al.*[98] and Calhoun *et al.*[100] each used two cut-offs but at different cut-points, one for titrating down (< 25 ppb, < 16 ppb and < 22 ppb respectively) and one for titrating up (50 ppb, > 26 ppb and > 35 ppb respectively), with an intermediate area in between where symptoms also guided treatment[98,101] or the dose remained the same.[100] Syk *et al.*[99] used three cut-offs, with different values for men and women (< 19 ppb, ≥ 24 ppb and ≥ 30 ppb for men; < 21 ppb, ≥ 25 ppb

TABLE 30 Adult management review: description of the intervention management strategies

Author, year	Decisions based on flow rate, device and cut-off points	Step-up/step-down protocol	Doses
Calhoun 2012[100]	Based on FeNO only Flow rate; device: flow rate NR; device NR (protocol states Niox) Cut-offs: well controlled < 22 ppb; controlled 22–35 ppb; undercontrolled > 35 ppb	< 22 ppb = well controlled = down one level; 22–35 ppb = controlled = maintain current level; > 35 ppb = undercontrolled = up one level	Dosing beclomethasone HFA: level 1 = 0 µg/day; level 2 = 80 µg q.d.; level 3 = 160 µg b.i.d.; level 4 = 320 µg b.i.d.; level 5 = 640 µg b.i.d.
Honkoop 2013[101]	Based on ACQ and FeNO Flow rate; device: protocol states NIOX MINO Cut-offs: FeNO low ≤ 25 ppb, FeNO intermediate > 25 ppb and < 50 ppb, FeNO high ≥ 50 ppb; ACQ strictly controlled ≤ 0.75, ACQ sufficiently controlled > 0.75 and < 1.50, ACQ uncontrolled ≥ 1.50	When ACQ ≤ 0.75: • if FeNO ≤ 25 ppb, step down • if FeNO > 25 ppb and < 50 ppb, no change • if FeNO ≥ 50 ppb, step up When ACQ > 0.75 and < 1.50: • if FeNO ≤ 25 ppb and time < 3 months, no change or change to LABA; if time > 3 months, step down ICS • if FeNO > 25 ppb and < 50 ppb, step up (treatment choice) • if FeNO ≥ 50 ppb, step up ICS by one level When ACQ ≥ 1.50: • if FeNO ≤ 25 ppb, step up LABA • if FeNO > 25 ppb and < 50 ppb, step up (treatment choice) • if FeNO ≥ 50 ppb, step up ICS by two levels	Step 1: SABA as needed; step 2: low-dose ICS or LTRA; step 3: low-dose ICS + LABA or medium- or high-dose ICS or low-dose ICS + LTRA; step 4: add one or both of medium- or high-dose ICS + LABA and LTRA; step 4: add one or both of OCS (lowest dose) and anti-IgE treatment
Shaw 2007[98]	Based on FeNO plus symptoms (Juniper score) Flow rate; device: 50 ml/second; device NR Cut-offs: intermediate 16–26 ppb; high > 26 ppb	Exhaled NO < 16 ppb on first occasion or exhaled NO 16–26 ppb on second occasion: • *and* Juniper score ≤ 1.57 = step down anti-inflammatory treatment, step down bronchodilator treatment once off steroids • *and* Juniper score > 1.57 = step down anti-inflammatory treatment, step up bronchodilator treatment	Hierarchy of anti-inflammatory treatment: (1) low-dose inhaled steroid (100–200 µg BDP b.i.d.), (2) moderate-dose inhaled steroid (200–800 µg BDP b.i.d.), (3) high-dose inhaled steroid (800–2000 µg BDP b.i.d.), (4) high-dose inhaled steroid (800–2000 µg BDP b.i.d.) plus LRTA, (5) higher-dose inhaled steroid (2000 µg BDP b.i.d.) plus leukotriene antagonist, (6) higher-dose inhaled steroid (2000 µg BDP b.i.d.) plus leukotriene antagonist plus oral prednisolone 30 mg for 2 weeks, then titrate dose, reducing by 5 mg/week

Author, year	Decisions based on flow rate, device and cut-off points	Step-up/step-down protocol	Doses
		Exhaled NO > 26 ppb: • *and* Juniper score ≤ 1.57 = step up anti-inflammatory treatment, no change in bronchodilator treatment • *and* Juniper score > 1.57 = step up anti-inflammatory treatment, step up bronchodilator treatment once on maximum anti-inflammatory treatment Safety measure: patients on 2000 µg/day of beclomethasone with > 26 ppb FeNO and had not fallen to 60% of baseline had sputum checked. If no eosinophilic inflammation, treatment reduced stepwise unless FeNO increased by > 60% of baseline	Hierarchy of bronchodilator treatment: (1) PRN SABAs, (2) LABAs, (3) LABAs plus theophylline, (4) LABAs plus theophylline plus nebulised bronchodilator
Smith 2005[97]	Based on FeNO, with a safety measure based on symptoms, bronchodilator use and spirometry Flow rate; device: 250 ml/second according to ATS 1999 guidelines;[133] assume Niox device[a] Cut-offs: equivalent to 35 ppb at 50 ml/second (≥ 15 ppb at 250 ml/second)[b]	FeNO < 35 ppb (equivalent at 50 ml/second) = asthma controlled FeNO ≥ 35 ppb = asthma uncontrolled. Safety measure: if one or more of the following clinical criteria are met, increase one step: (1) symptom score for previous 7 days ≥ 1 point more than mean run-in *and* minimum score of 2/5; (2) nocturnal wakening on ≥ 3 nights/week more than mean run-in; (3) mean daily bronchodilator use three or more times that of mean run-in *and* minimum use 15 occasions during previous 7 days; (4) diurnal peak flow variation ≥ 30% *and/or* FEV_1 of < 85% of baseline	Dose steps: placebo and inhaled fluticasone at 100 µg, 250 µg, 500 µg, 750 µg and 1000 µg Phase 1: until optimal dose reached. Optimal dose = one step higher than that at which control lost Phase 2: up-titrate one step at a time; down-titrate if controlled for two visits but not lower than optimal dose Patients had a personalised self-management plan that instructed them to take oral prednisone 40 mg/day when the morning peak flow fell below 70% of the mean run-in value, until it reached > 85%, at which time they took 20 mg/day for the same number of days
Syk 2013[99]	Based on FeNO only Flow rate; device: according to 2005 guidelines;[35] NIOX MINO Cut-offs: < 19 ppb (men), < 21 ppb (women); 19–23 ppb (men), 21–25 ppb (women); ≥ 24 ppb (men), ≥ 26 ppb (women); ≥ 30 ppb (men), ≥ 32 ppb (women)	FeNO < 19 ppb (men), < 21 ppb (women): decrease one step; FeNO 19–23 ppb (men), 21–25 ppb (women): no change; FeNO ≥ 24 ppb (men), ≥ 26 ppb (women): increase one step (no change in treatment step if on step 4 or 5 and using two or fewer inhalations of SABA per week); FeNO ≥ 30 ppb (men), ≥ 32 ppb (women): increase two steps (only if on treatment step 1). Grey zone of 5 ppb applied to avoid frequent dose changes	Steps 1–6: budesonide (µg/day): 0, 200, 400, 800, 800 + LTRA, 1600 + LTRA respectively; fluticasone (µg/day): 0, 100, 250, 500, 500 + LTRA, 1000 + LTRA respectively; mometasone (µg/day): 0, 100, 200, 400, 400 + LTRA, 800 + LTRA respectively

BDP, beclomethasone dipropionate; b.i.d., twice per day; IgE, immunoglobulin E; NR, not reported; PRN, not defined in source article; q.d., once per day.
a Donated by Aerocrine.
b Discussed and supported in journal article.[97]

and ≥ 32 ppb for women). Given the uncertain comparability in FeNO measurements between devices, it is difficult to assess how similar these cut-off points may in fact be.

Control *Table 31* provides details of the control interventions used in each study. As with the interventions, none of the studies used the same criteria, protocols or treatment doses for the management of asthma in the control arm of the studies. Generally speaking, the control arms considered symptoms, self-reported medication use and sometimes lung function to guide titration. In terms of similarity to UK practice, Shaw *et al.*[98] state that BTS/SIGN guidelines[8] were followed, using the Juniper scale to score symptoms. It is not clear how similar to UK practice other studies may be.

Estimates of efficacy

Exacerbations Exacerbations were reported in all studies but definitions varied (*Table 32*) and results were not entirely consistent across studies.

Major or severe exacerbations This outcome was defined differently across studies. Smith *et al.*[97] reported two such outcomes: 'major exacerbations' defined according to global daily asthma scores and exacerbations leading to a course of oral prednisone. A similar outcome, 'worsening requiring a course of oral prednisone', was also reported in Syk *et al.*[99] Shaw *et al.*[98] did not report rates of oral prednisone use alone but did report a composite outcome of 'exacerbations resulting in the use of oral prednisone or antibiotics'. Calhoun *et al.*[100] reported an outcome called 'exacerbations', which included exacerbations leading to oral prednisone use, increased ICS use or additional medication for asthma. This last definition may incorporate exacerbations that other studies would have classified as moderate or minor, although the study does define an additional outcome called 'treatment failure', which is likely to incorporate minor, moderate and major exacerbations. As such, the outcome 'exacerbations' in the study by Calhoun *et al.*[100] will be considered in this analysis. Honkoop *et al.*[101] reported courses of oral prednisone, as in Smith *et al.*[97] and Syk *et al.*[99]

Honkoop *et al.*[101] and Shaw *et al.*[98] reported lower rates per person-year of major/severe exacerbations in the intervention arm and Smith *et al.*[97] reported lower rates per person (data per person-year not reported) but the difference did not reach statistical significance compared with the control arm in any of the studies (these data were available only as odds ratios for Honkoop *et al.*[101]). Syk *et al.*[99] reported higher rates per person-year of oral prednisone use in the intervention arm, but the level of significance was not reported. Calhoun *et al.*[100] showed very similar rates per person-year of exacerbations in both arms of the trial, with no statistically significant difference between them. The best improvement in major/severe exacerbations per person-year was seen in the study by Shaw *et al.*,[98] at –21% (95% CI –57% to 43%; $p = 0.43$) (reviewer-calculated rate ratio 0.79, 95% CI 0.66 to 0.94), and the worst improvement was seen in the study by Syk *et al.*,[99] which reported a higher rate per person-year, although not statistically significantly so, in the intervention arm (0.113) than in the control arm (0.0875) (*p*-value not reported) (reviewer-calculated rate ratio 1.29, 95% CI 0.83 to 2.03).

Despite the high level of heterogeneity in study characteristics, an exploratory meta-analysis of the rates of major/severe exacerbations was performed. As data per person-year were not reported in or calculable for Smith *et al.*,[97] this study was excluded from the meta-analysis. The standard error (SE) was not reported in the study by Honkoop *et al.*[101] and analyses were performed without these data and with various imputed SEs. The pooled estimate of the rate ratio without the data from Honkoop *et al.*,[101] using random effects methods (*Figure 14a*), was 0.94 (95% CI 0.66 to 1.34), with a *p*-value of 0.73. This indicated no difference between the two intervention groups in major or severe exacerbations. The I^2 statistic was 52%, however, indicating moderate heterogeneity between studies.

TABLE 31 Adult management review: description of the control group management strategies

Author, year	Decisions based on	Step-up/step-down protocol	Doses
Calhoun 2012[100]	NHLBI guidelines[134] (US version of the SIGN guidelines)	Use severity classification chart, assessing both domains of impairment and risk, to determine initial treatment. Use asthma control chart, assessing both domains of impairment and risk, to determine if therapy should be maintained or adjusted (step up if necessary, step down if possible). Use multiple measures of impairment and risk: different measures assess different manifestations of asthma; they may not correlate with each other; and they may respond differently to therapy. Obtain lung function measures by spirometry at least every 1–2 years, more frequently for not well-controlled asthma. Asthma is highly variable over time and periodic monitoring is essential. In general, consider scheduling patients at 2- to 6-week intervals while gaining control; at 1–6 month intervals, depending on step of care required or duration of control, to monitor if sufficient control is maintained; at 3-month intervals if a step down in therapy is anticipated. Assess asthma control, medication technique, written asthma action plan, patient adherence and concerns at every visit	As for intervention
Honkoop 2013[101]			
Strict strategy	ACQ scores[135]	When ACQ ≤ 0.75: if < 3 months, no change; if > 3 months, step down When ACQ > 0.75 and < 1.50: step up (choice of treatments) When ACQ ≥ 1.50: step up (choice of treatments)	As for intervention
Sufficient strategy		When ACQ ≤ 0.75: step down When ACQ > 0.75 and < 1.50: no change When ACQ ≥ 1.50: step up (choice of treatments)	As for intervention
Shaw 2007[98]	BTS/SIGN guidelines[8] using the Juniper scale to score symptoms	Scored by Juniper scale. Treatment doubled if score > 1.57, treatment halved if score < 1.57 for 2 consecutive months	Step 1: SABA as required; step 2: add inhaled steroid 200–800 µg/day BDP equivalent; step 3: add inhaled LABA; step 4: increase ICS up to 2000 µg/day and addition of fourth drug, e.g. LTRA, theophylline, LABA; step 5: oral prednisolone, high-dose ICS, refer to specialist care
Smith 2005[97]	GINA guidelines;[136] symptoms, bronchodilator use, spirometry	GINA uncontrolled asthma criteria:[125] (1) symptoms present on > 2 days/week with 24-hour asthma score $\geq 2/5$; (2) More than one night-time waking/week; (3) bronchodilator use on more than four occasions/week or on > 2 days per week; (4) variation in PEFR > 20 (amplitude % of mean over previous 7 days); (5) $FEV_1 < 90\%$ of baseline	As for intervention but without the personalised management plan
Syk 2013[99]	Symptoms, lung function, beta-agonist use	Usual care (patient symptom report, SABA use, physical examination, pulmonary function tests)	Assume same doses as for intervention

BDP, beclomethasone dipropionate; NHLBI, National Heart, Lung, and Blood Institute.

TABLE 32 Adult management review: exacerbation and OCS use rates in adult patients with or without FeNO-guided management

Author, year, time of outcome	Definition of outcomes	*n*	Intervention per person-year	Control per person-year	Between-group comparison
Calhoun 2012[100]	Exacerbation: unscheduled medical contact for increased asthma symptoms that results in the use of OCSs, increased ICSs or additional medication for asthma	229	0.21 (97.5% CI 0.1 to 0.32)	0.23 (97.5% CI 0.1 to 0.37)	'Did not differ'
	Treatment failure defined as exacerbation or loss of control[a]		0.27 (97.5% CI 0.14 to 0.39)	0.43 (97.5% CI 0.23 to 0.64)	'Were not different'
Honkoop 2013[101] 12 months	Course of oral prednisone	611	0.20 per person-year	Strict: 0.29 per person-year; sufficient: 0.29 per person-year	Odds ratio: vs. strict: 0.52 (95% CI 0.20 to 1.30); vs. sufficient: 0.73 (95% CI 0.28 to 1.85)
Shaw 2007[98] 12 months	Course of oral steroids or antibiotics	118	0.33 (SD 0.69)	0.42 (SD 0.79)	–21% (95% CI –57% to 43%; $p = 0.43$)
Smith 2005[97] 3–12 months optimisation (exacerbation rates not reported for this period) plus 12 months titration	Minor: global daily asthma score[b] of 2 on ≥ 2 consecutive days	94	Minor:[c] 0.36	Minor:[c] 0.75	Minor: $p = 0.24$
	Major: global daily asthma score[b] of 3 on ≥ 2 consecutive days (or in one day, in the context of a minor exacerbation). Major exacerbation or medical emergency: global daily asthma score[b] of 4 in one day		Major:[c] 0.13	Major:[c] 0.14	Major: $p = 0.91$
	Any minor or major exacerbation		0.49 (95% CI 0.20 to 0.78)	0.90 (95% CI 0.31 to 1.49)	–45.6% (95% CI –78.6 to 54.5; $p = 0.27$)
	Course of oral prednisone		22 events in 46 patients (0.48 events per patient)	29 events in 48 patients (0.60 events per patient)	$p = 0.60$

TABLE 32 Adult management review: exacerbation and OCS use rates in adult patients with or without FeNO-guided management (*continued*)

Author, year, time of outcome	Definition of outcomes	*n*	Intervention per person-year	Control per person-year	Between-group comparison
Syk 2013[99] End points analysed from visit 2 to visit 6 (2–4 weeks to 12 months)	Moderate exacerbation[d] – need to step up controller treatment for at least 2 days with or without clinic visit. Prophylactic use before pollen season excluded	165	0.1	0.325	NR
	Severe exacerbation[d] – worsening requiring a course of OCSs		0.113	0.0875	Not significant
	Moderate or severe exacerbation		0.22	0.41	Total: $p = 0.024$

CI, confidence interval; NR, not reported.

a At-home measurements: any of the following three criteria, when not associated with the increased asthma symptoms, satisfies treatment failure criteria: (i) pre-bronchodilator morning PEFR of < 65% of the baseline on two consecutive mornings, scheduled measurements; (ii) post-bronchodilator PEFR of < 80% of baseline despite 60 minutes of rescue beta-agonist treatment; (iii) post-bronchodilator PEFR may be taken at any time of day. An increase in albuterol use of more than eight puffs per 24 hours over baseline use for a period of 48 hours or more than 16 puffs per 24 hours for more than 48 hours. In-clinic measurements: (i) pre-bronchodilator FEV_1 values from two consecutive sets of spirometric determinations measured 24–72 hours apart that are < 80% of the baseline pre-bronchodilator value (baseline value for adherence period: FEV_1 value at visit 3; baseline for randomisation period: FEV_1 value at visit 4); all participants found to have a FEV_1 of < 80% of baseline at any centre visit but who are not considered to meet treatment failure or exacerbation criteria must be seen again within 72 hours to have FEV_1 measured *or* (ii) physician judgement for patient safety *or* (iii) patient dissatisfaction with asthma control achieved by study regimen *or* (iv) requirement for open-label ICS or another (non-systemic corticosteroid) new asthma medication (e.g. montelukast) without the addition of systemic corticosteroids.

b Asthma scores: 0 (stable): morning PEFR > 75% of best PEFR in 14-day run-in period without deterioration in any symptom scores; 1 (mildly unstable): one or more of the following: (i) bronchodilator use on two or more occasions in 24 hours more than the rounded mean number of occasions during the run-in period, (ii) increase in symptom score of ≥ 1 point compared with the rounded mean during the run-in period, (iii) onset of or increase in nocturnal waking: one or more times in the previous 7 nights more than the rounded mean number of times during the run-in period *or* morning PEFR of 61–75% without deterioration in any of the above categories; 2 (minor deterioration): morning PEFR of 61–75% of the best PEFR during the run-in period and one or more criteria for an asthma score of 1 *or* morning PEFR of 41–60% without deterioration in any criteria for an asthma score of 1; 3 (major deterioration): morning PEFR of 41–60% of the best PEFR during the run-in period and one or more criteria for an asthma score of 1; 4 (major exacerbation or medical emergency): morning PEFR of ≤ 40% of the best PEFR during the run-in period regardless of symptoms *or* attendance at a clinician's office or emergency department because of severe asthma.

c Estimated from graph.

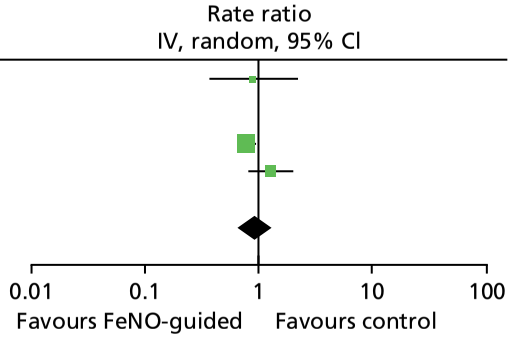
d ATS/ERS Task Force Criteria 2009.[137]

(a)

Study or subgroup	Log-rate ratio	SE	Weight	Rate ratio IV, random, 95% CI
Calhoun 2012[100]	−0.09097178	0.45116134	13.0%	0.91 (0.38 to 2.21)
Honkoop 2013[101]	−0.41726314	0.0476771	0.0%	0.66 (0.60 to 0.72)
Shaw 2007[98]	−0.24116206	0.0917899	55.2%	0.79 (0.66 to 0.94)
Syk 2013[99]	0.25762178	0.22857143	31.9%	1.29 (0.83 to 2.03)
Total (95% CI)			100.0%	0.94 (0.66 to 1.34)

Heterogeneity: $\tau^2=0.05$, $\chi^2=4.13$, df=2 ($p=0.13$); $I^2=52\%$

Test for overall effect: $z=0.34$ ($p=0.73$)



(b)

Study or subgroup	Log-rate ratio	SE	Weight	Rate ratio IV, random, 95% CI
Calhoun 2012[100]	−0.09097178	0.45116134	7.7%	0.91 (0.38 to 2.21)
Honkoop 2013[101]	−0.41726314	0.2	25.3%	0.66 (0.45 to 0.98)
Shaw 2007[98]	−0.24116206	0.0917899	45.4%	0.79 (0.66 to 0.94)
Syk 2013[99]	0.25762178	0.22857143	21.6%	1.29 (0.83 to 2.03)
Total (95% CI)			100.0%	0.85 (0.65 to 1.10)

Heterogeneity: $\tau^2=0.03$, $\chi^2=5.44$, df=3 ($p=0.14$); $I^2=45\%$

Test for overall effect: $z=1.24$ ($p=0.22$)

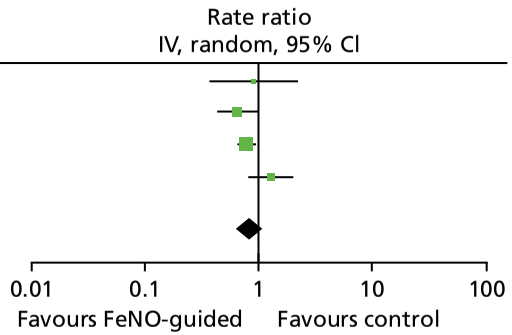


FIGURE 14 Random effects meta-analysis of the effects of FeNO-guided asthma management on major/severe exacerbation rates. IV, inverse variable. (a) All studies with data available, excluding Honkoop *et al.*[101] (unknown SE); and (b) all studies, imputing the SE for Honkoop *et al.*[101] at 0.2.

A SE of 0.1, 0.2, 0.3 or 0.4 was imputed for Honkoop *et al.*,[101] based on the range of errors observed in other studies. Depending on the error imputed, rate ratios ranged from 0.82 (95% CI 0.64 to 1.05; $p = 0.11$) to 0.89 (95% CI 0.67 to 1.17; $p = 0.40$), which is not statistically significant. *Figure 14b* presents the analysis imputing an error of 0.2.

In a prespecified sensitivity analysis, only studies that reported data relating to exacerbations resulting in the use of OCSs were included. Only Syk *et al.*[99] and Honkoop *et al.*[101] reported this outcome although Honkoop *et al.*[101] did not report SEs, leaving only the study by Syk *et al.*[99] This study reported a rate ratio of 1.29 (95% CI 0.83 to 2.03), indicating no significant difference between the intervention groups ($p = 0.26$) (*Figure 15*).

In further sensitivity analyses, SEs of 0.1, 0.2, 0.3 and 0.4 were imputed for Honkoop *et al.*[101] based on the range of errors observed in other studies. Depending on the error imputed, rate ratios ranged from 0.91 (95% CI 0.47 to 1.77; $p = 0.79$) to 1.00 (95% CI 0.53 to 1.90; $p = 1.00$), indicating no significant differences between the intervention groups. Heterogeneity statistics were high, ranging from 80% to 53% and reflecting the opposite direction of effect reported in these two studies.

Sensitivity analyses including imputed data for Smith *et al.*[97] were not conducted and it is unclear how the exclusion of these data affects the meta-analyses.

All exacerbations or treatment failures When considering other, wider definitions of exacerbation, as described in *Table 32*, three studies report composite outcomes that can be considered to be broadly similar and which represent what may be termed 'treatment failure'. In the studies by Smith *et al.*[97] and Syk *et al.*[99] this was 'any major or minor exacerbation', whereas in the study by Calhoun *et al.*[100] it was exacerbation or any loss of control by a variety of measures (see footnotes to *Table 32* for details). In the studies by Smith *et al.*[97] and Calhoun *et al.*,[100] FeNO-guided groups showed numerically but not statistically significantly lower rates of treatment failure. In the study by Syk *et al.*[99] the improvement was statistically significant, with a rate of 0.22 in the intervention arm compared with 0.41 in the control arm ($p = 0.024$) (reviewer-calculated rate ratio 0.52, 95% CI 0.44 to 0.61).

Despite the high level of heterogeneity in study characteristics, an exploratory meta-analysis of these rates using random effects methods (the I^2 statistic was 0%) was conducted (*Figure 16*). The pooled relative risk (RR) was 0.53 (95% CI 0.46 to 0.61), which represents a statistically significant effect in favour of using FeNO-guided management in asthmatics for this outcome ($p < 0.00001$).

Moderate and/or minor exacerbations Smith *et al.*[97] and Syk *et al.*[99] both reported the rates of less severe exacerbations separately from the rates of all exacerbations and from the rates of major/severe exacerbations (see *Table 32*). In both cases the point estimate reduction in minor/moderate exacerbations was far greater than the reduction in severe/major exacerbations. Smith *et al.*[97] reported 0.36 minor exacerbations per person-year in the intervention arm and 0.75 per person-year in the control arm, with a *p*-value of 0.24. Syk *et al.*[99] reported 0.1 moderate exacerbations per person-year in the intervention arm and 0.325 in the control arm. The *p*-value was not reported. When considering the results reported by Calhoun *et al.*[100] for exacerbations alone and the composite outcome treatment failure, it can be seen that the larger difference in rates of treatment failure in favour of the intervention arm is not driven by the exacerbation rates, which are very similar at 0.21 (97.5% CI 0.1 to 0.32) and 0.23 (97.5% CI 0.1 to 0.37), and it must therefore be due to a decrease in less severe exacerbations/loss of control in the intervention arm. The impact on quality of life and the costs of such exacerbations are much lower than for major/severe exacerbations.

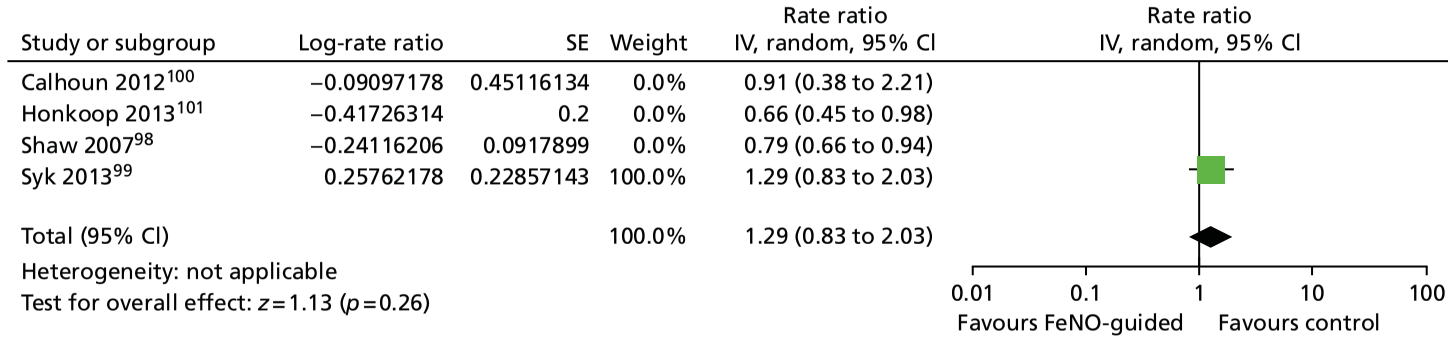


FIGURE 15 Sensitivity analysis removing studies with wider definitions of major/severe exacerbations: all studies with data available, excluding Honkoop *et al.*[101] (unknown SE). IV, inverse variable.

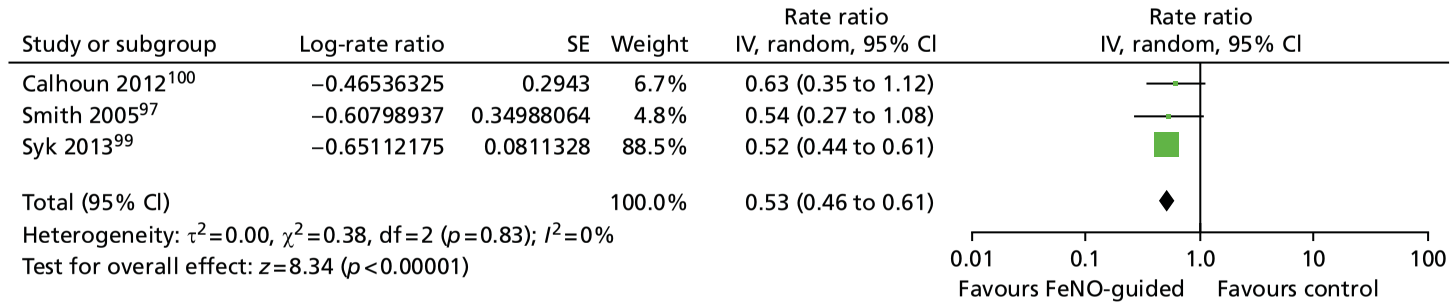


FIGURE 16 Meta-analysis of the effects of FeNO-guided asthma management on the composite outcome of major/severe, moderate and minor exacerbation rates/treatment failures. IV, inverse variable.

Inhaled corticosteroid use All studies except that by Honkoop *et al.*[101] provided some data on ICS use and these are presented in *Table 33*. Smith *et al.*[97] and Shaw *et al.*[98] reported ICS use as a mean per day at the end of the study, with mean differences of –270 µg/day (95% CI –430 µg/day to –112 µg/day; $p = 0.003$) and –338 µg/day (95% CI –640 µg/day to –37 µg/day; $p = 0.028$), respectively, in favour of FeNO-guided management. Syk *et al.*[99] reported median values that were not statistically significantly different. Means were supplied on request but without significance tests and showed a small increase in ICS use in the intervention arm [586 µg (SE 454 µg) vs. 540 µg (SE 317 µg) in the control arm]. Calhoun *et al.*[100] reported mean use per month, although it is unclear if this was an average over the whole course of the study or the mean for the final month of the study. The means were very similar at 1617 µg/month in the intervention group and 1610 µg/month in the control group. It should also be noted that this study managed and followed patients for only 9 months whereas the other studies did so for 12 months.

When looking at mean use over time (graphical data not reproduced here) in Smith *et al.*[97] and Syk *et al.*,[99] ICS use fell initially in the FeNO arm (both when compared with baseline and in comparison to the control arm) and then rose at the final measurement to a level above that in the control arm in Syk *et al.*[99] but staying below that in the control arm in Smith *et al.*[97] Conversely, in the Shaw *et al.*[98] study, ICS use initially rose and then fell at the final two measurement points to below the baseline level and below the control arm level. Only Shaw *et al.*[98] reported the AUC for ICS use and this showed an 11% greater use of ICSs in the FeNO group. Based on the 'mean use over time' figures, this is unlikely to be true for the study by Syk *et al.*,[99] in which a visual interpretation of the AUC would suggest very similar levels of total ICS use in both arms, with little change over time. Appropriate data were not available for the study by Calhoun *et al.*[100] or that by Smith *et al.*[97] These differences may be the result of the different titration protocols and cut-off values used in the studies and it is difficult to draw a generalised conclusion as to the direction of effect and the trends over time for ICS use. However, it would seem most likely that ICS use

TABLE 33 Adult management review: ICS use

Author, year	ICS measurement	Intervention	Control	Between-group difference expressed as intervention minus control[a]
Calhoun 2012[100]	ICS use (unclear if mean over whole study or final value)[b]	Mean 1617 µg/month	Mean 1610 µg/month	NR
Shaw 2007[98]	Final value ICS use[b]	557 µg	895 µg	Mean difference –338 µg/day (95% CI –640 µg to –37 µg; $p = 0.028$)
	Total used in study (AUC)			11% greater use in FeNO group (95% CI –15% to 37%)
Smith 2005[97]	Final value ICS use[c]	Baseline: mean 411 µg/day (95% CI 344 µg to 478 µg); end of phase 2: mean 370 µg/day (95% CI 263 µg to 477 µg)	Baseline: mean 491 µg/day (95% CI 403 µg to 579 µg); end of phase 2: mean 641 µg/day (95% CI 526 µg to 756 µg)	Mean difference –270 µg/day (95% CI –112 µg to –430 µg; $p = 0.003$)
Syk 2013[99]	ICS use[d]	Median 0 (IQR –400 to 400) µg; baseline: mean 604 (SE 370) µg; final value: 586 (SE 454) µg	Median 0 (IQR –200 to 200) µg; baseline: mean 626 (SE 391) µg; final value: 540 (SE 317) µg	0.945

CI, confidence interval; NR, not reported.
a Negative values indicate that the FeNO group had lower ICS use.
b Beclomethasone dipropionate or equivalent.
c Fluticasone or equivalent.
d The equivalent dose for budesonide when a different drug (e.g. fluticasone) has been used.

will either remain the same or fall in FeNO-managed groups when taken as an average over the course of the first year. The first year of titration is likely to be when the greatest gains are made, as patients reach a stable dose. It is unclear how ICS use will change in the following years as no study reported results beyond 1 year of follow-up, as the severity of the disease may progress, stay stable or remiss over time.

Despite the high level of heterogeneity in study characteristics, an exploratory meta-analysis of ICS use incorporating data from all four studies was conducted (*Figure 17*). As studies reported values for different ICSs (fluticasone, beclomethasone and budesonide), a standardised mean difference analysis was performed. A random-effects model was used as both clinical and statistical heterogeneity were high, but the I^2 statistic remained high at 75%. SDs for Calhoun *et al.*[100] were imputed based on consideration of the other three studies. Sensitivity analyses in which the imputed SDs were altered by an order of magnitude in either direction, and in which a value of 10,000 was used for the intervention arm and 5000 for the control arm (to mirror the SDs of Syk *et al.*[99]), did not have a big effect, with the pooled-analysis CIs crossing the line of no effect in every case and the pooled mean value ranging from –0.25 to –0.23 standardised mean difference. The results of the meta-analysis agree with the conclusions drawn from the narrative consideration of the data; it would seem most likely that ICS use will either remain the same or fall in FeNO-managed groups, probably depending on factors such as step-up/step-down protocols, cut-off values selected, treatments incorporated in the treatment protocol and comparator interventions.

Health-related quality of life

Syk *et al.*[99] Calhoun *et al.*[100] and Honkoop *et al.*[101] reported quality of life data. This was measured by the mini Asthma Quality of Life Questionnaire (mAQLQ) in Syk *et al.*[99] and the Asthma Quality of Life Questionnaire (AQLQ) in Calhoun *et al.*[100] and Honkoop *et al.*[101] In all studies the overall score, and in Syk *et al.*[99] three of four domains, did not show a statistically significant change over time. The symptoms domain did, however, show a relatively small but statistically significant between-group difference in change from baseline of 0.10 (*Table 34*) in Syk *et al.*[99] An exploratory meta-analysis of the overall scores (*Figure 18*) showed no effect, with a standardised mean difference of 0.00 (95% CI –0.20 to 0.20). In this case, data from the study by Honkoop *et al.*[101] were not included as there was not enough information provided to calculate a mean AQLQ score across the two control groups.

Asthma control and other medication use

Four studies reported data for asthma control.[97–100] Smith *et al.*[97], Calhoun *et al.*[100] and Shaw *et al.*[98] reported no change in asthma control, whereas Syk *et al.*[99] reported a statistically significant difference in change in ACQ score from visit 2 to visit 6 between the two trial arms (*Table 35*). This matches the change seen in the AQLQ symptoms domain previously mentioned. Smith *et al.*,[97] Calhoun *et al.*[100] and Syk *et al.*[99] reported use of other medications; Smith *et al.*[97] and Calhoun *et al.*[100] reported no significant difference between groups for bronchodilator use, although in the study by Calhoun *et al.*[100] there was a trend towards less use in the intervention arm, and Syk *et al.*[99] reported non-significant trends towards greater numbers using LTRAs and higher mean use of LTRAs and SABAs (significance not reported) in the FeNO-controlled arm.

Adverse events, mortality, compliance and test failure rates

No data were reported in the four studies for adverse events or mortality, although Calhoun *et al.*[100] reported one unrelated adverse event (hip surgery) in the control arm. Compliance was reported by Smith *et al.*[97] and Calhoun *et al.*[100] and was 85% and 89% in the intervention and control arms, respectively, in Smith *et al.*[97] and $\geq$ 95% (median) in both groups in Calhoun *et al.*[100] No test failure rates for NIOX MINO or NObreath were reported.

FIGURE 17 Meta-analysis of the effects of FeNO-guided asthma management on mean ICS use (standardised mean difference analysis). IV, inverse variable.

TABLE 34 Adult management review: HRQoL

Author, year	Intervention	Control	Between-group difference
Calhoun 2012[100]	AQLQ change from baseline 0.02 (97.5% CI –0.14 to 0.18), $p = 0.75$	AQLQ change from baseline 0.02 (97.5% CI –0.14 to 0.17), $p = 0.80$	AQLQ between-group difference 0.00 (97.5% CI –0.22 to 0.23), $p = 0.96$
Syk 2013[99]	Appears to be some data missing ($n = 78$–86) Total change over time in mAQLQ ($n = 80/87$), median (IQR): 0.23 (0.07 to 0.73); final mean (SE) value 6.07 (0.90) Visit 2 and visit 6 data, median (IQR): mAQLQ symptoms – visit 2: 5.60 (4.80 to 6.20), visit 6: 6.00 (5.60 to 6.60); activity limitation – visit 2: 6.50 (5.75 to 6.75), visit 6: 6.75 (6.00 to 7.00); emotional function – visit 2: 6.00 (4.67 to 6.67), visit 6: 6.33 (5.67 to 7.00); environmental stimuli – visit 2: 6.00 (5.00 to 6.67), visit 6: 6.33 (5.67 to 6.67) GQLI change ($n = 85/88$): 0.06 (–0.22 to 0.28)	Appears to be some data missing ($n = 77$–85) Total change over time in mAQLQ ($n = 77/78$), median (IQR): 0.07 (–0.20 to 0.80); final mean (SE) value 5.98 (0.83) Visit 2 and visit 6 data, median (IQR): mAQLQ symptoms – visit 2: 5.70 (4.80 to 6.40), visit 6: 6.00 (5.20 to 6.40); activity limitation – visit 2: 6.25 (5.50 to 7.00), visit 6: 6.50 (5.75 to 7.00); emotional function: visit 2: 6.00 (4.67 to 6.67), visit 6: 6.00 (5.33 to 6.67); environmental stimuli: visit 2: 5.67 (5.00 to 6.67), visit 6: 6.33 (5.33 to 6.67) GQLI change ($n = 78/78$): 0 (–0.39 to 0.39)	Analyses of median (IQR) change between visit 2 and visit 6: mAQLA overall: $p = 0.197$; mAQLQ symptoms: $p = 0.041$; activity limitation: $p = 0.544$; emotional function: $p = 0.596$; environmental stimuli: $p = 0.193$; GQLI: $p = 0.666$

CI, confidence interval; GQLI, Gothenburg Quality of Life Instrument.

FIGURE 18 Meta-analysis of HRQoL outcomes. IV, inverse variable.

TABLE 35 Adult management review: other outcomes

Author, year	Outcome	Intervention	Control	Between-group difference
Asthma control				
Calhoun 2012[100]	Night-time symptoms, difference from beginning to end of treatment period using model-based estimates (97.5% CI)	0.01 (–0.00 to 0.02), $p = 0.07$	0.01 (–0.00 to 0.02), $p = 0.11$	0.00 (–0.02 to 0.02), $p = 0.86$
	Daytime symptoms, difference from beginning to end of treatment period using model-based estimates (97.5% CI)	–0.00 (–0.02 to 0.02), $p = 0.86$	0.01 (–0.00 to 0.03), $p = 0.06$	–0.01 (–0.04 to 0.01), $p = 0.17$
	ACQ score, difference from beginning to end of treatment period using model-based estimates (97.5% CI)	–0.01 (–0.15 to 0.12), $p = 0.81$	0.03 (–0.10 to 0.16), $p = 0.64$	–0.04 (–0.23 to 0.15), $p = 0.62$
	ASUI score, difference from beginning to end of treatment period using model-based estimates (97.5% CI)	0.01 (–0.02 to 0.04) $p = 0.40$	0.01 (–0.02 to 0.03) $p = 0.64$	0.00 (–0.04 to 0.04) $p = 0.79$
Shaw 2007[98]	Asthma control	Data NR. No difference between groups in Juniper score throughout the study; however, in both groups the score decreased from baseline. Significance NR		
Smith 2005[97]	Symptom score (daily score previous 7 days): final scores, mean (95% CI)	0.4 (0.1 to 0.7)	0.6 (0.4 to 0.9)	$p = 0.23$
	Nocturnal waking (nights/week, previous 7 days): final scores, mean (95% CI)	0.2 (0.0 to 0.6)	0.2 (0.0 to 0.4)	$p = 0.89$
	Asthma score (% of days), mean (95% CI)	Score 0: 85.2 (78.4 to 92.0); score 1: 14.0 (7.4 to 20.6); score ≥ 2: 0.8 (0.3 to 1.3)	Score 0: 78.5 (70.4 to 86.6); score 1: 19.9 (12.3 to 27.5); score ≥ 2: 1.7 (0.3 to 3.1)	Between-group final scores (not change from baseline) $p = 0.19$
Syk 2013[99]	ACQ score change between visit 2 and 6, median (IQR)	–0.17 (–0.67 to 0.17) ($n = 81/88$)	0 (–0.33 to 0.50) ($n = 74/78$)	$p = 0.045$
Other medication use				
Calhoun 2012[100]	Albuterol rescue use (puffs/day), difference from beginning to end of treatment period using model-based estimates (97.5% CI)	–0.04 (–0.10 to 0.02), $p = 0.15$	0.02 (–0.03 to 0.08), $p = 0.30$	–0.06 (–0.14 to 0.02), $p = 0.08$
Shaw 2007[98]	Medication use	NR	NR	NR
Smith 2005[97]	Bronchodilator use (occasions/day, previous 7 days), mean (95% CI)	0.4 (0.1 to 0.7)	0.4 (0.1 to 0.6)	$p = 0.98$
	Safety buffer criteria used	16/436 assessments	NA	NA
Syk 2013[99]	LTRA use, *n*/*N* (%)	33/92 (35.9)	19/85 (22.4)	$p = 0.069$
	Mean months on LTRA	2.87 (4.42)	1.81 (3.89)	$p = 0.094$
	SABA use between visit 5 and visit 6 (8–12 months), median (IQR)	1.56 (0.06 to 5.18)	0.94 (0.03 to 2.81)	NR

ASUI, Asthma Symptoms Utility Index; CI, confidence interval; NA, not applicable; NR, not reported.

Children

Five studies[103–107] that recruited children (plus adolescents and/or young adults) and compared FeNO- guided management to non-FeNO-guided management were identified from the initial search and a further two studies[108,109] were identified during the update search. The study by Fritsch *et al.*[103] was based in Vienna, Austria; that by Szefler *et al.*[104] was based in the USA; that by Verini *et al.*[105] was based in Italy; that by Pijnenburg *et al.*[106] was based in Rotterdam, the Netherlands; that by Petsky *et al.*[107] was based in Australia; that by Peirsman *et al.*[109] was conducted in Belgium; and that by Pike *et al.*[108] was the first UK-based study identified on this topic in children. Fritsch *et al.*[103] received technical and analytical support from Aerocrine; one of the authors in the study by Szefler *et al.*[104] received speaker fees from Aerocrine; the study by Pijnenburg *et al.*[106] was supported by the Kroger Foundation/Sophia Children's Hospital Foundation, although Aerocrine had provided a grant to the department; the study by Petsky *et al.*[107] was funded by the Royal Children's Hospital Foundation, Asthma Foundation of Queensland; the study by Pike *et al.*[108] was funded by Sparks charity; the study by Peirsman *et al.*[109] was funded by Merck & Co., with equipment provided by Aerocrine; and Verini *et al.*[105] did not report their source of funding.

Quality assessment

Study quality varied, with no one study scoring well on every item and no item scoring well in every study (*Figure 19*). Of the studies included in the review, the study with the highest overall quality appeared to be that by Szefler *et al.*,[104] in which the only potential source of bias identified was study funding by a company with a commercial interest in FeNO measurement. The study with the lowest quality appeared to be that by

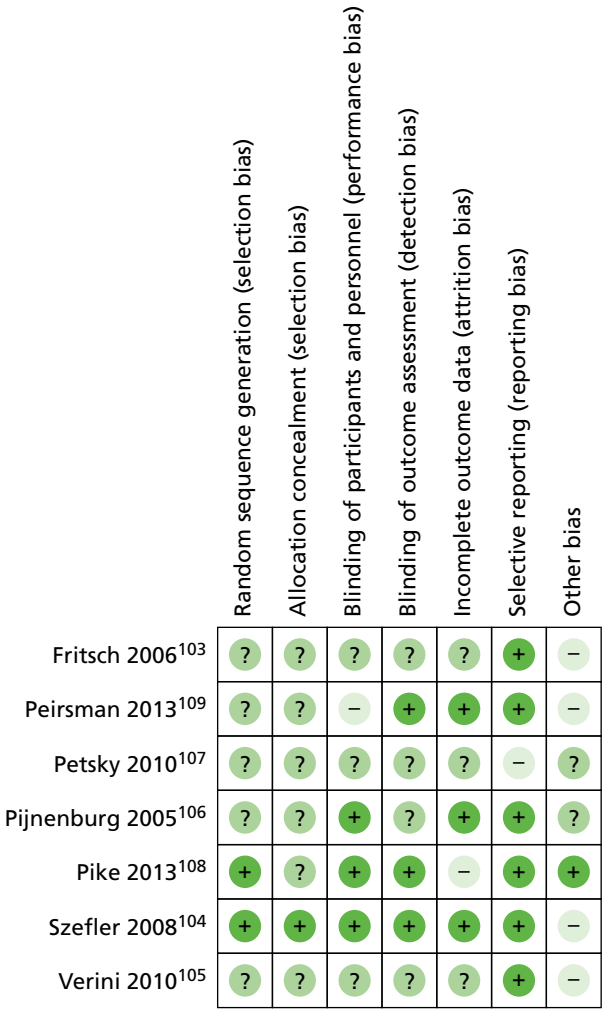


FIGURE 19 Methodological quality summary: review authors' judgements about each methodological quality item for all included studies. Dark green circles with + sign, low risk of bias; light green circles with – sign, high risk of bias; medium green circles with ?, unclear risk of bias.

Petsky *et al.*,[107] which was not scored as 'low risk' on any of the quality assessment items. As it was a conference abstract, Petsky *et al.*[107] was at especially high risk of selective reporting, whereas Verini *et al.*[105] was at risk of bias as the statistical comparison data were presented poorly (as discussed in the following sections). Potential sources of bias for the evidence base as a whole are discussed in the following sections.

Risk of selection bias All of the included studies were described as randomised. However, only the study by Szefler *et al.*[104] provided sufficient information on sequence generation and allocation concealment. Pike *et al.*[108] did demonstrate random sequence generation but the method of allocation concealment was unclear. In all other studies the method of sequence generation and allocation concealment was not reported.

Risk of performance bias In terms of blinding, Szefler *et al.*,[104] Pijnenburg *et al.*[106] and Pike *et al.*[108] appeared to have performed adequate blinding for both participants and study personnel. Fritsch *et al.*[103] blinded participants but did not report whether this was the case for study personnel and so this study was rated as 'unclear' on this item. Peirsman *et al.*[109] blinded participants but not personnel. Neither Petsky *et al.*[107] nor Verini *et al.*[105] provided sufficient information to make a judgement on participant and personnel blinding and so these studies were rated as 'unclear'. As many of the step-up/step-down protocols and criteria for exacerbations were based on participant symptom reporting and physician judgement, any potential lack of blinding in the studies could significantly affect the direction and size of the outcomes.

Risk of detection bias Szefler *et al.*,[104] Peirsman *et al.*[109] and Pike *et al.*[108] clearly stated that outcome assessment blinding had been performed. The poor reporting of outcome assessment blinding in the other studies means that unblinded outcome assessment may be a potentially important source of bias throughout this body of literature.

Risk of attrition bias In terms of outcome data completeness, Pijnenburg *et al.*,[106] Szefler *et al.*[104] and Peirsman *et al.*[109] appeared to be at low risk of bias. There may have been some bias in terms of outcome data completeness in the remaining four studies. Fritsch *et al.*[103] did not report the reasons for participant withdrawal or correction for missing FeNO values and there may have been missing outcome data in the study by Petsky *et al.*,[107] but this is unknown as only a conference abstract of this study was identified. In the study by Verini *et al.*[105] it was reported that 64 patients were recruited; however, it was unclear whether this was the total number after dropout or whether no participants dropped out. Consequently, the study was rated as 'unclear' on outcome data completeness. Pike *et al.*[108] reported 23% of dropouts in the intervention arm but only 7% in the control arm and was scored as being at high risk of attrition bias.

Risk of reporting bias Selective reporting risk may also have been present in some of the data. The study by Petsky *et al.*[107] was reported in a conference abstract and so this was rated as 'high risk' for this item. In the study by Fritsch *et al.*,[103] medication usage was reported as median (IQR) values rather than mean values and so these values could not be used in the planned meta-analysis; however, although planned, a meta-analysis was not possible because of study heterogeneity and so this bias did not affect the synthesis of data. The study by Verini *et al.*[105] was rated as having a low risk of bias for selective reporting; respiratory function and immunoallergological parameters were inadequately reported (i.e. no numerical data were provided; it was stated only that there were no significant between-group differences on these outcomes), but these outcomes were not of relevance to this review. Szefler *et al.*,[104] Pijnenburg *et al.*[106] Pike *et al.*[108] and Peirsman *et al.*[109] appear to have reported all of the outcomes that they set out to measure and so these studies were rated as 'low risk'.

Risk of other bias There were a number of further potential sources of bias in each of the studies. Fritsch *et al.*[103] and Szefler *et al.*[104] were both in receipt of sponsorship from the pharmaceutical industry and there was evidence of some such sponsorship in the studies by Peirsman *et al.*[109] and Pijnenburg *et al.*[106] The statistical comparison data reported in Verini *et al.*[105] was of poor quality in that most comparisons were presented as within-group longitudinal trends. Pike *et al.*,[108] Pijnenburg *et al.*,[106] Szefler *et al.*[104] and Fritsch *et al.*[103] all conducted run-in periods before randomisation, which have an unknown risk of bias attached to them. Finally, it was unclear whether there may have been additional sources of bias in the study by Petsky *et al.*,[107] as this research was presented as a conference abstract only.

Summary The quality of the sampled literature was variable, with selective reporting being the most common potential source of bias. The studies by Fritsch *et al.*,[103] Petsky *et al.*[107] and Verini *et al.*[105] were rated as 'unclear' on the majority of quality items. Such ratings were given for those aspects of study design that were not clearly presented within the articles themselves, meaning that it was unclear whether there is likely to be bias in the conduct of the studies themselves or whether the lack of clarity was a result of inadequate reporting. Other common potential sources of bias were random sequence generation, allocation concealment and outcome assessor blinding. Pharmaceutical industry sponsorship was declared as the source of funding by Fritsch *et al.*[103] and Szefler *et al.*[104] and at least partially funded the activities of one author in the studies by Pijnenburg *et al.*[106] and Peirsman *et al.*[109] The studies at lowest risk of overall bias appeared to be those by Szefler *et al.*[104] and Pike *et al.*[108] (low risk on six and five of seven items respectively) and the studies by Szefler *et al.*,[104] Pike *et al.*[108] and Pijnenburg *et al.*[106] were the only studies in which it was possible to confirm blinding of both participants and study personnel. Possible lack of participant blinding may be a particularly important source of bias given that the study outcomes were largely based on subjective measurements (i.e. self-reporting of symptoms); blinding of study personnel may also be an important source of bias as they decide whether a patient's medication step should be changed and there is some degree of interpretation in this decision. Finally, there was the possibility of selective reporting in Petsky *et al.*,[107] which may predispose the results to favour the intervention over the control.

Study details

Study design and timeline of studies All seven studies were RCTs, with varying degrees of blinding (see previous section). Study timelines are presented in *Table 36*. Study duration ranged from 6 months[103] to 12 months.[105,107–109] Pijnenburg *et al.*,[106] Szefler *et al.*,[104] Fritsch *et al.*[103] and Pike *et al.*[108] reported run-in periods of 2, 3, 4 and 4–16 weeks respectively. In Pijnenburg *et al.*[106] and Fritsch *et al.*,[103] details of the run-in period were not provided. In Szefler *et al.*[104] patients were provided with a treatment programme based on previous treatment, adherence and control and in Pike *et al.*[108] patients were stabilised when necessary. Verini *et al.*[105] and Petsky *et al.*[107] reported no run-in. In addition, the frequency of visits varied from study to study. Fritsch *et al.*[103] and Szefler *et al.*[104] reported visits every 6–8 weeks, Pike *et al.*[108] every 2 months, Pijnenburg *et al.*[106] and Peirsman *et al.*[109] every 3 months and Verini *et al.*[105] every 6 months. Petsky *et al.*[107] did not report the frequency of visits and provided outcomes for 12 months only.

Population The study and population characteristics are provided in *Table 37*. Eligibility criteria varied from study to study. With the exception of Verini *et al.*,[105] all studies included children with confirmed or persistent asthma. It is difficult to determine whether severity was comparable in the studies as scores have not been reported in a way that allowed comparison. Fritsch *et al.*[103] did not report severity; Szefler *et al.*[104] reported ACT scores; Verini *et al.*[105] and Peirsman *et al.*[109] classified participants on the basis of GINA scores; Pijnenburg *et al.*[106] reported mean daily symptom scores; and Pike reported exacerbations and OCS use in the previous year. Some insight into severity can be gained from considering the inclusion criteria and setting of each study. Three studies appeared to recruit patients who were uncontrolled.[104,105,107] Verini *et al.*[105] and Petsky *et al.*[107] recruited patients attending a specialist clinic, perhaps suggesting difficult to control patients, although in Verini *et al.*[105] patients had not yet started ICS therapy; an alternative explanation would be that all patients are sent to a specialist clinic before starting ICS therapy in this region and the patients were therefore not necessarily uncontrolled. Szefler *et al.*[104] recruited only patients with evidence of persistent or uncontrolled disease. Studies recruiting patients who are difficult to control are likely to capture the efficacy of FeNO for increasing control but not for decreasing ICS use in patients who are well controlled. Pike *et al.*[108] aimed to recruit patients with moderate to severe asthma and specified that children must be receiving therapy equivalent to stage 4 in the BTS/SIGN guidelines,[8] as well as a requirement to demonstrate responsiveness to a bronchodilator (i.e. an increase in FEV_1 of 15%). Fritsch *et al.*[103] recruited mild to moderate persistent asthma patients at an outpatients clinic. Pijnenburg *et al.*[106] recruited atopic asthma patients who were attending a children's hospital, although it is not clear if this was a scheduled appointment, an emergency admission or just the location of the study follow-up and it is therefore unclear what level of severity of asthma these patients may have. As they had all had a stable dose of ICS for the previous 3 months, it may be reasonable to assume that these patients were reasonably well controlled. Peirsman *et al.*[109] recruited the broadest spectrum of patients, including mild to severe persistent asthmatics.

TABLE 36 Children management review: study timelines

Author, year	Timeline of study	Final assessment
Fritsch 2006[103]	Visit 1: 4-week run-in. Visit 2: randomisation. Visit 3: visits at 6, 12, 18 and 24 weeks; symptoms, SABA use, anti-inflammatory treatment, FeNO and spirometry recorded. Bronchial challenge test (4.5% hypertonic saline) was carried out between the first and second visit	24 weeks
Peirsman 2013[109]	Visit 1: baseline. Visits 2–5: visit every 3 months; assessed symptom-free days (assessed daily), exacerbations, unscheduled asthma-related visits, hospital or emergency admissions, non-attendance at school and need for caregiver to take time off; FeNO recorded in all participants	12 months
Petsky 2010[107]	Spirometry, FeNO, QoL and asthma/cough diary every visit	12 months
Pijnenburg 2005[106]	Visit 0: 2-week run-in. Visit 1: randomisation, FeNO, FEV_1, PD20, diary card. Visits 2–4: visit every 3 months; FeNO and symptoms (diary card previous 2 weeks) recorded at each visit. Visit 5: FeNO, FEV_1, PD20, diary card	9 months
Pike 2013[108]	Unclear when baseline measurements performed. Visit 0: start of run-in period (4–16 weeks). Visit 1: randomisation. Visits 2–7: visit every 2 months for assessment – FeNO, exacerbations, symptoms and reliever use over previous 2 months recorded, treatment adherence assessed	12 months
Szefler 2008[104]	Visit 1: assessed asthma symptoms, pulmonary function, skin test, sensitivity, adherence and level of asthma control (NHLBI guidelines[134]). Run-in period of 3 weeks on a regimen based on standard treatment – physicians selected a treatment programme (one of six) based on previous treatment, adherence and asthma control. Included 10-minute session about adherence. Adherence measured during run-in period with Diskus inhaler and questionnaire. Centralised block randomisation and visit every 6–8 weeks for 46 weeks. Each visit: FeNO, days of symptoms, use of rescue drugs, pulmonary function, use of health care, adherence to treatment, missed days of school from asthma. Data were entered into computer and treatment option computed based on random allocation. In total, 546 were then randomly assigned to 46 weeks of either standard treatment or standard treatment modified on the basis of measurements of FeNO	46 weeks
Verini 2010[105]	Visit 1: baseline. Visit 2: 6 months. Visit 3: 12 months. ASS, asthma exacerbation frequency, asthma therapy score and immunoallergological and functional data recorded at each visit	12 months

ASS, Asthma Severity Score; NHLBI, National Heart, Lung, and Blood Institute; PD20, dose of methacholine causing a 20% fall in FEV_1 from baseline; QoL, quality of life.

TABLE 37 Child management review: study and population characteristics

Author, year	Study details	Inclusion/exclusion criteria	No. analysed/ no. recruited	Age (years), sex	Spirometry, mean (SD)	Severity	FeNO (ppb)	Atopic, smokers	Medication use
Fritsch 2006[103]	Setting: outpatient clinic, Vienna, Austria Funding: technical and analytical support from Aerocrine Study design: RCT, single blind, parallel groups	Patients with mild to moderate persistent asthma with a positive skin prick test (SPT) or radioallergosorbent test (RAST > 1) to at least one of seven common aeroallergens (cat, dog, house dust mite, alternaria, birch pollen, hazelnut pollen and mixed grass pollen) in past medical history or at the time of recruitment	47/52 I: 22 analysed, no. recruited unclear; C: 25 analysed, no. recruited unclear	Children and adolescents (6–18 years) Mean (SD) age: I: 11.3 (3.4); C: 12.1 (2.8) Male 28/47 (59.6%)	FEV_1%, median (IQR): I: 101 (91.1 to 107.5); C: 93.7 (83.8 to 99.6)	NR	Median (IQR): I: 34.6 (17.5 to 58.6); C: 31 (20.8 to 54.8); difference NS	Atopic: assume 100% Smokers: NR	ICS dose (µg/day), median (25%–75%): I: 230 (100 to 400); C: 140 (0 to 400) Beta-agonist puffs/day, median (IQR): I: 1 (0 to 7); C: 0 (0 to 2)
Peirsman 2013[109]	Setting: Belgium (seven sites) Funding: Investigator Initiated Studies Program of Merck & Co. Study design: multicentre, single-blind, parallel-group RCT	Mild to severe persistent asthma according to GINA guidelines[125] for ≥ 6 months, allergic sensitisation (i.e. positive skin prick test and/or specific IgE antibodies against inhaled allergens), elevated FeNO values in the presence of allergic airway inflammation. Exclusion: significant comorbidity, acute exacerbation or administration of experimental medication 4 weeks before screening, hospitalisation and/or systemic corticosteroids in 12 weeks before screening or OCS dependence	93/99 I: 47/49; C: 46/50	Children and young adolescent (5–14 years) Mean (SD) age: I: 10.6 (2.2); C: 10.7 (2.1) Male 66/99 (66.6%)	FEV_1% predicted: I: 92.9 (12.2); C: 89.0 (16.2); *t*-test: $p = 0.18$	Mild/moderate/ severe, *n* (%): I: 14 (28.6)/32 (65.3)/2 (4.1) (one missing value); C: 14 (28)/33 (66)/3 (6); chi-square: $p = 0.92$	Median (IQR): I: 32.5 (13.8 to 72.0); C: 27.5 (16.3 to 47.3)	Atopic: assume 100% Smokers (household exposure): I: 5/48 (one missing value); C: 8/49 (one missing value)	Daily ICS dose (µg), median (IQR): I: 320 (160 to 400); C: 320 (145 to 400) LABA use (*n*/*N*): I: 25/49; C: 23/50
Petsky 2010[107]	Setting: Australia (clinical setting NR) Funding: non-industry Study design: RCT	Children with asthma and on ICS attending a paediatric specialist clinic. Excluded if other cardiorespiratory illness, if poorly compliant or if unable to take ICS or LABA	63/63 I: 31/31; C: 32/32	Children (min. 4 years, max. NR) Mean age NR Male NR	FEV_1% predicted (95% CI): I baseline: 101.3 (90.9 to 111.7); I at 12 months: 106.1 (91.9 to 120.2); C baseline: 84.28 (63.9 to 104.7); C at 12 months: 91.16 (84.7 to 97.7)	NR	NR	Atopic: NR Smokers: NR	NR

continued

TABLE 37 Child management review: study and population characteristics (*continued*)

Author, year	Study details	Inclusion/exclusion criteria	No. analysed/ no. recruited	Age (years), sex	Spirometry, mean (SD)	Severity	FeNO (ppb)	Atopic, smokers	Medication use
Pijnenburg 2005[106]	Setting: children's hospital, Rotterdam, the Netherlands Funding: some non-industry plus grant from Aerocrine to department Study design: parallel-group, double-blind RCT	Children with atopic asthma who had been using ICS at a constant dose for previous 3 months	85/89 I: 39/42; C: 46/47	Children and adolescents (6–18 years) Mean (SD) age: I: 11.9 (2.9); C: 12.6 (2.8) Male $n = 55/85$ (64.7%)	FEV_1 % predicted: I 96 (14); C 99 (20)	Mean (SD) daily symptom score: I: 1.4 (2.0); C: 2.0 (2.4)	GM (range): I: 26.4 (5.6–134.9); C: 29.8 (3.1–117.5)	Atopic: I: 39/39 (100%); C: 46/46 (100%) Smokers: NR	Mean (SD) daily beta2-agonist puffs: I: 0.4 (0.6); C: 0.4 (0.5) Initial ICS dose (µg), mean (SD): I: 762 (335); C: 746 (410)
Pike 2013[108]	Setting: multiple outpatient clinics in the UK ($n = 4$) Funding: NR; authors state no conflict of interest Study design: RCT (assessor blinded)	Age 6–17 years, treatment with 400 µg/day beclomethasone/ budesonide or 200 µg/day fluticasone. Clinical asthma diagnosis based on symptoms including 15% increase in FEV_1 with bronchodilator or diurnal PEF variability ≥ 15%. Exclusion criteria: inability to perform spirometry or FENO, cigarette smoking, poor treatment adherence, life-threatening exacerbation or need for maintenance oral prednisolone	90/90 I: 34/44 completers (all analysed by ITT); C: 43/46 completers (all analysed via ITT)	Children and adolescents (6–17 years) Mean (SD) age: I: 10.51 (2.6); C: 11.42 (2.69) Male 51/90 (56.7%)	NR	Median (IQR) exacerbations in past year: I: 3.5 (2 to 8); C: 4.5 (2 to7) Median (IQR) OCSs in past year: I: 1 (0 to 3.5); C: 2 (0 to 3)	Median (IQR): NR	Atopic: I: 81.1%; C: 88.4% Smokers (household exposure): I: 9.1%; C: 13.0%	ICS dose (µg/day), median (25%–75%): I: 750 (400 to 1000); C: 800 (400 to 1000) Beta-agonist puffs/day, median (IQR): NR
Szefler 2008[104]	Setting: 10 sites, USA Funding: non-industry, although one author received speaker fees from Aerocrine Study design: multicentre, double-blind, parallel-group RCT	Eligibility restricted to residents of urban census tracts in which at least 20% of households had incomes below the federal poverty threshold. Eligible participants had been diagnosed with asthma by a physician. Those on long-term control included only if they had persistent asthma or evidence of uncontrolled disease; all others must have both symptoms of persistent asthma and evidence of uncontrolled disease. Excluded if adherence <25% or a smoker	534/546 I: 267/276; C: 267/270	Children and young adults (12–20 years) Mean (SD) age: 14.4 (2.1) Male 288/546 (53%)	FEV_1 (proportion of best FEV_1): I: 95.9 (15.5); C: 95.7 (15.9) FEV_1/FVC: I: 79.8 (9.0); C: 80.4 (8.3)	ACT score in last month (range 5–25), mean (SD): I: 21.1 (3.6); C: 21.3 (3.2)	Median (25%–75%): at enrolment: 31.7 (14.1–65.4); at randomisation: I: 20.5 (11.5–45.3), C: 19.7 (10.9–38.0)	Atopic: NR Smokers: 0%	NR

Author, year	Study details	Inclusion/exclusion criteria	No. analysed/ no. recruited	Age (years), sex	Spirometry, mean (SD)	Severity	FeNO (ppb)	Atopic, smokers	Medication use
Verini 2010[105]	Setting: secondary care hospital, Italy Funding: NR Study design: single-centre, parallel-group RCT	Patients referred for allergic asthma – not all already on ICS	64/64 I: 32/32; C: 32/32	Children and adolescents (6–17 years) Mean (SD) age: I: 10.7 (2.4); C: 11.3 (2.1) Male 36/64 (56.3)	NR	GINA score 0: I: 7; C: 7 GINA score 1: I: 18; C: 19 GINA score 2 or 3: I: 7; C: 6	Baseline, mean (SD): I: 13.78 (12.31); C: NR	Atopic: 64/64 (100%) Smokers: NR	NR

C, control group; CI, confidence interval; G, geometric mean; I, intervention group; IgE, immunoglobulin E; ITT, intention to treat; NR, not reported; NS, not significant; PEF, peak expiratory flow.

Interestingly, atopy is a known confounder to FeNO measurements as atopic subjects have raised FeNO levels regardless of asthma status. Asthmatic atopic patients are thought to have the highest levels overall and so FeNO is theoretically able to distinguish between controlled and uncontrolled atopic asthmatics as well as between controlled and uncontrolled non-atopic asthmatics.[138] However, atopic asthma patients tend to have ICS-responsive asthma more often than non-atopic patients and so studies recruiting atopic patients will have limited generalisability. It is unclear whether studies in atopic patients will over- or underestimate efficacy or have no impact at all, although clinical input to the assessment suggested that it would be expected to increase estimates of efficacy as atopy is correlated with ICS responsiveness. Atopic patients were recruited by Peirsman *et al.*,[109] Fritsch *et al.*,[103] Verini *et al.*[105] and Pijnenburg *et al.*[106] Pike *et al.*[108] recruited only patients who demonstrated responsiveness to bronchodilators, but not all were atopic.

Petsky *et al.*[107] was the only study to include young children only, with all other studies including adolescents and/or young adults as well as young children, or adolescents only in the case of Szefler *et al.*[104] The studies also varied in terms of size (range 52[103]–546[104]) and baseline FeNO was inconsistently reported.

Interventions *Table 38* describes the interventions used in each study. NIOX MINO was used in the two most recent studies;[108,109] the NIOX device was used in three of the studies;[103,104,106] Verini *et al.*[105] used the ECO MEDICS CLD 88 device; and it was unclear what device was used by Petsky *et al.*[107]

None of the studies used the same protocol or cut-off points for the management of asthma with FeNO. The protocol of Fritsch *et al.*[103] was based on FeNO readings only. Other studies used a combination of FeNO levels and symptoms, with various cut-off points and numbers of cut-off points: Szefler *et al.*[104] specified three levels of cut-off, Pike *et al.*[108] specified two cut-off points, Petsky *et al.*[107] did not report cut-offs and all other studies used just one cut-off point. These cut-off points ranged from 12 ppb to 40 ppb. Treatments indicated at each step were also highly heterogeneous across studies, with Pike *et al.*,[108] Peirsman *et al.*,[109] Fritsch *et al.*[103] and Szefler *et al.*[104] indicating doses for ICSs, LTRAs and LABAs and Pijnenburg *et al.*[106] indicating doses only for ICSs. Verini *et al.*[105] and Petsky *et al.*[107] did not report doses. The treatment in the study by Pike *et al.*[108] was most similar to that in the BTS/SIGN guidelines,[8] with some minor modifications. Importantly, in the studies by Szefler *et al.*,[104] Pike *et al.*[108] and Peirsman *et al.*,[109] step down could not occur on the basis of low FeNO levels if patients were still experiencing symptoms. This may have limited any potential reduction in ICS use for patients who were non-ICS responsive.

Control *Table 39* provides details of the control group interventions. As with the interventions, none of the studies used the same criteria, protocols or treatment doses for the management of asthma in the control arm of the study, but, when reported, they all used the same treatment steps in both arms of the study. Management was typically guided by symptom severity and/or FEV_1. Verini *et al.*[105] and Peirsman *et al.*[109] used GINA guidelines[136] as a control and Pike *et al.*[108] used BTS/SIGN guidelines[8] with some minor modifications.

TABLE 38 Child management review: description of the intervention management strategies

Author, year	Decisions based on flow rate, device and cut-off points	Step-up/step-down protocol	Doses
Fritsch 2006[103]	Based on FeNO readings only Flow rate; device: 50 ml/second with the single-breath online method; NIOX device Cut-off: FeNO > 20 ppb	In patients with stable asthma, an increased FeNO level was considered a sign of insufficient anti-inflammatory treatment (either because of insufficient dosing or because of low adherence to prescribed therapy); hence, aimed to improve adherence to therapy in patients on anti-inflammatory treatment with raised FeNO. These patients were provided with 2-week diary cards to record daily symptoms, beta-agonist use and controller medication requirements and telephone calls were made regularly to check adherence to therapy. Asymptomatic patients on therapy with beta-agonists on demand only, with normal lung function but increased FeNO levels, were prescribed low-dose steroids. Step up was performed irrespective of FeNO level if FEV_1% predicted was < 80% and/or there were severe symptoms over the last 4 weeks and/or beta-agonist use involved six or more 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 FEV_1% predicted was ≥ 80% and there were no or mild symptoms over the last 4 weeks and beta-agonist use involved fewer than six puffs over the last 14 days and FeNO was ≤ 20 ppb	Low-dose ICS: 2 × 100 µg fluticasone or 2 × 200 µg budesonide Low-dose ICS + LTRAs: 2 × 100 µg fluticasone or 2 × 200 µg budesonide + 5 mg montelukast once daily p.o. Low-dose ICS + LABAs: 2 × 100 µg fluticasone + 2 × 50 µg salmeterol or 2 × 200 µg budesonide + 2 × 12 µg formoterol High-dose ICS + LTRAs: 2 × 250 µg fluticasone or 2 × 400 µg budesonide + 5 mg montelukast once daily p.o. High-dose ICS + LABAs: 2 × 250 µg fluticasone + 2 × 50 µg salmeterol or 2 × 400 µg budesonide + 2 × 12 µg formoterol
Peirsman 2013[109]	Based on FeNO readings and symptoms Flow rate; device: 50 ml/second; NIOX MINO Cut-off: 20 ppb	Asthma classed as 'controlled' (≤ 20 ppb and symptoms controlled); 'partly controlled' (≤ 20 ppb and partly controlled symptoms); or uncontrolled (FeNO > 20 ppb regardless of symptoms). Medication changes were guided by participants' baseline therapies	Controlled: if on ICS only: step down ICS 100 µg/day, if already < 100 µg stop and add LTRA; if on LTRA only, no change; if on ICS + LTRA, step down ICS 100 µg/day, if already < 100 µg, stop ICS; if on ICS + LABA, stop LABA Partly controlled: if on ICS only, consider adding LTRA; if on LTRA only, consider adding ICS 100 µg/day (max. 200 µg/day); if on ICS + LTRA, consider ICS step up by 100 µg/day (max. 400 µg/day, then add LABA); if on ICS + LABA, consider adding LTRA Uncontrolled: if on ICS only, add LTRA; if on LTRA only, add ICS 100 µg/day (max. 200 µg/day); if on ICS + LTRA, step up ICS by 100 µg/day (max. 400 µg, then add LABA); if on ICS + LABA, replace LABA with LTRA
Petsky 2010[107]	Based on FeNO and atopy Flow rate; device: NR Cut-offs: NR	NR (treatment adjusted according to exhaled nitric oxide result, monthly for 4 months, then every second month for 8 months)	NR

continued

TABLE 38 Child management review: description of the intervention management strategies (*continued*)

Author, year	Decisions based on flow rate, device and cut-off points	Step-up/step-down protocol	Doses
Pijnenburg 2005[106]	Based on FeNO and symptoms Flow rate; device: presume 50 ml/second; NIOX analyser Cut-offs: > 30 ppb; ≤ 30 ppb + symptoms > 14 ≤ 30 ppb + symptoms ≤ 14	FeNO > 30 ppb = ICS increased; FeNO ≤ 30 ppb *and* symptoms > 14 = ICS stays the same; FeNO ≤ 30 ppb *and* symptoms ≤ 14 = ICS decreased	ICS doses: 100 µg: increase to 200 µg, decrease to 0 µg 200 µg: increase to 400 µg, decrease to 100 µg 400 µg: increase to 800 µg, decrease to 200 µg 500 µg: increase to 1000 µg, decrease to 250 µg 800 µg: increase to 1200 µg, decrease to 400 µg 1000 µg: increase to 1500 µg, decrease to 500 µg 1200 µg: increase to 1600 µg, decrease to 800 µg 1600 µg: increase to 2000 µg, decrease to 1200 µg 2000 µg: no further increase, decrease to 1000 µg
Pike 2013[108]	Based on FeNO readings and symptoms Flow rate; device: flow rate NR; NIOX MINO Cut-offs: ≤ 15 ppb; > 15 ppb and ≤ 25 ppb; ≥ 25 or FeNO doubled from baseline	FeNO ≥ 25 ppb or more than twice baseline: • poorly controlled: increase ICS or add LTRA if already at SIGN/BTS guidelines[8] step 4; if after increasing by two SIGN/BTS steps FENO remains high do not increase therapy further • asthma controlled or well controlled: increase ICS or add LTRA if already at SIGN/BTS guidelines[8] step 4 FeNO > 15 ppb and ≤ 25 ppb • poorly controlled: increase LABA therapy; if dose maximal, increase ICS or add LTRA if already at SIGN/BTS guidelines[8] step 4 • asthma controlled or well controlled: continue current treatment FeNO ≤ 15 ppb • poorly controlled: increase LABA; if dose maximal, increase ICS or add LTRA if already at SIGN/BTS guidelines[8] step 4 • asthma controlled or well controlled: if asthma controlled for 3 months, reduce ICS; if dose ≤ 400 µg, reduce LABA	Step 1: no ICS Step 2: beclomethasone 50 µg b.i.d. via spacer *or* budesonide 50 µg b.i.d. via spacer or turbohaler *or* fluticasone 50 µg once a day via spacer (or accuhaler) Step 3: beclomethasone 100 µg b.i.d. via spacer *or* budesamide 100 µg b.i.d. via spacer or turbohaler *or* fluticasone 100 µg once a day via spacer (or accuhaler) Step 4: beclomethasone 200 µg b.i.d. via spacer *or* budesamide 200 µg b.i.d. via spacer or turbohaler *or* fluticasone 100 µg once a day via spacer (or accuhaler) Step 5: trial of LABA. If ineffective, consider trial of LTRA Step 6: fluticasone 125 µg b.i.d. via spacer Step 7: fluticasone 250 µg b.i.d. via spacer Step 8: consider short course of prednisolone or other therapeutic options

TABLE 38 Child management review: description of the intervention management strategies (*continued*)

Author, year	Decisions based on flow rate, device and cut-off points	Step-up/step-down protocol	Doses
Szefler 2008[104]	Based on days/nights of symptoms (patient recall over past 2 weeks), FEV_1 as percentage of personal best, FeNO Flow rate; device: 50 ml/second; NIOX device Cut-offs: 0–20, 20.1–30, 30.1–40, > 40 ppb	Step up/down based on predefined levels of control: Level 1 – days of symptoms in past 2 weeks 0–3; nights of symptoms in past 2 weeks 0–1; % of personal best FEV_1 ≥ 80%; FeNO 0–20 ppb. Medication would not change at this level or if at level 1 for two consecutive visits it may be stepped down Level 2 – days of symptoms in past 2 weeks 4–9; nights of symptoms in past 2 weeks 2; % of personal best FEV_1 ≥ 80%; FeNO 20.1–30 ppb. Increase medication by one step Level 3 – days of symptoms in past 2 weeks 10–13; nights of symptoms in past 2 weeks 3–4; % of personal best FEV_1 70–79%; FeNO 30.1–40 ppb. Increase medication by two steps Level 4 – days of symptoms in past 2 weeks 14; nights of symptoms in past 2 weeks 5–14; % of personal best FEV_1 < 70%; FeNO > 40 ppb. Increase medication by three steps or two steps + prednisone	Step 0 – no controller medication; rescue treatment with salbutamol as needed Step 1 – fluticasone by dry powder inhaler 100 µg/day Step 2 – fluticasone by dry powder inhaler 100 µg b.i.d. Step 3 – fluticasone by dry powder inhaler 100 µg/day and salmeterol 50 µg b.i.d. Step 4 – fluticasone by dry powder inhaler 250 µg/day and salmeterol 50 µg b.i.d. Step 5 – fluticasone by dry powder inhaler 500 µg/day and salmeterol 50 µg b.i.d. Step 6 – fluticasone by dry powder inhaler 500 µg/day and salmeterol 50 µg b.i.d. plus either low-dose theophylline or montelukast every day
Verini 2010[105]	Based on GINA guidelines[136] plus FeNO values Flow rate; device: flow rate NR; CLD 88 Cut-off: 12 ppb	Values > 12 ppb lead to increased medication. Values < 12 ppb lead to a reduction in or maintenance of amount of drugs. Changes in drugs not reported. Unclear whether FeNO used at visit 2 only to guide therapy	NR

b.i.d., twice per day; p.o., by mouth.

TABLE 39 Child management review: description of the control group management strategies

Author, year	Decisions based on	Step-up/step-down protocol	Doses
Fritsch 2006[103]	Asthma control (symptoms, SABA use, lung function), as recommended in current (German) asthma guidelines[139]	A step down in therapy was performed if FEV_1% predicted was ≥ 80% and there were no or mild symptoms over the last 4 weeks and beta-agonist use involved fewer than six puffs over the last 14 days. A step up was performed in every other case	As intervention
Peirsman 2013[109]	Symptoms, need for rescue treatment in past 2 weeks, spirometry (FEV_1) based on GINA guidelines[136]	GINA guidelines[136] (specific step-up/step-down protocol not described) to determine if controlled, partly controlled or uncontrolled	As intervention
Petsky 2010[107]	Symptoms/FEV_1	Unclear	NR
Pijnenburg 2005[106]	Symptoms	Symptom score > 14 = ICS increase; symptom score ≤ 14 for first time = ICS stays the same; symptom score ≤ 14 for second time = ICS decrease Symptom score calculated as mean of daily scores for dyspnoea, wheezing and cough, during daytime and night-time, with each scored from 0 to 3, giving a max. score of 18, as well as use of beta2-agonists and percentage of symptom-free days. Calculated over previous 2 weeks for monitoring and over previous 4 weeks for end-point evaluation	As intervention
Pike 2013[108]	Symptom control	Therapy was stepped up if symptoms were poorly controlled and decreased if well controlled for ≥ 3 months, according to BTS/SIGN guidelines[8]	As intervention
Szefler 2008[104]	National Asthma Education and Prevention Program (symptoms, treatment use, lung function)[140]	Control group received standard treatment based on the guidelines of the National Asthma Education and Prevention Program[140] (i.e. as intervention but without FeNO measurements)	As intervention
Verini 2010[105]	GINA guidelines[136] (symptoms, SABA use, lung function)	GINA guidelines[136] (specific step-up/step-down protocol not described)	NR

b.i.d., twice per day; NR, not reported.

Estimates of efficacy

Exacerbations All seven studies provided some data on asthma exacerbations, although it was unclear in some cases what the precise definition of an exacerbation was (*Table 40*).

Hospitalisations Three studies[104,108,109] reported the number of patients (but not the rate per person-year) requiring hospitalisations. All three studies reported no difference between groups (see *Table 40*).

Exacerbations resulting in oral corticosteroid use Data on exacerbations resulting in OCS use were reported in three studies.[103,104,106] Szefler *et al.*[104] reported rates per year and Pijnenburg *et al.*[106] reported the number of courses per group. In both cases rates were lower in the intervention arm. In the study by Szefler *et al.*[104] the rate per year was 0.66 (SE 0.085) in the FeNO group and 0.84 (SE 0.085) in the control group. It is not clear if this analysis calculated rates per person-year to account for missing data points. The mean difference was not statistically significant (0.17, 95% CI −0.08 to 0.41; $p = 0.14$). In the study by Pijnenburg *et al.*[106] the reviewer-calculated mean number of exacerbations per person was 0.21 (eight courses in 39 patients) in the FeNO group and 0.39 (18 courses in 46 patients) in the control group.

TABLE 40 Child management review: exacerbation and OCS use rates in children and adolescents with or without FeNO-guided management

Author, year	Definition of outcomes	Intervention	Control	Between-group comparison
Hospital admission				
Peirsman 2013[109]	One or more hospital admission	1/43 (2.3%)	1/43 (2.3%)	Chi-square test: $p = 1.00$
Pike 2013[108]	Requiring ≥ 8 hours of admission	5 patients (11.4%)	3 patients (6.5%)	$p = 0.420$
Szefler 2008[104]	One or more hospital admissions	3.3% (SD 1.78%)	4.1% (SD 1.98%)	Mean difference –0.8 (95% CI –4.0 to 2.3), $p = 0.61$
Unscheduled use of health care				
Peirsman 2013[109]	One or more unscheduled uses of health care	6/44 (13.6%)	15/43 (34.9%)	Chi-square test: $p = 0.02$
Szefler 2008[104]	One or more unscheduled uses of health care	21.3% (SD 4.09%)	22.7% (SD 4.19%)	Mean difference –1.4 (95% CI –9.3 to 6.7), $p = 0.74$
OCS use				
Fritsch 2006[103]	OCS use (no. of patients/group)	$n = 2$	$n = 2$	$p =$ NS
Pijnenburg 2005[106]	Prednisone courses	Eight events in 1 year = 8/39 = 0.21 per patient	18 events in 1 year = 18/46 = 0.39 per patient	$p = 0.60$[a]
Szefler 2008[104]	Prednisone courses	Mean 0.66 (SE 0.085)	Mean 0.84 (SE 0.085)	Mean difference 0.17 (95% CI –0.08 to 0.41), $p = 0.14$
Any/wide definition of exacerbation				
Fritsch 2006[103]	Exacerbation defined as oral steroid courses because of asthma symptoms over the last 4 weeks and/or unscheduled visit because of asthma symptoms over the last 4 weeks and/or increase in asthma symptoms from a symptom score of 0 or 1 to a score of 2 and/or decline in $FEV_1 > 10\%$ compared with last visit (no. of patients/group)	17/88 observations (18.2%) [sic][b]	22/99 observations (21.2%) [sic][b]	$p =$ NS
Peirsman 2013[109]	Exacerbation as per GINA guidelines:[136] an episode of progressive increased shortness of breath, coughing, wheezing or chest tightness or a combination of these symptoms	18 per year[b]	35 per year[b]	Mann–Whitney test: $p = 0.02$
Petsky 2010[107]	Asthma exacerbations (severity not described)	6/31 (19.4%)	15/32 (46.9%)	$p = 0.021$[a]
Pike 2013[108]	Patients experiencing an exacerbation	37 patients (84.1%)[c]	38 patients (82.6%)[c]	$p = 0.850$
Szefler 2008[104]	Exacerbation defined as a composite outcome consisting of admissions to hospital, unscheduled visits and prednisone use	37.0% (SD 4.83%)	43.6% (SD 4.96%)	Mean difference –6.5% (95% CI –14.4 to 1.4), $p = 0.11$

continued

TABLE 40 Child management review: exacerbation and OCS use rates in children and adolescents with or without FeNO-guided management (*continued*)

Author, year	Definition of outcomes	Intervention	Control	Between-group comparison
Verini 2010[105]	ATS 2005 definition:[35] number of episodes of coughing, dyspnoea and wheezing requiring SABAs	0.83 (SD 0.98) per person-year	1.85 (SD 1.34) per person-year	Between-group comparison NR
Other outcomes				
Peirsman 2013[109]	Number of children with one or more exacerbation	11/46 (23.9%)	22/46 (47.8%)	Chi-square test: $p = 0.02$
Peirsman 2013[109]	One or more emergency room admission	2/45 (4.4%)	4/46 (8.7%)	Chi-square test: $p = 0.41$
Szefler 2008[104]	One or more prednisone course	32.1% (SD 4.67%)	42.0% (SD 4.94%)	Mean difference −10.3% (95% CI −18.5 to −2.2), $p = 0.01$

NS, not significant.
a *p*-value for number of patients having one or more events, not number of events.
b Unable to calculate rate per person-year as unclear how many patients were included in the analysis.
c Unable to calculate rate per person-year because of lack of data on absolute number of exacerbations per group.

The difference in the number of people experiencing an exacerbation in the study by Pijnenburg *et al.*[106] was non-significant. Fritsch *et al.*[103] reported no significant difference in the number of people requiring OCSs between groups.

Any/wide definition of exacerbation Fritsch *et al.*,[103] Szefler *et al.*,[104] Verini *et al.*,[105] Petsky *et al.*,[107] Pike *et al.*[108] and Peirsman *et al.*[109] all reported this outcome using a broad definition of exacerbation (sometimes called treatment failure), but used different definitions to one another. Pijnenburg *et al.*[106] did not report this outcome. Lack of data allowing calculation of rates per person-year precluded meta analysis.

Five studies reported numerically fewer exacerbations or treatment failures in the intervention arm, but these differences were statistically significant in only two studies. Fritsch *et al.*[103] used a composite outcome that appeared to include moderate to severe exacerbations. There were 17 exacerbations out of 88 observations in the intervention group (reported as 18.2% in Fritsch *et al.*[103]) compared with 22 exacerbations out of 99 observations in the control group (reported as 21.2% in Fritsch *et al.*[103]). These data were not convertible to rates as some data points were missing in the study. The difference was not significant at the $p < 0.05$ level. Szefler *et al.*[104] also used a composite outcome, which appeared also to relate to moderate to severe exacerbations. This study reported the percentage of patients in each group with more than one exacerbation; these were 37.0% in the intervention group and 43.6% in the control group (risk ratio −6.5, 95% CI −14.4 to 1.4; $p = 0.11$). Verini *et al.*[105] reported events leading to the use of SABAs, which appeared to be likely to incorporate minor to major exacerbations. Rates per person-year were 0.83 (SD 0.98) and 1.85 (SD 1.34) in the intervention arm and control arm respectively. No between-group comparisons were presented for this outcome. Pike *et al.*[108] reported the number of patients who had ≥ 48 hours of increased asthma symptoms or therapy and showed no difference between the groups, with 37 (84.1%) patients in the intervention arm and 38 (82.6%) in the control arm experiencing an exacerbation ($p = 0.850$).

The two studies that reported a significant between-group difference were those by Petsky *et al.*[107] and Peirsman *et al.*[109] In the study by Petsky *et al.*,[107] exacerbations were not clearly defined but occurred in six out of 31 participants in the intervention group (19.4%) and 15 out of 32 participants in the control group (46.9%; $p = 0.021$). Peirsman *et al.*[109] reported statistically significantly fewer exacerbations of any severity (as defined using GINA guidelines[136]) in the intervention arm (18 events) than in the control arm (35 events; $p = 0.02$), although rates were not calculable because of missing information about the number of participants included in the analysis.

Inhaled corticosteroid use *Table 41* provides details of ICS use in each study. Fritsch *et al.*[103] and Szefler *et al.*[104] reported statistically significantly higher ICS use in the intervention group, Pijnenburg *et al.*[106] reported very similar levels and the values in the remaining study[105] (in terms of absolute numbers using ICSs) were difficult to interpret. Fritsch *et al.*[103] reported median (IQR) end-point values for ICS use in the intervention and control groups as 316 (200 to 500) µg and 241 (26 to 607) µg respectively ($\beta = 0.20$, $p < 0.01$). Pijnenburg *et al.*[106] reported the mean (standard error of the mean) cumulative ICS dose from visit 1 to visit 5 as 4407 (367) µg in the intervention group and 4332 (383) µg in the control group ($p = 0.73$). Szefler *et al.*[104] reported the between-group difference in use of fluticasone, which was 119 µg/day greater in the FeNO group by the final visit (95% CI 49 µg to 189 µg; $p = 0.001$). Finally, Verini *et al.*[105] reported the absolute number of participants using ICSs from each group at each time point (intervention group: T1 20, T2 19, T3 19; control group: T1 15, T2 22, T3 19). However, the baseline values for the groups in this study were not comparable and the absolute numbers of participants using ICSs, without concomitant data on dosages used, provide little understanding of between-group ICS use.

TABLE 41 Child management review: ICS use

Author, year	ICS type and measurement definition	Intervention	Control	Between-group difference
Fritsch 2006[103]	Fluticasone and budesonide permitted. Data reported as median ICS dose (µg/day); unclear which ICS type the doses refer to	Baseline median (IQR) dose: 230 (100 to 400) µg; end point median (IQR) dose: 316 (200 to 500) µg	Baseline median (IQR) dose: 140 (0 to 400) µg; end point median (IQR) dose: 241 (26 to 607) µg	Repeated measures analysis: $\beta = 10.20$, $p < 0.01$
Peirsman 2013[109]	Budesonide or equivalent:			
	Median (IQR) cumulative ICS dose (calculated by summing daily ICS dose from visit 1 to visit 5)	Cumulative dose: 1280 (800 to 1800) µg	Cumulative dose: 1200 (675 to 1600) µg	p = NS
	Median (IQR) change in daily ICS dose from baseline	+100 (0 to +400) µg	0 (–200 to +80) µg	$p = 0.016$
Petsky 2010[107]	NR	NR	NR	NR
Pijnenburg 2005[106]	Budesonide (2 mg max. daily dose permitted). Cumulative steroid dose (sum of mean daily steroid doses from visit 1 to visit 5)	Cumulative end point: 4407 (367) µg	Cumulative end point: 4332 (383) µg	$p = 0.73$
Pike 2013[108]	Beclomethasone, fluticasone and budesonide permitted. Data reported as median (IQR) ICS dose (µg/day) in terms of baseline, end point, change and total dose. Unclear which ICS type the doses refer to	Baseline dose: 750 (400 to 1000) µg/day; end point dose: 800 (400 to 1000) µg/day; dose change: 0 (–200 to 300) µg/day	Baseline dose: 800 (400 to 1000) µg/day; end point dose: 500 (400 to 1000) µg/day; dose change: 0 (–300 to 0) µg/day	Mann–Whitney rank-sum tests: baseline dose: $p = 0.629$; end point dose: $p = 0.543$; dose change: $p = 0.297$
Szefler 2008[104]	Fluticasone	NR	NR	Difference 119 µg/day (95% CI 49 to 189 µg; $p = 0.001$) (higher in intervention group)
Verini 2010[105]	Unclear what ICS used. Measured in terms of absolute number of patients using per group at each time point	T1: 20, T2: 19, T3: 19	T1: 15, T2: 22, T3: 19	NR

CI, confidence interval; NR, not reported; T, time.

When studies recruiting patients who are or who are likely to be difficult to control[103,104] were compared with the study that recruited patients who had been on a stable dose of ICS for 3 months,[106] it was seen that the two studies recruiting the difficult to control groups saw an increase in ICS usage whereas the study that recruited stable patients saw similar levels of ICS use across both arms. This would be expected as the difficult to control group of patients is unlikely to need a dose reduction whereas patients who are stable may be eligible for such a reduction. In addition to this, the Szefler *et al.*[104] protocol did not allow step-down of ICSs on the basis of low FeNO levels if symptoms were still present, making step-down less likely to occur.

The two studies identified from the search update reported results that agree with previous findings. The study by Pike *et al.*,[108] which recruited more severe patients, saw a higher final median (IQR) ICS usage [800 (400 to 1000) µg vs. 500 (400 to 1000) µg] and higher upper and lower ends of the CIs [0 (–200 to 300) vs. 0 (–300 to 0) µg] for the median change from baseline in the intervention group, indicating that there was an increase in ICS use. However, the differences were not statistically significant. The study by Peirsman *et al.*,[109] which recruited a wider spectrum of patients but which also included severe asthmatics, also saw numerically higher doses in the intervention arm but, again, not statistically significantly so.

Health-related quality of life *Table 42* provides HRQoL data. Only Petsky *et al.*[107] provided data on HRQoL and it was unclear which quality of life tool was used. In the intervention group, the baseline mean was 84.38 (95% CI 77.27 to 91.48), which rose to 86 (95% CI 74.84 to 97.1) at 12 months. Conversely, in the control group, the baseline mean of 86 (95% CI 81.49 to 90.51) dropped to 83.75 at 12 months

TABLE 42 Child management review: other outcomes

Author, year	Outcome	Intervention, mean (SD)	Control, mean (SD)	Comparison
Asthma control				
Fritsch 2006[103]	Increase in symptoms to a score of 2 (severe), *n/N* (%)	10/88 (11.4)	11/99 (11.1)	NS at $p < 0.05$
	Unscheduled visits, *n/N* (%)	5/88 (5.7)	5/99 (5.1)	NS at $p < 0.05$
	FEV_1 decline > 10%, *n/N* (%)	7/88 (8.0)	13/99 (13.1)	NS at $p < 0.05$
Pijnenburg 2005[106]	Change in mean symptom severity scores between visit 1 and visit 5	0.1	0.6	Mean daily scores change $p = 0.40$
Szefler 2008[104]	Maximum days with symptoms	1.93 (2.60)	1.89 (2.69)	Mean difference 0.04 (95% CI –0.22 to 0.29), $p = 0.78$
	Days of wheeze	1.71 (2.52)	1.69 (2.64)	Mean difference 0.03 (95% CI –0.21 to 0.26), $p = 0.83$
	Days of interference with activities	0.87 (1.79)	0.95 (1.98)	Mean difference –0.08 (95% CI –0.26 to 0.10), $p = 0.38$
	Nights of sleep disruption	0.52 (1.30)	0.50 (1.25)	Mean difference 0.03 (95% CI –0.11 to 0.16), $p = 0.71$
	Days of school missed	0.19 (0.79)	0.23 (0.84)	Mean difference –0.04 (95% CI –0.12 to 0.05), $p = 0.38$
	ACT score in the last month	21.89 (2.83)	21.83 (2.88)	Mean difference 0.06 (95% CI –0.28 to 0.40), $p = 0.72$

TABLE 42 Child management review: other outcomes (*continued*)

Author, year	Outcome	Intervention, mean (SD)	Control, mean (SD)	Comparison
Verini 2010[105]	Symptom score (mean for ordinal data: intermittent asthma = 1; mild/moderate persistent asthma = 2; severe persistent asthma = 3)	T1: 1.09 (0.81); T2: 0.56 (0.75); T3: 0.75 (0.95)	T1: 1.09 (0.77); T2: 0.93 (0.61); T3: 0.92 (0.82)	NR
HRQoL				
Petsky 2010[107]	HRQoL (metric not specified), mean (95% CI)	Baseline: 84.38 (77.27 to 91.48); 12 months: 86 (74.84 to 97.1)	Baseline: 86 (81.49 to 90.51); 12 months: 83.75 (78.6 to 88.9)	NR
Other medication use				
Fritsch 2006[103]	Median (IQR) beta-agonist puffs/day	1 (0 to 7)	0 (0 to 2)	NR
	Montelukast (LTRA) (unclear if median or mean)	1.26 mg/day	0 mg/day	$p < 0.01$
Peirsman 2013[109]	Median (IQR) percentage of symptom-free days	83.7 (27.1 to 91.9)	79.6 (51.7 to 94)	Mann–Whitney test: $p = 0.58$
	Children who missed school, *n*/*N*, (%)	10/46 (21.7)	12/46 (26.1)	Chi-square test: $p = 0.63$
	Children whose caregivers had to take time off, *n*/*N*, (%)	6/45 (13.3)	8/46 (17.4)	Chi-square test: $p = 0.59$
	Nights of sleep disruption	0.52 (1.30)	0.50 (1.25)	0.03 (95% CI −0.11 to 0.16), $p = 0.71$
	Days of school missed	0.19 (0.79)	0.23 (0.84)	−0.04 (95% CI −0.12 to 0.05), $p = 0.38$
	ACT score in the last month	21.89 (2.83)	21.83 (2.88)	0.06 (95% CI −0.28 to 0.40), $p = 0.72$
Petsky 2010[107]	–	–	–	–
Pijnenburg 2005[106]	Beta-agonist use	NR	NR	$p = 0.28$
Pike 2013[108]	Change in FeNO (ppb), mean (95% CI)	+3.1 (–5.5 to 11.6)	+ 3.3 (–8.5 to 15.1)	NS at $p < 0.05$
Szefler 2008[104]	Salmeterol (mean difference from baseline), µg/day	–6.5	–12	NR
Verini 2010[105]	Mean of ordinal data, in which antihistamines, ketotifen and chromones = 1; specific immunotherapy, LABAs and LTRAs = 2; ICS = 3	T1: 1.5 (0.7); T2: 1.43 (0.7); T3: 1.53 (0.6)	T1: 1.03 (0.9); T2: 1.62 (0.6); T3: 1.4 (0.7)	NR
	Number of patients using LTRAs	T1: 8; T2: 8; T3: 11	T1: 3; T2: 8; T3: 7	NR
	Number of patients using no anti-inflammatory drugs	T1: 4; T2: 5; T3: 2	T1: 14; T2: 2; T3: 6	NR

CI, confidence interval; NS, not statistically significant; T, time.

(95% CI 78.6 to 88.9). If quality of life was measured with the European Quality of Life-5 Dimensions (EQ-5D), which seems likely, then higher values would indicate better quality of life and thus FeNO would be favoured. The end-point difference was statistically significant ($p = 0.042$), although it was unclear whether this comparison was for the change or for absolute end values.

Asthma control and other medication use

Table 42 provides details of outcomes relating to asthma control and medication use. Four studies provided some data on asthma control, none of which demonstrated any significant effects favouring either the intervention or the control, although in the study by Verini *et al.*[105] significance was not reported. Furthermore, there was lack of uniformity in how asthma control was measured. Fritsch *et al.*[103] recorded the absolute number of participants per group whose symptom severity score increased to 2 (i.e. severe symptoms). Ten participants in the intervention group (11.4%), and 11 in the control group (11.1%) fulfilled this criterion (difference not significant). These researchers also reported the absolute number of participants per group who experienced a decline in FEV_1 of > 10%: seven in the intervention group (8%) and 13 in the control group (13.1%; $p =$ not significant). Szefler *et al.*[104] presented between-group differences for a number of symptomatic indicators of control, with higher numbers favouring the intervention. The measure comprised days of wheeze (risk ratio 0.04, 95% CI −0.22 to 0.29; $p = 0.78$), days of interference with activities (risk ratio 0.03, 95% CI −0.21 to 0.26; $p = 0.83$), nights of sleep disruption (risk ratio −0.08, 95% CI −0.26 to 0.10; $p = 0.38$), days of school missed (risk ratio 0.03, 95% CI −0.11 to 0.16; $p = 0.71$) and ACT score in the last month (risk ratio −0.04, 955 CI −0.12 to 0.05; $p = 0.38$). Pijnenburg *et al.*[106] calculated symptom scores based on diary card data for dyspnoea, wheezing and cough. Day and night were scored separately and each symptom was scored between 0 and 3, giving a maximum possible total score of 18. The change in mean daily scores between baseline and visit 5 was 0.1 in the intervention group and 0.6 in the control group (between-group difference $p = 0.4$). Finally, Verini *et al.*[105] measured symptom control using the GINA scale,[136] which classified participants as having remission asthma (GINA score 0), intermittent asthma (GINA score 1) or persistent asthma (GINA score 2 or 3). The means (SDs) for these categorical data were presented for both groups at all three time points: at visit 1 the values were 1.09 (0.81) in the intervention group compared with 1.09 (0.77) in the control group; at visit 2 they were 0.56 (0.75) and 0.93 (0.61) respectively; and at visit 3 they were 0.75 (0.96) and 0.92 (0.82) respectively. No intergroup comparisons were conducted, although means in the intervention arm are numerically lower than those in the control arm.

With respect to additional medication use, three studies provided data using different metrics and mostly without formal comparison statistics. Szefler *et al.*[104] reported the mean difference from baseline in salmeterol usage; This was –6.5 µg/day in the intervention group and –12 µg/day in the control group (*p*-value not reported). Verini *et al.*[105] created a categorical measure of medication use in which antihistamines (e.g. ketotifen) and chromones = 1; specific immunotherapy, LABAs and LTRAs = 2; and ICSs = 3. The means (SDs) of these data were presented for both groups. In the intervention group the values were 1.5 (0.7) (visit 1), 1.43 (0.7) (visit 2) and 1.53 (0.6) (visit 3). For comparison, the values for the control group at the same time points were 1.03 (0.9), 1.62 (0.6) and 1.4 (0.7) respectively. Verini *et al.*[105] also provided absolute numbers using LTRA. For the intervention group these were 8, 8 and 11 at visits 1, 2 and 3 respectively and for the control group these were three, eight and seven respectively. Fritsch *et al.*[103] reported the median (IQR) number of beta-agonist puffs/day. In the intervention group this was one (0 to 7) whereas in the control group the number was zero (0 to 2). Overall, two studies reported numerically higher additional medication use in the intervention arm[104,105]

Studies found during the search update[108,109] agreed with previous observations as neither reported a statistically significant difference in metrics of asthma control.

Adverse events, mortality, compliance and test failure rates

Data on adverse events, mortality and compliance were reported only in Szefler *et al.*[104] No statistically significant differences between the groups were reported for any adverse events or for mortality. For the intervention and control groups, respectively, adverse events were reported for eyes, ears, nose and throat (8.3% vs. 8.1%; $p = 0.87$), gastrointestinal disorders (13.4% vs. 14.1%; $p = 0.78$), haematology disorders (27.2% vs. 28.9%; $p = 0.44$), infections

(55.8% vs. 52.2%; $p = 0.46$), musculoskeletal symptoms (15.9% vs. 18.5%; $p = 0.44$), nervous system disorders (34.4% vs. 33.7%; $p = 0.20$), respiratory signs and symptoms (33.7% vs. 34.1; $p = 0.92$) and skin symptoms (15.6% vs. 17.8%; $p = 0.18$). Medication compliance was shown to be 86% in the intervention group and 92% in the control group. No mortality was observed in either group.

Subgroups relevant to the review as defined in the scoping workshop

Pregnant women

Only one RCT of FeNO-guided management of asthmatic pregnant women was found.[102]

Study details The study by Powell *et al.*[102] was a double-blind, multicentre RCT conducted in Australia and funded from a number of industry and non-industry sources (including lecture fees from Aerocrine). In total, 203 participants were analysed out of 242 recruited. In the run-in period, patients not already using ICSs were started on budesonide at a dose of 200 µg twice a day. After randomisation, patients underwent monthly reviews and titration of the ICS dose. Patients were telephoned 2 weeks after each visit to assess symptoms and encourage adherence (*Table 43*). The study included no current smokers but did include 156/206 (75.7%) atopic patients (*Table 44*).

Quality assessment The study by Powell *et al.*[102] appeared to be at low risk of bias overall (see *Figure 13*). Randomisation and allocation concealment were performed well, meaning that the study was at low risk of selection bias. The study was double blind and made efforts to blind outcome assessors and is therefore at low risk of performance and detection bias. The study also seemed to be at low risk of attrition bias, with similar small numbers dropping out from each arm for reasons not related to treatment. Reporting bias did not seem to affect the study as far as could be ascertained from the journal publication. Commercial sponsorship puts the study at some risk of bias.

Intervention An ECO MEDICS device was used to measure FeNO. Patients were categorised according to their FeNO values, with cut-offs being < 16 ppb, 16–29 ppb and > 29 ppb. Step-up and step-down criteria are described in *Table 45*; decisions were based on a combination of FeNO and asthma control levels, with asthma control levels directing the dose of LABA (formoterol) and FeNO levels controlling the dose of ICS (budesonide).

Comparator Patients were managed according to asthma control as assessed by the ACQ (*Table 46*). Medication doses were somewhat different from those in the intervention arm, with different doses of budesonide and formoterol indicated.

TABLE 43 Pregnant women: study design and timelines

Author, year	Study details	Timeline of study
Powell 2011[102]	Setting: antenatal outpatients, Australia Funding: mixed; lecture fees from Aerocrine Study design: double-blind, parallel-group, multicentre RCT	Visit 1: FeNO, spirometry, ACQ, atopy (specific IgE to aeroallergen); optimised self-management skills including inhaler technique, knowledge, action plan and adherence; 2-week run-in period after visit 1 – continued use of ICS budesonide turbuhaler *or* uncontrolled patients not using ICSs started on budesonide 200 µg b.i.d. Visit 2: randomisation; asthma symptoms, FeNO, spirometry, ACQ, quality of life questionnaires. Then, monthly review with research assistant: recorded clinical symptoms, ACQ, present treatment, FeNO, FEV_1. FeNO, ACQ and treatment data sent to algorithm keeper who applied algorithm and sent treatment recommendation to research assistant who informed patient. If patient uncontrolled and at maximum dose, seen by investigator. Telephone assessments 2 weeks after visit to assess symptoms and encourage adherence

b.i.d. twice per day; IgE, immunoglobulin E.

TABLE 44 Pregnant women: study and patient characteristics

Author, year	Age (years), sex	No. analysed/ no. recruited	Inclusion/exclusion criteria	Spirometry, mean (95% CI)	Severity, median (IQR)	FeNO (ppb), median (IQR)	Smokers; atopic, *n*/*N* (%)	Medication use
Powell 2011[102]	Pregnant adults aged > 18 years Mean (SD) age 28 (5.4) Male 0/220 (0%)	203/242 WBR: 22; I: 100/111; C: 103/109	Doctor's diagnosis confirmed by respiratory physician's diagnosis of asthma; non-smoking pregnant women between 12 and 20 weeks' gestation with doctor's diagnosis of asthma and who were using inhaled therapy in the last year	FEV_1%: I: 95.1 (92.8 to 97. 4); C: 96.1 (93.5 to 98.7) FEV_1/FVC: I: 79.7 (75.4 to 78.0); C: 80.63 (79.3 to 82.0)	AQLQ-M: I: 0.8 (0.4 to 1.5); C: 1.0 (0.5 to 1.6) ACQ, mean (read off graph): I: 0.98; C: 1.01	I: 13.9 (6.6 to 32.0); C: 13.1 (7.5)	Current smokers: 0/203 (0); ex-smokers: 80/203 (39.4) Atopic: 156/206 (75.7)	Days using beta-agonist in past week, median (IQR): I: 1.0 (0 to 5); C: 2.0 (0 to 6) ICS users, *n*/*N* (%): I: 46/111 (41.4); C: 47/109 (43.1) BDP-equivalent ICS dose (µg/day), median (IQR): I: 800 (400 to 800); C: 800 (400 to 1600)

AQLQ-M, Asthma Quality of Life Questionnaire – Marks; BDP, beclomethasone dipropionate; C, control group; CI, confidence interval; I, intervention group.

TABLE 45 Pregnant women: details of intervention group management strategies

Author, year	Decisions based on flow rate, device and cut-off points	Step-up/step-down protocol	Doses
Powell 2011[102]	Based on FeNO and ACQ Flow rate; device: according to ATS guidelines 2005;[35] ECOMEDICS (Duernten, Switzerland) Cut-offs: < 16 ppb, 16–29 ppb, > 29 ppb	FeNO concentration used to adjust dose of ICS and ACQ used to adjust dose of LABA: • FeNO > 29 ppb – ICS increase one step, LABA no change • FeNO 16–29 ppb and ACQ ≤ 1.5 – ICS no change, LABA no change • FeNO 16–29 ppb and ACQ > 1.5 – ICS no change, LABA increase one step • FeNO < 16 ppb and ACQ ≤ 1.5 – ICS decrease one step, LABA no change • FeNO < 16 ppb and ACQ > 1.5 – ICS decrease one step, LABA increase one step If a patient had undergone two ICS dose increments and FeNO remained > 29 ppb, ICS was not increased further. If still symptomatic (ACQ > 1.5) formoterol 6 µg b.i.d. was added. For patients taking formoterol, the ICS dose could never be zero but would be reduced to 100 µg b.i.d. Patients who remained uncontrolled at maximum doses referred to respiratory physician	ICS – steps 1–5: budesonide 0, 100, 200, 400, 800 µg b.i.d. respectively LABA – step 1: salbutamol as required; steps 2–5: formoterol 6, 12, 24, 24 µg b.i.d. respectively

b.i.d., twice per day.

TABLE 46 Pregnant women: detail of the control group management strategies

Author, year	Decisions based on	Step-up/step-down protocol	Doses
Powell 2011[102]	ACQ guided	Well-controlled asthma (ACQ < 0.75) – reduce treatment one step; partially controlled asthma (ACQ 0.75–1.50) – no treatment change; uncontrolled asthma (ACQ > 1.5) – increase one step. Those at maximum dose referred to respiratory physician	Step 1: salbutamol as required; step 2: budesonide 200 µg b.i.d. + salbutamol as required; step 3: budesonide 400 µg b.i.d. + salbutamol as required; step 4: budesonide 400 µg + formoterol 12 µg b.i.d.; step 5: budesonide 800 µg b.i.d. + formoterol 24 µg b.i.d.

b.i.d., twice per day.

Outcomes

Table 47 provides details of all outcomes of relevance to the review.

Exacerbations

The composite outcome of all exacerbations (in this case defined as an unscheduled visit to a doctor, presentation to the emergency room or admission to hospital or when an OCS was used) was reduced in the intervention arm, with a rate ratio of 0.496 (95% CI 0.325 to 0.755) ($p = 0.001$). It should be noted that, unlike the other studies in adults, the composite outcome in this study did not include moderate or minor exacerbations, but more closely matched the definitions of severe exacerbations given in other adult studies. Data for each element of the composite outcome were reported individually and from this it can be seen that this difference is mostly driven by the rate of OCS use and the rate of visits to the doctor. Mean OCS use was 0.08 (95% CI 0.03 to 0.133) in the intervention arm and 0.19 (95% CI 0.08 to 0.31) in the control arm and, unlike other studies in adults, this did reach statistical significance, with a *p*-value of 0.042. Similarly, the rate of visits to the doctor was 0.26 (95% CI 0.16 to 0.36) in the intervention arm and 0.56 (95% CI 0.40 to 0.72) in the control arm, with a *p*-value of 0.002. The other

TABLE 47 Pregnant women: all outcomes

Time of outcome	Definition of outcomes	Intervention	Control	Between-group comparison
Exacerbations				
Monthly until birth (max. approx. 30 weeks)	Exacerbations: an unscheduled visit to a doctor, presentation to the ER or admission to hospital or when OCSs used. Events separated by ≥ 7 days were counted as a second event	0.288 per pregnancy [mean (SD) study time 17.8 (5.5) weeks]	0.615 per pregnancy [mean (SD) study time 18.8 (3.8) weeks]	Incidence rate ratio 0.496 (95% CI 0.325 to 0.755), $p = 0.001$
	OCS use, mean (95% CI)	0.08 (0.03 to 0.133)	0.19 (0.08 to 0.31)	*p*-value OCS use: 0.042
	Hospitalisations, mean (95% CI)	0 (0 to 0)	0.03 (–0.004 to 0.06)	$p = 1.0$
	ER/labour ward visits, mean (95% CI)	0.04 (0.001 to 0.07)	0.02 (–0.01 to 0.04)	$p = 0.399$
	Unplanned or unscheduled doctors' visits, mean (95% CI)	0.26 (0.16 to 0.36)	0.56 (0.40 to 0.72)	$p = 0.002$
ICS use				
	Difference in means (from baseline to last visit) (read off graph) (µg/day)	–210	50	$p = 0.043$
	BDP-equivalent ICS dose (µg/day), median (IQR)	200 (0 to 400)	0 (0 to 800)	$p = 0.079$
	ICS users, *n/N* (%)	76/111 (68.5)	46/109 (42.2)	$p < 0.0001$
Other outcomes				
	HRQoL, median (IQR)			
	SF-12 physical component summary (low 0, high 100)	47.7 (40.8 to 52.0)	46.9 (38.2 to 51.8)	$p = 0.89$
	SF-12 mental component summary (low 0, high 100)	56.9 (50.2 to 59.3)	54.2 (46.1 to 57.6)	$p = 0.037$
	AQLQ-M: total score (good 0, poor 10)	0.75 (0.38 to 1.25)	0.81 (0.38 to 1.63)	$p = 0.54$
	Asthma control (ACQ), mean (SD)	0.56 (0.67)	0.72 (0.80)	$p = 0.046$
	Beta2-agonist use in past week, median (IQR)	0 (0 to 3)	1 (0 to 5)	$p = 0.024$
	LABA users, *n/N* (%)	45/111 (40.5)	19/109 (17.4)	$p < 0.0001$
	Adverse events, mortality, compliance and test failure rates	NR	NR	NR

AQLQ-M, Asthma Quality of Life Questionnaire – Marks; BDP, beclomethasone dipropionate; CI, confidence interval; ER, emergency room; NR, not reported; SF-12, Short Form questionnaire-12 items.

components of the exacerbation outcome (hospitalisations and emergency room/labour ward visits) did not differ between groups.

Inhaled corticosteroid use The change in mean values from baseline to the final visit for ICS use was a decrease of 210 µg/day in the intervention arm and an increase of 50 µg/day in the control arm. This difference was statistically significant at $p = 0.043$. Interestingly, more women in the intervention arm were taking ICSs (68.5% vs. 42.2%) and the median (IQR) ICS dose as beclomethasone dipropionate equivalent (µg/day) was higher in the intervention arm [200 (IQR 0 to 400)] than in the control arm [0 µg/day (IQR 0 to 800)], but not statistically significantly so ($p = 0.079$).

Health-related quality of life The median scores and *p*-value indicate a small but statistically significant difference in the Short Form questionnaire-12 items (SF-12) mental component summary score in favour of the intervention arm, with a median (IQR) score of 56.9 (50.2 to 59.3) compared with 54.2 (46.1 to 57.6) in the control arm ($p = 0.037$); however, there were no statistically significant differences in the SF-12 physical component summary score or the Asthma Quality of Life Questionnaire – Marks (AQLQ-M) total score.

Asthma control and other medication use The ACQ score at the end of the study indicated good control in both groups, with the mean (SD) indicating statistically significantly better control in the intervention group [0.56 (0.67)] than in the control group [0.72 (0.80); $p = 0.046$]. Beta2-agonist use in the past week was higher in the intervention arm ($p = 0.024$) and there were statistically significantly more LABA users in the intervention arm ($p < 0.0001$).

Adverse events, mortality, compliance and test failure rates None of these outcomes was reported in the study.

An additional study by Mattes *et al.*,[124] a follow-up to the Powell *et al.*[102] study, was identified in the update search. This study was identified as a conference abstract although subsequent to the update search the full text was published. The study took the form of a prospective longitudinal birth cohort with the aim of determining the effect of better maternal asthma management on the number of episodes of wheezy illness in the first year of life. The abstract reports that children born to mothers who had been in the FeNO group were significantly less likely to suffer from recurrent bronchiolitis in the first year of life (OR 0.08, 95% CI 0.01 to 0.62; $p = 0.016$) than children born to mothers in the clinical treatment group. These results indicate that there may be wider benefits to asthma management with FeNO than have been captured in our economic model.

Conclusion In pregnant women, the outcomes of exacerbation rate as well as OCS use on its own and doctors' visits were all statistically significantly better in the intervention arm. ICS use and beta2-agonist use were also lower, although LABAs were used by more patients in the intervention arm than in the control arm. Asthma control was marginally better in the intervention arm and the mental component summary score of the SF-12 was also better, although the physical component summary score of the SF-12 and the total score for the AQLQ-M were not statistically significantly different between groups. In summary, the use of FeNO to guide asthma management in pregnant women appears to be as effective as if not more effective than the use of FeNO in other adults and appears to reduce exacerbations and ICS use. This may be because of increased efficacy in pregnant women or because of differences in step-up/step-down protocols. Notably, this protocol allowed for the step down of ICS use on the basis of FeNO levels alone, regardless of whether symptoms were still present or not. A follow-up study suggests that there may be more benefits for the children born to women who had asthma management with FeNO than have been captured in the economic model.

FeNO to assess compliance to treatment

One further study was identified for the management review.[141] This open-label RCT recruited patients aged 6–16 years with mild to moderate persistent asthma ($n = 54$) and excluded patients who had received

oral or inhaled steroid treatment during the last 2 months, who had acute upper airway infection, who had a history of bad compliance (< 65% of prescribed medication) or who had any other serious illness. The trial consisted of a 4-week run-in period, a 4-week washout phase and a final randomised treatment phase in which only one group was treated with inhaled budesonide and FeNO was used to attempt to distinguish these groups, that is, the study explored FeNO as a tool to assess patient compliance. The study showed that FeNO was able to distinguish those who had been treated with ICSs more successfully than conventional lung function parameters. However, as the study did not examine the efficacy of FeNO for guiding management per se, the data could not be compared with that from other studies in the management review. It should also be noted that this potential benefit of using FeNO in the management of asthma will have been captured in the other RCT trials if the management protocol included investigations of compliance before stepping treatment up or down.

The elderly

In the absence of RCTs, other study designs were included to gather evidence for the use of FeNO in the management of asthma in the elderly. Five observational studies (three cohort,[116–118] one nested case–control[119] and one cross-sectional[120] study), published between 2010 and 2012, were identified that evaluated the measurement of FeNO in elderly asthmatics. A further study[125] was identified during the search update and a journal article of the abstract by Columbo *et al.*[117] was also identified.[126] A summary of the design, patient characteristics and outcomes of the included studies is provided in *Table 48*. The studies by Columbo *et al.*,[117] Ross and Baptist[120] and Smith *et al.*[119] were based in the USA, that by Inoue *et al.*[116] was based in Japan, that by Roh[118] was based in Korea and that by Bozek *et al.*[125] was based in Poland. Three studies reported where the patients were recruited from: Inoue *et al.*[116] recruited patients from an outpatient clinic whereas Smith *et al.*[119] and Bozek *et al.*[125] recruited from primary care. All patients in the intervention group had a diagnosis of asthma; however, how asthma was defined was not reported in any of the studies apart from that by Smith *et al.*,[119] which used the GINA guidelines.[129] The mean disease duration of asthma was reported in three studies[116,117,120] and ranged from 14.4 years[116] to 35 years.[117] The mean age in the intervention group ranged from 68[119] to 73[120] years, apart from in the study by Bozek *et al.*,[125] which recruited only patients aged > 80 years and which had a mean age of 84.1 (± 3.9) years. All studies included both sexes, with a slightly higher proportion of female participants, apart from the study by Roh,[118] which had a higher proportion of male participants. Three studies had a comparative control group.[116,119,125] Bozek *et al.*[125] and Inoue *et al.*[116] compared FeNO values between elderly asthmatics and non-elderly asthmatics but with different age cut-offs and Smith *et al.*[119] compared asthmatics with non-asthmatics. The device for measuring FeNO was reported in four studies,[117,119,120,125,126] with all four using NIOX MINO.

The results of the included studies are summarised in *Table 48*. Four of the six studies generally indicated a trend showing that FeNO measurements may not be clinically valuable in elderly asthmatics. Smith *et al.*[119] found no statistically significant difference in FeNO levels in elderly asthmatic subjects (20.8 ± 17.3 ppb) compared with elderly non-asthmatics (18.3 ± 9.8 ppb) ($p = 0.5$). Furthermore, no statistically significant difference was observed in FeNO levels between ICS-treated (21.4 ± 20.4 ppb) and -untreated asthmatics (19.8 ± 14.3 ppb) ($p = 0.8$). Columbo *et al.*[117] followed up stable elderly asthmatic patients for 1 year and evaluated FeNO measurements at baseline and every 3 months for 1 year. No significant correlation was found between FeNO levels and spirometric values, ICS usage or asthma control. Two further studies[118,120] showed no correlation between FeNO levels and asthma control. Furthermore, one study,[116] which evaluated the pathophysiological characteristics of asthma in elderly patients, found that there was no difference in FeNO levels, the percentage of induced sputum eosinophils and neutrophils or methacholine airway sensitivity or reactivity between elderly asthmatics and non-elderly asthmatics.

Bozek *et al.*[125] observed differences in FeNO levels between elderly and non-elderly asthmatics and concluded that FeNO can be useful in the assessment of bronchial asthma in the elderly. However, this study did not report data relating to correlations between measures of asthma presence/absence/severity/control and FeNO levels and concluded only that FeNO may be higher in older asthmatic patients than in non-elderly asthmatics.

TABLE 48 Study design, patient characteristics and outcomes of studies in elderly asthmatics

Author, year	Study details	Population	FeNO (ppb)	Summary of outcomes
Bozek 2013[125] (new paper from updated search)	To assess the differences in the clinical features of atopic bronchial asthma between patients aged > 80 years old and youth Setting: primary care Country: Poland Funding: NR Design: observational study	Bronchial asthmatics aged at least 80 years ($n = 207$) EAs ≥ 80 years: $n = 105$; NEAs ≤ 32 years: $n = 102$ Mean age (years): EAs: 84.1 ± 3.9; NEAs: 22.1 ± 5.2 Sex male, *n/N* (%): EAs: 42/105 (40.0); NEAs: 67/102 (65.7)	EA: 41.2 ± 15.04; EA smokers: 46.09 ± 25.33; EA non-smokers: 38.03 ± 13.2; NEA: 32.74 ± 12.62; NEA smokers: 39.09 ± 15.66; NEA non-smokers: 27.8 ± 11.09 Device: NIOX MINO Flow rate: 50 ml/second Measured in triplicate	There was a statistical difference in FeNO levels ($p < 0.05$) between EAs and NEAs. The statistical difference between the two groups also extended to smokers and non-smokers. Authors' conclusion: FeNO can be useful in the assessment of bronchial asthma in the elderly. The higher FeNO level observed in the elderly may be evidence of more advanced inflammation in the airways
Columbo 2012[117] (abstract); Columbo 2013[126] (journal article)	Role of FeNO measurements in elderly asthmatics. Follow-up for 1 year with evaluation at baseline and every 3 months Setting: NR Country: USA Funding: NR Design: observational study	Stable elderly asthmatics ($n = 30$) (all asthmatics) Mean age (years): 71.6 ± 4.9 Sex male, *n/N* (%): 12/30 (40.0) Atopic, *n/N* (%): 21/30 (70.0) Rhinitis, *n/N* (%): 27/30 (90.0) GORD, *n/N* (%): 12/30 (40.0) Medication usage, *n/N* (%): ICS: 26/30 (86.7) (384 ± 378 µg/day); LABA: 20/30 (66.7); LTRAs: 19/30 (63.3); nasal steroids: 15/30 (50.0)	Baseline: 18.2 ± 14.3 Device: NR Flow rate: NR Measured in triplicate	FeNO was not elevated at baseline and did not significantly change throughout the follow-up period. No significant correlation was found between FeNO and FEV_1/FVC ($p > 0.55$; 0.25, 0.10 and 0.26, respectively, at each time point), other spirometric values, ICS or ACT at any time point. Authors' conclusion: in stable EAs, FeNO was not elevated and did not correlate with subjects' demographics, comorbidities, treatment symptoms or spirometric values. Routine measurements of FeNO may not be clinically valuable in EAs

continued

TABLE 48 Study design, patient characteristics and outcomes of studies in elderly asthmatics (*continued*)

Author, year	Study details	Population	FeNO (ppb)	Summary of outcomes
Inoue 2010[116] (abstract)	Pathophysiological characteristics of asthma in the elderly Setting: outpatient clinic Country: Japan Funding: NR Design: observational retrospective study	Clinically stable asthmatics, never or ex-smokers (< 5 pack-years) and receiving ICS therapy for at least 3 months ($n = 136$) EAs ≥ 65 years: $n = 49$; NEAs ≤ 60 years: $n = 51$ Mean age: NR Sex male, *n/N* (%): EAs: 12/49 (24.5); NEAs: 21/51 (41.2)	NR	There was no difference in FeNO levels, percentage of induced sputum eosinophils and neutrophils or methacholine airway sensitivity or reactivity between EAs and NEAs
Roh 2012[118] (abstract) (although described in text, data missing in table)	Patients performed spirometry and FeNO measurements and answered ACT questionnaire Setting: NR Country: Korea Funding: NR Design: observational study	Patients with diagnosis of asthma aged > 65 years ($n = 67$) (all asthmatics) ACT ≤ 15 (very poorly controlled): $n = 25$ (37.3%); ACT 16–19 (not well controlled): $n = 30$ (44.8%); ACT ≥ 20 (well controlled): $n = 12$ (17.9%) Mean age (years): 72.3 (65–89[a]) Sex male, *n/N* (%): 57/67 (85.1) Medication usage: NR	ACT ≤ 15: • FeNO: 41 ± 35 • FEV_1% predicted: 81.5 ± 21.5 ACT 16–19: • FeNO: 40 ± 36 • FEV_1% predicted: 89 ± 16.8 ACT ≥ 20: • FeNO: 44 ± 35 • FEV_1% predicted: 93.3 ± 16.8	No correlation was found between ACT/FeNO and FEV_1/FeNO variables ($p = 0.45$ and 0.41 respectively). Author's conclusion: in spite of these data, the clinical assessment of asthma should be based on a combined approach that involves clinical aspects, functional parameters and biomarkers of inflammation, because elderly patients may have reduced symptom perception and multiple comorbidities
Ross 2011[120] (abstract)	Baseline data were collected on objective measures of asthma, including spirometry and FeNO, and were correlated with asthma QoL and asthma control Setting: NR Country: USA Funding: NR Design: cross-sectional study	Subjects ≥ 65 years with a history of physician-diagnosed asthma ($n = 77$) (all asthmatics) Mean age (years): 73.2 Sex male, *n/N* (%): 16/70 (22.9) Medication usage: NR	NR Device: NIOX MINO Flow rate: NR	No correlation between spirometric/FeNO objective data and QoL or asthma control was noted

Author, year	Study details	Population	FeNO (ppb)	Summary of outcomes
Smith 2012[119]	Complete medical history taken and physical examination carried out. SPT of panel of common aeroallergens, spirometry and measurement of FeNO levels. Geriatric QoL and health status assessed through standardised questionnaire Setting: primary care (community-based family practice) Country: USA Funding: Department of Veterans Affairs Design: nested case–control study	Asthmatics: older adults aged ≥ 60 years with symptoms consistent with asthma; control: ≥ 60 years, age matched, without asthma No. analysed/no. recruited: asthmatics: 32/36; control: 39/41; 6/77 were unable to perform FeNO measurements Mean age (whole cohort) (years): 68.7 ± 7.2 years Sex male, *n/N* (%): 18/77 (23.4) Passive smokers, *n/N* (%): 24/77 (31.2); smoking history: 19 ± 19 pack-years Asthma medication usage, *n/N* (%): ICS 6/36 (16.7%); combination inhaler: 12/36 (33.3%); LTMA 8/36 (22.2%); theophylline 4/36 (11.1%); albuterol 18/36 (50%)	Asthmatics: 20.8 ± 17.3; control: 18.3 ± 9.8 ($p = 0.5$) Asthmatics treated with ICS: 21.4 ± 20.4; asthmatics not treated with ICS: 19.8 ± 14.3 ($p = 0.8$) Device: NIOX MINO Flow rate: 50 ml/second	No statistically significant difference was seen in FeNO levels between asthmatics and control subjects ($p = 0.5$). No statistically significant difference was seen between ICS-treated and ICS-untreated asthmatics ($p = 0.8$)

EA, elderly asthmatic; GORD, gastro-oesophageal reflux disease; LTMA, leukotriene-modifying agent; NEA, non-elderly asthmatic; NR, not reported; QoL, quality of life; SPT, skin prick test.
a Range definition not provided.

Overall, these results should be interpreted with caution as data were derived from studies with lower-quality designs that have greater potential to produce biased results. In addition, three of these studies were reported in abstract form only and hence provide limited data. However, the majority of studies appear to indicate that FeNO is not useful in the elderly.

Adult smokers

Four studies[5,121–123] were conducted in adult smokers. A summary of the design and patient characteristics of the four included studies is provided in *Table 49*. Two studies[5,121] were conducted in Belgium, one[123] in Serbia and one[122] in New Zealand. With the exception of the study by Hromis *et al.*,[123] which did not provide details of the funding source, all studies received funding from one or more commercial sponsor. Kostikas *et al.*[122] received an unrestricted research grant from Aerocrine; Michils *et al.*[121] received technical funding from AstraZeneca; and Schleich *et al.*[5] received an unrestricted grant from GlaxoSmithKline, AstraZeneca and Novartis.

Patients were recruited from a variety of settings including secondary care,[5] tertiary care[121] and outpatient clinics.[122] Eligibility criteria varied from study to study but all studies included smokers with confirmed or persistent asthma. The sample sizes of the included studies ranged from 83[123] to 470,[121] with the mean age of participants ranging from 38[121] to 50[122] years. Baseline FeNO levels were inconsistently reported: Schleich *et al.*[5] and Kostikas *et al.*[122] reported median values, Hromis *et al.*[123] reported mean values and Michils *et al.*[121] reported geometric means and ranges. All studies included patients who were being treated with ICSs except one study[5] in which treatment was unclear. In all studies except that by Hromis *et al.*,[123] asthma control was evaluated according to the GINA guidelines[129] and/or the ACT and Juniper's ACQ;[135] in the Hromis *et al.*[123] study it was unclear how asthma control was evaluated. The NIOX MINO device was used by Kostikas *et al.*,[122] Schleich *et al.*[5] used the Niox device, Michils *et al.*[121] used the LR2000 device and it was unclear which device was used by Hromis *et al.*[123] None of the studies used the same protocol or cut-off points for the management of asthma with FeNO.

The results are summarised in *Table 49*. In the study by Schleich *et al.*[5] the median FeNO level (17 ppb) in smokers was significantly lower than that in non-smokers (35 ppb) ($p = 0.003$). In addition, the FeNO threshold for identifying a sputum eosinophil count of $\geq 3\%$ was significantly lower in smokers (28 ppb, sensitivity 76% and specificity 62%) than in non-smokers (46 ppb, sensitivity 58% and specificity 82%) ($p = 0.066$).

Michils *et al.*[121] reported that baseline FeNO levels were reduced in smoking asthmatics (18.1 ppb vs. 33.7 ppb in non-smoking asthmatics). Furthermore, when patients were treated with high to medium doses of ICSs, FeNO no longer had the ability to reflect an improvement in asthma control for smoking patients, whereas for non-smoking patients its ability was only slightly reduced. However, the authors suggested that FeNO can reflect asthma control in smoking patients provided that changes in FeNO values detected by repeated measurements are considered. A decrease in FeNO of $< 20\%$ precludes asthma control improvement in non-smoking (NPV 78%) and smoking (NPV 72%) patients. An increase in FeNO of $< 30\%$ is unlikely to be associated with a deterioration in asthma control in both groups (NPV 86% and 84% for non-smoking and smoking patients respectively).

In the study by Kostikas *et al.*,[122] non-smokers who were either treated or not treated with ICSs reported higher FeNO values in uncontrolled asthma than in partly or well-controlled asthma. In contrast, smokers not treated with ICSs showed significant differences in FeNO values between uncontrolled and well-controlled asthma but no difference from partly controlled asthma. Smokers treated with ICSs showed no statistically significant differences ($p > 0.05$) in FeNO values between the controlled, partly controlled or uncontrolled asthma groups. The diagnostic performance of FeNO for the identification of not well-controlled (partly or uncontrolled) asthma was better in the non-smoker groups (FeNO cut-off > 22 ppb, sensitivity 87%, specificity 81%; FeNO cut-off > 27 ppb, sensitivity 64%, specificity 94%) than in the smoker groups (FeNO cut-off > 19 ppb, sensitivity 56%, specificity 75%; FeNO cut-off > 23 ppb, sensitivity 45%, specificity 87%).

TABLE 49 Study design, patient characteristics and outcomes of studies recruiting adult smokers with asthma

Author	Study details	Population	FeNO measurements (ppb)	Outcomes
Hromis 2012[123] (abstract)	Use of FeNO to assess asthma control in smoking patients; 4 weeks from the start of the study, a LABA (salmeterol, 30 non-smokers and 17 smokers) or an antileukotriene (montelukast 10 mg, 17 non-smokers and 14 smokers) was added. Changes in FeNO, FEV_1 and ACT at baseline and after 4 weeks of treatment were measured Setting: NR Country: Serbia Funding: NR Design: randomised, open-label study	Mild to moderate asthmatics with poor control ($n = 83$) Smokers: $n = 31$; non-smokers: $n = 52$ Age: NR Sex: NR Medication usage: low dose of ICS (400 µg beclomethasone dipropionate daily or equivalent)	Smokers: baseline: 57; after 4 weeks' treatment: 17 LABA added to ICS (reduction in FeNO): smokers: 22%, non-smokers: 32%; treated with antileukotriene (reduction in FeNO): smokers: 12%, non-smokers: 22% Device: NR Flow rate: NR	The sequential changes in FeNO could be a useful marker of asthma control, regardless of smoking status. FeNO level also depends on the applied treatment

continued

TABLE 49 Study design, patient characteristics and outcomes of studies recruiting adult smokers with asthma (*continued*)

Author	Study details	Population	FeNO measurements (ppb)	Outcomes
Kostikas 2011[122]	Patients sequentially undertook FeNO measurements, EBC collection and spirometry with dry spirometer according to ATS 2005 guidelines.[35] Subjects did not smoke for 2 hours before testing Setting: outpatient clinic Country: New Zealand Funding: Aerocrine Design: cohort study	Asthmatic patients ($n = 274$) Group 1: ICS-untreated non-smokers: $n = 48$; group 2: ICS-untreated smokers: $n = 32$; group 3: ICS-treated non-smokers: $n = 144$; group 4: ICS-treated smokers: $n = 50$ Mean (SD) age (years): 50 (17) Sex male, *n/N* (%): 109/274 (40) Medication usage, *n/N* (%): ICS 194/274 (71)	Median (IQR) Group 1: 30 (18–111) – well controlled 16 (14–21); partly controlled 40 (27–105),[a] uncontrolled 116 (63–145)[a,b] Group 2: 19 (14–22) – well controlled 16 (12–19); partly controlled 21 (15–38);[a] uncontrolled 22 (21–108)[a] Group 3: 23 (16–44) – well controlled 16 (12–20); partly controlled 28 (20–44);[a] uncontrolled 61 (35–78)[a,b] Group 4: 19 (14–25) – well controlled 17 (14–22); partly controlled 19 (13–25); uncontrolled 23 (17–74) Device: NIOX MINO Flow rate: 50 ml/second	There was a statistically significant difference in FeNO values between controlled, partly controlled and uncontrolled asthma ($p < 0.05$) in non-smokers (groups 1 and 3). In group 4 (smokers treated with ICSs) there was no statistically significant difference in FeNO values between the three asthma control groups ($p > 0.05$). In group 2 (smokers untreated with ICSs) there was a significant difference in FeNO values between uncontrolled and well-controlled asthma but no difference from partly controlled asthma. The diagnostic performance of FeNO for the identification of not well-controlled (partly or uncontrolled) asthma was better in the non-smoker groups (group 1 FeNO cut-off > 22 ppb, sensitivity 87%, specificity 81%; group 3 FeNO cut-off > 27 ppb, sensitivity 64%, specificity 94%) than in the smoker groups (group 2 FeNO cut-off > 19 ppb, sensitivity 56%, specificity 75%; group 4 FeNO cut-off > 23 ppb, sensitivity 45%, specificity 87%)
Michils 2009[121]	Evaluation of FeNO to predict asthma control in smoking patients. At each visit asthma treatment was adjusted according to GINA guidelines,[112] regardless of ACQ score or FeNO values Setting: tertiary asthma clinic Country: Belgium, Funding: AstraZeneca Design: Retrospective, post hoc analysis study	Adults with persistent asthma ($n = 470$) Current smokers: $n = 59$; non-smokers: $n = 411$ Mean (SD) age (years): smokers: 38 (11); non-smokers: 41 (16) Sex male, *n/N* (%): smokers: 34/59 (58); non-smokers: 195/411 (47) Medication usage: ICS dose (µg equivalents beclomethasone dipropionate per day), median (range): smokers: 500 (0–2000); non-smokers 250 (0–2000)	GM (range): smokers: 18.1 (6.9 to 47.5); non-smokers: 33.7 (14.3 to 79.2) Device: LR2000 chemiluminescence analyser Flow rate: 50 ml/second	Levels of FeNO were lower in smoking asthmatics. In smoking patients FeNO is unable to cross-sectionally discriminate for or against controlled vs. uncontrolled asthma ($p = 0.39$). FeNO cut-off was 50 ppb in non-smokers compared with 25 ppb in smokers. A decrease in FeNO of < 20% precludes asthma control improvement in non-smoking (NPV 78%) and smoking (NPV 72%) patients. An increase in FeNO of < 30% is unlikely to be associated with deterioration in asthma control in both groups. Authors' conclusion: even in smokers, sequential changes in FeNO have a relationship with asthma control. This study indicates that cigarette smoking does not obviate the clinical value of measuring FeNO in asthma among smokers

Author	Study details	Population	FeNO measurements (ppb)	Outcomes
Schleich 2010[5]	Use of FeNO to predict sputum eosinophil count of ≥ 3% Setting: secondary care Country: Belgium Funding: supported by the Interuniversity Project, GlaxoSmithKline, AstraZeneca and Novartis Design: retrospective, post hoc analysis	Asthmatic patients ($n = 295$) Smokers: $n = 58$; non-smokers: $n = 237$ Median (IQR) age: 47.3 (14 to 83) Sex male, *n/N* (%): 131/295 (44.4%) Medication usage: NR	Median (IQR): smokers: 17 (12 to 37); non-smokers: 35 ($p = 0.003$) Device: Niox (chemiluminescence) Flow rate: 50 ml/second	FeNO levels in smokers were significantly lower than in non-smokers ($p = 0.003$) (the median FeNO level was two times higher in non-smokers than in current smokers). The FeNO level that identified a sputum eosinophil count of ≥ 3% was lower in smokers than in non-smokers (28 ppb vs. 46 ppb) ($p = 0.066$), with a sensitivity of 76% and specificity of 62% in smokers and a sensitivity of 58% and specificity of 82% in non-smokers. When combining all variables in the logistic model, FeNO and smoking were independent predictors of sputum eosinophilia. The optimum cut-off for FeNO sputum eosinophil count > 3% (the FeNO level that identified a sputum eosinophil count of ≥ 3%) ranged from 15 ppb for smoking non-atopic patients receiving a high dose of ICS to 58 ppb for non-smoking atopic patients not treated with a high dose of ICS. When FeNO values were compared with values expected according to the Dressel equation, the observed values were much higher. Authors conclusion: FeNO threshold needs to be adjusted for smokers compared with non-smokers when identifying the presence of sputum eosinophilia in an unselected asthma population

EBC, exhaled breath condensate; GM, geometrical mean; NR, not reported.
a $p < 0.05$ compared with controlled asthma.
b $p < 0.05$ compared with partly controlled asthma.

Hromis *et al.*[123] showed that FeNO levels are low in asthmatic smokers (17 ppb) compared with levels in asthmatic non-smokers (57 ppb); however, when treated with a LABA a reduction in FeNO values was observed in both non-smokers and smokers (32% vs. 22% respectively). A similar pattern was observed when both groups were treated with an antileukotriene (reduction of 22% in non-smokers and 12% in smokers). The authors concluded that the sequential changes in FeNO could be a useful marker of asthma control, regardless of smoking status. FeNO level also depends on the applied treatment.

In addition, a study by Lehtimaki *et al.*[142] reported that smoking can cause a small and transient but statistically significant increase in FeNO at 1 and 5 minutes after smoking, highlighting the importance that smokers abstain from smoking before FeNO measurements are undertaken.

Overall, the findings suggest that FeNO levels in adults tend to be lower in asthmatic smokers than in asthmatic non-smokers and there is some evidence to suggest that, when this group of patients is treated with ICSs, FeNO can no longer detect asthma control. However, the use of repeated measures and within-patient change from baseline cut-offs may be worthy of further investigation in higher-quality studies, with two studies[121,123] providing promising data on this approach. However, as no high-quality RCT studies have been conducted in this group, the evidence on the effectiveness of using FeNO to guide the management of asthma in smokers is currently inconclusive.

Children exposed to tobacco smoke

A summary of the study design and patient characteristics of the three studies recruiting children exposed to tobacco smoke[111–113] is provided in *Table 50*. Two of the studies were conducted in the USA[112,113] and one in France.[111] None of the studies appeared to receive funding from commercial sponsors and all were observational studies. In the study by de la Riva-Velasco *et al.*,[113] which was a cohort study, the authors determined the relationship between FeNO levels and exposure to low levels of environmental tobacco smoke in children with asthma on ICS treatment. The study by Hanson *et al.*[112] was a retrospective chart review study that looked at the relationship between FeNO and multiple clinical variables in children aged 4–7 years. The study by Mahut *et al.*[111] was a cross-sectional study that evaluated whether exhaled FeNO was independently associated with underlying pathophysiological characteristics of asthma (e.g. airway tone and airway inflammation) and with clinical phenotypes of asthma. In two studies[111,113] patients were recruited from outpatient clinics and in one study[112] patients were recruited from an asthma allergy clinic. Eligibility criteria varied from study to study but all studies included children who had been exposed to tobacco smoke and who had a diagnosis of asthma. The sample sizes of the included studies ranged from 33[113] to 169,[111] with the mean age of participants ranging from 10[113] to 10.5[111] years. However, Hanson *et al.*[112] did not report the mean age but recruited children between the ages of 4 and 7 years. Baseline FeNO values were inconsistently reported (Mahut *et al.*[111] and de la Riva-Velasco *et al.*[113] reported median values and Hanson *et al.*[112] reported mean levels) and the studies also varied in terms of medication usage. De la Riva-Velasco *et al.*[113] included children who were being treated with ICSs[113] whereas Mahut *et al.*[111] included patients who were being treated with ICSs, LABAs or beta-agonists on demand. Hanson *et al.*[112] failed to provide details on medication usage. A range of devices was used to measure FeNO levels. Hanson *et al.*[112] used the NIOX MINO device; Mahut *et al.*[111] used the Niox device; and de la Riva-Velasco *et al.*[113] used the NIOX Flex device. None of the studies used the same protocol or cut-off points for the management of asthma with FeNO.

The results of the included studies were varied (see *Table 50*). Mahut *et al.*[111] reported that there was no statistically significant relationship between FeNO level and smoke exposure and concluded that FeNO is potentially helpful in asthma management. On the other hand, de la Riva-Velasco *et al.*[113] found that children on low to medium doses of ICSs with recent low-level environmental tobacco smoke exposure have lower median (IQR) FeNO levels [9.6 (5.1–15.8)] than subjects not exposed to environmental tobacco smoke [23.9 (15.2–34.5); $p = 0.008$]. The authors concluded that environmental tobacco smoke exposure or third-hand smoke (that which lingers after a cigarette is extinguished) may be an important variable to consider when interpreting FeNO levels in school-aged children with asthma.

TABLE 50 Study design, patient characteristics and outcomes of studies recruiting asthmatic children exposed to smoke

Author, year	Study details	Population	FeNO measurements (ppb)	Outcomes
de la Riva-Velasco 2012[113]	Relationship between FeNO and exposure to low-level environmental tobacco smoke in children with asthma on ICSs Setting: outpatient clinic Country: USA Funding: supported by the Children's Environmental Health Centre of the Hudson Valley and the Maria Fareri Children's Hospital Foundation (authors declared no competing interest) Design: cohort study	Children with clinically stable, mild or moderate persistent asthma taking a low or medium dose of ICS daily ($n = 33$) Subjects stratified based on urine cotinine levels: ≥ 1 ng/ml (ETS) $n = 10$; < 1 ng/ml (non-ETS) $n = 23$ Median (IQR) age (years): ETS exposed: 10.5 (9.5 to 10.9); non-ETS exposed: 10.0 (9 to 11) Sex male, *n/N* (%): ETS: 4/10 (40); non-ETS: 12/23 (52) Medication usage: $n = 26$ daily medium dose of ICS; $n = 7$ daily low dose of ICS	Median (IQR) ETS: 9.6 (5.1 to 15.8); non-ETS: 23.9 (15.2 to 34.5) ($p = 0.008$) Device: NIOX Flex Flow rate: 50 ml/second	Children on low to medium doses of ICSs with recent low-level tobacco smoke exposure have lower FeNO levels than subjects not exposed to tobacco smoke. Low-level ETS or third-hand smoke may be an important variable to consider when interpreting FeNO levels in school-aged children with asthma
Hanson 2012[112] (abstract)	Characterisation of FeNO in children aged 4–7 years and analysis of its relationship with multiple clinical variables Setting: asthma/allergy clinic Country: USA Funding: NR Design: retrospective chart review	Children aged 4–7 years who underwent FeNO testing ($n = 80$) Mean age: NR Sex: NR Medical usage: NR	Mean (range): 18.7 (2.5–89) Device: NIOX MINO Flow rate: NR	There was no statistically significant relationship between FeNO level and smoke exposure

continued

TABLE 50 Study design, patient characteristics and outcomes of studies recruiting asthmatic children exposed to smoke (*continued*)

Author, year	Study details	Population	FeNO measurements (ppb)	Outcomes
Mahut 2011[111]	To evaluate whether FeNO is associated with a phenotype of childhood asthma (exposure to tobacco) Setting: outpatient clinic Country: France Funding: NR (authors declared no competing interest) Design: cross-sectional study, single-centre cohort	Asthmatic children ($n = 169$) Cluster 1 (asthmatic boys, well-controlled asthma, unexposed to tobacco): $n = 79$; cluster 2 (asthmatic girls, well-controlled asthma, unexposed to tobacco): $n = 44$; cluster 3 (asthmatic boys or girls, uncontrolled asthma associated with increase in airway tone, unexposed to tobacco): $n = 11$; cluster 4 (asthmatic boys or girls, uncontrolled asthma associated with small airway to lung size ratio, exposed to parental smoking): $n = 35$ Mean (SD) age (years): 10.5 (2.6) Medication usage, *n/N* (%): ICS: 87/169 (51); LABA: 73/169 (43); beta-agonist on demand: 82/169 (49)	Median (25th–75th percentile) Cluster 1: 25 (14–45); cluster 2: 34 (19–51); cluster 3: 21 (9–49); cluster 4: 30 (14–52) ($p = 0.58$) Device: Niox Flow rate: 50 ml/second	FeNO levels were not decreased by tobacco exposure in univariate analysis. FeNO levels were not different in the four clusters ($p = 0.58$)

ERS, European Respiratory Society; ETS, exposed to tobacco smoke.

Overall, the findings suggest that the potential efficacy of using FeNO to inform the management of asthma in children exposed to environmental tobacco smoke may be similar to that in children who have not been exposed, but that it may be necessary to consider a child's exposure status when interpreting results as FeNO may be lower in these children. Whether this should involve the setting of lower cut-off points or whether a more qualitative interpretation should be made on a case-by-case basis or by comparing within-patient changes from baseline is unclear.

Discussion of the clinical evidence

Summary of key results

Equivalence of devices

The review of the equivalence of devices revealed that the level of agreement between devices is highly variable.

NIOX MINO compared with the Niox chemiluminescent device

There was most evidence available for a comparison between the Niox chemiluminescent device and NIOX MINO in adults. Devices gave similar mean FeNO values in five of eight studies, but higher values for NIOX MINO in three studies. Bland–Altman analysis (reported in four of eight studies) suggested that the limits of agreement were around 10 ppb in both directions when analysed on the absolute scale, with mean differences of between 0.5 and 1.5 ppb. Analysis on the log scale produced better limits of agreement in the study by Menzies *et al.*[39] but very wide limits in the study by Korn *et al.*[41] In a head-to-head comparison between two NIOX MINO devices,[40] there was also evidence that not all NIOX MINO devices produce equivalent readings to one another, although another study comparing three devices found them to be equivalent to one another.[45] There was also evidence that agreement between NIOX MINO and Niox is worse at higher FeNO values, with all studies in which cohorts had mean values of < 30 ppb reporting better agreement and most Bland–Altman plots showing a multiplicative relationship. Agreement looked acceptable in children, with all limits of agreement falling between –4.4 and 8.9 ppb.

NIOX MINO compared with other chemiluminescent devices

Correlation co-efficients were generally good, with a correlation between 0.76 and 0.96. However, cohort means were far more variable, with some devices reading higher and some lower than NIOX MINO. The highest difference between cohort mean FeNO values was 47 ppb. Although individual devices may show good agreement with NIOX MINO, it is not possible to draw any solid conclusions as most devices were tested in only one or two studies and, as was seen in the comparison between NIOX MINO and Niox, results between studies appear to vary considerably.

NObreath compared with the Niox chemiluminescent device and other chemiluminescent devices

In the one study that compared NObreath with the Niox chemiluminescent device, a good level of agreement was seen in Bland–Altman analysis, but cut-off values derived by this study for the diagnosis of asthma differed by 10 ppb according to which device was used.[65] Other devices generally appeared to read higher than NObreath, but not by a consistent amount.

NObreath compared with NIOX MINO

Both studies reporting this comparison[54,66] found that in most analyses NIOX MINO provided lower mean FeNO values than NObreath. This contradicts the available evidence for comparisons between NIOX MINO and Niox and between NObreath and Niox, in which NIOX MINO > Niox > NObreath.

NIOX VERO compared with NIOX MINO

Only one study provided data on this device. (Academic-in-confidence information has been removed.)

Test failure rates

The overall test failure rate for FeNO measurement in adults was generally low across all devices and most patients appear to be able to provide FeNO readings, provided that they are permitted sufficient measurement attempts. There may be a higher test failure rate in children using NIOX MINO.

Conclusion

Overall, it cannot be concluded that any two devices are equivalent in all situations. Although there may be situations in which they are similar, it appears to depend on the characteristics of the studies and cannot be generalised to all situations. Further research is required to identify what is driving the variability between studies and devices. However, as there is mostly a high degree of correlation between measurements across all devices, estimates of sensitivity and specificity are likely to be an accurate indication of the potential diagnostic accuracy of using FeNO to guide diagnosis, but the derived cut-off points are not likely to be interchangeable between devices.

Diagnostic accuracy of FeNO for the diagnosis of asthma

No end-to-end studies were identified and no cohort study provided a comparison between FeNO within a sequence of tests and a suitable reference standard of the same sequence of tests without FeNO. The review included 27 studies that estimated the diagnostic accuracy of either FeNO alone or FeNO in conjunction with another test compared with that of a variety of reference standards and in a variety of populations.

Adults presenting with symptoms of asthma (four studies)

It is difficult to draw any conclusion about the optimal cut-off for sensitivity and specificity because of the heterogeneity in the results, study designs and devices used.

- The cut-off for the highest sum of sensitivity and specificity ranged from 20 ppb to 47 ppb amongst the studies and even results produced by the same authors in studies with high levels of homogeneity varied widely (25 ppb and 46 ppb in Schneider *et al.*[69] and Schneider *et al.*[71,72] respectively). Sensitivities ranged from 32% to 88% and specificities from 75% to 93%.

A range of cut-offs was not reported in all studies and it was not clear if the highest sensitivity or specificity value was available. From those that were reported:

- when selecting the cut-off with the highest sensitivity, this ranged from 9 ppb to 15 ppb, with sensitivities ranging from 85% to 96% and specificities ranging from 13% to 48%
- when selecting the cut-off with the highest specificity, this ranged from 47 ppb to 76 ppb, with sensitivities ranging from 55.6% to 13% and specificities ranging from 88.2% to 100%.

The consistently smaller range and higher values of specificities than sensitivities reported suggest that FeNO may be a more reliable and useful parameter to base diagnostic decisions on as a rule-in test than as a rule-out test. However, this balance will depend on the clinical and cost consequences of being TP, TN, FP and FN in each scenario.

Subset of patients at position A compared with airway reversibility or airway hyper-responsiveness (two studies)

These studies did not produce estimates of diagnostic accuracy that were noticeably different from those in the studies that recruited a potentially broader spectrum of patients:

- The cut-off for the highest sum of sensitivity and specificity ranged from 27 to 36 ppb. Sensitivities from 77.8% to 87% and specificities from 60% to 92%.

A range of cut-offs was reported in only one study.[82] These reached 100% sensitivity and specificity at the lowest and highest cut-offs, respectively, in this cohort compared with this reference standard.

- when selecting the cut-off with the highest sensitivity, this was 25 ppb, with a sensitivity of 100% and a specificity of 46.7%
- when selecting the cut-off with the highest specificity, this was 100 ppb, with a sensitivity of 27.8% and a specificity of 100%.

Difficult-to-diagnose patients (four studies)

These studies all used some form of airway hyper-responsiveness as the reference standard. Surprisingly, estimates of sensitivity and specificity seemed largely comparable to those in the studies recruiting patients presenting to primary care with symptoms of asthma, with a reference standard of airway reversibility, ICS responsiveness and airway hyper-responsiveness.

Bobolea *et al.*[88] recruited a set of patients who were negative by MCT and compared FeNO with an adenosine challenge test:

- This study produced 100% sensitivity (29.2% specificity) at a cut-off of 30 ppb, meaning that FeNO is likely to operate well as a rule-out test.

The other studies used MCT challenge in patients who were negative for asthma in previous tests:

- Cut-offs for the highest sum of sensitivity and specificity ranged from 32 to 40 ppb compared with MCT, which is a slightly narrower range than those in the broader cohorts. Sensitivities ranged from 35.0% to 74.3% and specificities from 72.5% to 95%, which are similar ranges to those in the broader cohorts. This perhaps reflects the fact that airway reversibility is a highly accurate test for asthma and that the combined tests behave in a similar manner. If this is the case, it would also suggest that FeNO has similar diagnostic properties in difficult-to-diagnose patients as in the broader spectrum of patients.

A range of cut-offs was not reported in these studies.

Patients with chronic cough and difficult to diagnose (three studies)

These studies recruited patients with chronic cough who had tested negative for other causes. All three studies used a reference standard of ICS responsiveness. Cut-offs for the highest sum of sensitivity and specificity were also in the same range and sensitivity and specificity were somewhat better in two studies: 94.7% sensitivity and 76.3% specificity in Hsu *et al.*[73] and 90% sensitivity and 85% specificity in Hahn *et al.*[74] This is in accordance with the expectation that FeNO is a better marker of ICS responsiveness than of asthma itself. At this position in the pathway, FeNO may be a useful test to perform before ICS responsiveness to indicate which patients are likely to respond to a trial of treatment. Patients with a low FeNO level could go on for further asthma investigations (e.g. MCT) or be assumed to be non-asthmatic depending on whether a rule-in or a rule-out scenario is used.

Studies using FeNO in conjunction with another test as the index test (three studies)

These studies reported the diagnostic accuracy of FeNO in conjunction with another test. This evidence comes closest to testing FeNO in a diagnostic pathway but is still of very limited relevance to the decision problem. The improvements in diagnostic accuracy were modest (or negative when considering the sum of sensitivity and specificity) and necessitate the usual trade-off between sensitivity and specificity. As the two studies that reported accuracy data are derivation studies rather than validation studies, it is possible that the gains seen are an overestimate of increases in diagnostic accuracy. However, it would seem that using a combination of tests may have additional benefits to using FeNO on its own.

Children with symptoms of asthma (four studies)

In comparison to the adult cohorts, with a similar spectrum of patients and reference standards, the cut-offs derived are generally lower in studies in children but with similar ranges of estimates of sensitivity and specificity.

- There was a high degree of agreement as to the cut-off that produces the highest sum of sensitivity and specificity, despite the heterogeneity in devices and reference standards, with values between 19 ppb and 21 ppb, which are consistently lower than those in adults. Estimates of sensitivity at these cut-off points were also wide-ranging, at 49–86%, which is similar to estimates in adult studies (32–88%). Again, as in adults (range 75–93%), specificity was more similar between studies, ranging from 76% to 89%.
- When selecting the cut-off with the highest sensitivity, the results were similar to those in adult cohorts. Cut-offs ranged from 5 to 20 ppb (vs. 9–15 ppb in adults), sensitivity from 89% to 94% (vs. 85–96% in adults) and specificity from 14.1% to 70% (vs. 13–48% in adults).
- When selecting the cut-off with the highest specificity, results were also similar to, but perhaps a little lower than, those in adult cohorts, ranging from 30 to 50 ppb (vs. 47–76 ppb in adults). Sensitivity ranged from 20% to 50% (vs. 13–55.6% in adults) and specificity ranged from 92% to 100% (vs. 88.2–100% in adults).

Adult smokers

Two studies were identified. Both recruited an unusual spectrum of patients who reported symptoms of asthma in response to a questionnaire, rather than a population presenting with symptoms.

Cut-off values were generally lower in smokers than in cohorts consisting of never, ex- and current smokers and it may be useful to consider a patient's smoking status when interpreting results. It is difficult to determine how the fairly minor differences in cut-off points and diagnostic properties of FeNO across groups would affect cost-effectiveness and clinical utility in practice. However, it would appear that FeNO is able to distinguish between asthmatic and non-asthmatic smokers with similar accuracy as between non-smokers and ex-smokers, but different cut-off points may be required.

Children exposed to tobacco smoke

Evidence was limited with regard to children exposed to tobacco smoke and drew on studies reported in the section on the management of children exposed to tobacco smoke and from the above studies reported for adults. The overall conclusion was the same as for adult smokers: it may be necessary to consider a child's exposure status when interpreting the results of FeNO testing for the diagnosis of asthma, as FeNO levels may be lower in children exposed to tobacco smoke.

Pregnant women

No diagnostic accuracy studies in pregnant women were identified. A cross-sectional study compared mean FeNO values in pregnant asthmatic women, non-pregnant asthmatic women, healthy pregnant women and healthy non-pregnant women. The study concluded that pregnancy does not alter FeNO levels in asthmatic or non-asthmatic women and that FeNO can distinguish between asthmatic and non-asthmatic pregnant and healthy women. However, it is unclear whether diagnostic accuracy would be equivalent to that reported in other studies with non-pregnant participants or a mix of pregnant and non-pregnant participants.

The elderly

No diagnostic accuracy studies in the elderly were identified. A case–control study[115] investigated FeNO levels in elderly patients with eosinophilic airflow obstruction (sputum cell count > 3%) compared with elderly healthy controls. No significant difference was found in the mean FeNO values, suggesting that FeNO is not a good marker of eosinophilic airway inflammation in elderly patients. This indicates that FeNO is unlikely to act as a useful test for the diagnosis of asthma in the elderly.

FeNO-guided management in asthma

Adults (five studies)

There was a high degree of heterogeneity across studies in all aspects of study design, including levels of blinding, inclusion criteria, visit frequency, cut-off points selected, devices used, step-up/step-down protocols and medications controlled by the protocols. Only one study reported using UK guidelines in the comparator arm.[98]

Exacerbations All studies reported a fall in exacerbation rate, although it appeared that this was mostly driven by mild and moderate exacerbations and was not always statistically significant.

Severe exacerbations:

- An exploratory random-effects meta-analysis including all definitions of severe exacerbations (excluding the studies by Smith *et al.*[97] and Honkoop *et al.*[101]) produced a pooled estimate of 0.94 (95% CI 0.66 to 1.34; $p = 0.73$). Reviewer-calculated rate ratios for major/severe exacerbations ranged from 0.79 (95% CI 0.66 to 0.94) to 1.29 (95% CI 0.83 to 2.03).
- The addition of data from Honkoop *et al.*[101] with imputed SEs did not change the non-statistical significance of the estimate, with rate ratios ranging from 0.82 (95% CI 0.64 to 0.1.05; $p = 0.11$) to 0.89 (95% CI 0.67 to 1.17; $p = 0.40$).
- The impact of the exclusion of the study by Smith *et al.*[97] from the analysis is unknown.

In a prespecified sensitivity analysis removing studies with wider definitions of severe exacerbations, only that by Syk *et al.*[99] remained in the analysis, with a rate ratio in favour of the control group at 1.29 (95% CI 0.83 to 2.03), although the difference was not statistically significant ($p = 0.26$). The inclusion of the study by Honkoop *et al.*[101] using imputed SE values resulted in a range of rate ratios from 0.91 (95% CI 0.47 to 1.77; $p = 0.79$) to 1.00 (95% CI 0.53 to 1.90; $p = 1.00$), indicating no significant difference between the intervention groups. Heterogeneity statistics were high, ranging from 80% to 53% and reflecting the opposite direction of effect reported in these two studies. Differences in study characteristics, step-up/step-down protocols and patients may account for differences in the direction of effect.

All definitions of exacerbations:

- Three studies reported a composite outcome including all types of exacerbation.[97,99,100] Two reported fewer exacerbations in the FeNO arm, but the difference did not reach statistical significance.[97,100] Syk *et al.*,[99] however, did report a statistically significant difference in favour of the FeNO arm, with 0.22 exacerbations per person-year in the intervention arm and 0.41 in the control arm ($p = 0.024$).
- An exploratory pooled analysis showed a statistically significant effect with a rate ratio of 0.53 (95% CI 0.46 to 0.61; $p < 0.00001$, $I^2 = 0\%$).

Inhaled corticosteroid use All studies reported some data on ICS use. Smith *et al.*[97] and Shaw *et al.*[98] reported mean ICS use at the end of the study, with mean differences of –270 µg/day (95% CI –112 to –430 µg/day; $p = 0.003$) and –338 µg/day (95% CI –640 to –37 µg/day; $p = 0.028$), respectively, in favour of FeNO-guided management. Syk *et al.*[99] showed a small increase in ICS use in the intervention arm compared with the control arm [586 µg (SE 454) vs. 540 µg (SE 317)]. Calhoun *et al.*[100] reported the mean value per month, although it is unclear if this was an average over the whole course of the study or the mean for the final month of the study. The means were very similar, at 1617 µg/month in the intervention arm and 1610 µg/month in the control arm.

- An exploratory meta-analysis using standardised mean difference (as outcomes were not reported in a standardised way) showed an overall effect of –0.24 SDs in favour of the intervention, although this narrowly missed significance (95% CI –0.56 to 0.07; $p = 0.13$).
- This may indicate that some step-up/step-down protocols were better at decreasing ICS use than others or it may be related to the characteristics of the study populations.

Inhaled corticosteroid use and exacerbations are likely to be inversely related, regardless of the use of FeNO. Whether the effects of FeNO-based management on these two related factors represents a cost-effective exchange is assessed through cost-effectiveness modelling in *Chapter 4*.

Health-related quality of life Three studies used versions of the AQLQ to measure quality of life. All showed no effect on the global score, but one study investigated domains and found a statistically significant difference in the symptoms score.

Asthma control and other medication use

- Asthma control either did not change[97,98,100] or increased.[99]
- Smith *et al.*[97] and Calhoun *et al.*[100] reported no significant differences between groups in bronchodilator use and Syk *et al.*[99] reported greater numbers using and mean use of LTRAs (statistically non-significant) and SABAs (significance not reported) in the FeNO-controlled arm.

Adverse events and mortality No asthma-related adverse events or deaths were reported.

Conclusions for FeNO-guided management in adults Because of the high levels of heterogeneity with regard to multiple study characteristics and outcome definitions, it was not possible to draw any firm conclusions as to which step-up/step-down protocol or cut-off points offer the best efficacy. However, considering the evidence base as a whole, it would seem possible that FeNO-guided management of most descriptions may, during the first year of management, result in better management overall (fewer exacerbations), with the potential for no increase or a small reduction in ICS use.

Children (seven studies)

There was a high degree of heterogeneity across studies with regard to all aspects of study design, including levels of blinding, inclusion criteria, visit frequency, cut-off points selected, devices used, step-up/step-down protocols and medications controlled by the protocols. Only Pike *et al.*[108] reported using UK guidelines in the comparator arm.

- Two studies recruited patients who appeared to be poorly controlled.[104,107] Pike *et al.*[108] recruited moderate to severe patients, some of whom will have been uncontrolled.
- Peirsman *et al.*[109] recruited mild to severe asthmatics.
- One study recruited patients who were mild to moderate persistent asthmatics.[103]
- One study recruited patients who had had a stable dose of ICS for the previous 3 months, suggesting that they were reasonably well controlled.[106]
- It was not possible to tell whether patients in the study by Verini *et al.*[105] were controlled or uncontrolled.

Hospitalisations Three studies[104,108,109] reported the number of patients (but not the rate per person-year) requiring hospitalisations. All three studies reported no difference between groups..

Severe exacerbations Three studies reported data on exacerbations resulting in OCS use.[103,104,106] Two reported fewer OCS courses in the FeNO arm, but the difference between groups was not statistically significant in the study by Szefler *et al.*,[104] whereas significance was unreported in the study by Pijnenburg *et al.*[106] Fritsch *et al.*[103] reported similar numbers of OCS courses in both arms.

All definitions of exacerbations Fritsch *et al.*,[103] Szefler *et al.*,[104] Verini *et al.*,[105] Petsky *et al.*,[107] Pike *et al.*[108] and Peirsman *et al.*[109] all reported exacerbations that were not defined as either major or minor and which had different definitions from one another. Five studies reported numerically fewer exacerbations or treatment failures in the intervention arm, but these differences were statistically significant in only two studies.[107,109] All studies showed at least a trend in favour of fewer exacerbations in the intervention arm. In the study by Petsky *et al.*,[107] exacerbations were not clearly defined but occurred in six out of 31 participants in the intervention group (19.4%) and 15 out of 32 in the control group (46.9%; $p = 0.021$). Peirsman *et al.*[109]

reported statistically significantly fewer exacerbations of any severity (as defined using GINA guidelines[136]) in the intervention arm (18 events) than in the control arm (35 events; $p = 0.02$). Pijnenburg *et al.*[106] did not report this outcome.

Inhaled corticosteroid use With the exception of the study by Petsky *et al.*,[107] all of the studies provided some estimate of ICS use. Fritsch *et al.*[103] and Szefler *et al.*[104] reported statistically significantly higher ICS use in the intervention group; Pike *et al.*[108] and Peirsman *et al.*[109] reported higher levels of ICS use in the intervention group but not statistically significantly so; Pijnenburg *et al.*[106] reported very similar levels in the different groups; and the values in the remaining study (in terms of absolute numbers using ICSs) were difficult to interpret. The differences in the effects on ICS usage between studies may be the result of the specifics of the step-up/step-down protocols and/or the characteristics of the patients selected. In the case of the study by Pijnenburg *et al.*,[106] in which patients may have been generally better controlled at the outset, step down of ICS use may have been more likely than in the study by Szefler *et al.*,[105] in which patients were poorly controlled and ICS dose was perhaps more likely to be stepped up. Having said this, poorly controlled patients may be poorly controlled because they are non-responsive to corticosteroids, and use of FeNO testing may actually result in a decrease in ICS use if low FeNO levels always indicate a decrease in treatment. However, Szefler *et al.*,[104] Pijnenburg *et al.*,[106] Pike *et al.*[108] and Peirsman *et al.*[109] did not allow step down of ICS dose on the basis of low FeNO levels alone, meaning that uncontrolled ICS-unresponsive asthmatics for whom high doses of ICS were not appropriate could not have their doses lowered and mean ICS use may remain artificially high. It could be expected that this effect would be most pronounced in studies that recruited patients with severe asthma. As such, it may be that the increase in ICS usage in the study by Szefler *et al.*[104] is a function of the population selected as well as the management protocol.

Inhaled corticosteroid use and exacerbations are likely to be inversely related, regardless of the use of FeNO testing. Whether the effects of FeNO-based management on these two related factors represent a cost-effective exchange is assessed through cost-effectiveness modelling in *Chapter 4*.

Health-related quality of life This outcome was reported in only one study in abstract form[107] and using an unknown tool. No conclusions can be confidently drawn from these data.

Asthma control and other medication use Four studies provided some data on asthma control, none of which demonstrated any statistically significant effects favouring either the intervention or the control. With respect to additional medication use, three studies provided data and there did not appear to be a clear direction of effect within the data.

Adverse events, mortality, compliance and test failure rates Szefler *et al.*[104] reported no difference in adverse events between groups and no mortality was observed. The adverse events listed were disorders of the eyes, ears, nose and throat; gastrointestinal disorders; haematology disorders; infections; musculoskeletal symptoms; and skin symptoms.

Conclusions for FeNO-guided management in children Because of the high levels of heterogeneity with regard to multiple study characteristics and outcome definitions, it was not possible to draw any firm conclusion as to which step-up/step-down protocol or cut-off points offer the best efficacy. Results were generally not statistically significant, but this may be because of the small sample sizes in some cases; meta-analysis was precluded by the ability to calculate rate ratios. Because all but one study reported numerically smaller numbers or rates of exacerbations in the intervention arm, it would seem possible that FeNO-guided management of most descriptions could, during the first year of management, result in better management overall, despite the lack of statistically significant results in individual studies. Further larger studies are needed to clarify any treatment effect. It is unclear whether ICS use is likely to increase or decrease and this may depend on the details of the step-up/step-down protocols or the characteristics of the patients recruited to the trials in terms of control and severity.

Generalisability of the results to UK practice

Diagnostic review

Adults

Only studies with some relevance to UK practice were considered, of which not all used NIOX MINO or NObreath. The studies with the highest relevance to UK practice can be broken down into four types:

- Studies of all patients presenting with symptoms of asthma and using a reference standard that includes the most common tests in the UK pathway. The most relevant studies in this category are those by Schneider *et al.*[69] and Schneider *et al.*,[71,72] who used the NIOX MINO device, and those by Smith *et al.*[83] and Smith *et al.*,[86] who used the Niox chemiluminescent device and an unknown device respectively.
- Studies recruiting patients who are difficult to diagnose and using a reference test appropriate to UK practice:
  - Schleich *et al.*,[77] who used the Niox chemiluminescent device, and Pedrosa *et al.*[85] and Katsoulis *et al.*,[81] who used the NIOX MINO device.
  - Bobolea *et al.*,[88] who also used the NIOX MINO device and who selected a population of patients who were negative by MCT. The reference standard was the adenosine challenge test.
- Studies recruiting patients with chronic cough who have already undergone other tests. This includes the studies by Hsu *et al.*,[73] Hahn *et al.*[74] and Prieto *et al.*[76] These are useful studies in terms of demonstrating that FeNO can predict ICS responsiveness in these patients, rather than a diagnosis of asthma. None of these studies used the NIOX MINO device.
- Studies using FeNO in conjunction with another test compared with an appropriate reference standard:
  - Schleich *et al.*[77] recruited a difficult-to-diagnose group, combined FeNO with $FEV_1\% < 101\%$ and used a reference standard of MCT. It could be argued, however, that in the UK only patients negative by $FEV_1\%$ would receive a MCT, in which case this combination may not be a useful one.
  - Cordeiro *et al.*[87] recruited patients presenting with symptoms of asthma and combined FeNO with airway reversibility to administration of a bronchodilator. This would be equivalent to FeNO being used to prevent a MCT, but some of the included patients would not have received a MCT under the UK pathway anyway. As such, it is again unclear how useful this combination of tests would be in UK practice.

Children

Only studies with some relevance to UK practice were considered. These studies, of all patients presenting with symptoms of asthma and using a reference standard that includes the most common tests in the UK pathway, can be broken down into the following groups:

- Woo *et al.*,[96] who recruited patients in position A on the pathway and used the NIOX MINO device compared with a reference standard that roughly equates to UK practice.
- Linkosalo *et al.*,[93] who used a Sievers NOA280i chemiluminescence device for patients in position A on the pathway with a reference standard of an exercise challenge test. Not all presenting patients would receive this test in UK practice. FeNO testing would be positioned before the exercise challenge test and could triage patients away from this.
- Sivan *et al.*,[95] who used an ECO MEDICS device in patients at position A in the pathway compared with a reference standard similar to UK practice. In this study, FeNO replaces the whole pathway prior to ICS use.

Management review

Adults

Generalisability to UK practice is clear-cut in the study of adults by Shaw *et al.*,[98] which used UK guidelines as the comparator and was based in the UK. Patients were recruited from primary care and included mild to severe asthmatics (unless a severe exacerbation had been experienced in the previous 4 months) and atopic patients as well as non-atopic patients. Smokers were excluded and so the results may not be generalisable to this group. However, this study offers the best generalisability to UK practice in terms of setting, population and comparator.

However, if management protocols that are different from that used in Shaw *et al.*[98] were to be considered for recommendation, other studies may offer some useful data. Input from a clinician (Professor Ian Pavord, Nuffield Department of Medicine, University of Oxford, August 2013, personal communication) suggests that the management protocol described by Powell *et al.*,[102] in which symptoms control the LABA dose and FeNO levels control the ICS dose, is generally thought to be the best design. This study was conducted in pregnant women only and its generalisability to the whole asthma population is not assured. The protocol described by Shaw *et al.*[98] appears to be similar to this in that the FeNO level controls the ICS and LTRA doses whereas symptoms scored according to the Juniper scale control the SABA, LABA and theophylline doses. Importantly, this allows for low FeNO levels to result in a reduction in ICS dose regardless of symptoms. In practice, the extent of ICS dose reduction may be limited by current Commission on Human Medicine advice, which states that LABAs should not be prescribed without ICSs.[143]

Children

Generalisability in studies recruiting children was less clear-cut. Only the study by Pike *et al.*[108] was set in the UK and used UK guidelines, but this study also recruited only moderate to severe asthmatics and may therefore not be generalisable to the whole population. This study was identified during the update search and it was not possible to incorporate it into the model because of time constraints. From the studies identified in the original search, and on the basis of reported quality, that by Szefler *et al.*[104] was at lowest risk of bias and, for patients who are uncontrolled, this may be the best study to base generalisations on. However, clinical input to the project (Professor Ian Pavord, August 2013, personal communication) indicated that this study has been criticised for not allowing a step down of ICS dose on the basis of low FeNO levels if symptoms are still present. In addition, the patient population in this study was patients who were uncontrolled, which may introduce bias in that patients will be less likely to be indicated for a step down of ICS dose.

For patients who are mild to moderate asthmatics, the study by Fritsch *et al.*[103] may be the best study to select for modelling as the study by Pijnenburg *et al.*[106] uses only symptoms to guide asthma management in the control arm, whereas that by Fritsch *et al.*[103] uses symptoms, SABA use and lung function tests, which is probably more comparable with UK practice. However, Fritsch *et al.*[103] used only FeNO to guide management and it would seem more likely that clinicians would use other measures such as symptom control and lung function to guide treatment. This would allow the stepping down of treatment based on FeNO values, but may also be less sensitive than using a combination of factors. Unfortunately, there is not a study in children that addresses this particular problem by combining FeNO testing with other indicators in a protocol that allows step down in the presence of low FeNO levels regardless of symptomatic control. Fritsch *et al.*[103] did not report data in a way that allowed calculation of rates of exacerbation per person-year and this study is of limited use for this reason. The study by Pijnenburg *et al.*[106] provided the necessary data and this study was selected for modelling.

The study by Peirsman *et al.*[109] was identified in the update search. A broad spectrum of patients was recruited but the study did not allow for step down of ICS use on the basis of FeNO levels alone and the treatment protocol was different from UK practice. This study was not used in the modelling because of time constraints.

Chapter 4 The cost-effectiveness of FeNO testing for the diagnosis and management of asthma

Introduction

This chapter presents an assessment of the cost-effectiveness of FeNO testing for the diagnosis and management of asthma. The chapter consists of two main sections: (1) a review of existing evidence relating to the cost-effectiveness of FeNO testing in the diagnosis and management of asthma and (2) an exposition of the methods and results of two de novo health economic models developed by the EAG to evaluate the cost-effectiveness of FeNO testing for the diagnosis and management of asthma.

The chapter is set out as follows. The following section describes the aims and objectives of the economic analysis. *Review of existing evidence relating to the cost-effectiveness of FeNO testing for the diagnosis and management of asthma* presents the methods and results of a critical review of existing economic evidence on FeNO testing for asthma; this includes published studies as well as other economic evidence submitted by the manufacturers of the FeNO devices considered in this assessment. This section also includes a summary of methodological problems and concerns associated with undertaking economic analyses of interventions for the diagnosis and management of asthma. *Development of two de novo models to estimate the cost-effectiveness of FeNO testing for the diagnosis and management of asthma* presents the methods of the de novo economic analyses undertaken by the EAG and *De novo model results* summarises the main findings of the analyses. The final discussion section highlights the key uncertainties surrounding the evidence base used to inform the de novo analysis.

Aims and objectives of the health economic assessment of FeNO testing

The purpose of this chapter is to assess the expected cost-effectiveness of NIOX MINO, NIOX VERO and NObreath compared with current standard care for the diagnosis and management of asthma. Importantly, there is uncertainty not only with respect to whether FeNO testing might represent a cost-effective use of health-care resources but also with respect to how FeNO testing should be used in the most cost-effective manner within existing asthma pathways. Thus, the economic analysis attempts to address the following questions:

1. What is the cost-effectiveness of FeNO testing using NIOX MINO, NIOX VERO and NObreath compared with current standard tests for the diagnosis of asthma in England and Wales?

    i. Should FeNO testing be used *alongside* existing standard tests for the diagnosis of asthma?
    ii. Should FeNO testing be used *in place of* existing standard tests for the diagnosis of asthma?

2. What is the cost-effectiveness of FeNO testing using NIOX MINO, NIOX VERO and NObreath compared with standard guidelines for the management of asthma in England and Wales?
3. What are the key uncertainties relating to the cost-effectiveness of FeNO testing and how might these be resolved or reduced?

The next section presents the methods and results of a review of the existing evidence relating to the cost-effectiveness of FeNO testing.

Review of existing evidence relating to the cost-effectiveness of FeNO testing for the diagnosis and management of asthma

Purpose of the review

We undertook a systematic review of existing economic analyses of FeNO testing in the diagnosis of asthma and for the management of patients with diagnosed asthma. This also included a focused review of economic studies of other interventions for the diagnosis and/or management of asthma. The purpose of the review of existing health economic analyses was threefold:

1. to identify existing economic analyses of FeNO testing using NIOX MINO, NIOX VERO or NObreath for the diagnosis and/or management of asthma
2. to identify existing models that may be used to inform the structure of the de novo economic models developed by the EAG
3. to identify potentially relevant evidence sources to inform parameter values within the de novo economic models developed by the EAG.

Review methods

Methods used to identify existing economic studies

We undertook systematic searches across a range of electronic databases to identify published studies of FeNO testing for the diagnosis and/or management of asthma. We also searched for other economic studies of interventions for the diagnosis or management of asthma. All searches were undertaken by an information specialist (RW) during the period 30 May 2013 to 7 June 2013.

Four separate strands of searching were undertaken, which are detailed in the following sections.

Economic search 1: NIOX MINO/NObreath in either the diagnosis or the management of asthma (30 May 2013)

This search used free-text terms relating to NIOX MINO and NObreath (including manufacturer names), with the terms combined with a sensitive economic search filter.

Economic search 2: models of asthma and FeNO (30 May 2013)

This search used the search strategies developed for the management studies in the clinical effectiveness review (see *Chapter 3*, *Clinical reviews search methodology*) and combined these with a sensitive economic search filter. Studies that were found in the first search would also be retrieved in this search.

Economic search 3: asthma management models (3 June 2013)

This focused search used free-text terms for asthma combined with cost terms in the title and the economic model subject heading. A sensitive economic filter was not applied in this search.

Economic search 4: asthma diagnostic models (7 June 2013)

This focused search used free-text terms for asthma (as used in economic search 3) combined with a sensitive economic evaluations search filter and a diagnostic search filter.

These four searches are shown diagrammatically in *Figure 20*.

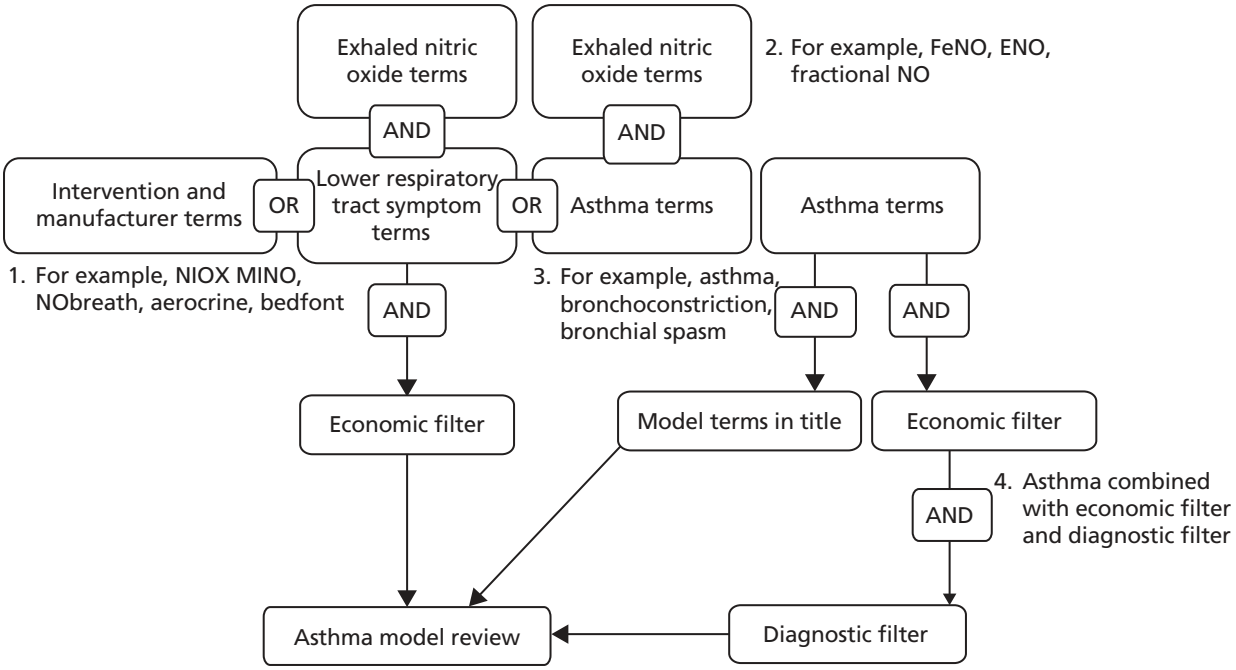


FIGURE 20 Diagrammatic representation of the search approach.

All of the above searches were performed within the following databases:

- MEDLINE and MEDLINE-In-Process & Other Non-Indexed Citations (Ovid): 1948–present
- EMBASE (Ovid): 1974–present
- The Cochrane Library (Wiley Interscience):
  - CDSR: 1996–present
  - HTA database: 1995–present
  - NHS EED: 1995–present
- SCIE (Web of Science): 1899–present
- CPCI-S (Web of Science): 1990–present.

The economic MEDLINE search strategy is detailed in *Appendix 13*.

As noted in *Chapter 3* (see *Additional search for NIOX VERO*), an additional separate search was also undertaken in August 2013 to identify evidence relating to NIOX VERO.

Inclusion and exclusion criteria for the review

Given the anticipated dearth of published economic analyses relating to FeNO, we adopted broad inclusion criteria for the review (*Box 1*).

Data sifting

The titles and abstracts of all records identified by the search were reviewed by one member of the research team (JM). The full texts of studies considered eligible for inclusion were then retrieved for a more detailed examination.

Critical appraisal methods

The identified studies of FeNO were critically appraised using the Drummond *et al.*[144] checklist for economic evaluations and the NICE reference case for diagnostic studies.[145] The identified studies were also informally assessed against current guidelines for the development and reporting of health economic models.[146]

BOX 1 Inclusion and exclusion criteria for the review of economic analyses of asthma diagnosis and management

Inclusion criteria

- Economic analyses of costs and consequences of interventions for the diagnosis and/or management of asthma in children and/or adults.
- Studies reporting on the cost-effectiveness of NIOX MINO, NIOX VERO or NObreath for the diagnosis and/or management of asthma.

Exclusion criteria

- Letters, commentaries and editorials.
- Economic studies that do not relate to diagnostic or management interventions.
- Studies that do not relate to asthma.
- Studies that do not involve (i) a model-based analysis, (ii) economic evaluations alongside trials or other forms of empirical clinical study or (iii) estimates of the costs and consequences of FeNO testing for the diagnosis of asthma.

Studies of other interventions for the diagnosis and/or management of asthma were not subjected to a formal critical appraisal but were instead used to inform the design and development of the de novo health economic analyses (detailed in *Development of two de novo models to estimate the cost-effectiveness of FeNO testing for the diagnosis and management of asthma*).

Results of the review of FeNO testing for asthma diagnosis and/or management

Number and type of studies included in the review

The results of the four economic searches are presented in *Table 51*. A total of 1898 potentially relevant citations were identified from the four searches. The full texts of 27 studies were retrieved for further examination. The full text of one of these studies could not be retrieved and was excluded. Of the remainder, only two studies[147,148] were identified that related to FeNO testing for the diagnosis and/or management of asthma. The focused searches did not identify any further cost–utility models of other interventions for the diagnosis of asthma. Sifting of the focused management model searches identified a further 13 studies[149–161] that were used more generally to inform the model structure, although none of these related to FeNO testing. In addition, one additional management study[13] that was detailed in the appendices of a UK HTA report was identified.

As part of the appraisal process, Aerocrine submitted evidence relating to the cost-effectiveness of NIOX MINO for the diagnosis and management of asthma (Aerocrine. *Submission to NICE – Assessing the Impact of FeNO in the Management and Diagnosis of Asthma*. Slideset and Microsoft Excel model, 2013). This submission included a Microsoft Excel 2010 spreadsheet model (Microsoft Corporation, Redmond, WA, USA) and a brief slideset. This submission is included as part of the economic review presented in this chapter. Aerocrine did not submit any economic evidence relating to the cost-effectiveness of the NIOX VERO device and Bedfont Scientific did not submit any evidence relating to either the effectiveness or the cost-effectiveness of the NObreath device.

TABLE 51 Summary of the results of the economic searches

Database	Search			
	1. NIOX MINO/NObreath	2. Asthma and FeNO models	3. Asthma management models	4. Asthma diagnostic models
MEDLINE and MEDLINE-In-Process & Other Non-Indexed Citations	2	29	311	338
EMBASE	7	144	420	590
CDSR	0	48	0	69
HTA database	4	8	4	0
DARE	0	2	3	14
NHS EED	1	2	119	12
SCIE	5	85	295	457
CPI-S	0	3	15	37
Total unique citations	14	269	567	1048

Existing economic analyses of FeNO testing for the diagnosis of asthma

Methods and results of the included diagnostic studies

The searches included only one UK model-based published economic analysis relating to the diagnosis of asthma;[147] this study assessed the cost-effectiveness of FeNO testing (specifically NIOX MINO) compared with standard diagnostic tests. This model has been published across two papers[147,148] and also forms the basis of the Aerocrine submission to NICE for this appraisal. The general model structure and many of the evidence inputs are the same across these three analyses.

An economic evaluation of NIOX MINO airway inflammation monitor in the United Kingdom: diagnostic model[147]

Description of the economic model and analysis Price *et al.*[147] presents the methods and results of two economic analyses: (1) a model to assess the cost savings associated with using NIOX MINO for the diagnosis of asthma and (2) a model to assess the cost-effectiveness of NIOX MINO for the management of asthma. The model of asthma management is reviewed in detail in *Existing economic analyses of FeNO testing for the management of asthma*.

The conceptual form of the Price *et al.*[147] diagnostic model is presented in *Figure 21*. Within the model, the costs and outcomes of competing diagnostic strategies are modelled using a simple deterministic decision tree based on the true underlying probability of asthma and the operating characteristics of a variety of tests used for the diagnosis of asthma in the NHS. The population under evaluation within the model is reported to relate to 'non-smoking adult patients with mild to severe asthma as seen in both primary and secondary care' (p. 433).[147] The intervention is defined in the base-case analysis as FeNO testing using NIOX MINO alone, although a secondary analysis is also reported for a joint diagnostic modality consisting of NIOX MINO plus spirometry using FEV_1 testing. The comparator within the base-case analysis is a blended comparison of standard diagnostic tests: (1) lung function testing, (2) reversibility test, (3) bronchial provocation and (4) sputum eosinophil count. The selection of tests included in the analysis was based on the BTS/SIGN asthma guidelines,[8] although the source for the proportionate weighting of each of these is unclear within the Price *et al.*[147] paper. It should also be noted that current BTS/SIGN guidelines[8] state that sputum induction is not in common usage and it currently remains a research tool. In contrast to the published Price *et al.*[147] model, the Aerocrine submission model does not adopt a blended comparison approach but instead evaluates each individual diagnostic test as a decision option in its own right.

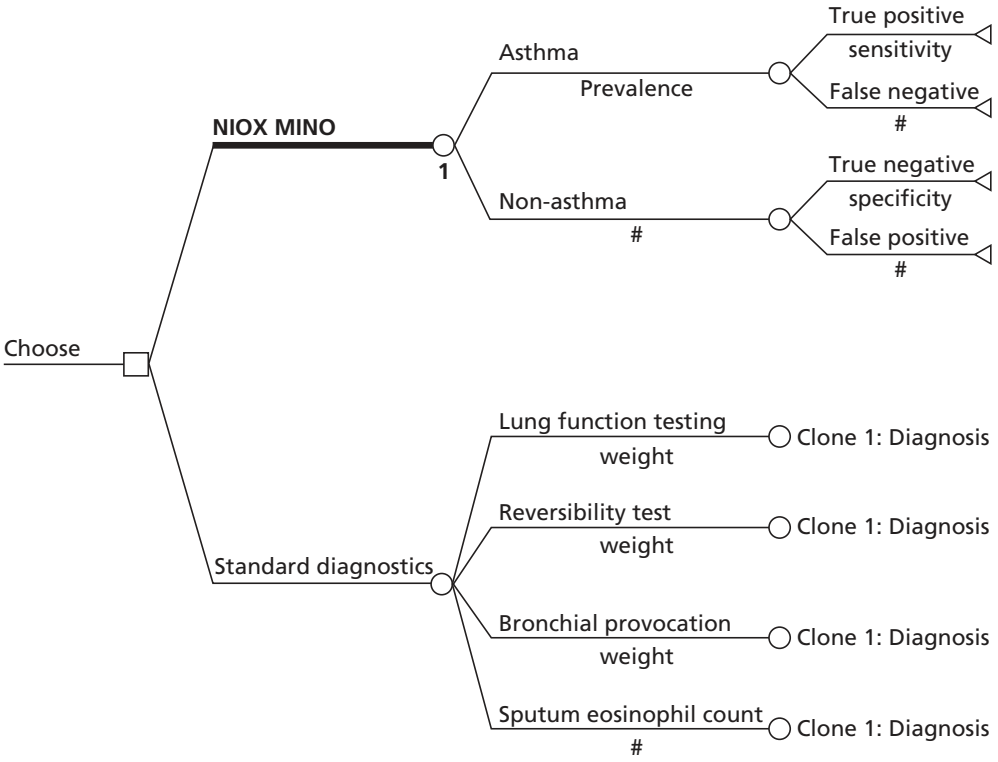


FIGURE 21 Model structure employed within the Price *et al.*[147] diagnostic model. Reproduced with permission from Price D, Berg J, Lindgren P. An economic evaluation of NIOX MINO airway inflammation monitor in the United Kingdom. *Allergy* 2009;**64**:431–8.[147] John Wiley & Sons. © 2009 The Authors. Journal compilation © 2009 Blackwell Munksgaard.

The model structure employs a single decision node whereby the model cohort is assumed to receive a single imperfect diagnostic intervention; those patients who receive an incorrect diagnosis are later assumed to achieve a correct diagnosis of either true asthma or not asthma. The published model estimates the costs associated with NIOX MINO compared with those of the blended comparison of standard diagnostic tests. The analysis takes the form of a comparative cost analysis and health outcomes are not explicitly considered in the published analysis (note that the number of misdiagnoses are not reported within the Price *et al.*[147] paper but could be easily calculated from the table of model input parameters). Diagnostic outcomes in terms of TPs, FPs, TNs and TPs are estimated explicitly within the Aerocrine model. Within the Price *et al.*[147] paper, costs are valued at 2005 prices. The model time horizon is undefined but relates to the time from presentation to correct diagnosis. No discounting is applied to costs.

The Price *et al.*[147] diagnostic model makes the following structural assumptions:

- NIOX MINO will replace existing diagnostic tests rather than be used alongside them
- time is not explicitly considered within the model with respect to the resolution of incorrect diagnoses (FPs or FNs)
- negative health consequences [quality-adjusted life-year (QALY) losses] associated with incorrect diagnoses are not quantified within the model
- all incorrect diagnoses are assumed to be corrected at the next outpatient visit.

The parameter values and evidence sources from which these are drawn are reported in *Table 52*.

The headline results of the economic analysis are presented as a simple cost difference between NIOX MINO and the blended comparison of standard tests for asthma diagnosis. Uncertainty surrounding model input parameters was explored using simple one-way sensitivity analyses. These analyses include varying model parameters describing test sensitivity, true underlying asthma prevalence in the modelled population, the costs of NIOX MINO and other diagnostic tests, the number of additional visits required to resolve an initially incorrect diagnosis, a comparison of NIOX MINO with reversibility testing plus peak expiratory flow (PEF) charting and a comparison of NIOX MINO plus FEV_1 and standard tests.

TABLE 52 All parameter values and evidence sources used in the Price *et al.*[147] diagnostic model

Parameter	Value	Source
Test operating characteristics		
Sensitivity FeNO testing (flow rate 50 ml/second; > 20 ppb)	0.88	Smith *et al.*[86]
Specificity FeNO testing (flow rate 50 ml/second; > 20 ppb)	0.79	
Sensitivity FeNO testing (flow rate 50 ml/second; > 33 ppb) + FEV_1 < 80% predicted	0.94	[a]Smith and Taylor[162]
Specificity FeNO testing (flow rate 50 ml/second; > 33 ppb) + FEV_1 predicted < 80%	0.93	
Sensitivity PEF A%M > 21.6%	0.43	Hunter *et al.*[163]
Specificity PEF A%M > 21.6%	0.75	
Sensitivity reversibility test: FEV_1 > 2.9% improvement after salbutamol	0.49	
Specificity reversibility test: FEV_1 > 2.9% improvement after salbutamol	0.70	
Sensitivity bronchial provocation: methacholine PC_{20} < 8 mg/ml	0.91	
Specificity bronchial provocation: methacholine PC_{20} < 8 mg/ml	0.90	
Sensitivity sputum eosinophil count > 1%	0.72	
Specificity sputum eosinophil count > 1%	0.80	
Disease characteristics		
Asthma prevalence	0.36	Smith *et al.*[86]
Comparator usage (blended comparison weightings)		
Proportion using PEF charting	0.485	BTS/SIGN[164]
Proportion using reversibility testing	0.485	
Proportion using bronchial provocation	0.025	
Proportion using sputum eosinophil count	0.005	
Cost parameters (£)		
Cost NIOX MINO	22.90	Aerocrine
Cost peak flow charting (two visits)	89.27	NHS Reference Costs[165]
Cost reversibility test	29.27	
Cost bronchial provocation	48.50	
Cost sputum eosinophil count	48.50	
Cost outpatient GP visit	30.00	Curtis and Netten[166]
Cost outpatient lung practitioner	44.00	

methacholine PC_{20} < 8 mg/ml, provocative concentration of methacholine causing > 20% fall in FEV_1; PEF, peak expiratory flow; PEF A%M > 21.6%, maximum within-day peak expiratory flow amplitude mean percentage (calculated from PEF measured twice daily over 14 days as the best of three blows).

a Note that this is a non-systematic review/opinion paper. Although Smith and Taylor[162] do state these sensitivity and specificity values and refer to two other empirical studies, neither includes the quoted estimates. The empirical source of the reported values for FeNO plus FEV_1 is unclear.

Diagnostic model results presented by Price et al.[147] The diagnostic model results reported by Price *et al.*[147] are summarised in *Table 53*. In the base-case analysis, the authors report that the cost of an asthma diagnosis made using NIOX MINO was £29 per patient, or £43 less than when using standard diagnostic tests (£72 per patient).

The results indicate that, within the base-case analysis, NIOX MINO is expected to produce cost savings (£43) compared with the blended comparison of standard diagnostic tests for asthma. These results do not account for potential health benefits associated with the improved accuracy of diagnosis. The sensitivity analysis indicates that NIOX MINO is expected to produce cost savings in all scenarios except (1) when the cost of NIOX MINO is increased by 200% and (2) within the comparison of NIOX MINO plus FEV_1 testing compared with the blended comparison of current standard diagnostic tests.

The authors note that 'is it is likely that, in practice, FeNO measurement will be used in conjunction with other tests rather than as their replacement. We examined this scenario and found that the combination of FeNO measurement plus lung function testing increased costs for diagnosing asthma by £42' (p. 435).[147] Given the authors' interpretation of the likely placement of NIOX MINO, it is unclear why the base-case analysis within the paper does not reflect this scenario and, given the proposed placement of FeNO within the existing pathway and the absence of quantified health outcomes within the Price *et al.*[147] diagnostic model, it is unclear whether the potential additional benefits associated with diagnosis using FeNO testing outweigh the opportunity costs associated with generating them.

TABLE 53 Summary of cost-minimisation results presented by Price *et al.*[147]

Scenario	NIOX MINO (£)	Standard tests (£)	Incremental cost (£)
Base case	29	72	–43
Variation in test sensitivity –50% (all tests simultaneously)	35	76	–40
Variation in test sensitivity +10% (all tests simultaneously)	29	72	–43
Variation in test sensitivity –50% (bronchial provocation and sputum only)	39	81	–42
Variation in test sensitivity +10% (bronchial provocation and sputum only)	28	71	–43
Asthma prevalence set to 10%	30	70	–40
Asthma prevalence set to 50%	29	74	–45
Asthma prevalence set to 90%	28	78	–50
NIOX MINO cost –50%	18	72	–54
NIOX MINO cost +200%	75	72	3
Cost of standard diagnostic tests +50%	29	72	–43
Cost of standard diagnostic tests +100%	29	102	–72
Cost of standard diagnostic tests +150%	29	131	–102
Cost of standard diagnostic tests +200%	29	161	–131
Two visits for false diagnosis	36	86	–50
Four visits for false diagnosis	49	113	–63
NIOX MINO vs. reversibility + PEF charting	29	131	–102
NIOX MINO + FEV_1 testing vs. standard tests	115	72	42

Source: reproduced with permission from Price D, Berg J, Lindgren P. An economic evaluation of NIOX MINO airway inflammation monitor in the United Kingdom. *Allergy* 2009;**64**:431–8.[147] John Wiley & Sons. © 2009 The Authors. Journal compilation © 2009 Blackwell Munksgaard.

The next section briefly outlines the economic analysis of NIOX MINO for asthma diagnosis as presented within the Aerocrine submission to NICE.

(ii) Additional analysis presented within the submitted Aerocrine diagnostic model

As noted earlier, Aerocrine also submitted a spreadsheet model to NICE as part of the appraisal process. The model was accompanied by a brief Microsoft PowerPoint slideset although this does not include a description of the intended base-case analysis results and little detail is provided supporting the structure, assumptions or choices regarding evidence used to inform the model parameters. The submitted Aerocrine model adopts a very similar structure and similar assumptions to those of the diagnostic model reported by Price *et al.*[147] It should be noted that, in the absence of a detailed written description of the Aerocrine submission model, it is difficult to provide a full critique of its methods and results. This task was further hindered as the worksheet tabs and many sets of calculations were structurally hidden within the Microsoft Excel worksheet, making formula auditing problematic.

The following differences should be noted between the Price *et al.* diagnostic model[147] and the Aerocrine diagnostic model:

1. *Differences in the specification of diagnostic options*. The Aerocrine model assesses a different set of options compared with Price *et al.*:[147]

   i. spirometry alone
   ii. spirometry and (if negative) MCT
   iii. spirometry and (if negative) FeNO testing
   iv. spirometry and FeNO testing
   v. FeNO testing alone
   vi. spirometry and (if negative) sputum induction.

   It should be noted that some of these options include sequences of diagnostic tests. These are implemented within the model by assuming that the probabilities of obtaining a positive or negative result from sequences of tests are uncorrelated with one another; in other words, the use of prior tests in a sequence will remove some candidates from the population, will alter the prevalence of true disease in the remaining population and may impact on the diagnostic accuracy of subsequent tests in that sequence. The validity of assuming no correlation between tests is questionable and no evidence is presented to support this. Within the Aerocrine submission model, all standard tests are evaluated as individual comparators in their own right rather than being combined and weighted within a blended comparison.
2. *Different assumptions relating to the cost impact of misdiagnosis and resolution*. The submitted model includes the costs of treating patients who are FP using ICSs over a 1-year time horizon; these treatment costs were not included in the Price *et al.*[147] diagnostic model. Conversely, the Aerocrine model does not include the assumptions made by Price *et al.*[147] regarding the costs of additional visits to resolve misdiagnosis.
3. *Different parameter values and evidence sources*. The Aerocrine diagnostic model includes some different parameter values from those in the Price *et al.*[147] diagnostic model. The parameter values and sources employed within the Aerocrine diagnostic model are detailed in *Table 54*.

TABLE 54 Key parameter values and evidence sources used in the Aerocrine diagnostic model

Parameter	Value	Source
Test operating characteristics		
Sensitivity spirometry alone	0.29	Schneider *et al.*[71]
Specificity PEF A%M > 21.6%	0.90	
Sensitivity FeNO testing + spirometry	0.94	[a]Smith and Taylor[162]
Specificity FeNO testing + spirometry	0.93	
Sensitivity FeNO testing alone	0.88	Smith *et al.*[86]
Specificity FeNO testing alone	0.79	
Sensitivity MCT	0.91	Hunter *et al.*[163]
Specificity MCT	0.90	
Sensitivity sputum induction	0.72	
Specificity sputum induction	0.80	
Disease characteristics		
Asthma prevalence	0.36	Smith *et al.*[86]
Cost parameters (£)		
Cost of spirometry	1	Source unclear
Cost of spirometry plus FeNO testing	11	Assumption
Cost of FeNO testing	10	Assumption
Cost of spirometry plus MCT	63	2005 NHS Reference Costs (reported in Price *et al.*[147]) uplifted to 2012 values
Cost of spirometry and sputum induction	63	2005 NHS Reference Costs (reported in Price *et al.*[147]) uplifted to 2012 values
Annual NHS cost for long-acting ICS (prescribing using standard guidelines)	138	BNF 51[167] (reported in Price *et al.*[147]) uplifted to 2012 values

BNF, *British National Formulary*; PEF A%M > 21.6%, maximum within-day peak expiratory flow amplitude mean percentage (calculated from PEF measured twice daily over 14 days as the best of three blows).

a Note that this is a non-systematic review/opinion paper. Although Smith and Taylor[162] do state these sensitivity and specificity values and refer to two other empirical studies, neither includes the quoted estimates. The empirical source of the reported values for FeNO testing plus FEV_1 is unclear.

It should be noted that the marginal per-test cost for NIOX MINO within the Aerocrine model is assumed to be £10.00; this is substantially lower than that assumed within the Price *et al.*[147] paper (£22.90). The manufacturer states that the model should mean this £10 cost can be amended depending on the aspects that local payers find relevant. The charge of £22.90 was noted by Price *et al.*[147] as is typical and includes all secondary care costs, but this cost also needs to be amended depending on the needs of to local payers. Most NHS costs are set; thus, the £22.90 charge may not be possible (Mr David Plotts, Director for Northern Europe & UK Managing Director, Aerocrine, 9 July 2013, personal communication).

Summary of the results of the Aerocrine diagnostic model

Table 55 provides the results presented within the Aerocrine diagnostic model. The results relate to a population of 840 patients; this population size is not justified within the model.

The Aerocrine diagnostic model suggests that the combination of spirometry plus FeNO testing is expected to result in the greatest number of correct diagnoses and the fewest number of incorrect diagnoses. This is because of the assumed sensitivity and specificity of this combination (sourced from the expert review paper by Smith and Taylor[162]), both of which are higher than the values for all other tests included in the analysis.

Critical appraisal of the Price *et al.*[147]/Aerocrine diagnostic models The use of the Price *et al.*[147]/Aerocrine diagnostic models to inform judgements about the cost-effectiveness of NIOX MINO compared with standard diagnostic tests for asthma is subject to a number of problems, which are detailed in the following sections.

Deviations from the National Institute for Health and Care Excellence reference case *Table 56* shows the extent to which the Price *et al.*[147] diagnostic model and the Aerocrine diagnostic model adhere to the NICE reference case for economic evaluations of diagnostic interventions.[145] Although the Price *et al.*[147] diagnostic model was not originally developed to inform this NICE appraisal, the model submitted by Aerocrine follows the same general approach and therefore should be interpreted in light of NICE's reference case.

TABLE 55 Results estimated within the Aerocrine diagnostic model

Diagnostic option	No. of correct diagnoses (TPs and TNs)	No. of incorrect diagnoses (FPs an FNs)	Difference	Cost of incorrect diagnoses (diagnosis cost only) (£)	No. of FP diagnoses	Cost of FP diagnoses (£)	Cost of FP steroid use (£)
Spirometry alone	572	268	303	268	54	54	7419
Spirometry and (if spirometry negative) MCT	719	121	597	4319	102	3102	14,096
Spirometry and (if spirometry negative) FeNO testing	659	181	478	1455	155	1171	21,441
Spirometry and FeNO testing combined	784	56	728	614	38	414	5193
FeNO testing alone	691	149	542	1492	113	1129	15,580
Spirometry and (if spirometry negative) sputum induction	629	211	419	9938	151	6150	20,773

TABLE 56 Adherence of the Price *et al.*[147]/Aerocrine diagnostic models to the NICE reference case

Element of HTA	Reference case	EAG comments
Defining the decision problem	The scope developed by the NICE	The Price *et al.*[147] diagnostic model was not developed specifically to inform the NICE diagnostic appraisal of FeNO, yet this same general model approach was employed within the Aerocrine submission. The intervention and comparators are generally in line with the NICE scope. However, the economic outcome does not include health consequences quantified in terms of health gains/losses. The population in both models is restricted to non-smoking adults with mild to severe asthma as seen in both primary and secondary care
Comparator	Therapies routinely used in the NHS, including technologies regarded as current best practice	Comparators include tests commonly used in the NHS for the diagnosis of asthma: bronchial provocation, lung function testing, reversibility testing and sputum eosinophil count. Sputum induction is not widely used in England and Wales. Importantly, the base-case analysis is presented as a blended comparison rather than as an incremental analysis between individual options. This is generally inappropriate as it may mask the most effective and/or the most cost-effective diagnostic option. Within the Aerocrine model, options are evaluated as individual diagnostic interventions. These include spirometry alone, spirometry and (if negative) MCT, spirometry and (if negative) FeNO, spirometry and FeNO, FeNO alone and spirometry and (if negative) sputum induction
Perspective on costs	NHS and Personal Social Services	A payer perspective was adopted by Price *et al.*;[147] however, this is restricted to short-term costs only – treatment costs for diagnosed asthma are not included. The Aerocrine diagnostic model includes costs of diagnostic tests and treatment costs for FPs. The time horizon for costing is not explicit. Personal Social Services costs are not considered in either model
Perspective on outcomes	All health effects on individuals	Health gains and losses associated with correct/incorrect diagnoses are not reported by Price *et al.*[147] The Aerocrine model reports numbers of TPs, FPs, TNs and FNs expected within a cohort of 840 patients
Type of economic evaluation	Cost–utility analysis	The Price *et al.*[147] diagnostic analysis represents a cost comparison; although diagnostic outcomes are calculable, these are not reported. The Aerocrine model quantifies numbers of correct/incorrect diagnoses but does not value these in terms of health gains or losses
Synthesis of evidence on outcomes	Based on systematic review	Price *et al.*[147] report that estimates of test sensitivity and specificity are based on three published papers identified by a systematic review of the literature.[86,162,163] The Aerocrine submission does not present any detail regarding methods used to identify or select evidence used to inform its parameters. The full range of empirical evidence relating to the diagnostic accuracy of FeNO used in combination with other tests is not captured in either model
Measure of health effects	QALYs	Neither the Price *et al.*[147] diagnostic model nor the Aerocrine diagnostic model measure or value health outcomes associated with correct/incorrect diagnoses

TABLE 56 Adherence of the Price *et al.*[147]/Aerocrine diagnostic models to the NICE reference case (*continued*)

Element of HTA	Reference case	EAG comments
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	HRQoL is not captured in either model
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	HRQoL is not captured in either model
Discount rate	An annual rate of 3.5% on both costs and health effects	In both models, costs and outcomes are not discounted
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	HRQoL is not captured in either model

Absence of quantified health consequences resulting from diagnostic decisions A key limitation of both the Price *et al.*[147] diagnostic model and the Aerocrine diagnostic model is that neither model attempts to value the health gains/losses resulting from correct/incorrect diagnoses of asthma. Although it may be reasonably inferred that a more sensitive and specific test will result in more correct diagnoses, and hence greater health gains from the use of that test, these factors are not captured within either model. Consequently, it is difficult to infer whether the health gains associated with a more sensitive and/or specific test outweigh the potential opportunity costs associated with displacing existing treatments and services.

Use of a blended comparison approach (Price et al.*[147] diagnostic model only)* The base-case analysis presented within the Price *et al.*[147] paper adopts a blended comparison approach. The results are not presented as an incremental comparison of the costs and consequences of NIOX MINO compared with individual comparator tests. This is misleading – although the base-case analysis suggests that NIOX MINO alone is more sensitive than the weighted mix of standard tests used to diagnose asthma, its sensitivity and specificity are both lower than those for bronchial provocation. It would be more appropriate to incrementally compare NIOX MINO against each individual diagnostic test; this is the approach adopted within the Aerocrine model submitted to NICE.

Anticipated use of NIOX MINO Both the Price *et al.*[147] diagnostic model and the Aerocrine diagnostic model reflect a situation in which NIOX MINO would replace existing standard tests for the diagnosis of asthma. The situation in which NIOX MINO is added to existing tests within the pathway, compared with those existing tests, as is suggested to be the more likely use of FeNO testing within the NHS by Price *et al.*,[147] is not adequately considered within the analysis. In addition, both models lack clarity with respect to the diagnostic setting in which the choice of diagnostic strategy is made (i.e. primary or secondary care).

Non-specific placement of NIOX MINO within the broader diagnostic pathway for asthma The Price *et al.*[147] analysis crudely compares NIOX MINO with individual diagnostic tests. In reality, some patients may achieve a positive or negative diagnosis only following a sequence of tests. This is undoubtedly an issue relating to the available evidence base at the time of model development; however, this limitation should be borne in mind when interpreting the results reported within the Price *et al.*[147] paper. In contrast, the submitted Aerocrine model includes some test sequences; however, these do not reflect potential correlations between each test in the pathway (sensitivity and specificity are assumed to be random and uncorrelated between tests).

Crude assumptions regarding the resolution of incorrect diagnoses The Price *et al.*[147] model assumes that incorrect diagnoses are resolved at the next visit. Conversely, the Aerocrine model does not include the costs of additional visits required to resolve incorrect diagnoses, but instead attempts to capture the costs associated with ICS use in patients who are FP. Both of these factors reflect relevant costs to the NHS and should be included in any economic analysis of FeNO testing. In addition, the time horizon over which incorrect diagnoses prevail is unclear and no discounting is applied to cost estimates.

Questionable validity of FeNO testing plus FEV_1 operating characteristics It is noteworthy that the estimates of test sensitivity and specificity for spirometry plus FeNO testing, the most favourable option within both diagnostic models included in this review, appear to have been derived from an expert review paper[162] rather than from an empirical study. The expert review paper does make reference to the sensitivity and specificity estimates of 0.93 and 0.94 as used in the models and does provide an apparent (yet ambiguous) reference to two other empirical studies.[86,168] However, neither the Dupont *et al.*[168] study nor the Smith *et al.*[86] study referenced by Smith and Taylor[162] report these estimates (or indeed any estimate of the joint sensitivity and specificity of FeNO testing plus FEV_1). The credibility of these estimates cannot be verified by the EAG and hence the credibility of the Price *et al.*[147]/Aerocrine model findings should be considered highly questionable.

Lack of clarity regarding methods to identify and select evidence Within the Aerocrine model, the sources of the costs of spirometry are unclear and the costs of NIOX MINO appear to be based solely on assumption (see earlier personal communication). The costs of NIOX MINO are substantially different between the two models (£22.90 vs. £10). It is unclear whether either estimate would reflect the true costs borne by the NHS. In addition, the methods used to identify and select evidence regarding test operating characteristics are particularly unclear within the Aerocrine model.

Limited consideration of uncertainty Both versions of the diagnostic model are evaluated deterministically using point estimates of parameters. Probabilistic sensitivity analysis (PSA) is not reported by Price *et al.*[147] and is not included in the submitted Aerocrine model.

It is reasonable to suggest that the existing evidence base relating to the cost-effectiveness of FeNO testing for the diagnosis of asthma is methodologically limited and should be interpreted with caution.

Existing economic analyses of FeNO testing for the management of asthma

Methods and results of included management studies

The Price *et al.*[147] study also included the methods and results of a separate model of the cost-effectiveness of FeNO testing using NIOX MINO for the management of asthma. The same model structure was also used in the German economic evaluation of FeNO testing for asthma reported by Berg and Lindgren.[148] In addition, the submission by Aerocrine also included an asthma management model based on the analysis published by Price *et al.*[147] No other published papers that evaluated FeNO testing for the management of asthma were identified.

An economic evaluation of NIOX MINO airway inflammation monitor in the United Kingdom:[147] management model

Description of the economic model and analysis The management model as described by Price *et al.*[147] uses a decision tree approach to evaluate the cost-effectiveness of NIOX MINO compared with standard guidelines for the management of asthma. The model adopts a UK health-care payer perspective and costs and outcomes are evaluated over a 1-year time horizon. The results are presented in terms of the

incremental cost per QALY gained. Patients within the model were assumed to be non-smokers with mild to severe diagnosed asthma. Patients were assumed to be at step 3 and above as per GINA[129] and BTS/SIGN[164] guidelines, that is, receiving ICSs and LABAs for asthma management. Patients were assumed to visit their GP four times per year to determine the appropriate ICS dosage; it is unclear whether this applies to both groups or the FeNO management group only.

The two management strategies compared within the model were:

- intervention: ICS dosage titration using NIOX MINO
- comparator: ICS dosage titration based on standard guidelines.

The model uses different sources to inform parameters relating to the baseline risks and relative risks of exacerbation and ICS use.[2,97,169] Only one of these three studies involved asthma management according to BTS/SIGN guidelines.[2]

The structure of the model is shown in *Figure 22*. The model assumes that patients are either well controlled or experience an exacerbation. Exacerbations are assumed to be either severe or mild to moderate. A proportion of the severe exacerbations are assumed to require hospitalisation whereas the remainder are assumed to be manageable on an outpatient basis. A mild to moderate exacerbation was defined as an exacerbation requiring a SABA in addition to usual medication; a severe exacerbation was defined as an exacerbation requiring corticosteroids (and, in some patients, hospitalisation). The successful control of exacerbations is assumed to be related to an improvement in HRQoL and a reduction in ICS use.

The parameter values and evidence sources listed in the Price *et al.*[147] management model are shown in *Table 57*.

In addition to the base-case analysis, the authors undertook 18 one-way sensitivity analyses. These include examining the impact of the baseline risk of exacerbations, health utilities, number of routine visits required per year, ICS dose reductions and costs of NIOX MINO on the cost-effectiveness of NIOX MINO compared with standard guidelines.

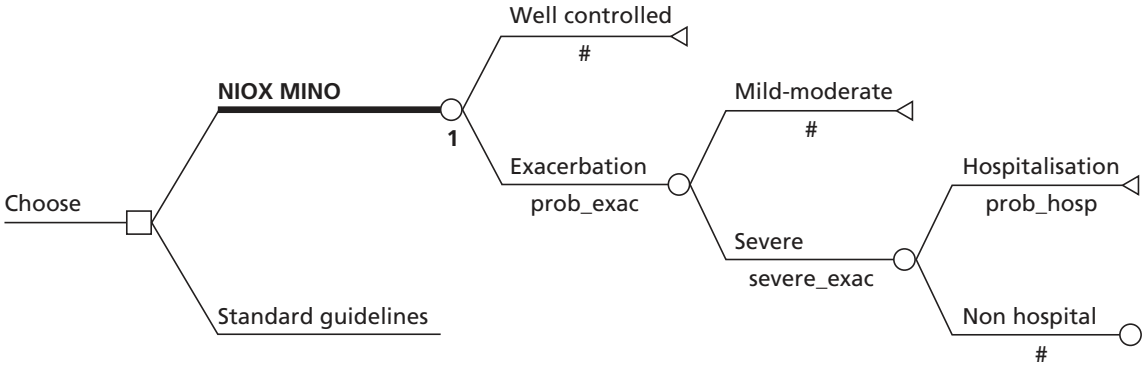


FIGURE 22 Model structure employed within the Price *et al.*[147] management model. Reproduced with permission from Price D, Berg J, Lindgren P. An economic evaluation of NIOX MINO airway inflammation monitor in the United Kingdom. *Allergy* 2009;**64**:431–8.[147] John Wiley & Sons. © 2009 The Authors. Journal compilation © 2009 Blackwell Munksgaard.

TABLE 57 Parameter values and evidence sources used in the Price *et al.*[147] management model

Parameters	Value	Source
Baseline event probabilities		
Exacerbation risk during 1 year	0.71	Jayaram *et al.*[169]
Proportion of exacerbations that are severe	0.23	Jayaram *et al.*[169]
Hospitalisation for severe exacerbations	0.23	Green *et al.*[2]
Proportion of severe exacerbations requiring an outpatient visit	0.75	Andersson *et al.*[170]
Mean number of severe exacerbations per year (overall population)	2	Jayaram *et al.*;[169] Tattersfield *et al.*[171]
Mean number of severe exacerbations per year (moderate to severe asthma)	4	Green *et al.*[2]
Impact of FeNO management		
Reduction in ICS dose	0.42	Smith *et al.*[97]
Relative risk reduction of exacerbation	0.29	Jayaram *et al.*[169]
Relative risk reduction of hospitalisation for severe exacerbation	0.83	Green *et al.*[2]
Utility values		
Well-controlled asthma	0.93	Szende *et al.*[172]
Mild/moderate exacerbation	0.65	Szende *et al.*[172]
Severe exacerbation	0.52	Szende *et al.*[172]
Resource cost parameters (£)		
Outpatient visit to GP	30.00	Curtis and Netten[166]
Outpatient visit to lung specialist	44.00	Curtis and Netten[166]
Hospitalisation for asthma	2231.45	BNF 51[167]
Maintenance therapy (1 year) with LABA	359.84	BNF 51[167]
Maintenance therapy (1 year) with ICS	109.00	BNF 51[167]
Rescue therapy (1 week) with SABA	7.38	BNF 51[167]
Rescue therapy (1 week) with oral prednisone	5.13	BNF 51[167]

BNF, *British National Formulary*.

Management model results presented by Price et al.[147] The model results reported by Price *et al.*[147] are presented in *Table 58*. For patients with moderate to severe asthma, FeNO monitoring was estimated to result in 0.004 additional QALYs compared with standard guidelines. FeNO monitoring was also estimated to result in cost savings of £554 per patient in this group. For patients with mild to moderate asthma, FeNO monitoring was estimated to result in 0.06 additional QALYs compared with standard guidelines. FeNO monitoring was also estimated to result in cost savings of £341 per patient in this group. Given its lower cost and increased QALY gain, FeNO monitoring was expected to dominate standard guidelines in both patient groups. It should be noted that the distinction between mild to moderate and moderate to severe in terms of input parameters is not entirely clear from the Price *et al.*[147] paper.

The results of the simple sensitivity analyses indicate that, for all but one scenario (NIOX MINO in addition to rather than instead of standard lung function tests), NIOX MINO is expected to dominate standard guidelines. Within the last scenario, NIOX MINO in addition to standard lung function tests is expected to cost £279 per QALY gained compared with standard guidelines.

Additional analysis presented within the submitted Aerocrine management model The schematic of the Aerocrine management model is presented in *Figure 23*.

Table 59 presents the parameter values and evidence sources used in the Aerocrine management model; the column on the right hand side indicates whether the source and parameter value are the same as those in the published Price *et al.*[147] management model.

The management model submitted by Aerocrine is similar to the published Price *et al.*[147] management model in terms of its structure and both models share many common parameter values. However, the two models do not make identical assumptions and hence do not provide identical estimates of incremental costs and effects of FeNO monitoring compared with standard guidelines.

Summary of the results of the Aerocrine management model Although the Aerocrine management model does not present the incremental cost-effectiveness ratio (ICER) for FeNO monitoring compared with standard guidelines in the main results worksheet, elsewhere the model indicates that FeNO monitoring is expected to produce an additional 0.045 QALYs and reduces costs by £103.11 compared with standard care.

Critical appraisal of the Price *et al.*[147]/Aerocrine management model The use of the Price *et al.*[147]/Aerocrine management models to inform judgements about the cost-effectiveness of NIOX MINO is subject to a number of methodological problems, as detailed in the following sections.

TABLE 58 Sensitivity analysis results reported by Price *et al.*[147]

Scenario	Cost (£)			QALYs			ICER
	NIOX MINO	Standard guidelines	Difference	NIOX MINO	Standard guidelines	Difference	
Moderate to severe asthma	628	1181	–554	0.730	0.726	0.004	Dominating
1-year baseline risk of exacerbation of 0.35 (base case 0.71)	589	915	–326	0.857	0.83	0.027	Dominating
Utility for moderate control of asthma of 0.76 (base case 0.65)	666	1007	–341	0.835	0.800	0.035	Dominating
Different number of monitoring visits per year for mild to severe asthma (base case four visits)							
Two visits per year	620	828	–208	0.785	0.726	0.059	Dominating
Six visits per year	712	1185	–473	0.785	0.726	0.059	Dominating
Different number of monitoring visits per year for moderate to severe asthma (base case, four visits)							
Two visits per year	582	1003	–421	0.730	0.726	0.004	Dominating
Six visits per year	673	1360	–687	0.730	0.726	0.004	Dominating
Different NIOX MINO cost for mild to severe asthma							
–50%	620	1007	–387	0.785	0.726	0.059	Dominating
+50%	712	1007	–295	0.785	0.726	0.059	Dominating
Different NIOX MINO cost for moderate to severe asthma							
–50%	582	1181	–599	0.730	0.726	0.004	Dominating
+50%	673	1181	–508	0.730	0.726	0.004	Dominating
Different level of ICS dose reduction for mild to severe asthma (base case 42%)							
10%	683	1007	–324	0.785	0.726	0.059	Dominating
80%	645	1007	–362	0.785	0.726	0.059	Dominating
Different level of ICS dose reduction for moderate to severe asthma (base case 42%)							
10%	639	1181	–543	0.730	0.726	0.004	Dominating
80%	616	1181	–565	0.730	0.726	0.004	Dominating
Different relative risk reduction for exacerbation for mild to severe asthma (base case 29%)							
10%	707	1007	–300	0.747	0.726	0.021	Dominating
50%	621	1007	–386	0.828	0.726	0.102	Dominating
Different relative risk reduction for hospitalisation for moderate to severe exacerbation (base case 0.83)							
10%	869	1181	–312	0.727	0.726	0.001	Dominating
100%	571	1181	–610	0.731	0.726	0.005	Dominating
NIOX MINO in addition to rather than instead of standard lung function tests (added costs)	1023	1007	17	0.785	0.726	0.059	£279 per QALY gained

ICER, incremental cost-effectiveness ratio.

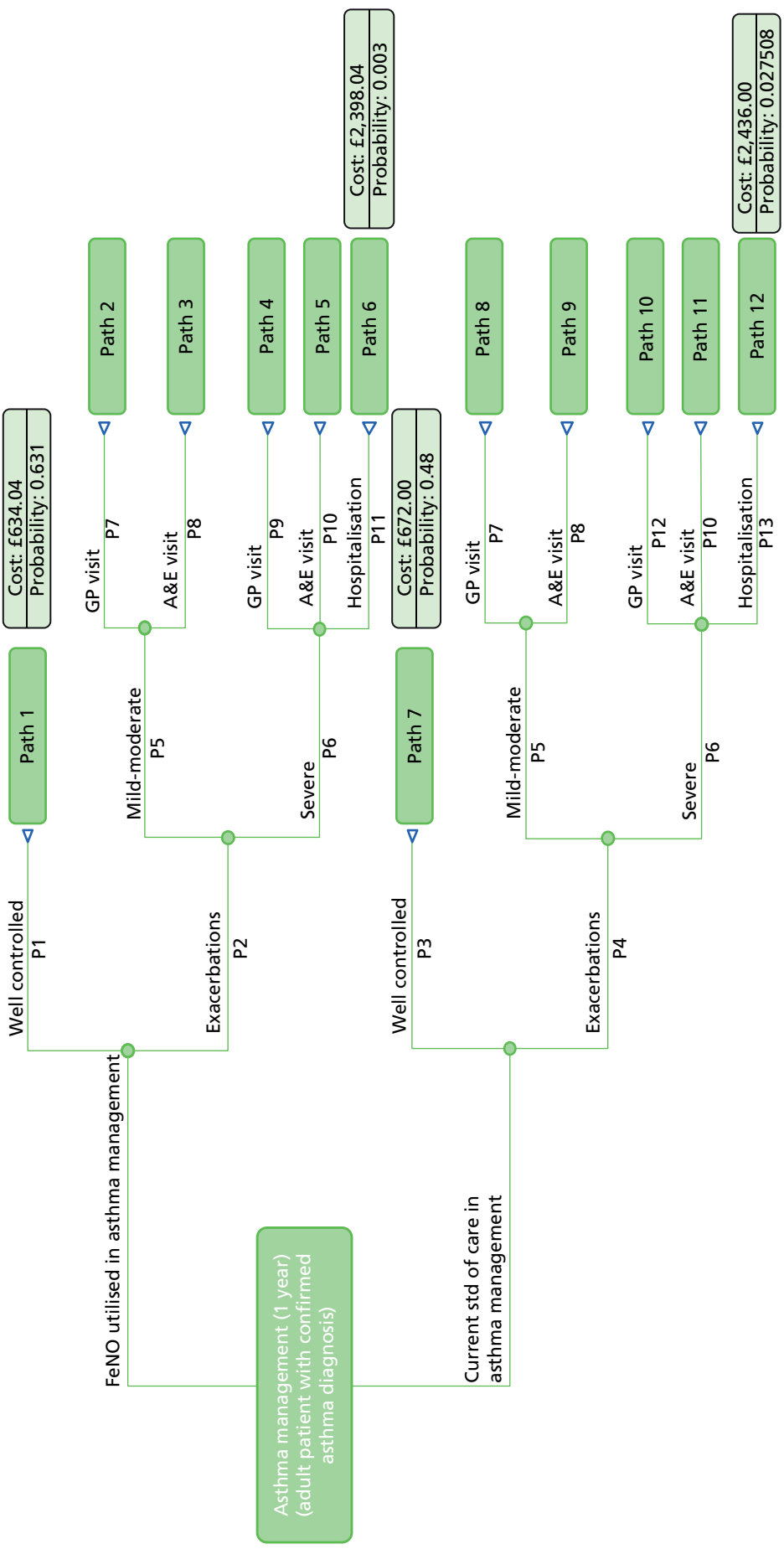


FIGURE 23 Management model submitted by Aerocrine. A&E, accident and emergency.

TABLE 59 Parameter values used in the Aerocrine management model

Variable ID	Variable description	Value	Source/justification	Same as Price *et al.*[147] model
P2	Likelihood of exacerbation using FeNO monitoring for management	0.369	Jayaram *et al.*[169]	No
P4	Likelihood of exacerbation using standard care guidelines for asthma management	0.520	Akinbami *et al.*[173]	No
P6	Likelihood that exacerbations will be moderate to severe	0.230	Green *et al.*[2]	Yes
P8	Likelihood that mild to moderate asthma exacerbations will be treated at an emergency room or urgent care centre	0.500	Expert opinion[a]	Unclear
P10	Likelihood that FeNO patient experiencing moderate to severe asthma exacerbations will be treated at an emergency room centre	0.750	Andersson *et al.*[170]	Yes
P13	Likelihood that standard care patient experiencing a moderate to severe exacerbation will require hospitalisation	0.230	Green *et al.*[2]	Unclear
F1	Reduction in ICS dose as a result of FeNO use	0.42	Smith *et al.*[97]	Yes
F2	Reduction in risk of hospitalisation for severe exacerbations as a result of FeNO use	0.83	Green *et al.*[2]	Yes
F3	Reduction in risk of exacerbations as a result of FeNO use	0.29	Jayaram *et al.*[169]	Yes
C1	Cost of FeNO monitoring	£10.00	Assumption	Unclear
C2	Cost of spirometry	£1.00	Source unclear	Unclear
C3	Annual cost of asthma medications for patients managed with FeNO	£536.04	BNF 51[167] (uplifted to 2012 prices)	Unclear
C4	Annual cost of asthma medications for patients managed using standard guidelines	£594.00	BNF 51[167] (uplifted to 2012 prices)	Unclear
C5	Cost per office visit to GP	£38.00	Curtis and Netten[166] (uplifted to 2012 prices)	Unclear
C6	Cost per office visit (referral) to lung specialist	£144.00	Curtis and Netten[166] (uplifted to 2012 prices)	Unclear
C7	Cost of A&E visit for asthma exacerbation	£81.00	NHS Reference Costs[174]	Unclear
C8A	Cost of rescue medications for moderate to severe exacerbations	£15.00	BNF 51[167] (uplifted to 2012 prices)	Unclear
C8B	Cost of rescue medications for mild to moderate exacerbations	£9.00	BNF 51[167] (uplifted to 2012 prices)	Unclear
C9	Average hospital cost for asthma admission because of exacerbation	£867.00	Weighted average of Healthcare Resource Group code DZ15A-F within NHS Reference Costs[174]	Unclear
C10	Annual number of check-ups for asthma management	2	Expert opinion[b]	Yes
C13	Average annual number of exacerbations	2	Jayaram *et al.*[169]	Yes
U1	Utility value of asthma patients with good control	0.93	Szende *et al.*[172]	Yes
U2	Utility value of asthma patients with mildly reduced control	0.76	Szende *et al.*[172]	Yes

TABLE 59 Parameter values used in the Aerocrine management model (*continued*)

Variable ID	Variable description	Value	Source/justification	Same as Price *et al.*[147] model
U3	Utility value of asthma patients with moderately reduced control	0.65	Szende *et al.*[172]	Yes
U4	Utility value of asthma patients with poor control	0.52	Szende *et al.*[172]	Yes

A&E, accident and emergency; BNF, *British National Formulary*.
a The text in the model states that the model authors were unable to find statistics specific to visits for mild/moderate exacerbations; an assumption was made that half will seek care in the emergency department setting and the other half will visit their doctor's surgery (GP or pulmonary specialist).
b An assumption was made that well-controlled asthma will result in two office visits per year.

Deviations from the National Institute for Health and Care Excellence reference case *Table 60* shows the extent to which the Price *et al.*[147]/Aerocrine management models adhere to the NICE reference case for economic evaluations of diagnostic interventions.[145]

Relative risk reduction for exacerbations Price *et al.*[147] argue that the relative risk reduction associated with using FeNO monitoring may be overly conservative as the data used were drawn from a patient population including patients with mild asthma whereas the relative risk reductions may be greater in patients with more severe asthma. The validity of this statement is unclear and evidence to support this assertion is not presented in the paper.

Impact of FeNO measurement on inhaled corticosteroid dosage Price *et al.*[147] also argue that some of the parameters, such as the effect of FeNO measurement on ICS usage, were based on patients in primary care, whereas other parameters, such as impact on exacerbations, were based on patients in secondary care.

Time horizon The model adopts a very short time horizon (1 year). The impact of mortality and discounting over a longer horizon may alter the cost-effectiveness estimates presented.

Failure to undertake probabilistic sensitivity analysis The authors did not undertake PSA. Instead, the results are presented based on the point estimates of parameters and uncertainty analysis is restricted to one-way sensitivity analyses. It should be noted that the economic evaluation of NIOX MINO from the German perspective did include a full probabilistic analysis.[148] The reason for the exclusion of PSA in the UK models is unclear.

Questionable methods for the selection of evidence used to inform the model parameters The methods used to identify and select evidence to inform the model parameters were not fully described in either the Price *et al.*[147] model or the Aerocrine model. It is unclear whether other evidence sources exist which indicate that different parameter values may be more appropriate. In particular, the model draws estimates of the relative reduction in exacerbations from FeNO monitoring from a study that used sputum induction monitoring rather than FeNO monitoring, hence assuming equivalence, despite the fact that exacerbation risk information was reported in the FeNO trial used to estimate reductions in ICS usage.[97]

Inappropriate sourcing of resource and cost estimates Several unit cost parameters within the Aerocrine model are based on those presented in the Price *et al.*[147] model, uplifted to 2012 values. For parameters such as drug costs and Healthcare Resource Groups, this is inappropriate as the *British National Formulary* and NHS Reference Costs are updated regularly to reflect current prices. Consequently, several of the cost estimates included in the submitted model may not reflect the prices paid by the NHS.

TABLE 60 Adherence of the Price *et al.*[147]/Aerocrine management models to the NICE reference case

Element of HTA	Reference case	EAG comments
Defining the decision problem	The scope developed by NICE	The patient population is defined in both models as non-smoking adults diagnosed with mild to severe asthma. This population excludes children and smokers. The intervention and comparator are in line with the NICE scope
Comparator	Therapies routinely used in the NHS including technologies regarded as current best practice	The comparator is standard care without FeNO monitoring. This is appropriate although it should be noted that the studies used to inform the model parameters did not all use BTS/SIGN guidelines[164] to guide treatment
Perspective on costs	NHS and Personal Social Services	The published Price *et al.*[147] management model purports to have adopted a payer perspective. It appears that the submitted Aerocrine model adopts the same perspective although this is not explicitly stated in the model workbook
Perspective on outcomes	All health effects on individuals	Health outcomes reflect those accrued by NHS patients. Health gains are assumed to be influenced only by the level of control achieved, which is in turn assumed to be directly related to the incidence of exacerbations
Type of economic evaluation	Cost–utility analysis	The models take the form of a decision tree-based cost–utility analysis. This adopts a short time horizon (1 year). Longer-term costs and outcomes associated with FeNO monitoring are not considered within the Aerocrine management model or the published Price *et al.*[147] management model
Synthesis of evidence on outcomes	Based on systematic review	Parameter values appear to have been selected in a non-systematic fashion. Estimates of relative reductions in exacerbations are drawn from different sources from estimates of reductions in medication use (the former relates to monitoring using sputum induction rather than FeNO testing but is assumed to be equivalent)
Measure of health effects	QALYs	The HRQoL impacts of different levels of control were estimated based on estimates from the literature
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	Health utilities were based on adequacy of asthma control rather than exacerbations per se, based on a study reported by Szende *et al.*[172] Within this study, 228 consecutive adult outpatients and inpatients at four Hungarian sites completed a variety of HRQoL instruments including the EQ-5D. Utilities related to control were then qualitatively mapped to the incidence of different severities of exacerbation
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Preference-based health utilities appear to have been generated using the UK EQ-5D tariff[175]
Discount rate	An annual rate of 3.5% on both costs and health effects	Because of the short time horizon, costs and outcomes are not discounted
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting was applied

Inflated baseline exacerbation rate without monitoring The Price *et al.*[147] management model and the Aerocrine management model assume a mean rate of two exacerbations per patient per year. It appears that this estimate was based on the results of a Phase II prospective trial of 117 adults reported by Jayaram *et al.*[169] This study reported that there was a total of 126 exacerbations in 63 patients, hence an average number of approximately two exacerbations per patient. However, the trial duration was > 1 year and the mean number of exacerbations per patient per year was reported by the study authors to be 0.75 in one arm of the trial and 1.02 in the other arm of the trial.[169] The Price *et al.* paper[147] also mentions a second study[171] used to inform this baseline exacerbation rate. In this latter study, the authors observed 425 severe exacerbations in 852 randomised patients over a 12-month period (approximate rate = 0.499 exacerbations per year). Both studies clearly indicate that the baseline exacerbation rate used in the Price *et al.*[147]/Aerocrine models is substantially overestimated; hence, the expected benefits of FeNO testing are likely to be artificially inflated.

Assumption that exacerbation determines health-related quality of life for the entire time horizon The Price *et al.*[147]/Aerocrine management models make an assumption that the incidence of exacerbations is directly related to the level of asthma control and apply health utilities according to the incidence of exacerbations. The models apply these health utilities over the modelled time horizon (1 year) rather than to the duration over which the exacerbation occurs (hours to weeks). This is likely to substantially overestimate the health benefits associated with reducing exacerbations through improved dose titration.

Use of expert opinion The Aerocrine management model includes the use of expert opinion to inform a small number of parameters for which the authors could not identify relevant evidence. Although expert opinion is a valid source of evidence in such circumstances, no details are provided with respect to the sources of these judgements or the methods used to elicit them. In the absence of a written submission that presents these details, the credibility of such judgements remains unclear.

The existing models of FeNO monitoring for asthma indicate that NIOX MINO is expected to dominate standard guidelines. However, given the methodological concerns identified within the critical appraisal, these findings should be interpreted tentatively.

Other studies relating to the cost-effectiveness of asthma management strategies

Given the limited number of studies of FeNO testing for the management of asthma, we also reviewed other studies of interventions for asthma management to inform the key disease-specific factors that should, or could, be included in a cost-effectiveness model of FeNO testing for the management of asthma.

Thirteen studies[149–154,157–161,176,177] (not related to FeNO testing) were included in the focused review of economic analyses of asthma management interventions; these studies are briefly summarised in *Table 61*.

TABLE 61 Summary of other identified economic analyses of asthma management interventions

Author, year	Summary description
Studies reporting QALYs	
Briggs 2006[150]	Cost–utility analysis undertaken alongside a clinical trial. The intervention was asthma treatment with salmeterol/fluticasone propionate in combination; the comparator was fluticasone propionate. Utility values for the model states were mapped from AQLQ scores. Within the GOAL study, patient treatment could be titrated upwards up to three times but not downwards. The amount of titration required was used to define three patient groups by asthma severity (stratum 1, stratum 2, stratum 3). The model states were 'totally controlled', 'well controlled', 'not well controlled but without an exacerbation' and 'exacerbation'. The cycle length was 1 week. A multinomial regression approach using individual patient-level data from the trial was used to estimate the transition probabilities of moving between states over the course of each week
Doull 2007[151]	Simple economic model comparing the cost-effectiveness of salmeterol xinafoate/fluticasone propionate combination inhalers with non-combination inhalers for adults and children with chronic asthma treated according to BTS/SIGN guidelines.[178] Clinical effectiveness was estimated from meta-analyses comparing the percentage of symptom-free days for each treatment (%SFD). The definition of SFD was assumed to be consistent with that provided in the GOAL study. The %SFD was assumed to be time invariant; hence, differences in clinical effectiveness between treatment options were assumed to be entirely due to this parameter. A 1-year time horizon was used. QALY gains were estimated from AQLQ data recorded in the GOAL study using a mapping algorithm to the EQ-5D
Paggiaro 2011[153]	A poster that discusses a patient-level Markov model. The decision problem concerns the cost-effectiveness of stepping down treatment according to GINA guidelines.[129] Very limited detail on the methods was available
Peters 2002[149]	UK technology assessment report evaluating submissions from several manufacturers of inhaler devices. Most (six out of eight) of the manufacturers submitted cost-minimisation analyses only. The assessment group did not develop a de novo model; instead, a QALY-based threshold analysis was performed
Wilson 2010[152]	Economic evaluation comparing the addition of either a LTRA or a LABA for patients who were already receiving ICSs as part of asthma management and for whom a decision to add on additional treatment to improve their condition had been made. The analysis was based on a pragmatic trial involving 53 primary care practices. Patients judged to need add-on therapy were randomly assigned to receive either a LTRA or a LABA. The trial duration was 2 years. The patient age range included children and adults. The differences in EQ-5D and ACQ scores between the LTRA group and the LABA group were reported, together with differences in resource use
Studies not based on QALYs	
Andersson 2000[177]	Poster abstract which argues that using 800 µg rather than 200 µg/day of budesonide is cost saving in patients with moderate asthma in the UK. Estimates were based on a survey of 20 physicians from the UK, Sweden and Spain
Barnes 1999[155]	Poster abstract that summarises a meta-analysis comparing fluticasone propionate and budesonide for the treatment of asthma. The study appears mainly to be a cost–consequence analysis as it refers to differences in clinical parameters, such as morning PEF rate, successfully treated weeks and symptom-free days. The poster concludes that fluticasone propionate is both more clinically effective and cheaper than budesonide
Booth 1995[154]	Cost comparison based on a RCT comparing fluticasone propionate (200 µg) via a diskhaler with budesonide (200 µg) via a reservoir dry powder device. The study provides estimates for the cost per successfully controlled week
Buxton 2004[159]	Economic evaluation based on a 3-year international prospective RCT, the Steroid Treatment as Regular Therapy (START) trial. The trial compared budesonide against placebo combined with usual asthma therapy. The trial included patients from the UK although all costs were converted to US dollars for comparability. ICERs were calculated for the UK as well as for other countries, with the measure of health benefit being symptom-free days. Estimates for UK costs were based on only 39 patients
Everden 2002[157]	Economic evaluation in children aged 6–17 years inclusive alongside a prospective multicentre open-label parallel-group study conducted in primary care in the UK and the Republic of Ireland (the FACT study). Most (> 95%) patients were at BTS step 1 or step 2 with a small proportion at step 3. The trial duration was 12 weeks. End points were change in SABA use (primary end point), PEF, number of poorly controlled days and quality of life evaluated using the Paediatric Asthma Quality of Life Questionnaire (PACLQ). When the clinical outcome was symptom-free days with no SABA use, use of eformoterol was estimated to rule out salmeterol by simple dominance, saving approximately 25 p per patient per day whilst resulting in approximately 10 additional symptom-free days over the 12-week period

TABLE 61 Summary of other identified economic analyses of asthma management interventions (*continued*)

Author, year	Summary description
Kemp 2010[161]	Economic evaluation based on a retrospective analysis of patients recorded in the UK General Practice Research Database (GPRD) from 1997 to 2007. Patients were included in the analysis if they had been registered at the same practice, had a diagnosis of persistent asthma and had been receiving treatment with ICSs. Two patient populations were identified: an initiation population who had started ICSs and a step-up population who had been prescribed an increased ICS dose. Both populations had to have been followed up for at least 12 months on their current regimen. The clinical effectiveness and cost-effectiveness of three inhaler technologies were compared for these patient populations. The clinical outcome was 'achieving asthma control within 1 year'. Asthma control was defined as a composite measure involving no hospital attendance for asthma, no OCS use and no consultation or hospital admission or attendance related to asthma
Price 2002[158]	Markov model based on a 12-week RCT of patients diagnosed with asthma aged 12–70 years (FEV_1 40–85% predicted). The main clinical outcome was the number of 'successfully controlled weeks'. The intervention arm received fluticasone propionate whereas the comparator arm received salmeterol/fluticasone propionate combination. Health states included in the model were 'successful control', 'hospital-managed exacerbation', 'primary care-managed exacerbation', 'suboptimal control' and 'treatment failure'
Price 2007[160]	Cost-minimisation analysis based on a 6-month, double-blind RCT. Resource use data were collected prospectively; these included medication costs and non-medication costs such as hospitalisations. The trial was international, with patients recruited from 16 countries. Costs were converted to 2004 UK costs. Patients were recruited if they were aged > 12 years at the time of recruitment and had been diagnosed with asthma at least 6 months previously and had been using ICSs continuously for at least 3 months. Compared with using ICSs alone, using budesonide/formoterol maintenance and reliever therapy was estimated to save the NHS around £90 per patient over the 6-month trial period

GOAL, Gaining Optimal Asthma control.

Health outcomes and form of economic evaluation

Of the 13 studies included in the focused management review, five reported QALYs gained as the measure of health benefit.[149–153] One of these studies[153] was published only in the form of a conference poster and provided very limited detail regarding the model structure. The study reported by Peters *et al.*[149] included only threshold analyses, indicating the necessary QALY impact to justify an incremental increase in cost. Of the eight studies that did not report QALYs, four were cost-effectiveness analyses. These studies reported health benefits in terms of:

- symptom-free days with no SABA use[157]
- successfully controlled weeks[158]
- symptom-free days[159]
- achieving asthma control within 1 year.[161]

Model structures

Several of the included economic evaluations were decision analyses conducted alongside clinical trials and did not explicitly involve the use of evidence synthesis or extrapolation. Three studies used Markov structures.[150,153,158] The Briggs *et al.*[150] and Price and Briggs[158] studies both used similar methodologies. Each was based primarily on data from a single, although different, study. The Price and Briggs[158] model categorised health states into five discrete categories: 'successfully controlled', 'suboptimal control', 'primary care-managed exacerbation', 'hospital-managed exacerbation' and 'treatment failure'. Treatment failure was an absorbing state; patients could transition between any of the other states during a given Markov cycle. The cycle length was 1 week and so the assumption was made that an individual could not have more than one exacerbation within 1 week. The time horizon of the model was 12 weeks (equal to the duration of the RCT) and the analysis did not extrapolate anticipated lifetime effects of treatment. The model used the number of exacerbation-free weeks as the measure of health benefit; this disease-specific

outcome measure is difficult to interpret from a policy context. The Briggs *et al.*[150] model was similar in that it was a model based on individual patient-level data from a single trial. This model adopted four discrete health states: 'totally controlled', 'well controlled', 'not well controlled' and 'exacerbation'. These health states differ from those in the Price and Briggs model[158] in that there were three non-exacerbation health states and only one exacerbation health state. This different categorisation implicitly reflects a different set of assumptions about the key factors that influence the clinical effectiveness and cost-effectiveness of different treatment options.

In addition to the studies identified by the search strategy described above, the *Health Technology Assessment* journal was searched from inception onwards for asthma management models. This search identified an additional asthma management model[13] that was similar in structure to the Price and Briggs[158] model. The report assessed the comparative effectiveness of different ICS treatments with or without LABAs for patients aged ≥ 12 years who had been diagnosed with chronic asthma. Unlike the Price and Briggs[158] model, this model was a cost–utility analysis and therefore measured health benefits in terms of QALYs gained. The intention of this model was to represent clinical practice, as described in the BTS/SIGN guidelines,[164] by including different separate health states to represent dosage levels corresponding to different BTS/SIGN treatment steps. For two steps, corresponding to step 2 and step 3 of the BTS/SIGN guidelines, the conceptual model is shown in *Figure 24*. The cycle length was 1 week and the time horizon was 5 years. The key disease-specific factors included in the model relate to whether the patient experiences an exacerbation within a model cycle and, if so, the severity of the exacerbation. By allowing transitions between different levels of treatment, however, changes in treatment in response to clinical events were also incorporated.

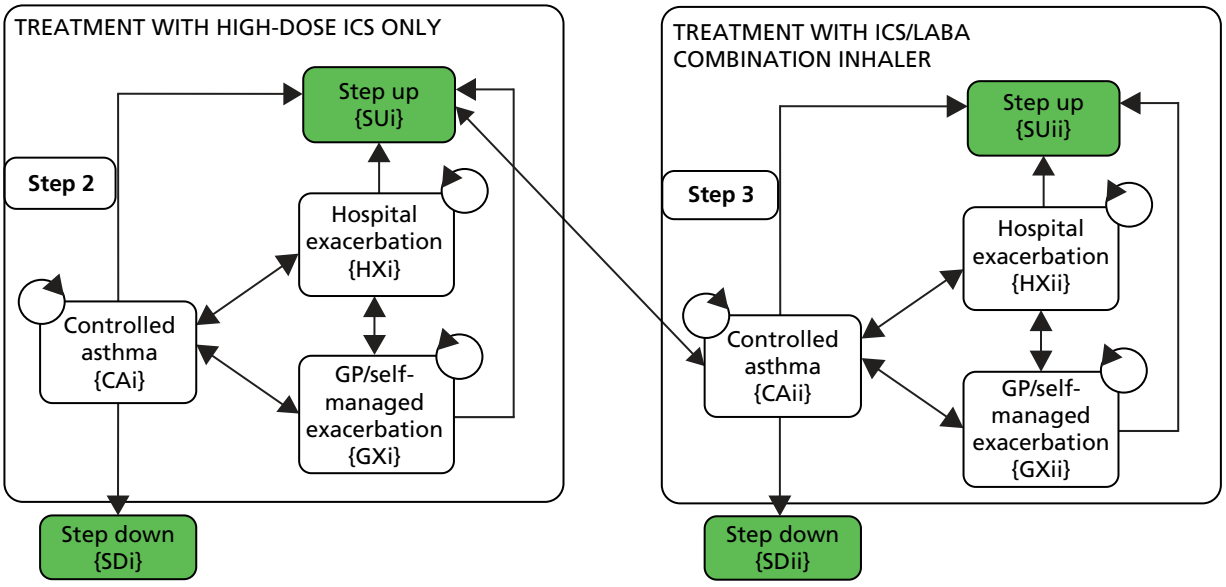


FIGURE 24 Conceptual model adopted by Shepherd *et al.*[13]

Discussion of the available economic evidence on the diagnosis and management of asthma using FeNO and other interventions

The review highlights a dearth of published studies reporting on the cost-effectiveness of FeNO testing for the diagnosis and/or management of asthma. Only one published UK cost-effectiveness model of asthma diagnosis was identified and included in the review;[147] this model estimates the incremental costs of FeNO testing compared with existing standard tests for asthma. No other cost-effectiveness models of FeNO or other diagnostic tests were identified by the searches. Similarly, the review of economic analyses of asthma management interventions identified only one UK-published study of FeNO monitoring.[147] Modified versions of these FeNO management and diagnostic models were submitted to NICE by Aerocrine. No evidence was submitted by Aerocrine with respect to the expected cost-effectiveness of NIOX VERO. Bedfont Scientific did not submit any economic evidence relating to the cost-effectiveness of NObreath.

The wider review of economic analyses of asthma management interventions identified a number of other economic analyses, although few were undertaken within a formal modelling framework involving evidence synthesis and/or extrapolation. These models have the following features in common: (1) the use of a Markov modelling approach with generally short cycle lengths, typically 1 week in duration; (2) short time horizons; and (3) separate states for asthma exacerbations. Only two of the model-based studies reported QALYs as the measure of health outcome.

The available economic evidence for FeNO testing suggests that, in the diagnostic setting, monitoring using NIOX MINO may reduce the costs of diagnosis (depending on how it is used) compared with standard tests, whereas in the management setting monitoring using NIOX MINO may dominate standard guidelines. However, this evidence is subject to a number of methodological problems, questionable assumptions and weak evidence. The results of these existing analyses should be interpreted with caution.

Development of two de novo models to estimate the cost-effectiveness of FeNO testing for the diagnosis and management of asthma

Rationale for developing de novo models

This section describes the de novo economic models developed by the EAG to estimate the cost-effectiveness of FeNO testing (specifically using NIOX MINO, NIOX VERO or NObreath) compared with standard care for the diagnosis and management of asthma. The EAG analysis involves the development of two models: (1) a de novo model to assess the expected cost-effectiveness of FeNO testing in addition to or in place of standard tests for the diagnosis of asthma and (2) a de novo model to assess the expected cost-effectiveness of FeNO plus standard guidelines compared with standard guidelines for the management of patients with diagnosed asthma. Although these models are distinct, they form part of the same overall asthma service pathway, hence they share a number of parameter values and assumptions.

The EAG models were developed to attempt to resolve the problems identified with respect to the existing economic analyses of NIOX MINO (see *Review of existing evidence relating to the cost-effectiveness of FeNO testing for the diagnosis and management of asthma*) and to address gaps in the evidence relating to the cost-effectiveness of NObreath and NIOX VERO. It should be noted that, because of the limitations in the evidence base (see *Chapter 3*), the structures of the models are necessarily simple.

The decision to develop two models rather than a single model was made because the NICE scope reflects two distinct decision problems. Although the FeNO devices are the same in both the diagnostic setting and the management setting, the relevant populations and the way in which FeNO may influence decisions about appropriate clinical options for patients differ between settings; these potential effects are summarised in *Table 62*.

TABLE 62 Clinical intent of FeNO testing in the diagnostic and management settings

Decision problem	Clinical population	Expected impact of FeNO testing
Diagnosis	Symptomatic patients with suspected asthma	FeNO testing, alone or in conjunction with other standard tests, may alter the proportion of correct and incorrect diagnoses amongst patients with suspected asthma. Changing the proportion of people with suspected asthma who are correctly/incorrectly diagnosed may then affect the expected downstream costs and health gains/losses
Management	Patients treated for diagnosed asthma	FeNO testing may influence the level of medication use and the rates of exacerbations experienced by patients diagnosed with asthma. This will influence the mean costs and health gains accrued by these patients

At the outset, the EAG had intended to model a scenario in which FeNO testing is used *both* as a diagnostic option and as a management option. However, this analysis was not possible because of the necessary differences in the structures of the EAG diagnostic and management models.

Complexity and uncertainty surrounding the economic analysis of FeNO testing for the diagnosis and management of asthma

Given the limitations of the available evidence base (see *Chapter 3*), evaluating the expected cost-effectiveness of FeNO testing alone or in conjunction with other tests for the diagnosis of asthma is difficult. The BTS/SIGN guidelines[8] for asthma diagnosis and management state that the absence of a gold standard definition of asthma means that it is impossible to make evidence-based recommendations on how to make a diagnosis of asthma. Further, differences in patient selection, methodological aspects of study design and the generalisability of studies to UK practice make the unbiased interpretation of the available diagnostic evidence extremely problematic. The current diagnostic pathway consists of a number of tests that may be used alone or in sequence; there is not a standard set of ways in which information from each of these tests should be evaluated and weighted when used together. The evidence base examined within this assessment, however, mostly relates to studies that estimate the operating characteristics of individual diagnostic tests used at particular points within this broader diagnostic pathway. In addition, the reference standards used within studies to estimate the sensitivities and specificities of other diagnostic tests are not always consistent or optimal, studies relate to different population groups and comparative (head-to-head) studies are few in number. As a consequence, there is considerable uncertainty surrounding the true diagnostic accuracy of FeNO testing and every other test used within the diagnostic pathway.

The uncertainty in the clinical evidence base is further compounded by the lack of available economic analyses. The review presented earlier (see *Review of existing evidence relating to the cost-effectiveness of FeNO testing for the diagnosis and management of asthma*) identified only one published economic model of options for asthma diagnosis[147] (note that the same general model was used in the German economic evaluation reported by Berg and Lindgren[148]). Within this study, the authors highlight a key limitation in the scope of their analysis, that is, the analysis considers FeNO testing as a *replacement* for existing diagnostic tests; this limitation is masked somewhat by the inappropriate use of a blended comparison of multiple diagnostic tests, the absence of quantified health losses associated with misdiagnosis and the absence of a full incremental analysis. If all diagnostic tests can be substituted for one another for all patients with symptoms of asthma, as is implied by the design of the economic comparisons presented in the Price *et al.*[147] paper, then the most clinically effective option will be the diagnostic test with the greatest sensitivity and specificity (depending on the balance of health losses avoided by obtaining TP and TN diagnoses). Subject to the per-test costs and the costs and consequences of downstream tests used to correct misdiagnoses, this may or may not also represent the most cost-effective option. Downstream costs, sequences of diagnostic pathways and consequences of incorrect diagnoses are not fully addressed by the Price *et al.*[147] diagnostic model. The existing economic evidence base does not provide any information on the *additional value* of FeNO testing in conjunction with current standard tests for asthma diagnosis.

As noted by Price *et al.*,[147] in reality, FeNO testing is likely to play a role as an adjunct to existing tests currently used within the diagnostic pathway. Although Price *et al.*[147] attempt to consider the combination of FeNO testing plus FEV_1, this is against the blended comparison of standard diagnostic tests and thus it still represents a replacement option. Current pathways for asthma diagnosis in adults and children are complex;[8] within the Price *et al.*[147] diagnostic model, this complexity is avoided by the neat assumption that all misdiagnoses are resolved at some later point in time with one subsequent test (i.e. following misdiagnosis, the subsequent test is assumed to have perfect sensitivity and specificity, thereby correcting all previously incorrect diagnostic decisions). This is a substantial simplification. In reality, there may be a number of potential places in the existing pathway at which FeNO testing may provide additional diagnostic information to improve the diagnostic accuracy of current standard tests (see *Figures 7* and *8*), and misdiagnoses may prevail for months, years or, in some patients, indefinitely. These misdiagnoses may incur unnecessary treatment costs and health losses. The Price *et al.*[147]/Aerocrine diagnostic models do not fully address these issues but instead ask the question, 'What is the least expensive test for the diagnosis of asthma?'

An alternative and more sophisticated approach to evaluating the cost-effectiveness of FeNO in the diagnostic setting would involve assessing the diagnostic accuracy and cost-effectiveness of FeNO *in addition* to existing tests within the pathway. Such an analysis would address the question, 'Where in the existing sequences of tests, if anywhere, should FeNO be added to provide the most cost-effective diagnostic pathway for patients with symptoms of asthma?' This would require either (1) a similar model structure to that employed by Price *et al.*,[147] populated using studies that assess the accuracy of the whole diagnostic pathway for children and adults with and without FeNO testing, or (2) the development of a model that estimates the diagnostic outcomes of sequences of tests at each point in the pathway, which simulates the impact of changes in the true underlying prevalence of asthma conditional on the results of each test undertaken and which fully takes into account the impact of potential correlations between tests that may result in non-random test outcomes in particular patients (e.g. if test A is negative would test B also be negative in patient C?). For the former approach to be reliable, one would require studies that have assessed FeNO plus other tests against a reference standard as well as the standard tests (without FeNO) against the same reference standard, either by direct comparisons within the same study or by indirect comparisons across multiple studies with similar populations and study protocols. Price *et al.*[147] note that such data simply do not exist. The review presented in *Chapter 3* did, however, identify several studies in which FeNO was used in conjunction with other tests within *part* of the diagnostic pathway. This evidence is, however, somewhat patchy. Interestingly, the Aerocrine diagnostic model does attempt to reflect sequential options – the latter modelling approach described above – despite the problems with the available evidence previously highlighted by Price *et al.*[147] The Aerocrine model thus assumes that sequential test outcomes are random and uncorrelated between tests. This represents a strong assumption that could lead to biased estimates of the cost-effectiveness of FeNO, the magnitude and direction of which are unclear.

These are important limitations relating to the evidence base that constrain what can be achieved through the development of any economic model of asthma diagnosis. It would be unfair to heavily criticise any model when the main limitations of that model are principally sourced from the weaknesses in the evidence used to inform it. Such weaknesses do, however, limit the confidence that can and should be placed in the results of the Price *et al.*[147]/Aerocrine diagnostic models. In light of these issues, the de novo EAG diagnostic model attempts to resolve those weaknesses in the Price *et al.*[147] diagnostic model that can be resolved. Problems relating to the heterogeneity in the evidence base cannot be resolved by the EAG; hence, the results of the de novo model should also be interpreted tentatively. Insofar as the available evidence allows, the EAG de novo diagnostic model attempts to simultaneously address the following two questions:

1. As a replacement test – is FeNO expected to be more cost-effective than other existing tests used for the diagnosis of asthma?
2. As an adjunctive test – is the use of FeNO in conjunction with existing tests expected to be more cost-effective than using existing tests alone?

The economic analysis of asthma management is subject to fewer complexities because of the availability of more robust direct evidence sourced from RCTs. However, there remains a number of methodological and evidence issues. The most notable of these relate to differences in the frequency of FeNO monitoring between the trials, uncertainty regarding the longer-term benefits of FeNO monitoring over standard care, differences between studies in terms of the step-up/step-down treatment protocols used and associated issues relating to the generalisability of non-UK treatment guidelines and symptom management strategies to UK clinical practice. The economic analysis of FeNO monitoring addresses the following question:

1. What is the cost-effectiveness of FeNO monitoring compared with standard guidelines in the management of asthma?

The External Assessment Group asthma diagnostic model

Logic underpinning the diagnostic model structure

The EAG diagnostic model hinges on the expected costs and health losses associated with the misdiagnosis of asthma. If a patient has been misdiagnosed, their treatment will not be clinically optimal until their misdiagnosis has been corrected. Misdiagnosis has different implications for those patients who are FP and for those patients who are FN. For patients who are FP, suboptimal treatment means receiving treatment with asthma medication that will provide no health benefits to them (because they do not have the underlying disease). This means there is an additional cost to the NHS without additional health benefits for the patients. Furthermore, a proportion of patients with a FP diagnosis of asthma may have other more serious pathology that goes undetected (e.g. cancer or tuberculosis) because of an incorrect diagnosis of asthma. Conversely, for patients who are FN, suboptimal treatment means not receiving treatment with asthma medication when in reality they would have benefited from the treatment. Until this misdiagnosis is corrected, patients may suffer from poor asthma control and hence lower HRQoL because of asthma symptoms without adequate treatment. Poor asthma control can impact on a patient's HRQoL during times without exacerbation and can also increase the duration of exacerbations. Clinically significant exacerbations are costly to the NHS and in the case of exacerbations requiring hospitalisation these costs may be substantial; hence, a patient with undiagnosed asthma may on balance be more costly to the NHS than a patient who is correctly treated for asthma. These patients may also go on to receive expensive and unnecessary tests such as imaging and referrals to specialists until their misdiagnosis is corrected.

An incorrect FN diagnosis may be corrected later following an asthma exacerbation, as a result of continued asthma-related symptoms that trigger subsequent appointments and investigations or even because of reconsideration of asthma after tests for other conditions produce negative findings. Similarly, an incorrect FP diagnosis may be corrected later as a result of the continued non-occurrence of exacerbations, a generally high level of HRQoL at very low treatment dosages, thus indicating that medications currently being taken by the patient may be unnecessary, or continued deterioration as a result of other more serious underlying pathology. Although it should be expected that the aggregate health consequences resulting from correct decisions should be better than those resulting from incorrect decisions, the implications for HRQoL and the costs of FP and FN diagnostic outcomes are not identical. Because of this, a diagnostic strategy that maximises the AUC on a receiver operating curve may not necessarily yield the most cost-effective strategy. The EAG diagnostic model is therefore intended to reflect the implications of test sensitivity and specificity for subsequent costs and health consequences for the full range of diagnostic options within the available evidence base.

Model structure and assumptions

Figure 25 presents the structure of the EAG diagnostic model. The model is implemented as a simple decision tree. The population under consideration may or may not have true underlying asthma (denoted θ in *Figure 25*). The model then uses estimates of sensitivity and specificity associated with each diagnostic test, or combination of tests, to estimate the expected probability that a patient will be diagnosed as having asthma or as not having asthma. Therefore, the model estimates the probability that a patient with asthma will be correctly or incorrectly diagnosed as TP or FN, respectively, and the probability that a patient without asthma will be correctly or incorrectly diagnosed as TN or FP respectively. The model makes the simplifying assumption that incorrect diagnoses (FNs and FPs) are resolved by subsequent tests after some period of time (see *Evidence used to inform the External Assessment Group diagnostic and management model parameters*). Unnecessary treatment costs and health losses resulting from misdiagnosis are explicitly captured in the model.

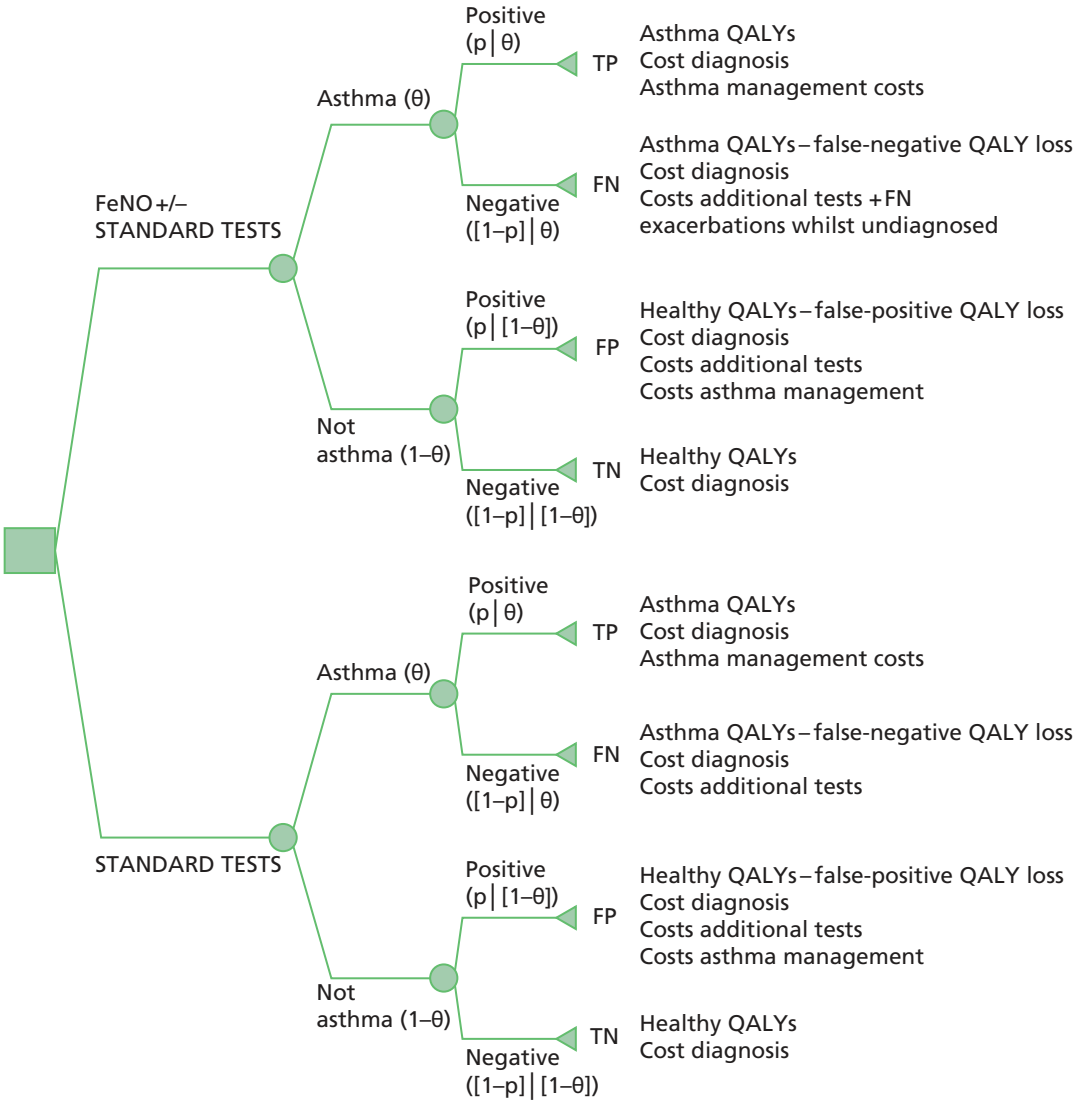


FIGURE 25 Conceptual form of the EAG diagnostic model structure.

The diagnostic model estimates costs and health outcomes for each diagnostic option across four groups:

1. Patients who are TP (test sensitivity × prevalence) are assumed to require the initial diagnostic test(s) with no subsequent tests and are assumed to have their asthma controlled using ICSs plus LABAs.
2. Patients who are TN [test specificity × (1 – prevalence)] are assumed to incur the cost of the initial test(s) with no subsequent tests and are assumed to have a normal (general population) health status for the remainder of the model time horizon.
3. Patients who are FP [(1 – test sensitivity) × (1 – prevalence)] are assumed to incur the cost of the initial test(s) plus the costs of subsequent tests to correct their initial misdiagnosis. These patients are assumed to incur a reduction in health status and the costs of ICSs and LABAs until their misdiagnosis is corrected.
4. Patients who are FN [(1 – test sensitivity) × prevalence] are assumed to incur the cost of the initial test(s) plus the costs of subsequent tests to correct their initial misdiagnosis. These patients are assumed to lose health because of poor control until their asthma is correctly diagnosed. These patients are assumed to incur asthma management costs after their asthma is diagnosed for the remainder of the model time horizon. These patients also accrue costs associated with an increased rate of exacerbations until their misdiagnosis is corrected.

The diagnostic model makes the following key structural assumptions:

- All misdiagnoses are eventually corrected within the patient's lifetime. This assumption will bias against those options with greater diagnostic accuracy. The time to correct a FP diagnosis may be different from the time to correct a FN diagnosis.
- The model time horizon for the analysis is set at 5 years. This exceeds the maximum time to correct a misdiagnosis in the base-case analysis (see *Evidence used to inform the External Assessment Group diagnostic and management model parameters*). In effect, this reflects a lifetime horizon because of the assumption that all misdiagnoses are corrected. Health benefits gained and costs accrued after the resolution of incorrect diagnoses will be the same between all competing diagnostic decision options.
- FNs at initial diagnosis experience the same level of HRQoL after their misdiagnosis is corrected as patients who are initially correctly diagnosed as TPs.
- FPs incur health losses until their misdiagnosis is corrected.
- The health consequences of other serious conditions that may be mistaken for the symptoms of asthma (e.g. lung cancer, tuberculosis, COPD) are not reflected in the model.
- Patients who are FN may experience an increased rate of exacerbations (compared with TPs) whilst their asthma remains uncontrolled.
- Improved diagnostic accuracy has no impact on mortality.
- All FeNO tests (NIOX MINO, NIOX VERO and NObreath) are assumed to have equivalent diagnostic accuracy.
- FeNO, spirometry and reversibility testing can be undertaken in primary care. Airway hyper-responsiveness testing (MCT) and sputum induction are undertaken in secondary care.
- Tests undertaken in primary care will involve two GP consultations and a nurse visit. Tests undertaken in secondary care will involve two attendances and a laboratory visit as well as a primary care visit for referral.
- One additional primary care visit, one laboratory visit and two additional secondary care visits are required to achieve resolution of an incorrect diagnosis.
- Because of a lack of evidence relating to the diagnostic accuracy of each test at each point in the pathway by patient age group, the model structure is 'blunt' in that differences between the diagnostic pathways for children and adults are not reflected.

Some of these assumptions are fairly strong and lack evidence to substantiate them. They are, however, relevant elements of the decision problem and thus require quantification. The impact of these assumptions is tested extensively in the sensitivity analysis (see *De novo model results*).

Table 63 summarises the calculations underpinning the expected costs and QALY gains associated with each terminal node within the model.

TABLE 63 Summary of calculations of expected costs and health outcomes for each test outcome

Diagnostic test outcome	Expected cost	Expected QALY gain
TP	Diagnostic test costs + (time horizon × cost asthma management)	Time horizon × utility_asthma
FP	Diagnostic test costs + additional tests + (time to correct FP diagnosis × costs of asthma management)	[(Timehorizon – time to correct FP diagnosis) × utility_healthy] + [time to correct FP diagnosis × (utility_ healthy–disutility_asthma)]
TN	Diagnostic test costs	Time horizon × utility_healthy
FN	Diagnostic test costs + additional tests + (time to correct FN diagnosis × cost of increased severe exacerbations) + [(time horizon – time to correct FN diagnosis) × (costs of asthma management)]	[(Time horizon – time to correct FN diagnosis) × (utility_asthma)] + (time to correct FN diagnosis × disutility poor control)

Scope of the External Assessment Group diagnostic model analysis

The model is intended to reflect a population of patients with symptoms of asthma as seen in primary and secondary care in England and Wales. *Table 64* details the test options included in the EAG diagnostic model analysis and the setting in which these tests are assumed to be undertaken.

All options are compared within a full incremental analysis. In line with the NICE reference case for diagnostic interventions,[145] all costs and health outcomes are discounted at a rate of 3.5%. All costs are valued at 2012/13 prices. No subgroup analyses were conducted because of evidence limitations (a narrative review of subgroup analyses within the FeNO studies is presented in *Chapter 3*). The base-case analyses are drawn from the results of the probabilistic model and hence reflect the expectation of the mean. Further sensitivity analyses were undertaken deterministically using point estimates of parameters. PSA was used to generate information on the likelihood that each test is expected to produce the greatest net benefit over a range of willingness-to-pay thresholds.

TABLE 64 Options included in the EAG diagnostic model

Test(s)	Setting
FeNO > 25 ppb (using NIOX MINO, NIOX VERO or NObreath)	Primary care
FeNO 34 ppb (using NIOX MINO, NIOX VERO or NObreath) + FEV_1	Primary care
FeNO 19 ppb (using NIOX MINO, NIOX VERO or NObreath) + sputum induction	Secondary care
FeNO > 27 ppb (using NIOX MINO, NIOX VERO or NObreath) + bronchodilator reversibility	Primary care
FEV_1/FVC	Primary care
PEF monitoring	Primary care
Bronchodilator reversibility	Primary care
Airway hyper-responsiveness (MCT)	Secondary care
Sputum induction	Secondary care

It should be noted that originally the model included an additional combination of diagnostic options – FeNO plus FEV_1 plus bronchodilator reversibility – based on the study reported by Fortuna *et al.*[70] However, as Fortuna *et al.*[70] reported that diagnostic accuracy was not improved compared with FeNO alone, incorporating this option into the model would result in a situation whereby it has the same modelled effectiveness and same modelled cost as FeNO testing alone. In reality, the use of spirometry, reversibility testing and FeNO testing would result in a small additional cost associated with consumables and/or minor drug costs compared with FeNO testing alone. Consequently, given the assumption of equivalence with FeNO testing alone and the expectation that test costs would be marginally higher than for FeNO testing alone, FeNO plus FEV_1 plus bronchodilator reversibility would always be dominated. Hence, this option was excluded from the final economic analysis.

The External Assessment Group asthma management model

Logic underpinning the management model structure

The EAG asthma management model is principally concerned with the potential benefits associated with using FeNO monitoring to enable better disease control in patients who have been diagnosed with asthma. Patients with diagnosed asthma may receive ICSs, LABAs and other pharmacological treatments to maintain control of symptoms, minimise the impact of the disease on HRQoL and reduce the risk of serious complications of asthma.[8] Treatment in the UK follows a stepped approach, with escalation of medication until control is reached. The incidence of exacerbations generally indicates poor asthma control; these exacerbations also impact on patient's HRQoL and may be expensive to manage. Monitoring of FeNO levels may provide information to allow for the better control of asthma, thereby resulting in a reduction in unnecessary medication use in patients who do not require such treatment, the maintenance of medication levels when appropriate and an increase in medication use in patients with poor disease control to avoid the health losses and costs associated with exacerbations.

Model structure

Figure 26 presents the structure of the de novo EAG management model. The model adopts a simple Markov framework with two states: (1) alive with diagnosed asthma and (2) dead. The model assumes that differences in HRQoL between treatment groups in the alive state are driven by the incidence of exacerbations whereas cost differences are influenced by the exacerbation rate and the mean level of medication use in each treatment group. Each exacerbation is associated with a reduction in HRQoL and a cost of management. Exacerbations that require hospitalisation are assumed to have a greater impact on HRQoL losses and are assumed to be more expensive to treat than other less severe exacerbations. Within each treatment group, the rate of exacerbations is modelled together with an estimate of required medication over time.

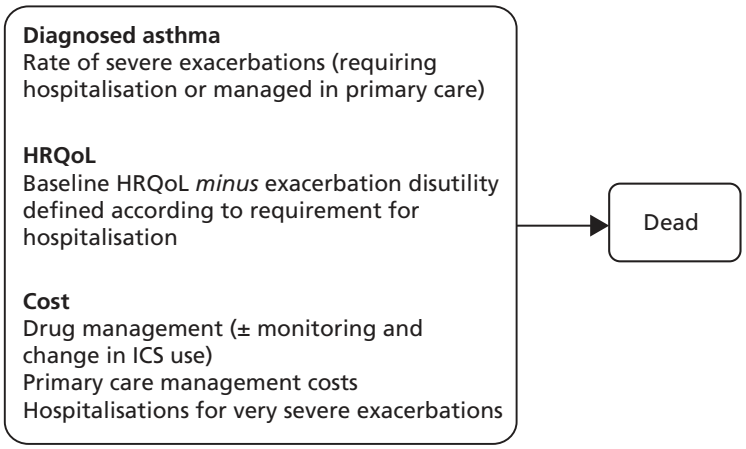


FIGURE 26 Conceptual form of the EAG asthma management model.

The management model makes the following key structural assumptions:

- Short-term impacts on exacerbations and medication use observed in the empirical studies associated with FeNO monitoring are assumed to be maintained in the longer term (indefinitely in the base case). Given the clinical evidence used to inform the analysis, this is a strong assumption that will favour FeNO.
- Impacts of FeNO monitoring on costs and health outcomes occur only during the period in which FeNO monitoring is used (this applies only to the sensitivity analysis).
- Exacerbations are associated with a short-term reduction in HRQoL.
- The use of FeNO monitoring leads to impacts on exacerbations.
- A proportion of severe exacerbations may require hospitalisation whereas the remainder may be managed in a primary care setting. Other less severe exacerbations may be managed at home.
- Improved asthma management has no impact on mortality.
- All FeNO devices (NIOX MINO, NIOX VERO and NObreath) are assumed to have an equivalent impact on dose titration decisions in the management setting.

Scope of the External Assessment Group management model analysis

The management model analysis compares the incremental costs of four options: FeNO monitoring using (1) NIOX MINO, (2) NIOX VERO and (3) NObreath against (4) standard guidelines in (a) children and (b) adults. It should be noted that each FeNO option also includes the use of guidelines, as determined by the clinical evidence used to inform the exacerbation rate and ICS use parameters. The starting age for the child subgroup is assumed to be 5 years whereas the starting age for the adult subgroup is assumed to be 18 years. The adult subgroup analysis also includes a separate subgroup analysis of FeNO monitoring in women who are pregnant. No further subgroup analyses were undertaken. The model adopts a lifetime horizon, all costs and health outcomes are discounted at 3.5% and all costs are valued at 2012/13 prices. The base-case analyses are drawn from the results of the probabilistic model and hence reflect the expectation of the mean. Further sensitivity analyses were undertaken deterministically using point estimates of parameters. PSA was used to generate information on the likelihood that each option is expected to produce the greatest net benefit over a range of willingness-to-pay thresholds.

Evidence used to inform the External Assessment Group diagnostic and management model parameters

Table 65 presents the parameter values, distributions and evidence sources used to inform the two models. These are described in more detail below.

TABLE 65 Parameters, distributions and evidence sources used in the de novo EAG models

Parameter	Distribution[a]	Mean	Param1	Param2	Source
Diagnostic model parameters *Diagnostic accuracy*					
FeNO – sensitivity	Beta	0.32	24.00	51.00	Schneider *et al.*[71,72]
FeNO – specificity	Beta	0.93	79.00	6.00	
FeNO + FEV_1 – sensitivity	Beta	0.24	20.00	62.00	Schleich *et al.*[77]
FeNO + FEV_1 – specificity	Beta	0.99	91.00	1.00	
FeNO + sputum induction – sensitivity	Beta	0.87	98.31	14.69	Sivan *et al.*[95]
FeNO + sputum induction – specificity	Beta	0.86	24.03	4.07	
FeNO + bronchodilator reversibility – sensitivity	Beta	0.87	36.54	5.46	Cordeiro *et al.*[87]
FeNO + bronchodilator reversibility – specificity	Beta	0.90	64.80	7.20	

continued

TABLE 65 Parameters, distributions and evidence sources used in the de novo EAG models (*continued*)

Parameter	Distribution[a]	Mean	Param1	Param2	Source
FEV_1/FVC – sensitivity	Beta	0.61	41.54	26.56	Hunter *et al.*[163]
FEV_1/FVC – specificity	Beta	0.60	11.37	7.58	
PEF – sensitivity	Beta	0.43	29.15	38.64	
PEF – specificity	Beta	0.75	14.21	4.74	
Bronchodilator reversibility – sensitivity	Beta	0.49	33.29	34.65	
Bronchodilator reversibility – specificity	Beta	0.70	13.28	5.69	
Airway hyper-responsiveness (MCT) – sensitivity	Beta	0.91	61.01	6.03	
Airway hyper-responsiveness (MCT) – specificity	Beta	0.90	22.43	2.49	
Sputum induction – sensitivity	Beta	0.72	48.91	19.02	
Sputum induction – specificity	Beta	0.80	15.26	3.81	
Disease and population parameters					
Prevalence of true asthma	Beta	0.47	412.00	469.00	Schleich *et al.*,[77] Sivan *et al.*,[95] Fortuna *et al.*,[70] Cordeiro *et al.*,[87] Schneider *et al.*[71,72]
Probability patient is male (children)	NA	0.55	–	–	Sivan *et al.*[95]
Probability patient is male (adults)	NA	0.40	–	–	Schneider *et al.*[69]
Patient age (years) at diagnosis (children)	NA	5	–	–	Assumption to reflect decision problem
Patient age (years) at diagnosis (adults)	NA	18	–	–	
Resource cost parameters					
NIOX MINO – marginal per-test cost	NA	£7.07	–	–	Based on information provided by Bedfont Scientific and Aerocrine
NIOX VERO – marginal per-test cost	NA	£6.36	–	–	
NObreath – marginal per-test cost	NA	£4.82	–	–	
Primary care GP visit	Normal	£43.00	£43.00	£4.30[b]	Curtis[179]
Primary care practice nurse visit	Normal	£13.69	£13.69	£1.39[b]	
Secondary care respiratory medicine outpatient visit	Normal	£204.29	£204.29	£30.64	NHS Reference Costs[174]
Secondary care laboratory visit	Normal	£203.29	£203.29	£30.49	NHS Reference Costs[174]
Number of additional primary care tests – FP	NA	1.00	–	–	Structural assumptions based on expert opinion
Number of additional secondary care tests – FP	NA	2.00	–	–	
Number of additional laboratory visits – FP	NA	1.00	–	–	
Number of additional primary care tests – FN	NA	1.00	–	–	
Number of additional secondary care tests – FN	NA	2.00	–	–	
Number of additional laboratory visits – FN	NA	1.00	–	–	

TABLE 65 Parameters, distributions and evidence sources used in the de novo EAG models (*continued*)

Parameter	Distribution[a]	Mean	Param1	Param2	Source
Annual rate of additional exacerbations in uncontrolled FNs	Normal	1.02	1.02	0.10[b]	Assumption based on Jayaram *et al.*[169]
Annual asthma drug management costs (children)	Normal	£201.00	£10.00	–	Main *et al.*[180]
Annual asthma drug management costs (adults)	Normal	£231.00	£10.00		Shepherd *et al.*[13]
QALY gain/loss parameters					
Time (years) until correct diagnosis – FP	Normal	1.50	1.50	0.26	Expert opinion
Disutility FP	Assumed to be equal to asthma disutility (see below)				
Time (years) until correct diagnosis – FN	Normal	0.67	0.67	0.17	Expert opinion
Disutility poor asthma control	Beta	0.04	1.39	33.35	McTaggart-Cowan *et al.*[181]
Disutility asthma	Beta	0.05	49.92	1027.40	Sullivan *et al.*[182]
HRQoL non-asthma population	Multivariate normal	0.96	–	–	Ara and Brazier[183]
Management model parameters *Exacerbation rate parameters*					
Duration (years) of FeNO monitoring benefit	NA	Lifetime	–	–	Assumption
FeNO annual exacerbation rate (children)	Log-normal	0.36	0.36	0.00	Szefler *et al.*[104]
FeNO annual exacerbation rate (adults)	Log-normal	0.33	0.33	0.09	Shaw *et al.*[98]
Guidelines annual exacerbation rate (children)	Log-normal	0.47	0.47	0.00	Szefler *et al.*[104]
Guidelines annual exacerbation rate (adults)	Log-normal	0.42	0.42	0.10	Shaw *et al.*[98]
HRQoL parameters					
Disutility severe hospitalised exacerbation[c]	Beta	0.56	1.21	3.84	Lloyd *et al.*[184]
Disutility severe non-hospitalised exacerbation	Beta	0.32	12.06	25.62	
Duration (years) severe hospitalised exacerbation	Gamma	0.08	15.62	0.00	Expert opinion
Duration (years) severe non-hospitalised exacerbation	Gamma	0.01	12.23	0.00	
Resource cost parameters					
Additional FeNO monitoring visits year 1	NA	4	–	–	Assumption based on BTS/SIGN[8] recommendations
Additional FeNO monitoring visits subsequent years	NA	4	–	–	
RDI ICS use year 1 FeNO (children)	Normal	0.98	0.98	0.05[b]	Szefler *et al.*[104]
RDI ICS use years 2+ FeNO (children)	Normal	0.97	0.97	0.05[b]	
RDI ICS use year 1 guidelines (children)	Normal	0.87	0.87	0.05[b]	
RDI ICS use years 2+ guidelines (children)	Normal	0.78	0.78	0.05[b]	
RDI ICS use year 1 FeNO (adults)	Normal	1.20	1.20	0.05[b]	Shaw *et al.*[98]
RDI ICS use years 2+ FeNO (adults)	Normal	0.77	0.77	0.05[b]	
RDI ICS use year 1 guidelines (adults)	Normal	1.06	1.06	0.05[b]	

continued

TABLE 65 Parameters, distributions and evidence sources used in the de novo EAG models (*continued*)

Parameter	Distribution[a]	Mean	Param1	Param2	Source
RDI ICS use years 2+ guidelines (adults)	Normal	1.27	1.27	0.05[b]	
Cost severe non-hospitalised exacerbation	Normal	£44.73	£44.73	–	Curtis,[179] BNF[185]
Cost severe hospitalised exacerbation	Normal	£1267	£1267	£253.34	NHS Reference Costs[174]

NA, not applicable; RDI, relative dose intensity.
a Normal distribution: param1 = mean, param2 = SE; log-normal distribution: param1 = mean, param2 = SE; beta distribution: param1 = alpha, param2 = beta; gamma distribution: param1 = alpha, param2 = beta; multivariate normal distribution: variance–covariance matrix not shown.
b SE determined subjectively.
c Mean reflects additive disutility for severe non-hospitalised + severe hospitalised.

Diagnostic test accuracy

Estimates of test accuracy for diagnostic tests were drawn from a number of separate studies[70–72,77,87,95,163] based on the results of the systematic review (see *Chapter 3*). *Tables 66* and *67* summarise the sources from which these estimates were derived and the actual values selected. As far as the evidence allows, the economic analysis included studies that presented estimates of the sensitivity and specificity of individual tests as well as combinations of FeNO plus other standard tests.

The study reported by Schneider *et al.*[71,72] was used to inform estimates of the sensitivity and specificity of FeNO alone; this study was selected because of its broad population and high study quality and because the reference standard broadly reflects the BTS/SIGN guidelines.[8] This study used the NIOX MINO device.

TABLE 66 Summary of studies used to inform test accuracy parameters

Author, year	Study design	Population	Setting	Reference standard	Age range
Cordeiro 2011[87]	Retrospective (analysis of prospective database)	114 patients referred to a general outpatient allergy clinic	Secondary care (the Netherlands)	History of typical respiratory symptoms and FEV_1% improvement of > 12% and > 200 ml or a provocative concentration of histamine causing a > 20% decrease in FEV_1% (PC_{20}) of ≤ 8 mg/ml, according to GINA guidelines[112]	Included those aged 7–83 years
Hunter 2002[163]	Cross-sectional case–control study	69 asthma patients, 20 pseudoasthma patients and 21 healthy subjects	Secondary care – single centre (UK)	Subjects with asthma had consistent clinical features, were symptomatic at the time of the investigations, had FEV_1 predicted values of > 65% and had one or more of the following conditions: a provocative concentration of a substance (methacholine) causing a > 20% fall in FEV_1 (PC_{20}) of < 8 mg/ml; a > 15% increase in FEV_1 10 minutes after receiving 200 µg of inhaled salbutamol; or a > 20% maximum within-day variability of PEF when measured twice daily for > 14 days	Mean age 44 years, range 15–70 years in asthma group

TABLE 66 Summary of studies used to inform test accuracy parameters (*continued*)

Author, year	Study design	Population	Setting	Reference standard	Age range
Schleich 2012[77]	Prospective cohort study	174 steroid-naive patients with respiratory symptoms	Secondary care (Belgium)	Asthma was diagnosed based on airway hyper-responsiveness demonstrated by inhaled concentration of methacholine provoking a 20% fall in FEV_1 (PC_{20}) of < 16 mg/ml	Range 20–59 years
Sivan 2009[95]	Prospective, consecutive patients	150 consecutive children referred for evaluation of possible asthma	Secondary care (Israel)	Patient's history of two or more clinical exacerbations of wheezing documented by a physician, dyspnoea or cough relieved by bronchodilators, documented variability in FEV_1 of ≥ 15% in response to bronchodilators at any time during the follow-up period (reversibility) or documented variability in FEV_1 of ≥ 15% over time with or without controller medications (ICS or montelukast). The results of provocation tests were included when available. Children in whom asthma did not manifest within 18 months of follow-up were considered as not having asthma	Range 5–18 years
[a]Smith 2004[86]	Prospective cohort study	47 consecutive patients referred by their GP to a pulmonary function laboratory for investigation of possible asthma	Secondary care (New Zealand)	Diagnosis of asthma made on the basis of the following: relevant symptom history (present in all patients) using the ATS criteria[113] and a positive test for bronchial hyper-responsiveness and/or a positive response to a bronchodilator	Range 8–75 years
Schneider 2009[71,72]	Prospective, consecutive cohort study	393 adults with symptoms suggestive of asthma	Private practice run by five pneumologists (Germany)	FEV_1/FVC < 0.7% or FEV_1% < 80% plus positive bronchodilator response = asthma. FEV_1/FVC > 0.7% or FEV_1% > 80% plus positive MCT = asthma	Unclear (adults)

a This study is used in the sensitivity analysis only.

TABLE 67 Summary of test operating characteristics used in the EAG models

Author, year	Test(s)	FeNO cut-off (ppb)	Sensitivity (%)	Specificity (%)
Cordeiro 2011[87]	FeNO + bronchodilator reversibility	> 27	87	90
Hunter 2002[163]	FEV_1/FVC	NA	61	60
	PEF	NA	43	75
	Bronchial reversibility	NA	49	70
	Airway hyper-responsiveness (MCT)	NA	91	90
	Sputum induction	NA	72	80
Schleich 2012[77]	FeNO + FEV_1	> 34	24	99
Schneider 2009[71,72]	FeNO	> 46	32	93
Sivan 2009[95]	FeNO + sputum induction	> 19	87	89

NA, not applicable.

The study reported sensitivity and specificity across a range of cut-offs. The cut-off of > 46 ppb had the highest sum of sensitivity and specificity (32% and 93% respectively); hence, this estimate was used in the model. Additional diagnostic interventions involving FeNO plus other standard tests were included according to their availability;[70,77,87,95] the FeNO cut-off values used from these studies were driven by the availability of reported estimates and were not based on choices made by the EAG. As noted earlier, the combination of FeNO + FEV_1 bronchodilator reversibility was excluded from the final model because, based on data from Fortuna *et al.*[70] and the model costing assumptions, it will always be dominated by FeNO alone. Estimates of the operating characteristics of other standard tests for asthma diagnosis were drawn from Hunter *et al.*[163] This is consistent with the manufacturer's economic analysis, although it should be noted that this study may introduce bias through the use of a case–control design. Sensitivity analyses were undertaken to examine whether the use of alternative estimates[86] of the sensitivity and specificity of existing tests alters the cost-effectiveness of FeNO testing (see *De novo model results*).

Across all diagnostic options, test operating characteristics were derived directly from data reported in the study publications. Uncertainty surrounding sensitivity and specificity estimates was modelled using independent beta distributions based on patient numbers reported in the studies.

Because of the limitations in the evidence base, the model necessarily makes a number of unadjusted (naive) indirect comparisons between the included studies. As a consequence, the results of the health economic analysis may be subject to bias and confounding because of differences between studies in terms of study design, recruited populations and reference standards. This same limitation is evident in the Price *et al.*[147]/Aerocrine diagnostic models and is unavoidable given the available evidence base. As the included studies did not provide sufficient information that would allow us to meaningfully discriminate between the sensitivity and specificity of all tests across population subgroups, we assumed that test operating characteristics were common to all patient populations. This assumption may not hold in reality.

Disease and population parameters

The true pre-test probability of asthma in undiagnosed patients was estimated as a weighted mean of the number of cases of asthma and non-asthma diagnosed in the studies used to inform the diagnostic test accuracy parameters.[69,70,77,86,87,95] We did not include the Hunter *et al.*[163] study in this calculation as it did not recruit consecutive patients because of its study design. Across these studies, 412 of 881 patients were diagnosed with asthma (probability = 0.47).

We estimated the probability that a patient is male using two studies.[69,95] This value is used only to estimate baseline HRQoL without asthma and thus does not impact on the model results.

Non-asthma utility

Preference-based HRQoL values for patients without asthma were estimated using a general population EQ-5D regression model reported by Ara and Brazier[183] (modelled EQ-5D = 0.9508566 + 0.0212126 × male – 0.0002587 × age – 0.0000332 × age^2). Uncertainty surrounding this regression equation was modelled using a multivariate normal distribution. As this parameter is common to all diagnostic comparator groups, it has no effect on the estimates of incremental health gain for the diagnostic tests included in the economic analysis.

Disutility associated with asthma

The disutility associated with asthma was taken from the catalogue of EQ-5D values reported by Sullivan *et al.*[182] Within this study, community-based UK preferences were applied to EQ-5D descriptive questionnaire responses in the US-based Medical Expenditure Panel Survey (MEPS). Sullivan *et al.*[182] used regression models to estimate the marginal disutility associated with a variety of diseases and conditions, assuming an additive model. Based on these models, the disutility for asthma was estimated to be –0.0463. Uncertainty surrounding this parameter was modelled using a beta distribution using bootstrapped confidence intervals provided in the supplementary appendices to the paper [available from http://mdm.sagepub.com/content/31/6/800/suppl/DC1 (accessed 1 August 2013)].

This disutility is applied indefinitely to all patients with asthma and to patients without asthma who test FP until their misdiagnosis is corrected. It should be noted that this disutility is unlikely to fully reflect health losses associated with the delayed diagnosis of more serious pathology such as cancer or tuberculosis.

Disutility associated with poor asthma control

The impact of poor asthma control on HRQoL was informed by a recent systematic review of studies that reported the use of the EQ-5D in patients with asthma.[186] Within this review, two studies were identified that reported the impact of loss of control on patients' health status.[172,181] Within the study reported by Szende *et al.*,[172] 228 consecutive adult outpatients and inpatients at four sites in Hungary completed the EQ-5D, the Short Form questionnaire-36 items (SF-36), the St George's Respiratory Questionnaire and a direct time trade-off question. The patients' level of asthma control was determined by physicians. EQ-5D estimates are reported for four health states: 'good control', 'mildly reduced control, 'moderately reduced control' and 'poor control'. EQ-5D estimates ranged from 0.93 for 'good control' to 0.52 for 'poor control'. Within the study reported by McTaggart-Cowan *et al.*,[181] 157 asthma patients completed the Health Utilities Index Mark 3 (HUI-3), the EQ-5D and the Short Form questionnaire-6 Dimensions (SF-6D). The degree of asthma control was self-reported by patients. The authors reported EQ-5D values for four health states: 'very well controlled', 'well controlled', 'adequately controlled' and 'not controlled'. EQ-5D estimates ranged from 0.90 for 'very well controlled' to 0.80 for 'not controlled'. The impact of loss of control is markedly different between these two studies. As Szende *et al.*[172] recruited inpatients and outpatients, it is very likely that a number of study subjects were identified because they were experiencing an exacerbation at the time at which they completed the questionnaire; this may overestimate their valuations of HRQoL. For this reason we derived disutilities from the study by McTaggart-Cowan *et al.*[181] We assumed that the health loss associated with poor control because of a FN diagnosis relates to the difference between the 'well controlled' state and the 'not controlled' state (mean disutility –0.04). Uncertainty surrounding this parameter was modelled using a beta distribution based on the mean difference between the two health states; this method ensures that the notionally better health state always has a monotonically better valuation than that for the notionally worse health state.

This disutility is applied to all patients with asthma who test FN until their misdiagnosis is corrected.

Time to resolution of incorrect diagnoses

There is a dearth of empirical evidence relating to the time required to resolve incorrect diagnoses (FPs and FNs); indeed, such studies would be difficult, if not impossible, to undertake prospectively. However, the time to resolve incorrect diagnoses is of direct relevance to the decision problem and must be quantified to evaluate the cost-effectiveness of alternative diagnostic options for asthma. Given the lack of empirical

evidence relating to these parameters, we attempted to elicit these quantities from clinical experts. We asked six clinical experts (see *Acknowledgements*) the following questions:

1. For someone who has been incorrectly diagnosed as 'not asthmatic', how long on average do you think it will take for this incorrect diagnosis to be corrected? What is your 95% confidence interval around this average?
2. For someone who has been incorrectly diagnosed as 'asthmatic', how long on average do you think it will take for this incorrect diagnosis to be corrected? What is your 95% confidence interval around this average?

A total of four experts provided responses. One expert suggested, with considerable uncertainty, that the time to resolve a FN diagnosis may be in the region of 4–12 months whereas the time to resolve a FP diagnosis may be in the region of 12 months or longer. This expert indicated substantial uncertainty around these estimates.

The second expert stated that, for FNs, the time to correct a misdiagnosis will:

> *mainly depend on chronicity and persistence of asthma: (a) In those with chronic persistent asthma (BTS step 2 or higher); [the] mean will only be a few weeks with relatively tight c.i., as the patient will presumably not be given treatment, will become symptomatic and demands further investigations/ treatment where the true diagnosis will be revealed by other methods i.e. lung function etc. (b) In those with mild intermittent/infection induced exacerbation, it may take much longer (mean [may be] months or even year or two with [a] wide CI) as they may not get regular symptoms so the diagnosis (no asthma) may seem correct until they are exposed to the trigger and become symptomatic or get an exacerbation.*

With respect to FPs, the second expert stated that:

> *this is even more difficult to estimate but here the means and c.i. may be in years. With an incorrect diagnosis of asthma, patients are put on treatment and they may become asymptomatic (for other reasons e.g. placebo effect) and it is presumed that they are better because of treatment and hence continued on it. There is a reluctance to reduce treatment if patient[s] are doing well. This was one of the argument of using eNO (to monitor, not to diagnose), that by titrating asthma treatment with eNO you can manage airway inflammation better with lower doses of inhaled steroids.*

The third expert stated that these questions were 'impossible questions to answer' but indicated that 'misdiagnosis may never be corrected [for] both false-positive and false-negative'. In addition, the third expert stated that 'patients may make the decision themselves and just stop going back to the doctor' and that 'asthmatic symptoms may come and go'. This expert also stated that a patient who has had asthmatic symptoms and who becomes asymptomatic might be considered an asymptomatic asthmatic or may be said to have had an incorrect diagnosis of asthma by someone who sees them when well. The expert also stated that these problems are the result of the absence of a reliable diagnostic test for asthma.

The fourth expert simply stated that these quantities are 'unknowable' but did suggest that the values quantified by the first expert were not unreasonable.

The fifth and sixth experts were not able to provide quantitative estimates.

Based on these responses, we assumed that the time to resolve a FN diagnosis has a mean of 8 months with a 95% CI of 4–12 months. We also assumed that the time to resolve a FP diagnosis has a mean of 18 months with a 95% CI of 12–24 months. Uncertainty surrounding these estimates was modelled using normal distributions. These estimates should be considered to be highly uncertain and are tested extensively in the sensitivity analysis.

Resource costs

Test costs

Calculating the likely marginal per-test cost for NIOX MINO, NIOX VERO and NObreath is somewhat complicated as the devices each have different lifetimes and test kits for each device are available at lower marginal costs if higher volumes of kits are purchased. The lifetimes of the NIOX MINO and NIOX VERO devices are determined either by time or by the number of tests undertaken (whichever limit is reached first).

The NIOX MINO device (Aerocrine) has a unit cost of £2100 and an effective unit lifetime of 3 years or 3000 tests (whichever comes first). The NIOX VERO device (Aerocrine) has a unit cost of £2310 and an effective unit lifetime of 5 years or 5000 tests (whichever comes first). The NObreath device (Bedfont Scientific) costs £1995 and, according to the manufacturer, has an unlimited unit lifetime.

Maintenance for NObreath is provided free of charge. No maintenance is required for NIOX MINO or NIOX VERO.

Test kits for NIOX MINO are available in packs of 300 at a price of £1350, in packs of 500 at a price of £2100 or in packs of 1000 at a price of £3950. Test kits for NIOX VERO are available in packs of 300 at a price of £1500, in packs of 500 at a price of £2200 or in packs of 1000 at a price of £4200. Mouthpieces for NObreath are available in packs of 50, 100, 300 or 1000 at prices of £195, £365, £995 and £2995 respectively.

The NObreath device requires replacement of the sensor unit every 2 years at a cost of £295. Besides test kits, NIOX MINO and NIOX VERO do not require any further consumables or incur any replacement costs.

Based on information provided by Bedfont Scientific and Aerocrine, *Table 68* presents the estimated annuatised marginal per-test costs assuming a usage of 300 tests per device per year (this estimate is based on estimates of mean usage provided by Aerocrine). All calculations are based on the lifetime of the specific device and the lowest cost estimates for the required number of test kits at the assumed level of throughput and lifetime of the device. We assumed that, although the NObreath device has an unlimited life, advances in technology would lead to replacement of the device within 10 years. Annuatisation was undertaken assuming a rate of 3.5%.

TABLE 68 Marginal per-test costs for FeNO devices

Item	NIOX MINO (£)	NIOX VERO (£)	NObreath (£)
Lifetime (years)	3	5	10
Total tests assumed per year	300	300	300
Equipment	2100.00	2310.00	1995.00
Test kits: 1000 mouthpieces	3950.00	4200.00	2995.00
Test kits: 500 mouthpieces	2100.00	2200.00	NA
Test kits: 300 mouthpieces	1350.00	1500.00	995.00
Test kits: 100 mouthpieces	NA	NA	365.00
Sensor replacements	NA	NA	295.00
Total cost over device lifetime	6150.00	8910.00	12,455.00
Annuatisation factor for specific device lifetime	2.90	4.67	8.61
Annuatised marginal per-test cost	7.07	6.36	4.82

NA, not available.

It should be noted that these marginal per-test costs do not include any costs associated with the education and training that may be required to teach NHS staff how to instruct patients to use the devices correctly to minimise test failure rates (see *Chapter 7*).

We assumed that spirometry, reversibility testing and FeNO testing can be carried out in primary care and would require two GP visits and one nurse visit. We assumed that sputum induction and airway hyper-responsiveness testing (MCT) would be undertaken in secondary care and would require two secondary care visits and one laboratory visit as well as an initial GP visit for referral (Dr John White, 17 July 2013, personal communication).

The unit cost of a GP visit was taken from Curtis *et al.*;[179] the economic analyses use an estimate of £43, which reflects the cost of an appointment lasting 11.7 minutes including direct staff costs and qualifications. Based on the same source[179] the cost of a GP practice nurse visit was assumed to be £13.69, assuming a visit duration of 15.5 minutes. The secondary care attendance cost was based on the Healthcare Resource Group code for respiratory medicine attendances (cost £204.29).[174] The cost of a laboratory visit was based on the Healthcare Resource Group code for simple bronchodilator studies (cost £203.29). We assumed that SEs around these estimates were normally distributed, with a SE equal to 15% of the mean.

As HRGs are calculated using full economic costing, we assumed that all visit costs include the costs associated with capital, training, staff costs and procedure costs associated with all existing diagnostic tests for asthma. For the strategies that include FeNO testing, the marginal per-test cost of FeNO measurement was added to these visit costs (see *Table 68*).

Costs associated with resolving misdiagnoses

We assumed that incorrect diagnoses would be resolved at a later point in time. We crudely assumed that one additional primary care attendance, two additional secondary care attendances and one laboratory visit would be required to correctly diagnose FP and FN results. This is an assumption and should be interpreted with some caution.

Costs associated with loss of control for false negatives

The model assumes that patients with asthma who initially test negative experience an increased rate of exacerbations compared with that in TP patients who are correctly diagnosed and who receive treatment. It is likely that ethical implications associated with the design of an empirical research study to collect this information would be prohibitive. We assumed that FN patients would experience one exacerbation each year in which they remain undiagnosed; this was loosely based on the higher absolute exacerbation estimate for diagnosed patients reported by Jayaram *et al.*[169] The model assumes that a proportion of these exacerbations will require hospitalisation (see below).

Costs of asthma management

We assumed that, on average, patients would be at step 3 in the BTS/SIGN asthma guidelines.[8] Current technology appraisal guidance from NICE[187,188] on the use of ICSs for children and adults recommends that the least expensive option is used and does not differentiate between drugs in terms of effectiveness. We derived estimates of the annual cost of combined inhalers from two previous HTA reports.[13,180] Main *et al.*[180] estimated the least expensive annual cost for combined inhalers to be £201 for children (Symbicort turbohaler). Shepherd *et al.*[13] estimated the least expensive annual cost of combined inhalers to be £231 for adults (Symbicort turbohaler). Scrutiny of the current version of the BNF[185] indicates that the annual cost of these inhalers has not changed since the original HTA reports were published.

Additional management model parameters

General population mortality

The probability of dying from all causes was taken directly from current interim life tables[189] and was applied according to the ratio of males to females with asthma.

Duration of benefit of FeNO monitoring

In the base-case analysis we assumed that the impact of FeNO monitoring on dose titration and exacerbations would be retained indefinitely over the patient's lifetime. Although this is plausible, there is no long-term RCT evidence to support or refute this assumption. We examine the impact of this assumption within the sensitivity analysis.

Annual exacerbation rates with FeNO monitoring and standard care

Annual exacerbation rates with and without FeNO testing were derived for children from the RCT reported by Szefler *et al.*[104] and for adults from the RCT reported by Shaw *et al.*[98] Changes in ICS use with/without FeNO monitoring for the child and adult subgroups were also drawn from these trials.

The RCT reported by Shaw *et al.*[98] was selected for use in the adult subgroup as it was the only UK-based study included in the systematic review for adults (see *Chapter 3*), because it reflects BTS/SIGN guidelines[8] and because it reported data on severe exacerbation rates and changes in ICS use (the relevant parameters for the model). The population within this RCT relates to adult non-smokers and never smokers who were deemed to be compliant with medication and who had not experienced a severe exacerbation within 4 weeks of study entry. This allowed for the inclusion of a broader range of severity compared with the other studies. Patients were aged between 20 and 81 years and were treated and followed up for 12 months.

Of the studies included in the systematic review for children (see *Chapter 3*), the study reported by Szefler *et al.*[104] appears to most closely reflect current UK practice; hence, this study was selected to inform the exacerbation rates and ICS use parameters for the child subgroup. Within this study, patients were either on long-term control treatment with symptoms of persistent asthma or evidence of uncontrolled disease or not on long-term control treatment with symptoms of persistent asthma and evidence of uncontrolled disease. Patients were treated and followed up for 46 weeks. This trial was undertaken in the US.

Szefler *et al.*[104] reported that 32.1% (SD 4.67%) of 276 patients in the FeNO group and 42.0% (SD 4.94%) of 270 patients in the control group received one or more courses of prednisone over the 46-week study period; this was taken as a proxy for severe exacerbations. The authors also reported that 3.3% (SD 1.78%) of patients in the FeNO group and 4.1% (SD 1.98%) of patients in the control group were hospitalised at least once. We used these data to estimate the annual rate of exacerbations for each arm (0.36 for the FeNO arm and 0.47 for the standard care arm). It should be noted that the data available in the paper relate to the number of patients experiencing exacerbation events rather than the number of exacerbation events. We calculated the probability that an exacerbation required hospitalisation by pooling the exacerbation and hospitalisation data for the two study arms (probability = 0.04).

Shaw *et al.*[98] reported 18 exacerbations in 12 patients from the FeNO group ($n = 58$) and 26 exacerbations in 19 patients from the control group ($n = 60$) over 42 weeks. This corresponds to an annual exacerbation rate per patient of 0.33 (SD 0.69) for the FeNO group and 0.42 (SD 0.79) for the control group. Shaw *et al.*[98] did not report the proportion of severe exacerbations requiring hospitalisation and so this probability was assumed to be the same as that observed in the Szefler *et al.* study.

Exacerbation rates were assumed to follow a log-normal distribution. The probability that an exacerbation requires hospitalisation was modelled using a beta distribution.

Impact of exacerbations on health-related quality of life

The impact of exacerbations on HRQoL was based on a valuation study reported by Lloyd *et al.*;[184] this study was identified from the systematic review reported by Davis.[186] Lloyd *et al.*[184] reported the impact of exacerbations on HRQoL in patients with moderate to severe asthma (BTS/SIGN levels 4 and 5) in the UK. Within this study, 112 patients completed a variety of health status questionnaires including the EQ-5D. Disutilities associated with severe non-hospitalised and severe hospitalised exacerbations (compared with 'no exacerbation') were calculated based on the differences between the valuations for the three states. Uncertainty surrounding these parameters was modelled using beta distributions based on the difference

between each state and the next worst state; this method ensures that the notionally better health state always has a monotonically better valuation than that for the notionally worse health state. The disutility of a severe exacerbation resulting in hospitalisation (compared with no exacerbation) was estimated to be –0.56 whereas the impact of other exacerbations that do not result in hospitalisation (compared with no exacerbation) was estimated to be –0.32. Disutilities are assumed to be additive and are therefore not influenced by the baseline level of HRQoL.

Severe exacerbations not resulting in hospitalisation were assumed to last for 4 days whereas major exacerbations resulting in hospitalisation were assumed to last for 4 weeks. These quantities were based on subjective estimates provided by experts. These durations were assumed to follow gamma distributions with SEs fitted to capture the range of estimates elicited (2–6 weeks for exacerbations requiring hospitalisation and 3–7 days for other severe exacerbations).

Resource costs: additional costs of FeNO monitoring

We assumed that FeNO monitoring would be undertaken during routine GP visits and would require one additional nurse visit once every 3 months.[8] The marginal cost of FeNO monitoring was applied as the per-test cost plus the cost of a primary care nurse appointment.

Changes in medication (inhaled corticosteroid) use over time

We derived estimates of change in ICS use with and without FeNO monitoring in children from the RCT reported by Szefler *et al.*[104] and in adults from the RCT reported by Shaw *et al.*[98] We assumed that, during the period for which ICS use was observed in each study (12 months in the study by Shaw *et al.*[98] and 46 weeks in the study by Szefler *et al.*[104]), ICS use would reflect the observed mean, with the relative dose intensity (RDI) calculated as the mean over the observed period divided by the baseline ICS dosage for each study arm. Beyond this point, we assumed that ICS use would remain constant at the level of the last observation for each study arm for the remainder of the duration over which FeNO monitoring impacts on exacerbations and titration decisions (*Table 69*).

Costs of managing exacerbations

We assumed that a proportion of exacerbations would require hospitalisation whereas the remainder could be managed in primary care. We assumed that severe exacerbations that do not require hospitalisation would require one GP attendance (cost £43.00) plus oral steroids for 5 days (cost £1.73), based on an earlier HTA report.[180] We derived the cost of asthma hospitalisation from current NHS Reference Costs[174] (cost £1266.72).

TABLE 69 Estimated ICS dose (relative to baseline)

Parameter	FeNO monitoring	Guidelines
Children[104]		
Mean RDI first 39 weeks	0.98	0.87
Mean RDI subsequent	0.97	0.78
Adults[97]		
Mean RDI first 12 months	1.20	1.06
Mean RDI subsequent	0.77	1.27

Model evaluation

The model was evaluated probabilistically using standard Monte Carlo sampling techniques over 5000 random samples. Central estimates of cost-effectiveness are presented based on the expectation of the mean. Headline results are presented as ICERs, cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs). In addition, a large number of deterministic sensitivity analyses (DSAs) were undertaken; these analyses are detailed in the following sections. All incremental analyses were carried out using an automated tabular algorithm developed by one of the study authors (PT).

Deterministic sensitivity analyses undertaken using the diagnostic model

Scenario D1: point estimates of parameters

The model was evaluated using point estimates of parameters rather than the expectation of the mean.

Scenarios D2 and D3: alternative discount rates

The model was evaluated with discount rates of 0% for costs and QALYs (scenario D2) and 6% for costs and QALYs (scenario D3).

Scenario D4: all tests undertaken in secondary care

The model was run assuming that all tests are undertaken in a secondary care setting.

Scenarios D5 and D6: alternative asthma control disutilities for false negatives

The model was run assuming different disutilities for patients who are FN. In scenario D5, the most extreme disutility from the study by McTaggart-Cowan *et al.*[181] was assumed ('very well controlled' to 'not controlled' state disutility = –0.10). In scenario D6, the most extreme disutility from the study by Szende *et al.*[172] was assumed ('good control' to 'poor control' state disutility = –0.41).

Scenarios D7 and D8: alternative disutilities for false positives

The model was run assuming different disutilities for patients who are FP. In scenario D7, the base-case disutility applied to FPs was doubled whereas in scenario D8 this disutility was halved.

Scenarios D9 and D10: FeNO test costs

The model was evaluated assuming that the marginal per-test costs for all FeNO devices (NIOX MINO, NIOX VERO and NObreath) are double (scenario D9) or half (scenario D10) those assumed in the base-case analysis.

Scenarios D11–D13: alternative assumptions concerning the lifetime of the NObreath device

Within the base-case analysis, the NObreath device is assumed to have a fixed lifetime of 10 years (for costing purposes). In scenario D11 the analysis is repeated assuming a maximum lifetime for the NObreath device of 3 years (equal to the maximum lifetime of the NIOX MINO device). In scenario D12 the analysis is repeated assuming a maximum lifetime for the NObreath device of 5 years (equal to the maximum lifetime of the NIOX VERO device). In scenario D13 the analysis is repeated assuming a maximum lifetime for the NObreath device of 20 years (double that assumed in the base case). These alternative assumptions result in marginal per-test costs for the NObreath device of £14.32, £8.88 and £2.32 for scenarios D11, D12 and D13 respectively.

Scenarios D14 and D15: test visit costs

The model was evaluated assuming that all primary and secondary care visit costs are double (scenario D14) or half (scenario D15) those assumed in the base-case analysis. This includes the costs of initial visits and subsequent visits to resolve misdiagnosis.

Scenarios D16 and D17: false-negative exacerbation rate

The model was evaluated assuming that the base-case incremental exacerbation rate for FNs is double (scenario D16) or half (scenario D17) that assumed within the base-case analysis.

Scenarios D18 and D19: asthma treatment costs

The model was evaluated assuming that asthma treatment costs are double (scenario D18) or half (scenario D19) those assumed in the base-case analysis.

Scenarios D20–D25: time to resolve misdiagnosis

The model was evaluated assuming a range of different times to resolve initial misdiagnoses (both FNs and FPs) (2×, 3×, 4×, 5×, 10× and 0.5× the base-case time to correct diagnosis parameters in scenarios D20–D25 respectively). In these analyses the time horizon was set to be equal to the maximum time to resolve FP and FN results (note that this does not affect the incremental model results).

Scenarios D26 and D27: alternative sources for the diagnostic accuracy of FeNO monitoring alone

The base-case analysis used estimates of the diagnostic accuracy of FeNO monitoring from Schneider *et al.*[71,72] In scenario D26, the model was evaluated using alternative estimates from Schleich *et al.*;[77] at a cut-off of 34 ppb, the sensitivity and specificity of FeNO monitoring were 0.35 and 0.95 respectively. In DSA scenario D27, the model was evaluated using alternative estimates from Pedrosa *et al.*;[85] at a cut-off of 40 ppb, the sensitivity and specificity of FeNO monitoring were 0.74 and 0.73 respectively. Both of these studies include a difficult-to-diagnose population, although it should be noted that this is not the case for the other comparators in this scenario analysis.

Scenario D28: alternative source for the diagnostic accuracy of non-FeNO monitoring comparators

The base-case analysis draws estimates of sensitivity and specificity for individual comparators from the study reported by Hunter *et al.*[163] In scenario D28, the model was evaluated using estimates of diagnostic accuracy for FEV_1/FVC, PEF and sputum induction from the comparative diagnostic study reported by Smith *et al.*[86]

Scenarios D29–D31: 'rule-out' diagnostic decision approach

In scenarios D29–D31, the model was evaluated assuming a 'rule-out' diagnostic approach for all diagnostic tests. In these scenarios any patient who tests negative is 'ruled out' and treated as being not asthmatic (as per the base-case structure), whereas any patient testing positive is assumed to immediately undergo further tests to confirm the diagnosis. As a consequence, no patient loses health from initially testing FP. The 'rule-out' approach was evaluated over three scenarios: scenario D29 – base-case test characteristics for FeNO monitoring options; scenario 30 – best sensitivity for FeNO monitoring options; and scenario 31 – best specificity for FeNO monitoring options.

Scenarios D32–D34: 'rule-in' diagnostic decision approach

In scenarios D32–D34, the model was evaluated assuming a 'rule-in' diagnostic approach for all diagnostic tests. In this scenario any patient who tests positive is 'ruled in' and treated as being asthmatic (as per the base-case structure), whereas any patient testing negative is assumed to immediately undergo further tests to confirm the diagnosis. As a consequence, no patient loses health from initially testing FN. The 'rule-in' approach was evaluated over three scenarios: scenario D32 – base-case test characteristics for FeNO monitoring options; scenario D33 – best sensitivity for FeNO monitoring options; and scenario D34 – best specificity for FeNO monitoring options.

Deterministic sensitivity analyses undertaken using the management model

Scenario M1: point estimates of parameters

The model was evaluated using point estimates of parameters rather than the expectation of the mean.

Scenarios M2 and M3: alternative discount rates

The model was evaluated with discount rates of 0% for costs and QALYs (scenario M2) and 6% for costs and QALYs (scenario M3).

Scenario M4: pregnant women subgroup analysis

In this scenario the model was evaluated specifically for a subgroup consisting of women who are pregnant. This analysis was based on the RCT reported by Powell *et al.*[102] We estimated annual exacerbation rates of 0.58 and 1.26 for the FeNO monitoring and guidelines groups respectively. Mean ICS use over the study period was estimated to be approximately 77% of the baseline dose for the FeNO group and 102% of the baseline dose for the guidelines group. These estimates were assumed to apply for the first 5 months (the observed period in the trial). The final observations of 73% and 105% for the FeNO and guidelines groups, respectively, were assumed to be carried forward over the remainder of the time horizon.

Scenario M5: alternative source of exacerbation rates and ICS use for children

In scenario M5, the model was evaluated using alternative estimates of exacerbation rates and ICS use over time, based on the RCT reported by Pijnenburg *et al.*[106] We estimated exacerbation rates of 0.18 and 0.39 for the FeNO and guidelines groups respectively. ICS use over the 1-year follow-up period was similar in both groups: the RDI compared with the baseline dose was estimated to be 1.16 in both groups. Beyond the first year, the RDI was estimated to be 1.23 for the FeNO group and 1.22 for the guidelines group.

Scenarios M6 and M7: alternative sources of exacerbation rates and ICS use for adults

In scenarios M6 and M7, the model was evaluated using alternative estimates of exacerbation rates and ICS use over time, based on the RCTs reported by Smith *et al.*[119] (scenario M6) and Syk *et al.*[99] (scenario M7).

Using data from Smith *et al.*,[119] we estimated severe exacerbation rates of 0.16 and 0,17 for the FeNO and guidelines groups respectively. ICS use in the first year, relative to the first observation, was estimated to be 0.85 and 1.08 for the FeNO and guidelines groups respectively. ICS use based on the last observation was estimated to be 0.90 and 1.30 for the FeNO and guidelines groups respectively.

Using data from Syk *et al.*,[99] we estimated exacerbation rates of 0.09 and 0.07 for the FeNO and guidelines groups respectively. ICS use in the first year, relative to the first observation, was estimated to be 0.97 and 0.96 for the FeNO and guidelines groups respectively. ICS use based on the last observation was estimated to be 0.88 and 0.99 for the FeNO and guidelines groups respectively.

Scenarios M8–M17: alternative assumptions regarding the duration of impact of FeNO monitoring

A number of scenarios were undertaken to examine the impact of assuming alternative durations over which FeNO monitoring would impact on ICS use and exacerbations. The durations examined were 1 year, 2 years, 3 years, 4 years, 5 years, 10 years, 15 years, 20 years, 30 years and 40 years (scenarios M8–M17 respectively).

Scenarios M18 and M19: FeNO test costs

The model was evaluated assuming that the marginal per-test costs for all FeNO devices (NIOX MINO, NIOX VERO and NObreath) are double (scenario M18) or half (scenario M19) those assumed in the base-case analysis.

Scenarios M20–M22: alternative assumptions concerning the lifetime of the NObreath device

In scenario M20, the model was evaluated assuming a maximum lifetime for the NObreath device of 3 years (equal to the maximum lifetime of the NIOX MINO device). In scenario M21, the analysis was repeated assuming a maximum lifetime for the NObreath device of 5 years (equal to the maximum lifetime of the NIOX VERO device). In scenario M22, the analysis was repeated assuming a maximum lifetime for the NObreath device of 20 years (double that assumed in the base case). These result in marginal per-test costs for the NObreath device of £14.32, £8.88 and £2.32 for scenarios M20, M21 and M22 respectively.

Scenarios M23 and M24: nurse visits

The model was evaluated assuming that the number of nurse visits for the FeNO group was double (scenario M23) or half (scenario M24) the number applied in the base-case analysis.

Scenarios M25 and M26: alternative assumptions regarding exacerbation rates

The model was evaluated assuming that the exacerbation rates for the FeNO and guidelines groups are double (scenario M25) or half (scenario M26) those rates assumed in the base-case analysis.

Scenarios M27 and M28: alternative assumptions regarding exacerbation disutility

The model was evaluated assuming that the exacerbation disutilities for the FeNO and guidelines groups are double (scenario M27) or half (scenario M28) those disutilities assumed in the base-case analysis.

Scenario M29: mean observed inhaled corticosteroid use projected forward

The model was evaluated assuming that mean ICS use observed within the clinical trials is maintained over the remainder of the model time horizon.

Scenarios M30 and M31: alternative assumptions regarding inhaled corticosteroid dose change over time

The model was evaluated assuming that the mean RDI for ICSs in the FeNO and guidelines groups is double (scenario M30) or half (scenario M31) that assumed in the base-case analysis.

With the exception of scenarios M4–M7, all DSAs within the management model were undertaken in both the child subgroup and the adult subgroup.

Model validation methods

We took a number of measures to ensure the credibility of the models and their results. The conceptual models were discussed extensively amongst the EAG before implementation. The lead modeller (PT) checked the integrity of all model calculations and VBA (Visual Basic for Applications) programming whilst developing the model. The models were rechecked once they were complete. PT also rebuilt deterministic versions of both models in a more disaggregated form to ensure that all calculations were implemented as intended; these replicated models gave exactly the same results as the full models. All model input parameters and pre-model analyses were checked and inputted values were compared against the sources from which they were derived. The results of the models were compared against our a priori expectations, given the model structures and input parameters, and any discrepancies were investigated. A large number of sensitivity analyses and black-box tests were undertaken to ensure that the models were behaving as expected. Finally, the assessment report was peer reviewed by clinical experts, other researchers within the School of Health and Related Research (ScHARR), University of Sheffield, and NICE (see *Acknowledgements*).

De novo model results

Diagnostic model results (all patients)

Central estimates of cost-effectiveness: diagnosis (all patients)

Table 70 presents the central estimates of cost-effectiveness based on the probabilistic version of the diagnostic model. The results suggest that, across the 17 diagnostic options included in the economic analysis, the expected difference in QALY gains is likely to be very small. NIOX MINO and NIOX VERO, alone or in combination with other tests, are expected to be dominated as their marginal per-test cost is higher than that for NObreath. Airway hyper-responsiveness (MCT) is expected to produce the greatest QALY gain; this is because this option has both the highest sensitivity and the highest specificity of all of the tests included in the economic analysis. With the exception of FeNO (NObreath) plus bronchodilator reversibility, all other options are expected to be ruled out by simple dominance. The incremental cost-effectiveness of airway hyper-responsiveness compared with FeNO plus bronchodilator reversibility is expected to be approximately £1.125M per QALY gained. This information is presented on the absolute cost-effectiveness plane in *Figure 27*.

TABLE 70 Central estimates of cost-effectiveness: diagnosis

Option	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	Incremental cost per QALY gained (£)
Airway hyper-responsiveness (MCT)	4.2834	1226.00	0.0005	539.92	1,125,074
FeNO + bronchodilator reversibility (NObreath)	4.2829	686.08	–	–	–
FeNO + bronchodilator reversibility (NIOX VERO)	4.2829	687.61	–	–	Dominated
FeNO + bronchodilator reversibility (NIOX MINO)	4.2829	688.33	–	–	Dominated
FeNO + sputum induction (NObreath)	4.2812	1265.78	–	–	Dominated
FeNO + sputum induction (NIOX VERO)	4.2812	1267.32	–	–	Dominated
FeNO + sputum induction (NIOX MINO)	4.2812	1268.03	–	–	Dominated
FeNO + FEV_1 (NObreath)	4.2783	810.14	–	–	Dominated
FeNO + FEV_1 (NIOX VERO)	4.2783	811.67	–	–	Dominated
FeNO + FEV_1 (NIOX MINO)	4.2783	812.38	–	–	Dominated
Sputum induction	4.2774	1328.28	–	–	Dominated
FeNO (NObreath)	4.2771	819.94	–	–	Dominated
FeNO (NIOX VERO)	4.2771	821.47	–	–	Dominated
FeNO (NIOX MINO)	4.2771	822.18	–	–	Dominated
PEF	4.2719	877.91	–	–	Dominated
Bronchodilator reversibility	4.2710	886.27	–	–	Dominated
FEV_1/FVC	4.2686	907.71	–	–	Dominated

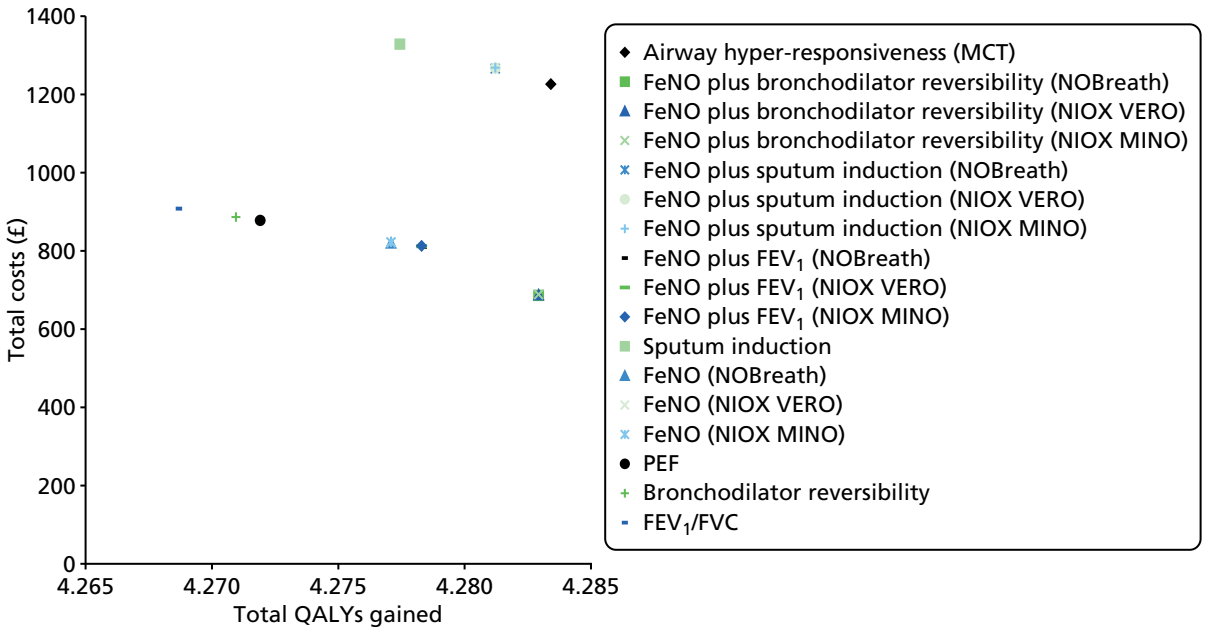


FIGURE 27 Cost-effectiveness plane: diagnosis (all patients).

Uncertainty analysis: diagnosis (all patients)

Figure 28 presents CEACs for the diagnostic options. Assuming a willingness-to-pay threshold of £20,000 per QALY gained, FeNO plus bronchodilator reversibility (using NObreath) has the highest probability of producing the greatest amount of net benefit (probability = 0.98). Assuming a willingness-to-pay threshold of £30,000 per QALY gained, FeNO plus bronchodilator reversibility (using NObreath) also has the highest probability of producing the greatest amount of net benefit (probability = 0.95). These results are also summarised in *Table 71*.

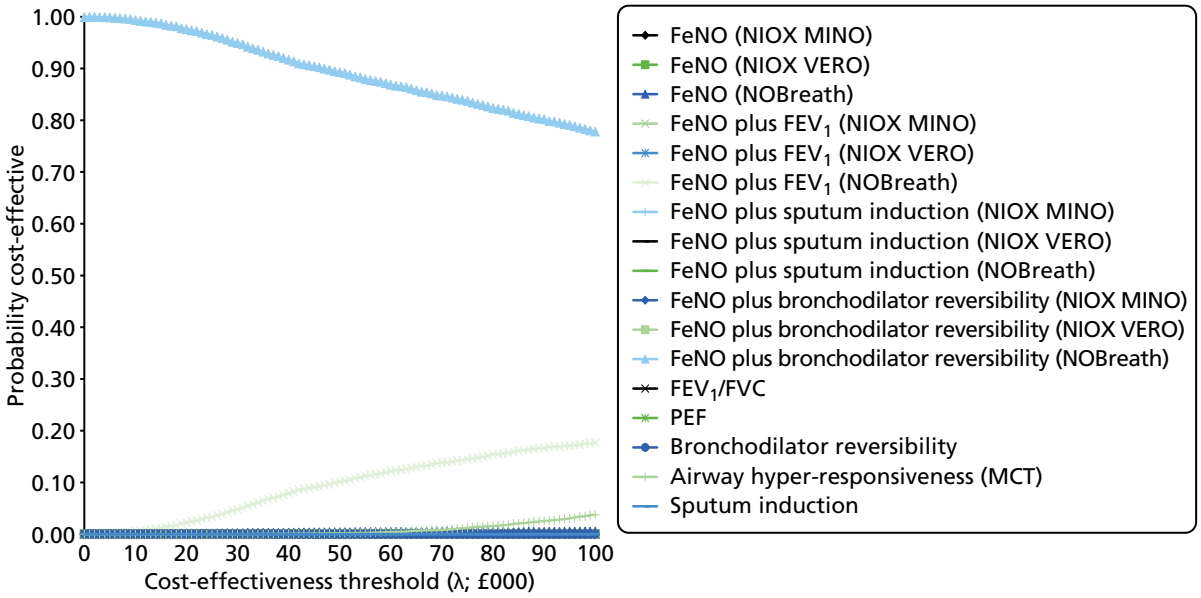


FIGURE 28 Cost-effectiveness acceptability curves: diagnosis (all patients).

TABLE 71 Probability of optimality: diagnosis (all patients)

Option	Probability optimal: λ = £20,000 per QALY gained	Probability optimal: λ = £30,000 per QALY gained
FeNO (NIOX MINO)	0.00	0.00
FeNO (NIOX VERO)	0.00	0.00
FeNO (NObreath)	0.00	0.00
FeNO + FEV_1 (NIOX MINO)	0.00	0.00
FeNO + FEV_1 (NIOX VERO)	0.00	0.00
FeNO + FEV_1 (NObreath)	0.02	0.05
FeNO + sputum induction (NIOX MINO)	0.00	0.00
FeNO + sputum induction (NIOX VERO)	0.00	0.00
FeNO + sputum induction (NObreath)	0.00	0.00
FeNO + bronchodilator reversibility (NIOX MINO)	0.00	0.00
FeNO + bronchodilator reversibility (NIOX VERO)	0.00	0.00
FeNO + bronchodilator reversibility (NObreath)	0.98	0.95
FEV_1/FVC	0.00	0.00
PEF	0.00	0.00
Bronchial reversibility	0.00	0.00
Airway hyper-responsiveness (MCT)	0.00	0.00
Sputum induction	0.00	0.00

Deterministic sensitivity analysis: diagnosis (all patients)

Tables 72–77 present the results of the DSAs. In all analyses the rank ordering of non-dominated options is maintained except when indicated by square brackets.

The DSAs indicate the following:

- Across the majority of scenarios, the cost-effectiveness frontier presented in the base-case analysis [which includes only airway hyper-responsiveness (MCT) and FeNO plus bronchodilator reversibility] is maintained. In most scenarios the majority of options are expected to be ruled out because of simple dominance.
- The results based on the point estimates of parameters are similar to the results of the probabilistic analysis.
- Discounting does not have a substantial effect on the cost-effectiveness of the non-dominated diagnostic options.
- The disutility associated with loss of control in FNs has a substantial impact on the incremental cost-effectiveness of airway hyper-responsiveness (MCT) compared with FeNO plus bronchodilator reversibility.
- The FP exacerbation rate has no impact on the results as both non-dominated options have the same specificity.
- The cost of the various FeNO devices has only a negligible impact on the cost-effectiveness results for non-dominated options.
- Longer misdiagnosis correction times substantially improve the cost-effectiveness of airway hyper-responsiveness (MCT) compared with FeNO plus bronchodilator reversibility.
- The use of other sources for the operating characteristics of FeNO monitoring and standard tests does not impact on the cost-effectiveness of non-dominated options.
- The use of a 'rule-out' decision approach may improve the comparative effectiveness and cost-effectiveness of FeNO monitoring in combination with either bronchodilator reversibility or FEV_1.
- The use of a 'rule-in' decision approach may improve the effectiveness of FeNO monitoring plus FEV_1; however, the ICER for this option (compared with FeNO monitoring plus bronchodilator reversibility) is in excess of £63,000 per QALY gained.

TABLE 72 Deterministic sensitivity analyses: diagnosis (all patients) – scenarios D1–D6 (cost per QALY gained)

Option	D1: point estimates of parameters (£)	D2: undiscounted costs and outcomes (£)	D3: discount rate = 6% (£)	D4: all tests in secondary care (£)	D5: disutility from McTaggart-Cowan *et al.*[181] (£)	D6: disutility from Szende *et al.*[172] (£)
Airway hyper-responsiveness (MCT)	1,094,325	1,081,089	1,103,827	Dominating	437,730	106,763
FeNO + bronchodilator reversibility (NObreath)	–	–	–	Dominated	–	–
FeNO + bronchodilator reversibility (NIOX VERO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + bronchodilator reversibility (NIOX MINO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + sputum induction (NObreath)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + sputum induction (NIOX VERO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + sputum induction (NIOX MINO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + FEV_1 (NObreath)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + FEV_1 (NIOX VERO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + FEV_1 (NIOX MINO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
Sputum induction	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO (NObreath)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO (NIOX VERO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO (NIOX MINO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
PEF	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
Bronchodilator reversibility	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FEV_1/FVC	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated

TABLE 73 Deterministic sensitivity analyses: diagnosis (all patients) – scenarios D7–D13 (cost per QALY gained)

Option	D7: FP disutility doubled (£)	D8: FP disutility halved (£)	D9: FeNO marginal per-test cost doubled (£)	D10: FeNO marginal per-test cost halved (£)	D11: NObreath lifetime = 3 years (£)	D12: NObreath lifetime = 5 years (£)	D13: NObreath lifetime = 20 years (£)
Airway hyper-responsiveness (MCT)	1,094,325	1,094,325	1,084,543	1,094,325	1,091,809	1,093,539	1,093,576
FeNO + bronchodilator reversibility (NObreath)	–	–	–	–	–	–	–
FeNO + bronchodilator reversibility (NIOX VERO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + bronchodilator reversibility (NIOX MINO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + sputum induction (NObreath)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + sputum induction (NIOX VERO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + sputum induction (NIOX MINO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + FEV_1 (NObreath)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + FEV_1 (NIOX VERO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + FEV_1 (NIOX MINO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
Sputum induction	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO (NObreath)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO (NIOX VERO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO (NIOX MINO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
PEF	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
Bronchodilator reversibility	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FEV_1/FVC	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated

TABLE 74 Deterministic sensitivity analyses: diagnosis (all patients) – scenarios D14–D19 (cost per QALY gained)

Option	D14: visit costs doubled (£)	D15: visit costs halved (£)	D16: FN exacerbation rate doubled (£)	D17: FN exacerbation rate halved (£)	D18: asthma treatment costs doubled (£)	D19: asthma treatment costs halved (£)
Airway hyper-responsiveness (MCT)	2,196,057	543,459	1,090,925	1,096,025	1,100,100	1,091,438
FeNO + bronchodilator reversibility (NObreath)	–	–	–	–	–	–
FeNO + bronchodilator reversibility (NIOX VERO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + bronchodilator reversibility (NIOX MINO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + sputum induction (NObreath)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + sputum induction (NIOX VERO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + sputum induction (NIOX MINO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + FEV_1 (NObreath)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + FEV_1 (NIOX VERO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + FEV_1 (NIOX MINO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
Sputum induction	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO (NObreath)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO (NIOX VERO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO (NIOX MINO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
PEF	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
Bronchodilator reversibility	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FEV_1/FVC	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated

TABLE 75 Deterministic sensitivity analyses: diagnosis (all patients) – scenarios D20–D25 (cost per QALY gained)

Option	D20: misdiagnosis correction times ×2 (£)	D21: misdiagnosis correction times ×3 (£)	D22: misdiagnosis correction times ×4 (£)	D23: misdiagnosis correction times ×5 (£)	D24: misdiagnosis correction times ×10 (£)	D25: misdiagnosis correction times halved (£)
Airway hyper-responsiveness (MCT)	556,717	377,547	287,986	234,270	126,982	2,169,614
FeNO + bronchodilator reversibility (NObreath)	–	–	3201	5111	8523	–
FeNO + bronchodilator reversibility (NIOX VERO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + bronchodilator reversibility (NIOX MINO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + sputum induction (NObreath)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + sputum induction (NIOX VERO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + sputum induction (NIOX MINO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + FEV_1 (NObreath)	Dominated	Dominated	–	–	–	Dominated
FeNO + FEV_1 (NIOX VERO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + FEV_1 (NIOX MINO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
Sputum induction	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO (NObreath)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO (NIOX VERO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO (NIOX MINO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
PEF	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
Bronchodilator reversibility	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FEV_1/FVC	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated

TABLE 76 Deterministic sensitivity analyses: diagnosis (all patients) – scenarios D26–D28 (cost per QALY gained)

Option	D26: FeNO operating characteristics from Schleich *et al.*[77] (£)	D27: FeNO operating characteristics from Pedrosa *et al.*[85] (£)	D28: other test operating characteristics from Smith *et al.*[86] (£)
Airway hyper-responsiveness (MCT)	1,094,325	1,094,325	1,094,325
FeNO + bronchodilator reversibility (NObreath)	–	–	–
FeNO + bronchodilator reversibility (NIOX VERO)	Dominated	Dominated	Dominated
FeNO + bronchodilator reversibility (NIOX MINO)	Dominated	Dominated	Dominated
FeNO + sputum induction (NObreath)	Dominated	Dominated	Dominated
FeNO + sputum induction (NIOX VERO)	Dominated	Dominated	Dominated
FeNO + sputum induction (NIOX MINO)	Dominated	Dominated	Dominated
FeNO + FEV_1 (NObreath)	Dominated	Dominated	Dominated
FeNO + FEV_1 (NIOX VERO)	Dominated	Dominated	Dominated
FeNO + FEV_1 (NIOX MINO)	Dominated	Dominated	Dominated
Sputum induction	Dominated	Dominated	Dominated
FeNO (NObreath)	Dominated	Dominated	Dominated
FeNO (NIOX VERO)	Dominated	Dominated	Dominated
FeNO (NIOX MINO)	Dominated	Dominated	Dominated
PEF	Dominated	Dominated	Dominated
Bronchodilator reversibility	Dominated	Dominated	Dominated
FEV_1/FVC	Dominated	Dominated	Dominated

TABLE 77 Deterministic sensitivity analyses: diagnosis (all patients) – scenarios D29–D34 (cost per QALY gained)

Option	D29: rule-out decision approach (base case) (£)	D30: rule-out decision approach (best sensitivity for FeNO) (£)	D31: rule-out decision approach (best specificity for FeNO) (£)	D32: rule-in decision approach (base case) (£)	D33: rule-out decision approach (best sensitivity for FeNO) (£)	D34: rule-in decision approach (best specificity for FeNO) (£)
Airway hyper-responsiveness (MCT)	1,119,170	1,119,170	1,119,170	63,533	63,533	Dominated
FeNO + bronchodilator reversibility (NObreath)	6965	6965	6965	–	–	Dominated
FeNO + bronchodilator reversibility (NIOX VERO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + bronchodilator reversibility (NIOX MINO)	Dominated	Dominated	Dominated	Dominated	Dominated	– [rank 3]
FeNO + sputum induction (NObreath)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + sputum induction (NIOX VERO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + sputum induction (NIOX MINO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + FEV_1 (NObreath)	–	–	5719	Dominated	Dominated	63,533 [rank 2]
FeNO + FEV_1 (NIOX VERO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO + FEV_1 (NIOX MINO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
Sputum induction	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO (NObreath)	Dominated	Dominated	–	Extendedly dominated	Dominated	94,020 [rank 1]
FeNO (NIOX VERO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FeNO (NIOX MINO)	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
PEF	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
Bronchodilator reversibility	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated
FEV_1/FVC	Dominated	Dominated	Dominated	Dominated	Dominated	Dominated

Management model results (children)

Central estimates of cost-effectiveness: management (children)

Table 78 presents the central estimates of cost-effectiveness based on the probabilistic version of the child management model. The results suggest that FeNO testing is expected to produce a small health benefit compared with guidelines alone (0.05 QALYs). FeNO testing is also expected to be more expensive than guidelines alone; this is because of the projected ICS use for the FeNO groups. The results also indicate, as expected, that NIOX MINO and NIOX VERO are expected to be dominated by NObreath because of their slightly higher marginal per-test cost. The incremental cost-effectiveness of NObreath compared with guidelines is expected to be approximately £45,213 per QALY gained. This information is presented on the absolute cost-effectiveness plane in *Figure 29*.

TABLE 78 Central estimates of cost-effectiveness: management (children)

Option	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	Incremental cost per QALY gained (£)
Guidelines plus FeNO monitoring (NObreath)	23.6767	8148.59	0.0506	2288.53	45,213
Guidelines plus FeNO monitoring (NIOX VERO)	23.6767	8314.30	–	–	Dominated
Guidelines plus FeNO monitoring (NIOX MINO)	23.6767	8391.53	–	–	Dominated
Guidelines	23.6261	5860.06	–	–	–

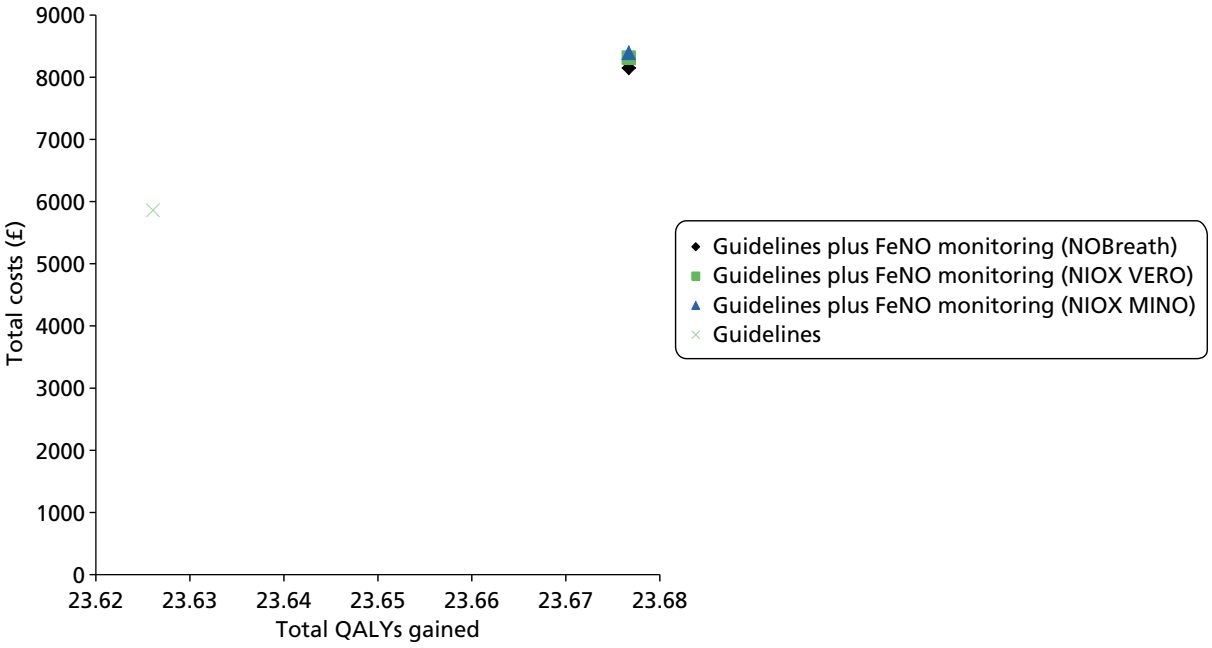


FIGURE 29 Cost-effectiveness plane: management (children).

Uncertainty analysis: management (children)

Figure 30 presents CEACs for the management options in the child subgroup. These data are also summarised in *Table 79*. Assuming a willingness-to-pay threshold of £20,000 per QALY gained, use of guidelines alone has the highest probability of producing the greatest amount of net benefit (probability = 0.99). Assuming a willingness-to-pay threshold of £30,000 per QALY gained, use of guidelines alone also has the highest probability of producing the greatest amount of net benefit (probability = 0.91).

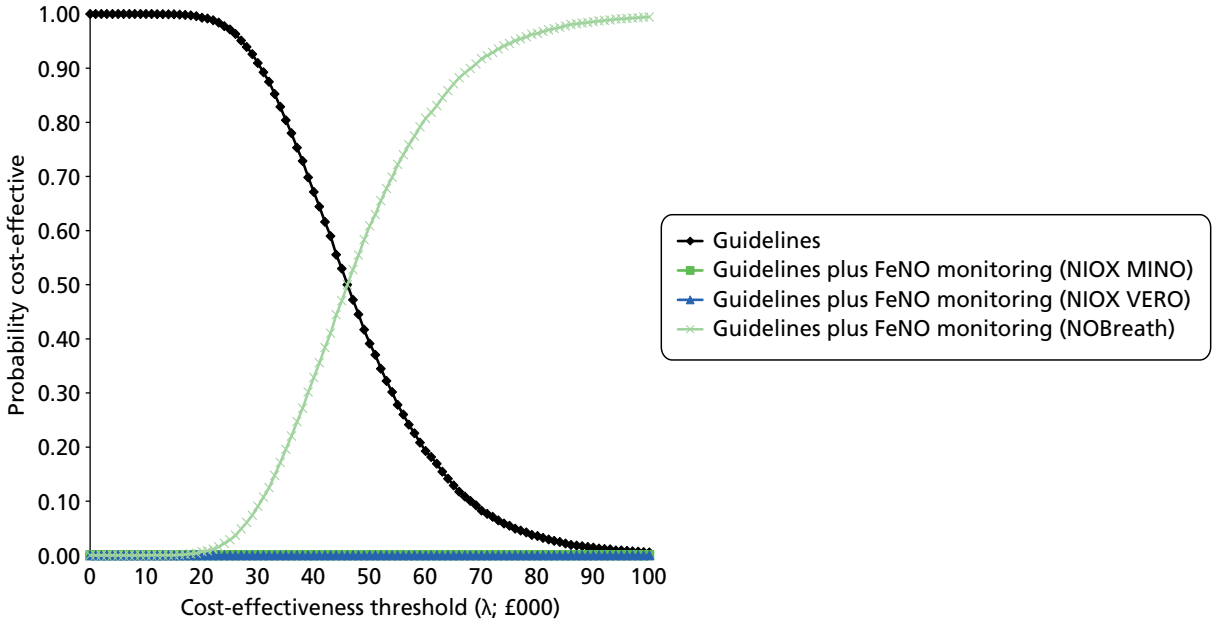


FIGURE 30 Cost-effectiveness acceptability curves: management (children).

TABLE 79 Probability of optimality: management (children)

Option	Probability optimal: λ = £20,000 per QALY gained	Probability optimal: λ = £30,000 per QALY gained
Guidelines	0.99	0.91
Guidelines plus FeNO monitoring (NIOX MINO)	0.00	0.00
Guidelines plus FeNO monitoring (NIOX VERO)	0.00	0.00
Guidelines plus FeNO monitoring (NObreath)	0.01	0.09

λ, willingness-to-pay threshold.

Deterministic sensitivity analysis results

Table 80 presents the results of the DSAs.

The DSAs indicate the following:

- The results of the analysis using point estimates of parameters are similar to those produced using the probabilistic model.
- NIOX MINO and NIOX VERO are expected to be consistently dominated by NObreath because of their higher marginal per-test costs.
- Although the marginal per-test cost influences which device would be preferred, it does not have a substantial impact on the overall cost-effectiveness of FeNO monitoring compared with guidelines.
- Discounting has little impact on the cost-effectiveness of FeNO monitoring.
- The duration over which FeNO monitoring is assumed to impact on exacerbations and ICS use is a key parameter within the child subgroup. Shorter durations of impact improve the cost-effectiveness of FeNO monitoring.
- The analysis based on data from Pijnenburg *et al.*[106] suggests a considerably more favourable ICER for FeNO monitoring compared with guidelines in children. This may be explained by the fact that the Szefler *et al.*[104] study was undertaken in uncontrolled patients and the study protocol did not allow therapy to be stepped down on the basis of low FeNO levels alone. This may in part explain why ICS use was higher for FeNO monitoring than for guidelines alone.
- The model is sensitive to the rate of exacerbations (and associated health loss) and assumptions regarding the number of monitoring visits in which FeNO monitoring is used.

TABLE 80 Deterministic sensitivity analyses: management (children) (cost per QALY gained)

Scenario		Guidelines plus FeNO (NObreath) (£)	Guidelines plus FeNO (NIOX VERO) (£)	Guidelines plus FeNO (NIOX MINO) (£)	Guidelines (£)
M1	Point estimates of parameters	45,138	Dominated	Dominated	–
M2	Undiscounted costs and outcomes	46,894	Dominated	Dominated	–
M3	Discount rate = 6%	44,555	Dominated	Dominated	–
M5	Analysis based on Pijnenburg *et al.*[106]	18,963	Dominated	Dominated	–
M8	FeNO impact = 1 year	Dominating	Dominated	Dominated	Dominated
M9	FeNO impact = 2 years	Dominating	Dominated	Dominated	Dominated
M10	FeNO impact = 3 years	Dominating	Dominated	Dominated	Dominated
M11	FeNO impact = 4 years	Dominating	Dominated	Dominated	Dominated
M12	FeNO impact = 5 years	7598	Dominated	Dominated	–

TABLE 80 Deterministic sensitivity analyses: management (children) (cost per QALY gained) (*continued*)

Scenario		Guidelines plus FeNO (NObreath) (£)	Guidelines plus FeNO (NIOX VERO) (£)	Guidelines plus FeNO (NIOX MINO) (£)	Guidelines (£)
M13	FeNO impact = 10 years	27,660	Dominated	Dominated	–
M14	FeNO impact = 15 years	34,337	Dominated	Dominated	–
M15	FeNO impact = 20 years	37,674	Dominated	Dominated	–
M16	FeNO impact = 30 years	41,025	Dominated	Dominated	–
M17	FeNO impact = 40 years	42,721	Dominated	Dominated	–
M18	Marginal per-test FeNO cost doubled	55,409	Dominated	Dominated	–
M19	Marginal per-test FeNO cost halved	40,003	Dominated	Dominated	–
M20	NObreath lifetime = 3 years	47,780	Dominated	Dominated	–
M21	NObreath lifetime = 5 years	45,963	Dominated	Dominated	–
M22	NObreath lifetime = 20 years	45,925	Dominated	Dominated	–
M23	FeNO nurse visits doubled	84,564	Dominated	Dominated	–
M24	FeNO nurse visits halved	25,425	Dominated	Dominated	–
M25	Exacerbation rates doubled	19,891	Dominated	Dominated	–
M26	Exacerbation rates halved	95,632	Dominated	Dominated	–
M27	Exacerbation disutility doubled	31,479	Dominated	Dominated	–
M28	Exacerbation disutility halved	52,844	Dominated	Dominated	–
M29	ICS observed mean carried forward	37,452	Dominated	Dominated	–
M30	ICS change doubled	56,206	Dominated	Dominated	–
M31	ICS change halved	39,604	Dominated	Dominated	–

Management model results (adults)

Central estimates of cost-effectiveness: management (adults)

Table 81 presents the central estimates of cost-effectiveness based on the probabilistic version of the adult management model. FeNO testing is expected to produce a small incremental health gain compared with standard guidelines (0.04 QALYs). The results also suggest that NIOX MINO and NIOX VERO are expected to be dominated by NObreath (again, this is because of the slightly lower marginal per-test cost for this device). In this population subgroup, the NObreath device plus guidelines compared with guidelines alone is expected to cost approximately £2146 per QALY gained. This information is presented on the absolute cost-effectiveness plane in *Figure 31*.

TABLE 81 Central estimates of cost-effectiveness: management (adults)

Option	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	Incremental cost per QALY gained (£)
Guidelines plus FeNO monitoring (NObreath)	21.9397	7377.61	0.0379	81.31	2146
Guidelines plus FeNO monitoring (NIOX VERO)	21.9397	7535.43	–	–	Dominated
Guidelines plus FeNO monitoring (NIOX MINO)	21.9397	7608.99	–	–	Dominated
Guidelines	21.9018	7296.30	–	–	–

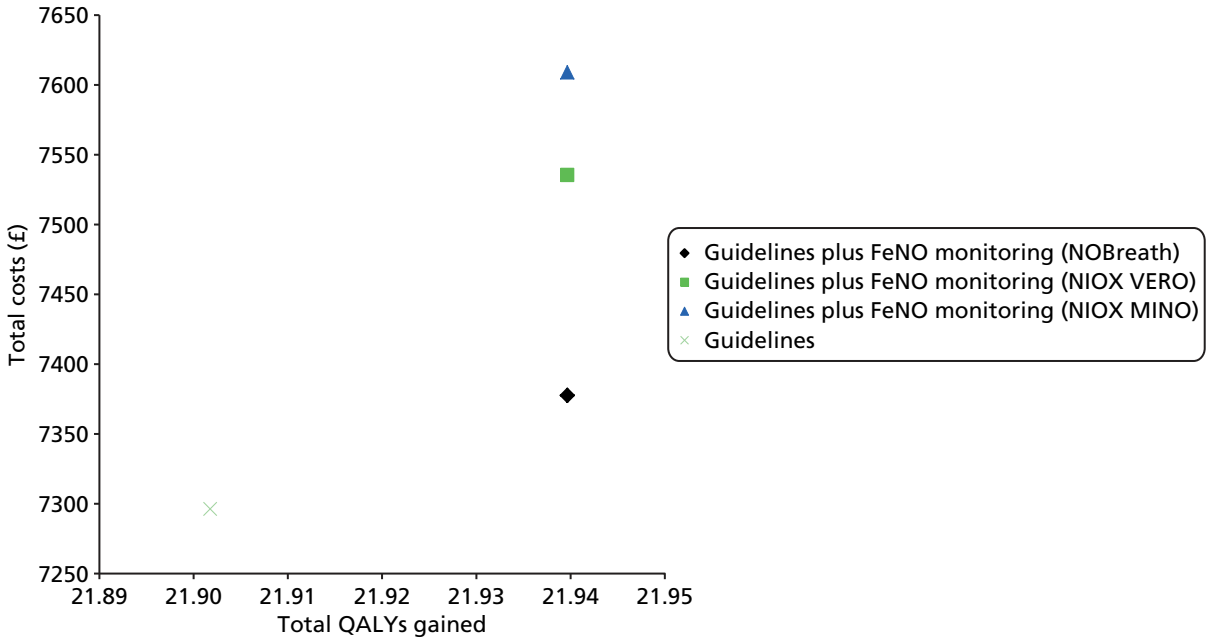


FIGURE 31 Cost-effectiveness plane: management (adults).

Uncertainty analysis: management (adults)

Figure 32 presents CEACs for the management options in the adult subgroup. Assuming a willingness-to-pay threshold of £20,000 per QALY gained, FeNO monitoring using NObreath plus guidelines has the highest probability of producing the greatest amount of net benefit (probability = 0.82). Assuming a willingness-to-pay threshold of £30,000 per QALY gained, FeNO monitoring using NObreath plus guidelines also has the highest probability of producing the greatest amount of net benefit (probability = 0.87). These results are summarised in *Table 82*.

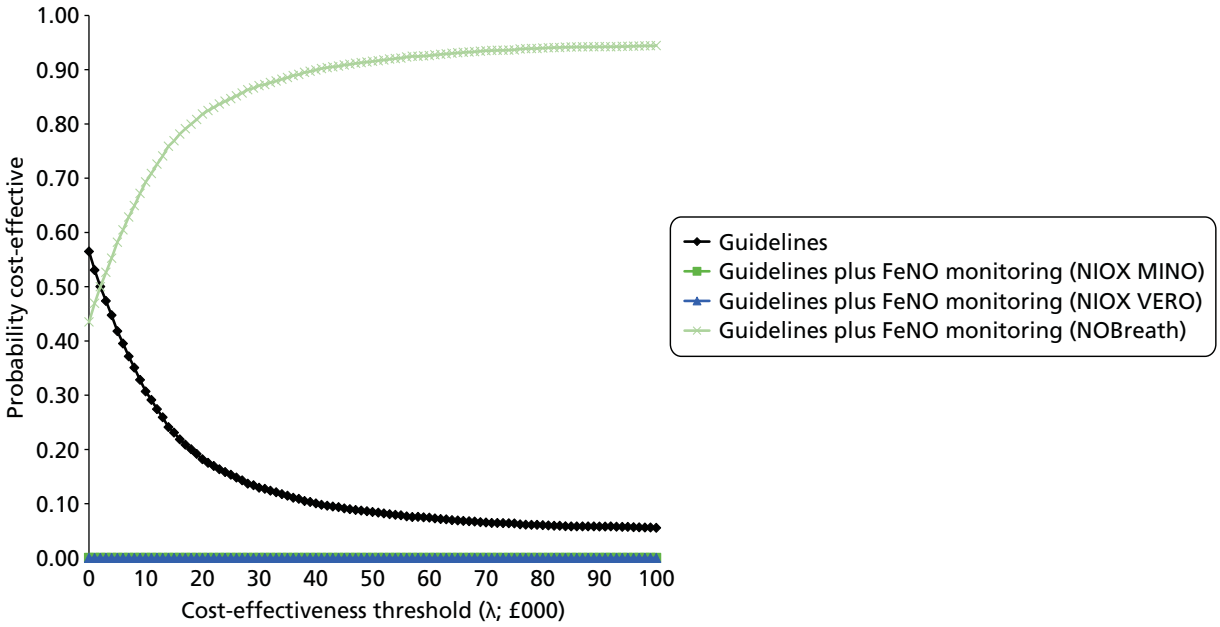


FIGURE 32 Cost-effectiveness acceptability curves: management (adults).

TABLE 82 Probability of optimality: management (adults)

Option	Probability optimal: λ = £20,000 per QALY gained	Probability optimal: λ = £30,000 per QALY gained
Guidelines	0.18	0.13
Guidelines plus FeNO monitoring (NIOX MINO)	0.00	0.00
Guidelines plus FeNO monitoring (NIOX VERO)	0.00	0.00
Guidelines plus FeNO monitoring (NObreath)	0.82	0.87

λ, willingness-to-pay threshold.

Deterministic sensitivity analyses

Table 83 presents the results of the DSAs.

The DSAs indicate the following:

- The results of the analysis using point estimates of parameters are very similar to those produced using the probabilistic version of the model.
- NIOX MINO and NIOX VERO are expected to be consistently dominated by NObreath because of their higher marginal per-test costs.
- FeNO monitoring using NObreath is expected to dominate standard guidelines in the subgroup of women who are pregnant.
- Discounting has little impact on the cost-effectiveness of FeNO monitoring.
- Although the marginal per-test cost influences which device would be preferred, it does not have a substantial impact on the overall cost-effectiveness of FeNO monitoring compared with guidelines.
- The use of exacerbation rates from Syk *et al.*[99] and Smith *et al.*[119] has a substantial negative impact on the cost-effectiveness of FeNO monitoring.
- The duration over which FeNO monitoring is assumed to impact on exacerbations and ICS use is a key driver of cost-effectiveness. It is noteworthy that, in the adult subgroup, cost-effectiveness *improves* over longer time horizons whereas the opposite is true in the child subgroup, in which cost-effectiveness *worsens* over longer time horizons. This is driven entirely by the observed differences in relative ICS use for FeNO monitoring and guidelines at the last observed time point in the trials.
- The cost-effectiveness of FeNO monitoring is markedly less favourable when projected ICS use is modelled according to the mean ICS use observed in the trial reported by Shaw *et al.*[98]

TABLE 83 Deterministic sensitivity analyses: management (adults) (cost per QALY gained)

Scenario		Guidelines plus FeNO (NObreath) (£)	Guidelines plus FeNO (NIOX VERO) (£)	Guidelines plus FeNO (NIOX MINO) (£)	Guidelines (£)
M1	Point estimates of parameters	2248	Dominated	Dominated	–
M2	Undiscounted costs and outcomes	740	Dominated	Dominated	–
M3	Discount rate = 6%	3534	Dominated	Dominated	–
M4	Pregnant women subgroup	Dominating	Dominated	Dominated	–
M6	Analysis based on Smith *et al.*[119]	184,095	Dominated	Dominated	–
M7	Analysis based on Syk *et al.*[99]	Dominated	Dominated	Dominated	Dominating
M8	FeNO impact = 1 year	885,451	Dominated	Dominated	–
M9	FeNO impact = 2 years	434,284	Dominated	Dominated	–
M10	FeNO impact = 3 years	283,954	Dominated	Dominated	–
M11	FeNO impact = 4 years	208,833	Dominated	Dominated	–
M12	FeNO impact = 5 years	163,795	Dominated	Dominated	–
M13	FeNO impact = 10 years	73,975	Dominated	Dominated	–
M14	FeNO impact = 15 years	44,320	Dominated	Dominated	–

TABLE 83 Deterministic sensitivity analyses: management (adults) (cost per QALY gained) (*continued*)

Scenario		Guidelines plus FeNO (NObreath) (£)	Guidelines plus FeNO (NIOX VERO) (£)	Guidelines plus FeNO (NIOX MINO) (£)	Guidelines (£)
M15	FeNO impact = 20 years	29,707	Dominated	Dominated	–
M16	FeNO impact = 30 years	15,531	Dominated	Dominated	–
M17	FeNO impact = 40 years	8898	Dominated	Dominated	–
M18	Marginal per-test FeNO cost doubled	15,273	Dominated	Dominated	–
M19	Marginal per-test FeNO cost halved	Dominating	Dominated	Dominated	–
M20	NObreath lifetime = 3 years	5598	Dominated	Dominated	–
M21	NObreath lifetime = 5 years	3294	Dominated	Dominated	–
M22	NObreath lifetime = 20 years	3246	Dominated	Dominated	–
M23	FeNO nurse visits doubled	52,246	Dominated	Dominated	–
M24	FeNO nurse visits halved	Dominating	Dominated	Dominated	–
M25	Exacerbation rates doubled	Dominating	Dominated	Dominated	–
M26	Exacerbation rates halved	9958	Dominated	Dominated	–
M27	Exacerbation disutility doubled	1563	Dominated	Dominated	–
M28	Exacerbation disutility halved	2634	Dominated	Dominated	–
M29	ICS observed mean carried forward	66,453	Dominated	Dominated	–
M30	ICS change doubled	Dominating	Dominated	Dominated	–
M31	ICS change halved	23,392	Dominated	Dominated	–

Discussion

Summary of cost-effectiveness evidence

There is very limited evidence available on the cost-effectiveness of FeNO testing for the diagnosis and/or management of asthma. The systematic review presented in this chapter identified one published UK model of FeNO testing in the diagnostic setting and one published model of FeNO testing in the management setting. These models were published within the same paper.[147] Aerocrine submitted a model of FeNO testing for diagnosis and a model of FeNO testing for management; these models were similar to, but not the same as, the published Price *et al.*[147] models.

The Price *et al.*[147] diagnostic model indicates that NIOX MINO is likely to be cost saving in comparison to other tests routinely used in the diagnosis of asthma. The model analysis presented by Price *et al.*[147] also suggests that NIOX MINO is expected to be more expensive than standard diagnostic tests when used in conjunction with other tests. The EAG critique of this model highlighted a number of problems including the use of a blended comparison, the questionable selection of evidence used to inform the model's parameters and the absence of any quantified health consequences associated with diagnostic test outcomes. The Aerocrine diagnostic model is similar in structure to the published version but does not use a blended comparison approach and includes some updated parameter values. However, the Aerocrine model also fails to reflect the health consequences associated with correct or incorrect diagnostic outcomes. Because of their limited scope, these diagnostic models do not provide any information regarding the economic trade-off between potential additional health gains resulting from the more accurate diagnosis of asthma and the health loss associated with displacing existing services.

The Price *et al.*[147] management model compares FeNO monitoring using NIOX MINO with guidelines. This model was evaluated within a cost–utility framework and indicates that NIOX MINO produces more health gain at a lower cost than guidelines; in other words, NIOX MINO dominates management using guidelines alone. Aerocrine submitted a similar management model that included some different data and assumptions but ultimately produced the same conclusion as the published analysis reported by Price *et al.*[147] The EAG critique of these management models highlighted a number of problems including the use of a short time horizon, the selective use of efficacy evidence, the assumptions made regarding equivalence between sputum count monitoring and FeNO and invalid assumptions regarding the health losses associated with exacerbations. No economic evidence was submitted by the manufacturers for either NIOX VERO or NObreath. The EAG takes the view that neither the published Price *et al.*[147] models nor the submitted Aerocrine models represent a suitable basis for informing decision-making about the use of FeNO testing for the diagnosis or management of asthma.

In light of the problems with the available evidence, the EAG developed two de novo models:

1. a model to assess the cost-effectiveness of FeNO testing using NIOX MINO, NIOX VERO and NObreath in addition to, or in place of, existing tests compared with other diagnostic options commonly used in the diagnosis of asthma
2. a model to assess the cost-effectiveness of NIOX MINO, NIOX VERO and NObreath plus guidelines compared with guidelines alone for the management of asthma.

The EAG diagnostic model suggests that, across the diagnostic options included in the economic analysis, the expected difference in QALY gains is likely to be very small. Airway hyper-responsiveness (MCT) is expected to produce the greatest QALY gain; this is because this option has the highest sensitivity of all of the tests included in the economic analysis. All options that include NIOX MINO or NIOX VERO are expected to be dominated as their marginal per-test cost is higher than that for NObreath (assuming a device lifetime of 10 years). In the base-case analysis, all options except airway hyper-responsiveness (MCT) and FeNO monitoring (NObreath) plus bronchodilator reversibility testing are expected to be ruled out by simple dominance. The incremental cost-effectiveness of airway hyper-responsiveness (MCT) compared with FeNO monitoring (using NObreath) plus bronchodilator reversibility is expected to be £1.125M per

QALY gained. The results of the analysis are particularly sensitive to assumptions about the duration of time required to resolve misdiagnoses, assumptions about health losses incurred by patients who are FNs, the costs of asthma management and the use of 'rule-in' and 'rule-out' diagnostic decision rules.

The EAG management model was evaluated across two subgroups: (1) children and (2) adults. Within both the child and the adult subgroup base-case analyses, FeNO testing is expected to produce a small incremental QALY gain compared with guidelines alone. In both subgroups, NIOX MINO and NIOX VERO are expected to be dominated as their marginal per-test costs are higher than that for NObreath. Within the child subgroup, the incremental cost-effectiveness of guidelines plus FeNO monitoring using NObreath compared with guidelines alone is expected to be approximately £45,200 per QALY gained. This ICER is influenced considerably by the assumed change in ICS use, which is applied over a lifetime horizon. Within the adult subgroup, FeNO monitoring using NObreath compared with guidelines alone is expected to cost approximately £2100 per QALY gained. A similarly favourable result was produced within a further analysis based on a subgroup of women who are pregnant.[102] Importantly, these positive results are not held when alternative trials are used to inform the analysis.[99,119] The results in the child and adult subgroups 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.

Limitations of the External Assessment Group models

Although the EAG models presented here do resolve many of the problems identified within the Price *et al.*[147]/Aerocrine models, the results drawn from these models remain subject to considerable uncertainty. These are briefly discussed in the following sections.

Limitations of the diagnostic model

The following represent the key limitations and uncertainties within the EAG diagnostic model:

- *Use of naive indirect comparisons*. Limitations in the diagnostic evidence base meant that naive indirect comparisons across studies that assess the diagnostic accuracy of different tests were used in the model. The review presented in *Chapter 3* highlighted considerable heterogeneity between these studies. As such, the results of the economic analysis of FeNO monitoring in the diagnostic setting should be interpreted with caution.
- *Non-systematic approach to including non-FeNO comparators*. We did not undertake a systematic review of evidence concerning the diagnostic accuracy of existing tests used in the diagnosis of asthma but instead relied on studies picked up by our systematic review of FeNO studies.[86,163] Although a formal review of other tests (excluding FeNO monitoring) would be valuable, this was beyond the scope of the assessment and the time and resources available to the EAG precluded this work. It is likely that other studies exist and it is possible that these could be considered more relevant than the studies used in the EAG model.
- *Use of a 'blunt' model structure*. We adopted a similar model structure to that of Price *et al.*,[147] which assesses options at a particular point in the diagnostic pathway rather than attempting to simulate the entire sequence of tests used throughout the pathway. This model development decision was taken because of limitations in the available evidence.
- *Uncertainty surrounding health losses associated with misdiagnosis*. We crudely elicited estimates of the duration required to resolve a FN/FP diagnosis. Only one of our experts was able to tentatively quantify the likely values of these parameters. These estimates are very uncertain. There is also uncertainty surrounding the magnitude of the HRQoL loss as well as the duration over which this loss is incurred. It is possible that health losses associated with FP diagnoses in patients with more serious underlying pathology are underestimated. It is not clear how this uncertainty could be resolved empirically.

Limitations of the management model

The following represent the key limitations and uncertainties within the EAG management model:

- *Use of effectiveness evidence*. The model uses individual studies within the child and adult subgroups. These studies were deemed by the EAG to most closely reflect asthma management in England and Wales. However, the Szefler *et al.*[104] study was undertaken in the USA and does not fully match BTS/SIGN guidelines[8] on dose titration. Only the use of guidelines in the comparator group within the Shaw *et al.*[98] study can be considered as 'standard' within the UK.
- *Uncertainty surrounding the duration over which FeNO monitoring impacts on dose titration*. In line with the NICE reference case, the EAG model reflects a lifetime horizon. There is, however, considerable uncertainty with respect to the duration over which FeNO monitoring would result in different exacerbation rates and ICS use compared with guidelines alone. Within the base-case analysis we assumed that this impact would be sustained indefinitely. The sensitivity analysis shows that this parameter is a key driver of cost-effectiveness.

Both the EAG diagnostic model and the EAG management model assume that all FeNO devices have the same diagnostic properties in terms of absolute FeNO measurements and how this translates into sensitivity and specificity. This necessary assumption may not hold in reality.

Areas for further research

Further research would be valuable to reduce some of the uncertainties detailed in the previous sections. In particular, comparative studies that include FeNO monitoring alongside the range of existing standard tests with a common population and a common reference standard of long-term follow-up of at least 1 year would be useful in assessing the comparative accuracies of these alternative diagnostic strategies. In addition, longer-term studies of FeNO monitoring in combination with standard UK management guidelines would be beneficial to better understand the long-term impacts on asthma medication use and exacerbations.

Chapter 5 Assessment of factors relevant to the NHS and other parties

Beyond its likely clinical effectiveness and cost-effectiveness, a number of other factors relating to the implementation of FeNO testing in the NHS require consideration.

Training and education

The introduction of FeNO testing for the diagnosis and/or management of asthma has implications for training and education in terms of teaching NHS staff how to instruct patients to use the devices correctly to minimise test failure rates. Repeatability and accuracy of the devices are not dependent on patient performance as the devices will not produce a measurement if flow rate and length of exhalation limits are not met. The precise training and education requirements associated with introducing FeNO testing are dependent on whether it is routinely recommended and, if so, the setting that such recommendations relate to. Training may be required for primary care nurses and GPs or for secondary care staff or for both. It should be noted that these additional costs are *not* reflected in the marginal per-test costs used within the economic analysis presented in *Chapter 4*.

Purchasing of equipment and consumables

The diffusion of FeNO testing into routine NHS practice would involve the purchasing of additional equipment either for GP surgeries or for hospitals. Equipment costs include the costs of the devices, the replacement parts (NObreath only) and other consumables (test kit mouthpieces). The NIOX MINO and NIOX VERO devices both have a finite lifetime and would need to be replaced at a maximum of 3 years and 5 years respectively. The NObreath device does not have a finite lifetime but does require replacement sensor cells every 2 years. Each FeNO device requires the purchase of test kit mouthpieces; the volume purchased and the number of tests undertaken will influence the overall marginal per-test cost of each device for GP surgeries and trusts. Maintenance of the NObreath device is expected to be free of charge to the NHS. Aerocrine did not mention the cost of maintenance in its cost estimates.

Replacement of the NIOX MINO device with the newer NIOX VERO device

It is anticipated that the NIOX MINO device will soon be replaced with the newer NIOX VERO device. Both FeNO devices will be available for some time but, in the long term, the NIOX MINO device will eventually become redundant. It is likely that the NIOX VERO device will be less expensive (per test) than the NIOX MINO device and hence the justification for purchasing the NIOX MINO device is unclear.

Impact on the demand for current standard diagnostic tests

The introduction of FeNO testing in a diagnostic setting will likely have an impact on the demand for other existing standard tests currently used in the diagnosis of asthma. This change in the level of demand for existing standard tests will be dependent on how FeNO testing is incorporated into the existing asthma diagnosis pathway.

FeNO testing in children

The diagnostic and clinical evidence considered in this assessment is restricted to patients aged ≥ 5 years. The potential diagnostic/management benefit of FeNO use in younger children is unknown.

FeNO testing in older adults

Monitoring of FeNO levels does not seem to be a useful test in the diagnosis or management of older adults with asthma. In this population, other current standard tests and management approaches may be more applicable.

Patients with respiratory tract infections

Most studies included in this assessment (see *Chapter 3*) purposefully excluded patients with a recent respiratory tract infection. The diagnostic utility of FeNO testing in these patients is unclear. It may be more appropriate either to use standard diagnostic tests in these patients or to allow a period of recovery before using FeNO testing.

Chapter 6 Discussion

Statement of principal findings

Equivalence of devices

Although there was often a good correlation between FeNO measurement devices, equivalence of readings could not necessarily be assumed in all situations. Many studies concluded that the comparability of measurements between devices was within clinically acceptable limits; however, others went on to produce correction equations to correct for systematic bias in measurements. There was also no common justified definition of clinically acceptable differences and 95% limits of agreement were sometimes very wide (around 20 ppb). There seemed to be a generally consistent observation of poorer equivalence between FeNO devices at higher FeNO levels. The direction of disagreement varied between studies and between comparator devices.

However, as there is mostly a high degree of correlation between measurements across all devices, estimates of sensitivity and specificity are likely to be a reasonable indication of the potential diagnostic accuracy of using FeNO monitoring to guide diagnosis and management, but the derived cut-off points are not likely to be interchangeable between devices. As such, for the purpose of this assessment, sensitivities and specificities will be assumed to be interchangeable, but it cannot be assumed that the cut-off points that should be used to achieve them will be the same in each device, and there is still some doubt whether the same diagnostic accuracy would be achievable in all devices. This is an important issue that should be considered in the interpretation of the diagnostic accuracy review and the findings of the health economic analysis assessment presented within this report.

Test failure rates were generally low for all devices in adults, with the highest reported rate being 3.3%. With regard to children, there may be some problems with using the NIOX MINO device in younger children, with failure rates ranging from 5.5% to 27%. One study used the NObreath device with children and reported no test failures.

Diagnostic accuracy review

This review identified several groups of studies that were similar to one another in terms of the position of the patients in the UK pathway and the reference standards used. Groups were adults presenting with symptoms of asthma compared with most of or the entire UK pathway; a subset of adults presenting with symptoms of asthma compared with airway hyper-responsiveness; difficult-to-diagnose patients compared with airway hyper-responsiveness; patients with chronic cough who were difficult to diagnose compared with ICS responsiveness; and children with symptoms of asthma compared with various reference standards.

No meta-analysis was conducted in any group as clinical heterogeneity between studies was generally extremely high. Estimates of sensitivity and specificity were not consistent within groups and ranged widely in rule-in scenarios, rule-out scenarios and when the pair with the highest sum of sensitivity and specificity were selected. *Table 84* summarises the results across studies and groups of studies. Given the wide-ranging estimates of sensitivity and specificity, together with heterogeneous cut-off points, it is difficult to draw any firm conclusions as to the diagnostic accuracy of FeNO monitoring in any situation and at any given cut-off point. Interestingly, there did not appear to be an obvious difference between the diagnostic accuracy of FeNO monitoring compared with the whole or parts of the UK pathway in patients who present with symptoms of asthma and the diagnostic accuracy of FeNO monitoring compared with airway hyper-responsiveness in patients who are difficult to diagnose. The large variation in estimates within groups may obscure any true underlying differences in the accuracy of FeNO monitoring between groups and compared with different reference standards.

TABLE 84 Summary of diagnostic accuracy studies

Patients	Reference standard	Number of studies	Highest sum of sensitivity and specificity			Rule-out scenario			Rule-in scenario		
			Range of cut-offs (ppb)	Range of sensitivity values (%)	Range of specificity values (%)	Range of cut-offs (ppb)	Range of sensitivity values (%)	Range of specificity values (%)	Range of cut-offs (ppb)	Range of sensitivity values (%)	Range of specificity values (%)
Adults with symptoms of asthma	Part or whole of the UK pathway	4	20–47	32–88	75–93	9–15	85–96	13–48	47–76	13–55.6	88.2–100
Subset of patients at position A	Airway reversibility or airway hyper-responsiveness	2	27–36	77.8–87	60–92	25	100	46.7	100	27.8	100
Difficult-to-diagnose patients	Airway hyper-responsiveness	4	32–40	24.4–74.3	72.5–98.9	NR	NR	NR	NR	NR	NR
Patients with chronic cough, difficult to diagnose	ICS responsiveness	3	20–38	53–94.7	63–85	NR	NR	NR	NR	NR	NR
Children with symptoms of asthma	Various	4	19–21	49–86	76–89	5–20	89–94	14.1–70	30–50	20–50	92–100

NR, not reported.

However, some limited observations can be made. It would appear that FeNO monitoring was more often able to reach 100% specificity than 100% sensitivity and that ranges of specificity were generally tighter. This may indicate that it has the most potential for use as a rule-in test. It would also appear that FeNO cut-off points should probably be lower in children than in adults.

In addition to the above, two studies were found that reported results for FeNO monitoring in conjunction with another test in adults, one in those difficult to diagnose[77] and one in patients of all ages with symptoms of asthma.[87] In both cases the addition of another test to the diagnostic protocol resulted in a change in diagnostic accuracy, but as this involved the usual trade-off between sensitivity and specificity it is difficult to tell if this represents an increase or decrease in clinical effectiveness and cost-effectiveness.

Evidence was limited in the subgroups defined a priori, namely pregnant women, the elderly and smokers/those subjected to environmental tobacco exposure.

- *Smokers*. FeNO monitoring appeared to be able to distinguish between asthmatic and non-asthmatic adult smokers with similar accuracy as for non-smokers and ex-smokers. It would seem likely that the FeNO level is generally lower in smokers than in mixed cohorts and it may be useful to consider a patient's smoking status when interpreting results or to select lower cut-off points for smokers. Limited data in children support the same conclusion as for adults.
- *The elderly*. Available data were extremely limited and did not always provide appropriate comparisons between elderly asthmatics and elderly non-asthmatics. A case–control study indicated that FeNO monitoring is unlikely to be a useful test in the diagnosis of asthma in the elderly.
- *Pregnant women*. A cross-sectional study indicated that pregnancy does not alter FeNO levels in asthmatics or non-asthmatics and that FeNO monitoring can distinguish between asthmatic and non-asthmatic pregnant and healthy women.

FeNO-guided management of asthma

Five studies on FeNO-guided management of asthma in adults were identified. There were high levels of heterogeneity in multiple study characteristics and outcome definitions and as such it was not possible to draw any firm conclusions as to which step-up/step-down protocol or cut-off points offer the best efficacy. All studies reported a fall in exacerbation rates per person-year, although it appeared that this was mostly driven by mild and moderate exacerbations and was statistically significant in only one study.[99] Exploratory pooled analyses showed no statistically significant difference for severe exacerbations and a statistically significant decrease in exacerbations in the intervention groups when considering the composite outcome of any severity of exacerbation. The effects on ICS use were heterogeneous, with two studies showing statistically significant decreases in ICS use in the FeNO-guided management groups, one study showing a very minor increase (significance not reported) and another showing very similar levels of use in each arm. This may indicate that some step-up/step-down protocols were better at decreasing ICS use than others or it may be because of the characteristics of the study populations. Pooled analysis showed decreased ICS use in the intervention arm, but the difference was not statistically significant. HRQoL was infrequently reported; two studies used versions of the AQLQ to measure quality of life and both showed no effect of FeNO monitoring on the global score, but one investigated domains and found a statistically significant difference in the symptoms score.

Despite the heterogeneity in the results, and the lack of statistically significant findings in individual studies, it would seem possible that, on the basis of an exploratory class-effects meta-analysis in adults, FeNO-guided management protocols of some or most designs may, during the first year of management, result in better management overall (considering all exacerbations), with either a small or a zero reduction in ICS use. Further larger studies are needed to clarify any treatment effects. There was no evidence relating to whether these effects would be maintained over a longer time period.

In pregnant women, the use of FeNO monitoring to guide asthma management appears to be as effective if not more effective than the use of FeNO monitoring to guide asthma management in other adults and appears to reduce exacerbations and ICS use. This may be because of increased efficacy in pregnant women or because of differences in step-up/step-down protocols. Notably, this protocol allowed for the step-down of ICS use on the basis of FeNO levels alone, regardless of whether symptoms were still present or not. A follow-up study suggests that there may be benefits to the children born to women who had FeNO-guided asthma management that have not been captured in the economic model.

Studies looking at FeNO-guided asthma management in the elderly were limited by study quality. The majority of studies suggest that FeNO monitoring is not useful in the elderly because of a lack of difference in FeNO levels between elderly asthmatics and elderly non-asthmatics and no correlation between FeNO levels, sputum eosinophils, asthma control, quality of life and so on in elderly asthmatics.

Levels of FeNO in smokers appeared to be generally lower than those in non-smokers but still appeared to be responsive to changes in control and eosinophils. Lower cut-off values for management might be necessary in smokers.

Seven studies in children were identified. One study appeared to recruit a group of patients who were well controlled whereas two others recruited patients who appeared to be poorly controlled. Both reported fewer severe exacerbations in the intervention arm, but not statistically significantly so. All studies reported a decrease in exacerbations (however defined) in the intervention arm, but only one reported a statistically significant reduction. The effects on ICS use were heterogeneous, with two studies showing a statistically significant increase in ICS use, one showing no difference, one being difficult to interpret and one further study not reporting this outcome. HRQoL was only reported within one study, although insufficient details were reported.

Because of the high levels of heterogeneity in multiple study characteristics and outcome definitions, it was not possible to draw any firm conclusions as to which step-up/step-down protocol or cut-off points offer the best efficacy for management. Results were generally not statistically significant but this may be because of small sample sizes in some cases; meta-analysis was precluded by the ability to calculate rate ratios. However, because all but one study reported numerically smaller numbers or rates of exacerbations in the intervention arm, it would seem possible that FeNO-guided management protocols of most descriptions could, during the first year of management, result in better management (fewer exacerbations) overall, despite the lack of statistically significant results in individual studies. Further larger studies are needed to clarify any treatment effect. It is unclear whether ICS use is likely to increase or decrease and this may depend on the details of the step-up/step-down protocols or the characteristics of the patients recruited to the trials in terms of control and severity.

Independent assessment of cost-effectiveness

The EAG developed two de novo models. The first model assesses the cost-effectiveness of FeNO testing using NIOX MINO, NIOX VERO and NObreath in addition to, or in place of, existing tests compared with other diagnostic options commonly used in the diagnosis of asthma. The second model assesses the cost-effectiveness of NIOX MINO, NIOX VERO and NObreath plus guidelines compared with guidelines alone for the management of asthma.

The EAG diagnostic model suggests that, across the 17 options included in the analysis, airway hyper-responsiveness (MCT) is expected to produce the greatest QALY gain. All options that include NIOX MINO or NIOX VERO are expected to be dominated as their marginal per-test costs are higher than that for NObreath. The incremental cost-effectiveness of airway hyper-responsiveness (MCT) compared with FeNO testing (using NObreath) plus bronchodilator reversibility is expected to be £1.125M per QALY

gained. All other options are ruled out of the analysis because of simple dominance. The results of the analysis are particularly sensitive to assumptions about the duration of time required to resolve misdiagnoses, assumptions about health losses incurred by patients who are false-negative, the costs of asthma management and the use of 'rule-in' and 'rule-out' diagnostic decision rules.

The EAG management model was evaluated separately for the child and adult subgroups. Within both the child and adult subgroup analyses, FeNO monitoring plus guidelines is expected to produce a small incremental QALY gain compared with guidelines alone. NIOX MINO and NIOX VERO are expected to be dominated as their marginal per-test costs are higher than that for NObreath. Within the adult subgroup, FeNO monitoring using NObreath compared with guidelines alone is expected to cost approximately £2100 per QALY gained. A similarly favourable result was produced within a further analysis based on a subgroup of women who are pregnant.[102] Importantly, these positive results for the adult subgroup do not hold when alternative trials are used to inform the analysis.[97,99] Within the child subgroup, the incremental cost-effectiveness of guidelines plus FeNO monitoring using NObreath compared with guidelines alone is expected to be approximately £45,200 per QALY gained. A more favourable ICER was produced when the analysis was based on the trial reported by Pijnenburg *et al.*;[106] this may reflect differences in the characteristics of patients recruited to these trials, with the former trial being uncontrolled. The results in the child and adult subgroups are particularly sensitive to assumptions regarding changes in ICS use over time, the annual number of nurse visits for FeNO monitoring and the duration over which FeNO monitoring is assumed to impact on exacerbation rates and ICS use.

Generalisability of the results

Generalisability of the evidence relating to FeNO monitoring in the diagnosis of asthma

- The clinical evidence was heterogeneous in terms of clinical characteristics and results and studies were selected for modelling based on their similarity to UK practice and similarity to the subgroups of interest as defined in the protocol (i.e. those who are difficult to diagnose or the wider population of those presenting with symptoms of asthma). As such, no single study can be generalised to the whole population and this should be noted when interpreting the results of this assessment.
- Some of the subgroups of interest to the appraisal were not modelled. These groups were the elderly, pregnant women and smokers/those exposed to environmental tobacco smoke. This was because of limitations in the identified evidence. Only inferences as to the generalisability of results from other studies to these populations can be made.
- The EAG model is 'blunt' in that it assumes that all misdiagnoses are assumed to be later corrected by subsequent tests. The model is not specific about what these tests are.
- In addition, all but one[95] of the studies used to inform the diagnostic accuracy parameters were undertaken in adults. As a consequence, the EAG model does not fully capture differences in the likely diagnostic pathways between child and adult subgroups.

Generalisability of the evidence relating to FeNO monitoring in the management of asthma

- In adults, the studies used in the model were those by Shaw *et al.*,[98] Smith *et al.*[97] and Syk *et al.*[99] Each study has its own merits in terms of generalisability.
    - Shaw *et al.*[98] followed UK practice in terms of the comparator arm management strategy. They also recruited a population from primary care and included mild to severe asthmatics regardless of atopic status. Smokers were excluded and so it is not clear if the results can be generalised to the UK smoking population. It was also not clear which FeNO device was used.

  - Smith *et al.*[97] recruited what is likely to be a population with mild to moderately severe asthma and used a different step-up/step-down protocol in the control arm and the intervention arm. It is unclear to what extent this study could be generalisable to the UK population but it nevertheless provides some insight into the impact that different but plausible efficacy inputs have on the cost-effectiveness estimates.
  - The study by Syk *et al.*[99] is most notable for having recruited only atopic patients, only non-smokers and only mild to moderate asthmatics. This study is unlikely to have wide generalisability. However, again, it nevertheless provides some insight into the impact that different but plausible efficacy inputs have on the cost-effectiveness estimates.

- In children, the two studies that were modelled were those by Szefler *et al.*[104] and Pijnenburg *et al.*,[106] largely because these two studies reported the most complete sets of data and recruited different populations. Again, each study has its own merits in terms of generalisability.

  - The study by Szefler *et al.*[104] had the lowest risk of bias amongst the studies available. It also recruited patients who were difficult to treat, one of the subgroups identified in the scope as being of special interest, and so generalisability may be limited to this group. However, the step-up/step down protocol within this trial did not allow for ICS use to be decreased on the basis of low FeNO levels alone, making it less likely that a decrease in ICS use will be seen in the intervention arm than in some other protocols. Therefore, the generalisability of this study largely depends on what type of step-up/step-down protocol is likely to be adopted in the UK.
  - Pijnenburg *et al.*[106] adopted inclusion criteria that were likely to result in a population of asthmatics who have more stable disease. The step-up/step-down protocol also does not allow for ICS use to be decreased on the basis of low FeNO levels alone, requiring that symptoms are also low. As such, the generalisability of this study also largely depends on what type of step-up/step-down protocol is likely to be adopted in the UK.

- One study was found that recruited pregnant women. The management strategy allowed step down of ICS use on the basis of FeNO levels alone. This study can be generalised within the population of pregnant women.

Equivalence of devices

- As the equivalence of devices is not assured, the generalisability of these results to all three devices is also not assured.
- It is thought that estimates of diagnostic accuracy and efficacy in managing asthma are probably achievable by all devices, as correlation between measurements is good. However, the actual values that should be used as cut-offs in diagnosis and management are much more difficult to generalise and further research may be required to estimate the most appropriate values.

Strengths and limitations of the assessment

Strengths of the assessment

The assessment includes systematic reviews of the equivalence of devices, diagnostic accuracy, management efficacy and test failures, which have been undertaken according to robust and high-quality methods.

The scope of the assessment was agreed by NICE and the SCMs during an extensive scoping exercise.

The existing economic evidence base models have been formally critiqued using the Drummond *et al.*[144] checklist and assessed in terms of adherence of the individual studies to the NICE reference case.[145]

The two economic models have been developed to a high standard and are based on the decision problem rather than being limited by the available empirical evidence. Both EAG models explicitly address the trade-off between expected additional health gains resulting from the more accurate diagnosis of asthma and the health losses associated with displacing existing services. Although many of the parameters included in these models are subject to considerable uncertainty, the use of a modelling framework helps elucidate which parameters are likely to be most important for decision-making.

The assessment report has been peer reviewed by NICE, other experienced HTA researchers and leading experts in the diagnosis and management of inflammatory airways diseases.

Limitations of the assessment

This assessment is subject to several limitations. It is important to note that these limitations are principally sourced in the evidence base rather than in the methods used to interrogate and evaluate it. Overall, the evidence base for this assessment was not of the highest quality. No end-to-end studies were found that estimated the clinical utility of FeNO testing in the diagnosis of asthma and no studies were found that used NIOX VERO or NObreath. As such, clinical validity studies were included and a review of the equivalence of devices was conducted. This leads to the following limitations:

- The benefits and harms associated with the diagnosis of asthma using FeNO testing have been estimated based on modelling of the consequences of being TP, TN, FP and FN. This includes a large number of assumptions and extrapolations, many of which cannot be substantiated with empirical evidence.
- The equivalence of devices is assumed and this may not hold true in practice. As such, FeNO cut-off values reported in the primary research may not be applicable to measurements using other devices.
- The NObreath device will always dominate other devices as its efficacy has been assumed to be equivalent but its unit cost is less.

No study provided estimates relating to the additional diagnostic value of FeNO testing to the whole UK diagnostic pathway. This limits the scope of the economic analysis.

No short-term diagnosis of asthma is 100% accurate and as such all diagnostic studies included in the review had a flawed reference standard. However, in the absence of any alternative, these reference standards were considered to be 100% accurate. A better reference standard would have been long-term follow-up of patients; however, only one study[95] used such a reference standard.

None of the management studies in children included a step-up/step-down protocol that allowed ICS use to be stepped down on the basis of FeNO levels alone. This will limit the degree to which ICS use can be reduced and means that one of the major putative benefits of FeNO management has not actually been assessed empirically: the identification of ICS non-responsive asthmatics who can be taken off ICS therapy with no loss of control.

The EAG diagnostic model is based on evidence identified through the systematic review of FeNO monitoring. The diagnostic accuracy of other non-FeNO comparators [spirometry, airway reversibility (MCT) and bronchodilator reversibility] was based on comparative studies identified through the review process. It is possible that other studies not identified within the review could be considered relevant to the model. The use of the Hunter *et al.*[163] case–control study does, however, mean that all non-FeNO diagnostic options are assessed consistently within the same study.

The EAG diagnostic model and the Price *et al.*[147]/Aerocrine diagnostic models draw a number of naive indirect comparisons across studies; this is a limitation of the evidence base rather than of the assessment. It does, however, limit the confidence that can and should be placed in the findings of these diagnostic models.

The EAG management model is based on short-term evidence of the comparative efficacy of FeNO testing compared with guidelines. The extrapolation of these benefits to the longer term is subject to considerable uncertainty. Again, this limitation reflects the evidence base rather than the model itself.

Two previous systematic reviews of the effectiveness of FeNO monitoring to guide management were identified. Petsky *et al.*[31] performed a Cochrane review in 2008, which was updated with data from two new studies in 2009. A total of six studies were included in the update (two adult studies[83,98] and four studies in children/adolescents[103,104,106,190]), all of which compared adjustments in asthma therapy based on FeNO monitoring with those based on conventional methods (typically clinical symptoms and spirometry). A meta-analysis was performed for seven outcomes: number of patients with more than one exacerbation, exacerbation rates, FEV_1% predicted at the final study visit, FeNO level at the final visit, symptom score, ICS dose at the final visit and geometric mean change in FeNO level from baseline. There was some suggestion of benefits associated with FeNO monitoring for several outcomes, in particular the number of subjects with more than one exacerbation, exacerbation rates, FEV_1% predicted at the final visit and geometric mean change in FeNO level from baseline; however, none of these results was statistically conclusive. There were also some results that suggested inconsistent effects between adult and child cohorts. FeNO monitoring appeared to have some beneficial effects on the symptom score in adults (mean difference –0.14, 95% CI –0.42 to 0.14) but not children (mean difference 0.04, 95% CI –0.11 to 0.20) and FeNO management lowered the ICS dose in adults (mean difference –450.03 µg, 95% CI –676.73 µg to –223.34 µg) but not children (mean difference 140.18 µg, 95% CI 28.94 µg to 251.43 µg). Furthermore, there were some limitations to the meta-analysis, particularly with respect to the studies in children. There was substantial clinical heterogeneity among the study cohorts, with no two studies using exactly the same step-up/step-down protocols. The study by de Jongste *et al.*,[190] which included a telemedical component, was not of relevance to our current assessment, making the results of this meta-analysis not directly applicable to this review.

It can be seen that there is a high degree of agreement between the Petsky *et al.*[31] review and our own review, especially with relation to the lack of statistically significant effects and some differences between adults and children. The strength of our review lies in the inclusion of subsequently published studies, the focus on exacerbation rates rather than the number of people with an exacerbation and the a priori separation of both children and pregnant women into different subgroups.

The second review was an academic-in-confidence manufacturer's submission to NICE (Aerocrine. *Meta Analysis of Asthma Exacerbation Rates with FeNO Guided Asthma Management*. Aerocrine submission to NICE, 2013). This review has subsequently been published.[191] This review updated the meta-analyses of the number of patients with more than one exacerbation and exacerbation rates from the aforementioned Cochrane review[31] with a study of FeNO-guided asthma management in pregnant women.[102] Inclusion of this study resulted in improvements on all measures of exacerbations, especially asthma exacerbation rates in adults (mean difference –0.27, 95% CI –0.42 to –0.12) and relative rate of asthma exacerbations in adults (relative rate 0.57, 95% CI 0.41 to 0.80). However, as it is known that pregnancy can substantially affect the course of asthma,[192] it was arguably inappropriate to include the cohort of pregnant women in meta-analyses of adults with asthma. Indeed, in the current review of FeNO-guided management, we have interpreted the results of the Powell *et al.*[102] study of pregnant women separately from the main results for just this reason.

Research recommendations

This appraisal has been limited by several key evidence gaps that would benefit from further research. It could be argued that this technology is currently under-researched and that any conclusions drawn at this stage may be unduly affected by this lack of evidence. However, some of the problems with the evidence base seem intractable in terms of practicalities and it could also be argued that the available evidence does point towards some benefits of the technology, albeit benefits that are difficult to quantify with certainty.

Some key problems and suggested research priorities are listed here:

- The equivalence of devices is not assured. There are several ways that this problem could be addressed, none of which offers a panacea:
  - Additional extensive equivalence testing of all devices in relation to one another to ascertain what is driving the heterogeneity in study results. This may be expensive and time-consuming and may still reveal high levels of disagreement between studies because of the evidence of variability between devices of the same design.
  - A network meta-analysis of the existing evidence. This was precluded in this project because of time and resource constraints. There is likely to be a high degree of uncertainty in any such analysis based on current evidence and its results may not be useful.
  - Derivation and validation studies conducted using the devices in question to develop unique cut-off points for each device for management and diagnosis. This may also be expensive and time-consuming.
  - Exploration of the option of using intrasubject relative change to assess control when managing asthma. There is already evidence relating to this approach but it appears to be in the comparatively early stages of development. This is not likely to be a useful option in diagnosis.
- Cut-off values are highly variable and are largely based on derivation studies not validation studies. This is related to problems with the equivalence of devices. Possible research priorities relating to this include large validation studies (possibly preceded by derivation studies) to determine cut-off values in all populations of interest, using a number of available devices. Although expensive and time-consuming, these studies could be very valuable.
- The clinical utility of the diagnosis of asthma using FeNO monitoring compared with the diagnosis of asthma using current practice is not informed by direct evidence. Possible research priorities relating to this include a study that charts the clinical utility of the diagnosis of asthma using FeNO monitoring compared with the diagnosis of asthma using current guidelines against a reference standard of long-term follow-up of diagnosis to correct for the misdiagnoses of both diagnostic approaches.
- It is unclear which step-up/step-down protocol offers the best efficacy. Possible research priorities relating to this include:
  - Studies that compare different management protocols with one another. It may be that different protocols are necessary in different populations.
  - Studies that aim to derive the best cut-off points for management protocols. This may be influenced by the specifics of the step-up/step-down protocols.
- It is unclear how treatment effects will progress over time. Long-term studies following patients for a number of years could address this evidence gap.

Larger RCTs of FeNO monitoring for asthma management are needed to clarify whether studies are failing to report significant effects because of underpowering.

Conclusions

There is considerable uncertainty associated with all analyses within this assessment. This is largely because of the limitations in the evidence base.

Studies using the devices that are the focus of this review were not available for all analyses and, in the absence of an alternative, equivalence has been assumed between devices. However, there is not a strong indication across the literature to support this assumption.

The clinical evidence relating to the use of FeNO monitoring for the diagnosis of asthma is highly heterogeneous and difficult to interpret in the context of the insertion of FeNO monitoring into a diagnostic pathway. This is compounded by a lack of certainty as to the equivalence of the devices used in the primary research studies to the devices that are the focus of this assessment.

The health economic analysis indicates that FeNO monitoring could have value in both the diagnostic setting and the management setting. In particular, the diagnostic model indicates that FeNO monitoring plus bronchodilator reversibility dominates many other diagnostic tests and may render airway hyper-responsiveness cost-ineffective. In the management setting, FeNO-guided management has the potential to appear cost-effective, although this is largely dependent on the expected duration over which it continues to impact on medication decisions. The conclusions drawn from both models require strong technical value judgements with respect to several aspects of the decision problem in which little or no empirical evidence exists.

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About the School of Health and Related Research (ScHARR)

The School of Health and Related Research is one of the nine departments that comprise the Faculty of Medicine, Dentistry and Health at the University of Sheffield. ScHARR specialises in health services and public health research and the application of health economics and decision science to the development of health services and the improvement of public health.

The ScHARR Technology Assessment Group (ScHARR-TAG) synthesises research on the clinical effectiveness and cost-effectiveness of health-care interventions for the National Institute for Health Research (NIHR) Health Technology Assessment programme on behalf of a range of policy-makers, including NICE. ScHARR-TAG is part of a wider collaboration of a number of units from other regions including the Health Economics Research Unit and Health Services Research Unit, University of Aberdeen; the Southampton Health Technology Assessment Centre (SHTAC), University of Southampton; the Liverpool Reviews & Implementation Group (LRiG), University of Liverpool; the Peninsula Technology Assessment Group (PenTAG), University of Exeter; the NHS Centre for Reviews and Dissemination, University of York; Warwick Evidence, University of Warwick; the BMJ Technology Assessment Group (BMJ-TAG), BMJ Evidence Centre; and Kleijnen Systematic Reviews Ltd, York.

Contribution of authors

Sue E Harnan (Research Fellow in Systematic Reviewing) acted as Principal Investigator for this assessment.

Sue E Harnan, **Munira Essat** (Research Associate in Systematic Reviewing) and **Tim Gomersall** (Research Associate in Systematic Reviewing) undertook the reviews of clinical effectiveness.

Paul Tappenden (Reader in Health Economic Modelling) and **Jon Minton** (Research Associate in Health Economic Modelling) undertook the review of existing health economic analyses.

Ruth Wong (Information Specialist) developed the electronic search strategies.

Paul Tappenden designed, developed and analysed the de novo EAG models.

Ian Pavord (Consultant Physician and Honorary Professor of Medicine), **Mark Everard** (Professor of Paediatric Respiratory Medicine) and **Rod Lawson** (Respiratory Physician) provided clinical guidance and commented on and edited the report.

Data sharing statement

Data relating to the clinical review chapter of this report can be obtained by request from the corresponding author, Sue Harnan. Data relating to the economic chapter can be obtained from Paul Tappenden (p.tappenden@sheffield.ac.uk). All other data can be obtained from the corresponding author, Sue Harnan.

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Appendix 1 Search strategies for the clinical review

Shading indicates sets of related terms within the search strategy.

Management review: MEDLINE

1. NIOX MINO.mp.
2. aerocrine.mp.
3. (niox adj5 (monitor$ or chemiluminescence or analyser$ or sensor or device$ or desktop)).mp.
4. NObreath.mp.
5. bedfont.mp.
6. or/1-5
7. exp cough/
8. cough$.mp.
9. phlegm.mp.
10. sputum.mp.
11. mucus.mp.
12. wheez$.mp.
13. chest pain/
14. chest pain$.mp.
15. (chest adj5 tight$).tw.
16. ((lower respiratory or lrt) adj5 symptom$).tw.
17. (lower airway adj5 symptom$).tw.
18. ((trache$ or wind pipe or lung$ or bronch$) adj3 symptom$).tw.
19. exp lung/ or trachea/
20. symptom$.tw.
21. 19 and 20
22. or/7-18,21
23. exp asthma/
24. asthma$.mp.
25. exp respiratory hypersensitivity/
26. exp bronchial hyperreactivity/
27. bronchial spasm/
28. bronchospas$.mp.
29. exp Bronchoconstriction/
30. bronchoconstric$.mp.
31. (bronch$ adj3 constrict$).mp.
32. (bronch$ adj5 spas$).mp.
33. (airway$ adj5 (obstruct$ or inflammation$)).mp.
34. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
35. or/23-34
36. Nitric Oxide/
37. nitric oxide.mp.
38. 36 or 37
39. (exhal$ or expir$ or alveolar or fractional).mp.

40. 38 and 39 (5228)
41. exhaled NO.mp.
42. eno.mp.
43. fe?no$.mp.
44. (fractional adj2 NO).mp.
45. or/40-44
46. 22 and 45
47. 35 and 45
48. 6 or 46 or 47
49. limit 48 to yr="2009 -Current"

Systematic reviews search: MEDLINE

1. NIOX MINO.mp.
2. aerocrine.mp.
3. (niox adj5 (monitor$ or chemiluminescence or analyser$ or sensor or device$ or desktop)).mp.
4. NObreath.mp.
5. bedfont.mp.
6. or/1-5
7. exp cough/
8. cough$.mp.
9. phlegm.mp.
10. sputum.mp.
11. mucus.mp.
12. wheez$.mp.
13. chest pain/
14. chest pain$.mp.
15. (chest adj5 tight$).tw.
16. ((lower respiratory or lrt) adj5 symptom$).tw.
17. (lower airway adj5 symptom$).tw.
18. ((trache$ or wind pipe or lung$ or bronch$) adj3 symptom$).tw.
19. exp lung/ or trachea/
20. symptom$.tw.
21. 19 and 20
22. or/7-18,21
23. exp asthma/
24. asthma$.mp.
25. exp respiratory hypersensitivity/
26. exp bronchial hyperreactivity/
27. bronchial spasm/
28. bronchospas$.mp.
29. exp Bronchoconstriction/
30. bronchoconstric$.mp.
31. (bronch$ adj3 constrict$).mp.
32. (bronch$ adj5 spas$).mp.
33. (airway$ adj5 (obstruct$ or inflammation$)).mp.
34. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
35. or/23-34
36. Nitric Oxide/
37. nitric oxide.mp.
38. 36 or 37
39. (exhal$ or expir$ or alveolar or fractional).mp.

40. 38 and 39 (5228)
41. exhaled NO.mp.
42. eno.mp.
43. fe?no$.mp.
44. (fractional adj2 NO).mp.
45. or/40-44
46. 22 and 45
47. 35 and 45
48. 6 or 46 or 47
49. meta-analysis as topic/
50. (meta analy$ or metaanaly$).tw.
51. Meta-Analysis/
52. (systematic adj (review$1 or overview$1)).tw.
53. "Review Literature as Topic"/
54. or/49-53 (96944)
55. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or bids or cancerlit).ab.
56. ((reference adj list$) or bibliograph$ or hand-search$ or (relevant adj journals) or (manual adj search$)).ab.
57. ((selection adj criteria) or (data adj extraction)).ab.
58. "review"/
59. 57 and 58
60. comment/ or editorial/ or letter/
61. Animals/
62. Humans/
63. 61 not (61 and 62)
64. 60 or 63
65. 54 or 55 or 56 or 59
66. 65 not 64
67. 48 and 66

Randomised controlled trials search: MEDLINE

1. NIOX MINO.mp.
2. aerocrine.mp.
3. (niox adj5 (monitor$ or chemiluminescence or analyser$ or sensor or device$ or desktop)).mp.
4. NObreath.mp.
5. bedfont.mp.
6. or/1-5
7. exp cough/
8. cough$.mp.
9. phlegm.mp.
10. sputum.mp.
11. mucus.mp.
12. wheez$.mp.
13. chest pain/
14. chest pain$.mp.
15. (chest adj5 tight$).tw.
16. ((lower respiratory or lrt) adj5 symptom$).tw.
17. (lower airway adj5 symptom$).tw.
18. ((trache$ or wind pipe or lung$ or bronch$) adj3 symptom$).tw.
19. exp lung/ or trachea/

20. symptom$.tw.
21. 19 and 20
22. or/7-18,21
23. exp asthma/
24. asthma$.mp.
25. exp respiratory hypersensitivity/
26. exp bronchial hyperreactivity/
27. bronchial spasm/
28. bronchospas$.mp.
29. exp Bronchoconstriction/
30. bronchoconstric$.mp.
31. (bronch$ adj3 constrict$).mp.
32. (bronch$ adj5 spas$).mp.
33. (airway$ adj5 (obstruct$ or inflammation$)).mp.
34. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
35. or/23-34
36. Nitric Oxide/
37. nitric oxide.mp.
38. 36 or 37
39. (exhal$ or expir$ or alveolar or fractional).mp.
40. 38 and 39 (5228)
41. exhaled NO.mp.
42. eno.mp.
43. fe?no$.mp.
44. (fractional adj2 NO).mp.
45. or/40-44
46. 22 and 45
47. 35 and 45
48. 6 or 46 or 47
49. Randomized controlled trials as Topic/
50. Randomized controlled trial/
51. Random allocation/
52. randomized controlled trial.pt.
53. Double blind method/
54. Single blind method/
55. Clinical trial/
56. exp Clinical Trials as Topic/
57. controlled clinical trial.pt.
58. or/49-57
59. (clinic$ adj25 trial$).ti,ab.
60. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$ or mask$)).tw.
61. Placebos/
62. Placebo$.tw.
63. (allocated adj2 random).tw.
64. or/59-63
65. 58 or 64
66. Case report.tw.
67. Letter/
68. Historical article/
69. 66 or 67 or 68
70. exp Animals/
71. Humans/

72. 70 not (70 and 71)
73. 69 or 72
74. 65 not 73
75. 48 and 74

Diagnostic studies search: MEDLINE

1. NIOX MINO.mp.
2. aerocrine.mp.
3. (niox adj5 (monitor$ or chemiluminescence or analyser$ or sensor or device$ or desktop)).mp.
4. NObreath.mp.
5. bedfont.mp.
6. or/1-5
7. exp cough/
8. cough$.mp.
9. phlegm.mp.
10. sputum.mp.
11. mucus.mp.
12. wheez$.mp.
13. chest pain/
14. chest pain$.mp.
15. (chest adj5 tight$).tw.
16. ((lower respiratory or lrt) adj5 symptom$).tw.
17. (lower airway adj5 symptom$).tw.
18. ((trache$ or wind pipe or lung$ or bronch$) adj3 symptom$).tw.
19. exp lung/ or trachea/
20. symptom$.tw.
21. 19 and 20
22. or/7-18,21
23. exp asthma/
24. asthma$.mp.
25. exp respiratory hypersensitivity/
26. exp bronchial hyperreactivity/
27. bronchial spasm/
28. bronchospas$.mp.
29. exp Bronchoconstriction/
30. bronchoconstric$.mp.
31. (bronch$ adj3 constrict$).mp.
32. (bronch$ adj5 spas$).mp.
33. (airway$ adj5 (obstruct$ or inflammation$)).mp.
34. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
35. or/23-34
36. Nitric Oxide/
37. nitric oxide.mp.
38. 36 or 37
39. (exhal$ or expir$ or alveolar or fractional).mp.
40. 38 and 39 (5228)
41. exhaled NO.mp.
42. eno.mp.
43. fe?no$.mp.
44. (fractional adj2 NO).mp.

45. or/40-44
46. 22 and 45
47. 35 and 45
48. 6 or 46 or 47
49. exp "Sensitivity and Specificity"/
50. sensitivity.tw.
51. specificity.tw.
52. ((pre-test or pretest) adj probability).tw.
53. post-test probability.tw.
54. predictive value$.tw.
55. likelihood ratio$.tw.
56. or/49-55
57. 48 and 56

Analytical validity studies search: MEDLINE

1. NIOX MINO.mp.
2. aerocrine.mp.
3. (niox adj5 (monitor$ or chemiluminescence or analyser$ or sensor or device$ or desktop)).mp.
4. NObreath.mp.
5. bedfont.mp.
6. or/1-5

Trial registers and websites search

ClinicalTrials.gov (www.clinicaltrials.gov/)

21 March 2013

16 studies found for niox

10 studies found for mino l asthma

12 studies found for aerocrine

No studies found for NObreath

No studies found for bedfont

31 studies found for fractional exhaled nitric oxide l asthma

meta*Register of Controlled Trials (www.controlled-trials.com/mrct/)*

Three studies found for niox

Three studies found for mino

Two studies found for aerocrine

No studies found for NObreath

One study found for bedfont

Two studies found for fractional exhaled nitric oxide

Manufacturer and User Facility Device Experience (MAUDE) database (www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm)

Report date 1 January 2010–28 February 2013

No records were found with NIOX MINO

No records were found with aerocrine

No records were found with NObreath

No records were found with bedfont

EuroScan International Network (http://euroscan.org.uk/)

Two results for NIOX MINO

No records were found with aerocrine

No records were found with bedfont

No records were found with NObreath

13 results for fractional exhaled nitric oxide asthma

Appendix 2 Clarification of the scope: communication with specialist committee member clinicians

Queries on scope and study selection	Study Reference Manager IDs[a]	Our thoughts	Clifford Godley	John White	Hasan Arshad	Our decision
Population						
1. Unselected populations (not selected on the basis of asthmatic symptoms but patients with symptoms may be selected from the wider cohort to establish diagnostic cut-off), e.g. birth cohorts, a school year, a college year, a group in a particular profession	483, 525, 654, 661, 1109, 3011, 6204	*We would like to exclude these as they do not reflect how the device would work in UK clinical practice and the population selected would likely impact on the estimates of sensitivity and specificity*	*Agreed*	*Agree*	*Agree*	*Exclude unselected populations*
2. Very young children – what is the minimum age? a. Patients with infant wheeze – if we are including very young children, are these patients equivalent to patients with suspected asthma?	6047, 5136	*We would like to exclude studies where patients are > 10% under 4 years of age, in line with Aerocrine's CE documentation. Bedfont do not state a minimum age. Alternatively, we could consider a cut-off of 5 years, as the UK guidelines draw this distinction in their protocols, as children under this age cannot reliably perform spirometry, a key stage in the diagnostic process*	*Agreed*	*It would be good if there were an alternate measure but practical difficulties mean cut-off at 5 reasonable as you suggest*	*NO can be measured reliably in younger children. Potentially, it could be a very useful test (if it works) precisely because other diagnostic methods (spirometry, reversibility and bronchial hyper-responsiveness) are not practical. However, in the absence of 'Gold standard' it is difficult to conclude if NO is a useful diagnostic test. So agree to keep the minimum age 5 years*	*Exclude studies with > 10% of patients under 5 years of age*

Queries on scope and study selection	Study Reference Manager IDs[a]	Our thoughts	Clifford Godley	John White	Hasan Arshad	Our decision
3. All patients already have asthma and the reference standard is one of: a. responsiveness to ICS b. EIB c. severe asthma d. methacholine/ mannitol responsiveness e. high levels of sputum eosinophilia	350, 613, 6014, 6164, 7500	*a. Responsiveness to ICS studies could be seen to fall in-between diagnosis and management – see attached 'Diagnostic pathway for asthma in children' – is this useful? Is this diagnostic or management? Do any of the other reference standards have any potential use in patients already diagnosed with asthma? We would probably like to exclude if not*	*Responsiveness to ICS is effectively a diagnostic trial, a positive response to which lends support to the postulated diagnosis. I would therefore like to keep this group, particularly if symptoms relapse off steroids*	*It is both – initially diagnostic. Yes as they might suggest lack of 'control' like FeNO*	*'Response to steroid' is primarily a management issue (although it can be argued that the test can be used to 'diagnose' steroid responsive asthma). I think this question is better considered with other management issues*	*No clear consensus – but keep these studies in, present separately. Latterly think only include if they are being used diagnostically for asthma*
4. Patients with chronic cough – are these patients equivalent to patients with asthma symptoms? These studies usually diagnose ICS responsiveness (but not whether they have asthma or not) or cough-variant asthma	328, 5878, 6383, 6385	*Unsure what to do with these*	*Raised N > O > will be a useful diagnostic signpost in the investigation of chronic cough. Normal N > O > will not preclude cough variant asthma but will make it less likely*	*Include as area of clinical relevance*	*Keep this as it might be useful to know if NO helps to diagnose 'cough variant asthma'*	*Keep in if diagnose CVA [cough variant asthma], present separately*

Queries on scope and study selection	Study Reference Manager IDs[a]	Our thoughts	Clifford Godley	John White	Hasan Arshad	Our decision
5. Study includes only children with positive skin prick test (no asthma symptoms necessarily)	6345	*We would like to exclude – includes only atopic children, not on basis of asthma symptoms, so does not match the population we are interested in in UK practice*	*Agreed*	*Others will have clearer view on this. I would include – sorry!*	*Agree*	*Exclude studies which select patients on the basis of positive skin prick test only*
6. Study includes only patients with severe refractory asthma or moderate asthma. Reference standard is one of: a. ICS responsiveness b. eosinophilic phenotype	6321, 6257	*a. Responsiveness to ICS studies could be seen to fall in-between diagnosis and management – see attached 'Diagnostic pathway for asthma in children' – is this useful? Is this diagnostic or management?* *b. Is eosinophilic phenotype a useful outcome? Management or diagnostic?*	*I think it is used diagnostically in the first instance. If they have asthma I would include*	*As above. Yes as relates to accurate diagnosis and management strategy*	*a. As suggested above, responsiveness to steroid is more of a management issue* *b. NO is closely associated with eosinophilic asthma but in itself it is not a useful outcome in terms of management*	*Include studies which select patients with asthma and diagnose ICS responsiveness and/or eosinophilic phenotype. Present separately*
7. Study includes only patients with suspected occupational asthma; reference standard is positive specific inhalation challenge	387	*Is this population too specific or is it useful?*	*Should be included – useful*	*Emphasis on this area, e.g. NICE QS [Quality Standards]. It could be useful*	*This population is distinct and it could be useful to see if NO can help to diagnose occupational asthma*	*Include studies in patients with occupational asthma*

Queries on scope and study selection	Study Reference Manager IDs[a]	Our thoughts	Clifford Godley	John White	Hasan Arshad	Our decision
8. Patients with suspected Western red cedar asthma or suspicion of any other very specific type of asthma (e.g. occupational asthma)		*Is this population too specific or is it useful?*	*Useful*	*Think I might let you off here*	*Western red cedar asthma is too specific and targets a small population. However, occupational asthma in general is a significant problem*	*Include with occupational asthma studies*
9. Only patients diagnosed with occupational asthma – reference standard/diagnostic target of ICS responsiveness	617	*Is this population too specific or is it useful?*	*Useful*	*See 7*	*See above*	*As 7*
10. Study includes patients with rhinitis *and* asthma symptoms – useful group to include?	106	*Is this population too specific or is it useful?*	*Useful*	*See 7 include*	*Asthma and rhinitis coexist in significant proportion of patients. This is therefore a large group and useful to include*	*Include studies in patients with rhinitis and asthma*

Queries on scope and study selection	Study Reference Manager IDs[a]	Our thoughts	Clifford Godley	John White	Hasan Arshad	Our decision
11. Population a little odd – see data in column 3	6184	*Inclusion criteria states 'children 6 to 16 years of age referred to our pulmonary outpatient clinic for further diagnostic work-up of possible reactive airway disease', but the results section then states 'the major complaints leading to referral were: exercise-induced shortness of breath, physician diagnosed asthma, chronic cough or miscellaneous leading symptoms', i.e. some patients were already diagnosed with asthma. Is this a relevant cohort? Is a physician diagnosis of asthma sufficiently unreliable to class these patients as 'patients with symptoms suggestive of asthma'? Some other studies excluded such patients*	*My understanding is that more than 75% of patients with unexplained chronic cough referred to clinics are ultimately considered to have airways disease. Physicians diagnosed asthma patients should be included. This heterogeneous group of patients compromise the real world population. Raised NO is a most invaluable result*	*It's mainly a clinical diagnosis – supported by response to Rx [medical prescription] etc. Recommendation is further tests if this doesn't help. This is a further test!*	*I think this is an appropriate population of childhood asthma. I did not find the inclusion criteria unusual*	*Include this study*

Queries on scope and study selection	Study Reference Manager IDs[a]	Our thoughts	Clifford Godley	John White	Hasan Arshad	Our decision
12. Are patients with chronic cough and $FEV_1 > 80\%$ predicted equivalent to the hard-to-diagnose group?	6169	*If so, we can include this study*	*Yes*	*Yes*	*Yes*	*Include this study*
Intervention						
13. Offline measurements – can we exclude studies that use this?	6204, 7038, 525	*We would have to conduct an review of comparability between methods in order to include these studies and they would just add another source of heterogeneity to the results. We have enough data without including these studies. We would like to exclude*	*Agreed*	*I don't know what offline means. Maybe that's what I am, hence lack of understanding*	*Agree*	*Exclude offline measurement*
14. Tidal breathing measurements – can we exclude these (mostly in very young children)		*If we are only including those aged 4 and up, this is irrelevant. We would like to exclude*	*Agreed*	*OK*	*Agree*	*Exclude tidal breathing methods*
15. Studies that use a different flow rate but convert to FeNO 50 (FeNO measured at a flow rate of 50 ml/second) – can we exclude (this specifically relates to a RCT management study that was included in the Cochrane review – attached to e-mail)	7704, Smith 2005	*We would like to exclude – not convinced that the 'equivalence' can be assured*	*Agreed*	*OK*	*As far as I can see the study is sound; so no reason to exclude the study*	*Include, but maybe do a subgroup analysis where the results are excluded*

Queries on scope and study selection	Study Reference Manager IDs[a]	Our thoughts	Clifford Godley	John White	Hasan Arshad	Our decision
16. Weird flow rate – please see attached study	617	*Unsure what to do*		*Prob exclude*	*Could not find the study in the attachment*	*Send again to clinicians*
17. Alveolar and bronchial NO measurements – can we exclude?		*We would like to exclude – not the use intended by the manufacturer in this application*	*Agreed*	*OK. Not relevant or likely to be to routine practice*	*Agree*	*Exclude alveolar and bronchial NO measurements*
18. Exhaled breath condensate – we have excluded these		*We would like to exclude*	*Agreed*	*OK – as above*	*Agree*	*Exclude exhaled breath condensate studies*
19. Laser spectroscopy – this is not in scope correct?		*We would like to exclude*	*Agreed*	*OK*	*Agree*	*Exclude laser spectroscopy*
20. Nasal NO measurements – can we exclude?		*We would like to exclude*	*Agreed*	*Might tell you something different. Used in CF I think OK to exclude*	*Agree*	*Exclude nasal NO measurements*
21. Portable FeNO devices other than NIOX MINO and NObreath: NO Vario and Medisoft devices – should we include these in the same way that we are including chemiluminescence evidence, as equivalent? We may not have any analytical validity study data to support the equivalence of devices		*We would like to exclude, unless they provide data on a subgroup that we have no other data for. This is because we would have to review the equivalence evidence for these devices as well as NIOX MINO and NObreath, which widens the scope of that review*	*Agreed*	*Keen to see this as generic FeNO but would need equivalence data to allow that. If can't be done then excluded by default*	*I am not sure of the validity or equivalency of NO Vario and Medisoft devices. I have not used them and have no experience. Unless the companies can provide these data, it might be better to exclude these studies*	*Include if we have equivalency studies that allow the comparison of NO Vario and Medisoft devices*

Queries on scope and study selection	Study Reference Manager IDs[a]	Our thoughts	Clifford Godley	John White	Hasan Arshad	Our decision
Reference standard/outcome/diagnostic target						
22. Is exercise-induced asthma/ bronchoconstriction a useful diagnostic target? Are they the same thing even? Are they the same as the 'airway hyper-responsiveness testing' listed in UK guidelines?	5171, 6014 (population all asthmatics), 6047 (population wheezy children)	*Unsure what to do. If same as UK airway hyper-responsiveness testing, we can include*	*This is a form of hyperresponsivness testing along with methacholine and histamine challenge. It is diagnostic for asthma. Include*	*May not be the same. Suggest include*	*Exercise induced bronchial challenge provides a valid outcome. It estimates bronchial hyperresponsiveness just like methacholine or histamine bronchial challenge. For childhood asthma in general and exercise induced asthma in particular, it might be superior to other types of bronchial challenges*	*Include studies which use EIB as the reference standard*
23. Studies that diagnose asthma severity, usually in an already diagnosed asthma population		*Unsure if useful to diagnose asthma severity – where population is all asthmatic, this may occupy an intermediate position between the diagnostic strategy and the management strategy that has not yet been captured in the review – as discussed above in 'population' item 3a*	*Useful if it facilitated the diagnosis of asthma or helps identify uncontrolled asthma*	*Not sure how this helps really*	*If NO can provide an objective indication of asthma severity in those already diagnosed with the condition, then this might be a valid use of the test*	*Include diagnosis of asthma severity in already diagnosed population. Exclude diagnosis of asthma severity in an undiagnosed population, unless this facilitates diagnosis of asthma or uncontrolled asthma*

Queries on scope and study selection	Study Reference Manager IDs[a]	Our thoughts	Clifford Godley	John White	Hasan Arshad	Our decision
24. Studies that diagnose ICS responsiveness in a variety of populations, e.g.: a. chronic cough b. diagnosed asthmatics c. suspected asthma d. severe refractory asthma e. moderate asthma	e.g. 6169, 613, 617, 5878, 6164, 6321 (sputum cell count), chronic cough papers 328, 6383, 6385	*For chronic cough, we would have to present this data separately, as the diagnosis may not always be one of asthma, just one of ICS responsiveness. However, it may be better to exclude for consistency. Would this data be useful to the committee? For asthmatic populations, this may occupy an intermediate position between the diagnostic strategy and the management strategy that has not yet been captured in the review – as discussed above in 'population' item 3a*	*Data would be very useful. I feel I am comfortable to consider that patients with chronic cough who demonstrate ICS responsiveness should be considered to have cough variant asthma*	*Data are pleural so 'these data'. Sorry again! Anyway, ICS responsiveness will effectively be asthma though not all asthma is ICS responsive. Include if possible*	*Yes, it would be useful to know if NO can provide a reliable indication of steroid responsiveness in those with chronic cough. For other asthmatic populations, it would be useful to assess the value of NO in estimating steroid responsiveness, although, the answer is probably yes in most asthma phenotypes*	*Include studies which diagnose ICS responsiveness in those with or without asthma*

Queries on scope and study selection	Study Reference Manager IDs[a]	Our thoughts	Clifford Godley	John White	Hasan Arshad	Our decision
25. Asthma (as opposed to ICS responsiveness, i.e. diagnoses both eosinophilic and non-eosinophilic asthma)		*This will influence the estimates of sensitivity and specificity we will get out of the review – if we are using ICS responsiveness as a reference standard, FeNO is likely to give higher diagnostic accuracy than if we are using a broader definition of asthma as the reference standard, if we believe that it is better at identifying eosinophilic asthma. It may be best to present both sets of data? Another thing to consider is what will be useful to the model – some of the RCT studies recruit atopic patients – so if we are matching data from the diagnostic review to the RCT data for the modelling, would we need to use the diagnostic studies which identify ICS responsive asthmatics to lead into the modelling of the management strategy?*	*Certainly it will be more important to highlight the differences between eosinophilic and neutrophilic asthma with regard to NO levels and likely steroid responsiveness*	*Agree probably*	*Agree, it would be better to present both sets of data. Studies show that NO is better in diagnosing atopic than non-atopic asthma. Indeed, some studies show that it is a marker for atopy, more than it is for asthma. Hence, it would be useful to assess the usefulness of NO (as a diagnostic test) separately in atopic and non-atopic asthma. I suspect the result will be very different*	*Include studies which use asthma as the diagnostic reference standard*

Queries on scope and study selection	Study Reference Manager IDs[a]	Our thoughts	Clifford Godley	John White	Hasan Arshad	Our decision
26. Studies that use methacholine/ mannitol or bronchial hyper-responsiveness challenge as the reference standard	1109, 7500, 6184		*Include*	*Include*	*That is valid if the result of methacholine or mannitol bronchial challenge (bronchial hyperresponsiveness) is combined with symptoms and not used alone as a diagnostic marker of asthma*	*Include studies which use methacholine/ mannitol or bronchial hyperresponsiveness challenge as the reference standard where this is combined with symptoms*
27. Studies that use exposure to trigger (occupational asthma) as a specific inhalation challenge as the reference standard	387	*Is the reference standard equivalent to a diagnosis of asthma?*	*Usually diagnosis of occupational asthma is more robust than the clinical diagnosis of non occupational asthma*	*Not always!*	*Fine, but need to consider this as a distinct asthma phenotype (occupational asthma)*	*Include studies in occupational asthma which use specific inhalation challenge as the reference standard, but present separately*
28. Eosinophilic and phenotype	6257, 6164	*Similar to diagnosing ICS responsiveness and asthma – does this sit between diagnosis and management? Is it useful?*	*Sorry – couldn't identify these papers*		*No, it is not useful*	*Send to clinicians again*

Queries on scope and study selection	Study Reference Manager IDs[a]	Our thoughts	Clifford Godley	John White	Hasan Arshad	Our decision
29. Sputum eosinophilia	350	*Is this a relevant reference standard?*	*Yes*	*Ian Pavord would say so*	*For eosinophilic asthma, yes. But that is not a useful phenotype to diagnose in terms of management in day to day practice*	*Include studies which use eosinophilia as the reference standard. Present separately*
30. Variety of possibly useless reference standards	6345 (also recruited only children with positive skin prick test)	*See* Table 1 *in attached document ID 6345 – are any of these a useful reference standard?*	*Sorry – couldn't identify these papers*	*Can't see it on any list*	*Could not find* Table 1. *As suggested before, studies recruiting those with positive skin test only i.e. atopy if combined with asthma should be considered separately as this asthma phenotype (atopic asthma) is likely to be sensitive to NO*	*Sent to clinicians*

a References available on request.

Appendix 3 Data extraction forms

Review type	Data extracted for Study background	Methods and devices	Study sample characteristics	Results
Analytical validity	• Author/year • Source of funding/conflicts of interest • Study design • Setting • Inclusion/exclusion criteria • Code for population (e.g. asthmatics; asthmatics and healthy) • Code for age (adults, children, adolescents)	• Devices used: NIOX MINO, NObreath, others • Comparisons made: NIOX MINO vs. chemiluminescence, NObreath vs. chemiluminescence, NIOX MINO vs. NObreath, NIOX MINO vs. other • Method of FeNO recording (i.e. guidelines used) • Authors' conclusions • Statistical methods	• Total *N* patients recruited • Number withdrawn (with reasons) • Number analysed • Mean (±SD) age • Sex male, *n/N* (%) • Diagnosis • FEV_1% predicted • Medication usage • Smokers (current smokers/ex-smokers) • Atopic status	• Test failure rates • Mean FeNO (ppb): NIOX MINO, NObreath, chemiluminescence • Comparison data • Correlation coefficient • Regression • Bland–Altman statistic • Comparability of AUC • Comparability of cut-off values • Correction equation
Diagnostic	• Author/year • Source of funding • Study design (prospective/retrospective) • Validation or derivation • Dates • Description of study timeline • Setting • Inclusion/exclusion criteria • Inclusion age range • Code for age (children, adolescents, adults) • Code for population (e.g. symptoms of asthma; difficult to diagnose) • Medication permitted during study	• Name of device • Code for device (NIOX Mino, NObreath, chemiluminescence) • Code for FENO measurement method (e.g. ATS/ERS 2005,[35] bespoke) • Measurement method details if bespoke • FeNO cut-off points • Description of reference standard • Code for reference standard (e.g. ATS/ERS 2005[35]) • Definition of asthma	• Total *N* patients recruited • Number not followed up (with reasons) • Number of patients analysed • Mean (±SD) age • Sex male, *n/N* (%) FEV_1% predicated • Mean (±SD) FeNO measured in ppb at a flow rate of 50 ml/second • Symptoms Smokers • Atopic/allergic status • Other symptoms • Statistical methods	Prevalence of asthma Prevalence of positive result by reference standard: • cut-off value • TP • FP • FN • TN • sensitivity asthma (95% CI) • specificity asthma (95% CI) Prevalence of ICS responsiveness: • TP • FP • FN • TN • sensitivity ICS responsiveness (95% CI) • specificity ICS responsiveness (95% CI)

Review type	Data extracted for			
	Study background	**Methods and devices**	**Study sample characteristics**	**Results**
Management	• Author/year • Source of funding • Study design • Timeline of study • Setting • Inclusion/exclusion criteria • Asthma diagnosis method • Inclusion age range • Code for population • Code for subgroup	• Description of intervention • Concomitant treatments • Code for intervention (e.g. control plus FeNO) • FeNO measurement method • Code for device and method • FeNO cut-off • Description of control • Code for control (e.g. symptoms, spirometry) • Step-up/step-down protocol • Definition of exacerbation	• Total *N* patients recruited • Number of patients not followed up[a] • Number of patients analysed[a] • Mean (±SD) age[a] • Sex male, *n/N* (%)[a] • FEV_1% predicted[a] • Symptom/severity score[a] • FeNO level[a] • Medication usage[a] • Smokers (current smokers and ex-smokers)[a] • Symptoms[a] • Atopic/allergic status[a] • Statistical methods • Time of outcome measurement	• Number of exacerbations[b] • HRQoL[b] • Asthma control[b] • Clinical complications associated with exacerbations[b] • Use of OCSs[b] • Levels and use of ICSs[b] • Levels and use of other medications[b] • Adverse events[b] • Mortality rate[b] • Compliance[b] • Test failure rate[b]

a When available, data were extracted separately for the whole cohort, the intervention group and the control group.
b When available, data were extracted separately for the intervention and control groups and for any reporting of between-group comparisons.

Appendix 4 Quality assessment scoring criteria

Diagnostic studies

Risk of bias in diagnostic studies (for both child and adult populations) was assessed and described using the Bristol University QUADAS-2 tool.[38] The QUADAS-2 tool is structured around four domains of potential sources of bias in primary diagnostic studies: patient selection, index test, reference standard and flow and timing. There are signalling questions within each of these domains that allow researchers to overview the potential sources of bias therein and a summary domain score can be generated to provide an indication of the overall potential for bias in each aspect of a study's methodology. These signalling questions, and our approach to scoring them, are detailed in the following sections. It should be noted that, in our risk of bias tables, we report only the domain summary scores, although we also narratively summarise our responses to signalling questions in the review text to support these judgements.

Domain 1: patient selection

Signalling question 1: Was a consecutive or a random sample of patients enrolled?

- Score 'yes' if the report states that enrolment was consecutive or random.
- Score 'no' if the report states that another method of sampling was used.
- Score 'unclear' if insufficient information was provided to make a judgement.

Signalling question 2: Was a case–control design avoided?

- Score 'yes' if the study was not a case–control study.
- Score 'no' if the study was a case–control study.
- Score 'unclear' if insufficient information was provided to make a judgement.

Signalling question 3: Did the study avoid inappropriate exclusions?

With respect to the current review, the population of interest was patients presenting with clinical characteristics of asthma or those who are 'difficult to diagnose', that is, patients who have already undergone some of the tests for asthma in the UK pathway and who have not yet been confirmed to have asthma. The review scope also sought data on subgroups, in particular women during pregnancy, older people and smokers/passive smokers. Hence, this question was answered with respect to these groups. When there were ambiguities, two reviewers would discuss whether the population was appropriate.

- Score 'yes' if the study had appropriately selected patients conforming to the groups outline above.
- Score 'no' if the study made inappropriate exclusions from the group it set out to select.
- Score 'unclear' if insufficient information was provided to make a judgement.

Summary domain score: Could the selection of patients have introduced bias?

- Score as 'low risk' if the study scored 'yes' on all of signalling questions above.
- Score as 'high risk' if the study scored 'no' or 'unclear' on two or more of the individual items or on either of the case–control design or inappropriate exclusions questions.
- Score as 'unclear risk' if the study scored 'no' or 'unclear' on signalling question 1.

Domain 2: index test

Signalling question 1: Were the index test results interpreted without knowledge of the results of the reference standard?

- Score 'yes' if the index test results were interpreted blind to the reference standard results or the index test results were clearly interpreted before the reference standard results were known.
- Score 'no' if the results of the reference standard (UK guidelines pathway) were already known or if parts of the reference standard results downstream of the position of the test in the UK pathway were already known. This will need to be scored with reference to the patient population.
- Score 'unclear' if unclear.

Signalling question 2: If a threshold was used, was it prespecified?

- Score 'yes' if prespecified cut-off values were used (validation study).
- Score 'no' if cut-off values were fitted to the data (derivation study).
- Score 'unclear' if unclear.

Summary domain score: Could the conduct or interpretation of the index test have introduced bias?

- Score as 'low risk' if the study scored 'yes' on both signalling questions.
- Score as 'high risk' if cut-off values were fitted to the data (as derivation studies are likely to overestimate the true diagnostic accuracy of a technology relative to clinical practice) or if the study scored 'no' or 'unclear' on both signalling questions.
- Score as 'unclear' if the study scored 'no' or 'unclear' on signalling question 1 only.

Domain 3: reference standard

Signalling question 1: Is the reference standard likely to correctly classify the target condition?

No reference standard for asthma is 100% sensitive or specific. Possibly the only way that this could be achieved is with long-term follow-up, but even this might be confounded by the fact that asthma can remiss and develop (e.g. as a comorbidity) over time. Hence, this item was scored with respect to UK guidelines:

- Score 'yes' if the reference standard conforms with all or part of the UK guidelines.
- Score 'no' if the reference standard does not conform with UK guidelines, that is, it uses a test that is not within the UK guidelines.
- Score 'unclear' if unclear.

Signalling question 2: Were the reference standard results interpreted without knowledge of the results of the index test?

- Score 'yes' if the reference standard results were interpreted blind to the index test results or the reference standard results were clearly interpreted before the index test results were known.
- Score 'no' if the results of the index test were known.
- Score 'unclear' if unclear.

Summary domain score: Could the conduct or interpretation of the index test have introduced bias?

- Score as 'low risk' if the study scored 'yes' on both signalling questions.
- Score as 'high risk' if the study scored 'no' or 'unclear' on both signalling questions.
- Score as 'unclear' if the study scored 'no' or 'unclear' on either of the two signalling questions.

Domain 4: flow and timing

Signalling question 1: Was there an appropriate interval between the index test(s) and the reference standard?

- Score 'yes' if the tests were conducted consecutively.
- Score 'no' if the index test and the reference test were conducted > 1 week apart.
- Score 'unclear' if unclear.

Signalling question 2: Did all patients receive a reference standard?

- Score 'yes' if yes.
- Score 'no' if no.
- Score 'unclear' if unclear.

Signalling question 3: Did patients receive the same reference standard?

- Score 'yes' if yes.
- Score 'no' if no.
- Score 'unclear' if unclear.

Signalling question 4: Were all patients included in the analysis?

- Score 'yes' if yes.
- Score 'no' if no.
- Score 'unclear' if unclear.

Summary domain score: Could the patient flow have introduced bias?

- Score as 'low risk' if the study scored 'yes' on all signalling questions.
- Score as 'high risk' if the study scored 'no' or 'unclear' on three or more items.
- Score as 'unclear risk' if the study scored 'no' or 'unclear' on up to two items.

Management studies

The quality of the FeNO-guided management studies in adults and children was assessed using the Cochrane Collaboration's tool for assessing risk of bias in RCTs.[36] The tool is designed to address seven domains of bias: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and 'other issues'. The tool provides a two-part assessment for risk of bias: the first part describes what was reported in the study for each domain and the second part consists of the review authors' categorisation of the study as 'low', 'high' and 'uncertain' risk of bias (*Table 85*).

The criteria for risk of bias judgements as outlined in the *Cochrane Handbook*[36] (*Table 86*) were used to assign study ratings. As recommended by the *Cochrane Handbook*,[36] we did not assign an overall numerical score for risk of bias in each study but discussed how potential sources of bias may be likely to affect the outcomes of the study.

TABLE 85 The Cochrane Collaboration's tool for assessing risk of bias[36]

Domain	Description	Review authors' judgement
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Was the allocation sequence adequately generated?
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment	Was allocation adequately concealed?
Blinding of participants, personnel and outcome assessors [assessments should be made for each main outcome (or class of outcomes)]	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data [assessments should be made for each main outcome (or class of outcomes)]	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with the total number of randomised participants), reasons for attrition/ exclusions when reported and any re-inclusions in analyses performed by the review authors	Were incomplete outcome data adequately addressed?
Selective outcome reporting	State how the possibility of selective outcome reporting was examined by the review authors and what was found	Are reports of the study free of the suggestion of selective outcome reporting?
Other sources of bias	State any important concerns about bias not addressed in the other domains of the tool. If particular questions/entries were prespecified in the review's protocol, responses should be provided for each question/entry	Was the study apparently free of other problems that could put it at a high risk of bias?

TABLE 86 Criteria for judging risk of bias in the risk of bias assessment tool (from the *Cochrane Handbook*)[36]

Sequence generation: Was the allocation sequence adequately generated? (Short form: Adequate sequence generation?)	
Criteria for a judgement of 'yes' (i.e. low risk of bias)	The investigators describe a random component in the sequence generation process such as: • referring to a random number table • using a computer random number generator • coin tossing • shuffling cards or envelopes • throwing dice • drawing of lots • minimisation* *Minimisation may be implemented without a random element, and this is considered to be equivalent to being random
Criteria for the judgement of 'no' (i.e. high risk of bias)	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, e.g.: • sequence generated by odd or even date of birth • sequence generated by some rule based on date (or day) of admission • sequence generated by some rule based on hospital or clinic record number Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorisation of participants, e.g.: • allocation by judgement of the clinician • allocation by preference of the participant • allocation based on the results of a laboratory test or a series of tests • allocation by availability of the intervention
Criteria for the judgement of 'unclear' (uncertain risk of bias)	Insufficient information about the sequence generation process to permit judgement of 'yes' or 'no'
Allocation concealment: Was allocation adequately concealed? (Short form: Allocation concealment?)	
Criteria for a judgement of 'yes' (i.e. low risk of bias)	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: • central allocation (including telephone, web-based and pharmacy-controlled randomisation) • sequentially numbered drug containers of identical appearance • sequentially numbered, opaque sealed envelopes
Criteria for the judgement of 'no' (i.e. high risk of bias)	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: • using an open random allocation schedule (e.g. a list of random numbers) • assignment envelopes used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered) • alternation or rotation • date of birth • case record number • any other explicitly unconcealed procedure
Criteria for the judgement of 'unclear' (uncertain risk of bias)	Insufficient information to permit judgement of 'yes' or 'no'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement, e.g. if the use of assignment envelopes is described but it remains unclear whether envelopes were sequentially numbered, opaque and sealed
Blinding of participants, personnel and outcome assessors: Was knowledge of the allocated interventions adequately prevented during the study? (Short form: Blinding?)	

continued

TABLE 86 Criteria for judging risk of bias in the risk of bias assessment tool (from the *Cochrane Handbook*)[36] (*continued*)

Criteria for a judgement of 'yes' (i.e. low risk of bias)	Any one of the following: • no blinding but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding • blinding of participants and key study personnel ensured and unlikely that the blinding could have been broken • the participants or some key study personnel were not blinded but the outcome assessment was blinded and the non-blinding of others is unlikely to introduce bias
Criteria for the judgement of 'no' (i.e. high risk of bias)	Any one of the following: • no blinding or incomplete blinding and the outcome or outcome measurement is likely to be influenced by lack of blinding • blinding of key study participants and personnel attempted but likely that the blinding could have been broken • participants or some key study personnel were not blinded and the non-blinding of others is likely to introduce bias
Criteria for the judgement of 'unclear' (uncertain risk of bias)	Any one of the following: • insufficient information to permit judgement of 'yes' or 'no' • the study did not address this outcome
Incomplete outcome data: Were incomplete outcome data adequately addressed? (Short form: Incomplete outcome data addressed?)	
Criteria for a judgement of 'yes' (i.e. low risk of bias)	Any one of the following: • no missing outcome data • reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias) • missing outcome data balanced across intervention groups, with similar reasons for missing data across groups • for dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk not enough to have a clinically relevant impact on the intervention effect estimate • for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on the observed effect size • missing data have been imputed using appropriate methods
Criteria for the judgement of 'no' (i.e. high risk of bias)	Any one of the following: • reasons for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups • for dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk enough to induce clinically relevant bias in the intervention effect estimate • for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in the observed effect size • 'as-treated' analysis carried out with substantial departure of the intervention received from that assigned at randomisation • potentially inappropriate application of simple imputation
Criteria for the judgement of 'unclear' (uncertain risk of bias)	Any one of the following: • insufficient reporting of attrition/exclusions to permit judgement of 'yes' or 'no' (e.g. number randomised not stated, no reasons for missing data provided) • the study did not address this outcome
Selective outcome reporting: Are reports of the study free of the suggestion of selective outcome reporting? (Short form: Free of selective reporting?)	

TABLE 86 Criteria for judging risk of bias in the risk of bias assessment tool (from the *Cochrane Handbook*)[36] (*continued*)

Criteria for the judgement of 'yes' (i.e. high risk of bias)	Any of the following: • the study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way • the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon)
Criteria for the judgement of 'no' (i.e. high risk of bias)	Any one of the following: • not all of the study's prespecified primary outcomes have been reported • one or more of the primary outcomes are reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified • one or more of the reported primary outcomes are not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect) • one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis • the study report fails to include results for a key outcome that would be expected to have been reported for such a study
Criteria for the judgement of 'unclear' (uncertain risk of bias)	Insufficient information to permit judgement of 'yes' or 'no'. It is likely that the majority of studies will fall into this category
Other potential threats to validity: Was the study apparently free of other problems that could put it at a risk of bias? (Short form: Free of other bias?)	
Criteria for a judgement of 'yes' (i.e. low risk of bias)	The study appears to be free of other sources of bias
Criteria for the judgement of 'no' (i.e. high risk of bias)	There is at least one important risk of bias, e.g. the study: • had a potential source of bias related to the specific study design used or • stopped early because of some data-dependent process (including a formal stopping rule) or • had an extreme baseline imbalance or • has been claimed to have been fraudulent or • had some other problem
Criteria for the judgement of 'unclear' (uncertain risk of bias)	There may be a risk of bias but there is either: • insufficient information to assess whether an important risk of bias exists or • insufficient rationale or evidence that an identified problem will introduce bias

Appendix 5 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[193] flow diagram (adapted) for the reviews of clinical evidence and for the update of clinical evidence conducted in September 2013. Additional search for NIOX Vero included in numbers for original search

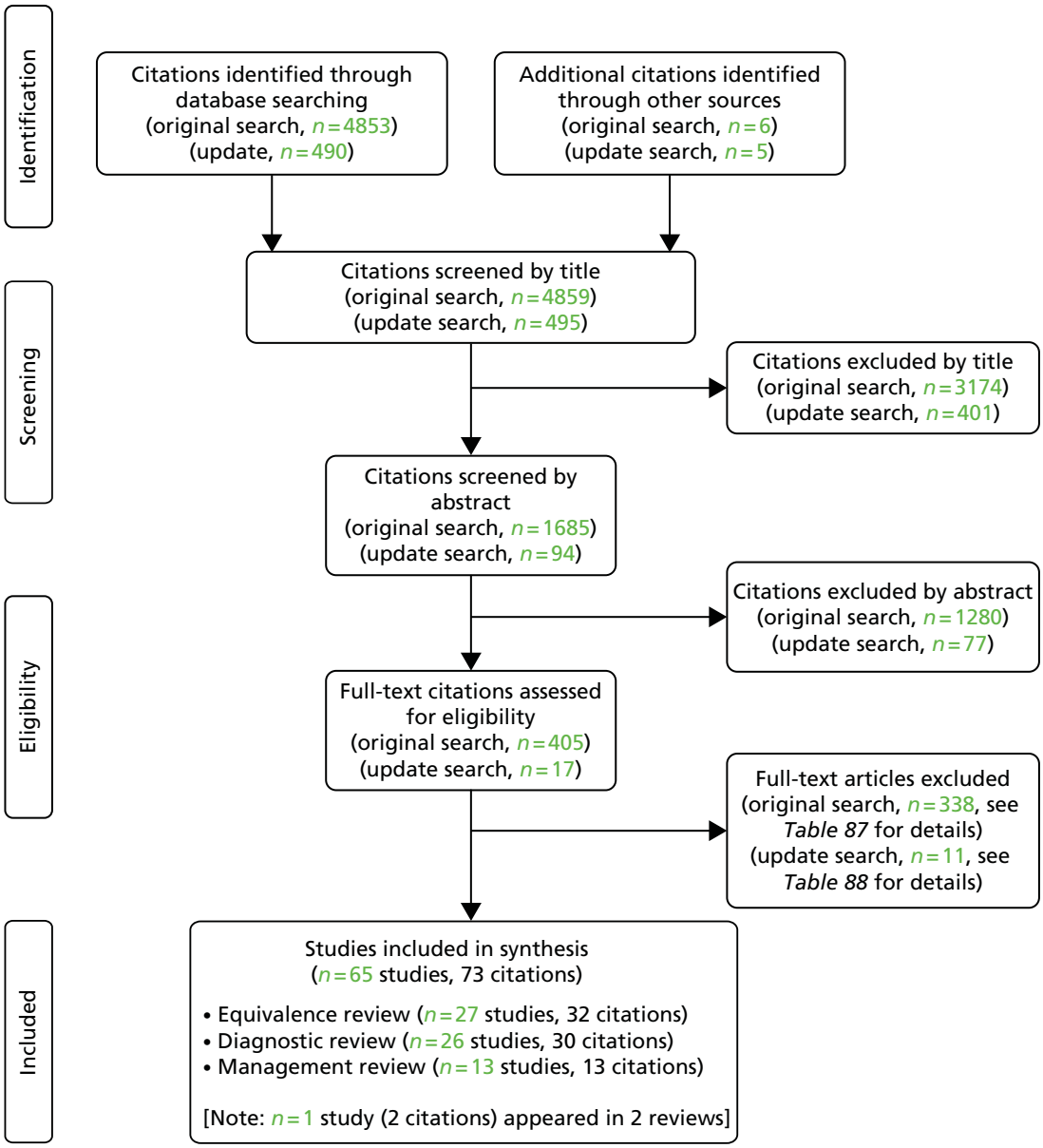

TABLE 87 Analytical validity review, management review and diagnostic review: table of excluded studies with rationale

	Study	Reason for exclusion
1	National Institute of Allergy and Infectious Diseases. Evaluation of an asthma treatment strategy based on exhaled nitric oxide measurements in adolescents. *ClinicalTrials.gov* 2005	Trial protocol
2	Abba AA, Habib SS, Beg MFS, Al Zoghaibi M. A comparative study of fraction of exhaled nitric oxide in stable chronic obstructive pulmonary disease and steroid naive asthma. In *New Horizons Allergy Asthma Immunology* 2009. pp. 199–204	Not a RCT
3	Acembekiroglu S, Altintas D, Seydaoglu G, Ceter T, Yilmaz M, Bingol KG, *et al.* Seasonal variation of exhaled nitric oxide levels in children with allergic asthma that is sensitive to inhaled allergens. *Allergy* 2011;**66**:201	Not a RCT
4	Agache I, Ciobanu C. Predictive value of lung function trend and FeNO for difficult asthma in children. *J Invest Allergol Clin Immunol* 2012;**22**:419–26	Not a RCT
5	Alvarez-Gutierrez FJ, Medina-Gallardo JF, Perez-Navarro P, Martin-Villasclaras JJ, Etchegoren BM, Romero-Romero B, *et al.* Comparison of the Asthma Control Test (ACT) with lung function, levels of exhaled nitric oxide and control according to the Global Initiative for Asthma (GINA). *Arch Bronconeumol* 2010;**46**:370–7	Foreign language
6	Anderson WJ, Lipworth BJ. Does body mass index influence responsiveness to inhaled corticosteroids in persistent asthma? *Ann Allergy Asthma Immunol* 2012;**108**:237–42	Not a RCT
7	Andregnette-Roscigno V, Fernandez-Nieto M, Garcia Del Potro M, Aguado E, Sastre J. Correlation between tests to measure bronchial hyperreactivity and exhaled nitric oxide levels in asthmatic children. *Allergy* 2011;**66**:154	No useable diagnostic data
8	Arnold DH, Gebretsadik T, Abramo TJ, Hartert TV, Arnold DH, Gebretsadik T, *et al.* Noninvasive testing of lung function and inflammation in pediatric patients with acute asthma exacerbations. *J Asthma* 2012;**49**:29–35	Emergency care
9	Arochena L, Fernandez-Nieto M, Andregnette V, Garcia Del PM, Aguado E, Sastre J. Bronchial hyperresponsiveness in sportschildren; different methods to reach a diagnosis. *J Allergy Clin Immunol* 2012;**129**(2 Suppl. 1):AB2	No useable diagnostic data
10	Artlich A, Hagenah JU, Jonas S, Ahrens P, Gortner L. Exhaled nitric oxide in childhood asthma. *Eur J Pediatr* 1996;**155**:698–701	Wrong flow rate
11	Avital A, Uwyyed K, Berkman N, Godfrey S, Bar-Yishay E, Springer C. Exhaled nitric oxide and asthma in young children. *Pediatr Pulmonol* 2001;**32**:308–13	Offline
12	Awabdy B, Balasubramanyam V, Parikh B, Peled N. Performance of the new insight ENO system to measure exhaled nitric oxide – comparison to chemiluminescence technologies. *Am J Respir Crit Care Med* 2010;**181**:A4283	Wrong device
13	Ayars AG, Potter-Perigo S, Wight TN, Tilles SA, Altman LC. Comparative sensitivity of various indices in evaluating improvement in mild persistent asthma. *J Allergy Clin Immunol* 2012;**129**(2 Suppl. 1):AB75	Not a RCT
14	Badzakova MG, Obocki K. Exhaled nitric oxide fraction in asthmatic children – well correlated with clinical control of asthma (in primary care). *Allergy* 2011;**66**:588	Not a RCT
15	Baek HS, Kim HJ, Kim YD, Oh JW, Shin JH, Lee HB. Exhaled nitric oxide correlates with post-betaronchodilator improvement of FEV_1 in chronic childhood asthma. *J Allergy Clin Immunol* 2010;**125**(2 Suppl. 1):AB50	Not a RCT
16	Balinotti JE, Colom A, Kofman C, Teper AM. Association between nitric oxide and a clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2011;**183**:A5475	Infants
17	Baptist AP, Sengupta R, Pranathiageswaran S, Wang Y, Ager J. Evaluation of exhaled nitric oxide measurements in the emergency department for patients with acute asthma. *Ann Allergy Asthma Immunol* 2008;**100**:415–19	Emergency care
18	Baptist AP, Shah B, Wang Y, Ager J, Badr MS. Exhaled nitric oxide levels during treatment in patients hospitalized with asthma. *Allergy Asthma Proc* 2008;**29**:171–6	Emergency care
19	Baptist AP, Khan FI, Wang Y, Ager J. Exhaled nitric oxide measurements in hospitalized children with asthma. *J Asthma* 2008;**45**:670–4	Emergency care

TABLE 87 Analytical validity review, management review and diagnostic review: table of excluded studies with rationale (*continued*)

Study		Reason for exclusion
20	Bar-Yishay E, Matyashchuk E, Mussaffi H, Prais D, Steuer G, Mei-Zahav M, *et al.* Fractional exhaled nitric oxide does not correlate with functional measures in pre-school wheezy children. *Am J Respir Crit Care Med* 2010;**181**:A3922	No usable diagnostic data
21	Baraldi E, Scollo M, Zaramella C, Zanconato S, Zacchello F. A simple flow-driven method for online measurement of exhaled NO starting at the age of 4 to 5 years. *Am J Respir Crit Care Med* 2000;**162**:1828–32	NO analytical data
22	Baraldi E, Azzolin NM, Zanconato S, Dario C, Zacchello F. Corticosteroids decrease exhaled nitric oxide in children with acute asthma. *J Pediatr* 1997;**131**:381–5	Not a RCT
23	Baraldi E, Azzolin NM, Cracco A, Zacchello F. Reference values of exhaled nitric oxide for healthy children 6–15 years old. *Pediatr Pulmonol* 1999;**27**:54–8	Tidal breathing
24	Barben J, Strippoli MP, Trachsel D, Schiller B, Hammer J, Kuehni CE, *et al.* Effect of mannitol dry powder challenge on exhaled nitric oxide in children. *PLOS ONE* 2013;**8**:e54521	Not FeNO testing for diagnosis
25	Barreto M, Villa MP, Olita C, Martella S, Ciabattoni G, Montuschi P, *et al.* 8-Isoprostane in exhaled breath condensate and exercise-induced bronchoconstriction in asthmatic children and adolescents. *Chest* 2009;**135**:66–73	Not a RCT
26	Barreto M, La Penna F, Prete A, Bonafoni S, Negro V, Chialant D, *et al.* Exhaled breath temperature and other exhaled markers in children with asthma and rhinitis. *Am J Respir Crit Care Med* 2011;**183**:A1897	No useable diagnostic data
27	Bastain TM, Islam T, Berhane KT, McConnell RS, Rappaport EB, Salam MT, *et al.* Exhaled nitric oxide, susceptibility and new-onset asthma in the Children's Health Study. *Eur Respir J* 2011;**37**:523–31	Offline
28	Bautista AP, Eisenlohr CP, Lanz MJ. Nasal nitric oxide and nasal eosinophils decrease with levocetirizine in subjects with perennial allergic rhinitis. *Am J Rhinol Allergy* 2011;**25**:383–7	Not asthma
29	Bayo AL, Tordera MP, Perez EM, Gisbert VM. Contribution of exhaled nitric oxide measurements to abbreviated bronchial challenge test protocols. *Arch Bronconeumol* 2008;**44**:402–7	Population asthma and non-asthma
30	Becher G, Dietze S, Steinhaeusser W, Schmidtmann S, Beck E, Timm-Labsch B. Can we measure exhaled NO accurate and reproducible? *Am J Respir Crit Care Med* 2010;**181**:A4280	No analytical data
31	Beigelman A, Mauger DT, Phillips BR, Zeiger RS, Taussig LM, Strunk RC, *et al.* Effect of elevated exhaled nitric oxide levels on the risk of respiratory tract illness in preschool-aged children with moderate-to-severe intermittent wheezing. *Ann Allergy Asthma Immunol* 2009;**103**:108–13	Offline
32	Belda J, Parameswaran K, Lemiere C, Kamada D, O'Byrne PM, Hargreave FE, *et al.* Predictors of loss of asthma control induced by corticosteroid withdrawal. *Can Respir J* 2006;**13**:129–33	Not a RCT
33	Bell MC, Evans MD, Tisler CJ, Gern J, Lemanske J, Jackson DJ. Early aeroallergen sensitization is associated with higher fractional exhaled nitric oxide levels in school age children independent of asthma diagnosis. *J Allergy Clin Immunol* 2013;**131**(2 Suppl. 1):AB46	No useable diagnostic data
34	Berkman N, Avital A, Breuer R, Bardach E, Springer C, Godfrey S. Exhaled nitric oxide in the diagnosis of asthma: comparison with bronchial provocation tests. *Thorax* 2005;**60**:383–8	Wrong flow rate
35	Berlyne GS, Parameswaran K, Kamada D, Efthimiadis A, Hargreave FE. A comparison of exhaled nitric oxide and induced sputum as markers of airway inflammation. *J Allergy Clin Immunol* 2000;**106**:638–44	Wrong flow rate

continued

TABLE 87 Analytical validity review, management review and diagnostic review: table of excluded studies with rationale (*continued*)

	Study	Reason for exclusion
36	Bernstein JA, Davis B, Alvarez-Puebla MJ, Nguyen D, Levin L, Olaguibel JM, *et al.* Is exhaled nitric oxide a useful adjunctive test for assessing asthma? *J Asthma* 2009;**46**:955–60	No useable diagnostic data
37	Berry MA, Shaw DE, Green RH, Brightling CE, Wardlaw AJ, Pavord ID, *et al.* The use of exhaled nitric oxide concentration to identify eosinophilic airway inflammation: an observational study in adults with asthma. *Clin Exp Allergy* 2005;**35**:1175–9	Wrong flow rate
38	Bisgaard H, Loland L, Oj JA. NO in exhaled air of asthmatic children is reduced by the leukotriene receptor antagonist montelukast. *Am J Respir Crit Care Med* 1999;**160**:1227–31	Wrong flow rate
39	Bivins J, Ownby D, Waller J, Tingen M. Exhaled nitric oxide level and school absenteeism in rural high school students with current asthma. *J Allergy Clin Immunol* 2013;**131**(2 Suppl. 1):AB64	No useable diagnostic data
40	Blain EA, Craig T, Weyant K. Exhaled nitric oxide (eNO) should not be used to exclude the diagnosis of asthma. *Ann Allergy Asthma Immunol* 2009;**103**(5 Suppl. 3):A60	Case study
41	Bloemen K, Koppen G, Govarts E, Colles A, Van Den Heuvel R, Nelen V, *et al.* Application of non-invasive biomarkers in a birth cohort follow-up in relation to respiratory health outcome. *Biomarkers* 2010;**15**:583–93	No useable diagnostic data
42	Bodini A, Peroni DG, Zardini F, Corradi M, Alinovi R, Boner AL, *et al.* Flunisolide decreases exhaled nitric oxide and nitrotyrosine levels in asthmatic children. *Mediators Inflamm* 2006;**2006**:31919	Not a RCT
43	Bodini A, Peroni D, Loiacono A, Costella S, Pigozzi R, Baraldi E, *et al.* Exhaled nitric oxide daily evaluation is effective in monitoring exposure to relevant allergens in asthmatic children. *Chest* 2007;**132**:1520–5	Not a RCT
44	Bohadana AB, Hannhart B, Ghezzo H, Teculescu D, Zmirou-Navier D. Exhaled nitric oxide and spirometry in respiratory health surveillance. *Occup Med (Oxford)* 2011;**61**:108–14	Unselected population
45	Bommarito L, Migliore E, Bugiani M, Heffler E, Guida G, Bucca C, *et al.* Exhaled nitric oxide in a population sample of adults. *Respiration* 2008;**75**:386–92	Offline
46	Boon M, Meyts I, Warnier G, Boeck KD. Exhaled nitric oxide: offline tidal breathing measurements are feasible in children and correlate with online single breath measurements. *Pediatr Allergy Immunol Pulmonol* 2010;**23**:201–6	Online vs. offline
47	Boon M, Proesmans M, Meyts I, De Boeck K. Do composite scores of nNO and FENO improve diagnostic value? *J Cyst Fibrosis* 2012;**11**:S96	Case–control study
48	Boot JD, de Kam ML, Mascelli MA, Miller B, van Wijk RG, de Groot H, *et al.* Nasal nitric oxide: longitudinal reproducibility and the effects of a nasal allergen challenge in patients with allergic rhinitis. *Allergy* 2007;**62**:378–84	Nasal NO
49	Bora M, Alpaydin AO, Yorgancioglu A, Akkas G, Isisag A, Coskun AS, *et al.* Does asthma control as assessed by the asthma control test reflect airway inflammation? *Multidiscip Resp Med* 2011;**6**:291–8	Not a RCT
50	Bosque-Garcia M, Asensio-De La Cruz O, Jaramillo-Hidalgo D, Valdesoiro-Navarrete L, Costa-Colomer J, Penas-Aguilera A, *et al.* Exhaled nitric oxide and asthma control measured by clinical score and exerciseinduced bronchoconstriction. *Allergy Eur J Allergy Clin Immunol* 2011;**66**:577–8	Not a RCT
51	Bossley CJ, Saglani S, Kavanagh C, Payne DN, Wilson N, Tsartsali L, *et al.* Corticosteroid responsiveness and clinical characteristics in childhood difficult asthma. *Eur Respir J* 2009;**34**:1052–9	Not a RCT
52	Bozek A, Jarzab J. Nasal nitric oxide measurements in patients with seasonal allergic rhinitis. *Allergy Eur J Allergy Clin Immunol* 2010;**65**:155	No usable diagnostic data
53	Bozek A, Filipowska-Gronska A, Werynska-Kalemba M, Jarzab J. Nasal nitric oxide measurements in patients with seasonal allergic rhinitis of different age groups. *Postepy Dermatol Alergol* 2010;**27**:96–100	Foreign language

TABLE 87 Analytical validity review, management review and diagnostic review: table of excluded studies with rationale (*continued*)

Study		Reason for exclusion
54	Bozek A, Krajewska J, Jarzab J. Nasal nitric oxide and other diagnostic procedures in seasonal allergic rhinitis: elderly vs juvenile patients. *Am J Otolaryngol* 2011;**32**:105–8	Nasal NO
55	Bratton DL, Lanz MJ, Miyazawa N, White CW, Silkoff PE. Exhaled nitric oxide before and after montelukast sodium therapy in school-age children with chronic asthma: a preliminary study. *Pediatr Pulmonol* 1999;**28**:402–7	Wrong flow rate
56	Brightling CE, Green RH, Pavord ID. Biomarkers predicting response to corticosteroid therapy in asthma. *Treat Respir Med* 2005;**4**:309–16	Review
57	Brindicci C, Ito K, Barnes PJ, Kharitonov SA. Differential flow analysis of exhaled nitric oxide in patients with asthma of differing severity. *Chest* 2007;**131**:1353–62	FeNO testing did not guide step-up/step-down therapy
58	Brooks CR, Brogan SB, van Dalen CJ, Lampshire PK, Crane J, Douwes J, *et al.* Measurement of exhaled nitric oxide in a general population sample: a comparison of the Medisoft HypAir FE(NO) and Aerocrine NIOX analyzers. *J Asthma* 2011;**48**:324–8	Wrong device
59	Bruce CT, Zhao D, Yates DH, Thomas PS. AMP challenge induces a decrease in FE(NO) in asthmatic subjects modulated by nedocromil. *Eur J Clin Invest* 2006;**36**:899–905	FeNO testing did not guide step-up/step-down therapy
60	Bruce CT, Zhao D, Yates DH, Thomas PS. L-arginine reverses cigarette-induced reduction of fractional exhaled nitric oxide in asthmatic smokers. *Inflammopharmacology* 2010;**18**:9–16	FeNO testing did not guide step-up/step-down therapy
61	Brusselle GG, Kardos P, Louis R, Schmoller T, Jorgensen L, Aubier M, *et al.* Budesonide/formoterol maintenance and reliever therapy at two different maintenance doses: effect on fractional excretion of nitric oxide (FENO). *Am J Respir Crit Care Med* 2010;**181**:A5407	No useable diagnostic data
62	Buchvald F, Eiberg H, Bisgaard H. Heterogeneity of FeNO response to inhaled steroid in asthmatic children. *Clin Exp Allergy* 2003;**33**:1735–40	FeNO testing did not guide step-up/step-down therapy
63	Buchvald F, Hermansen MN, Nielsen KG, Bisgaard H. Exhaled nitric oxide predicts exercise-induced bronchoconstriction in asthmatic school children. *Chest* 2005;**128**:1964–7	All asthmatic not diagnostic
64	Buchvald F, Baraldi E, Carraro S, Gaston B, De Jongste J, Pijnenburg MW, *et al.* Measurements of exhaled nitric oxide in healthy subjects age 4 to 17 years. *J Allergy Clin Immunol* 2005;**115**:1130–6	Measurement in healthy subjects
65	Bukstein D, Luskin AT, Brooks EA. Exhaled nitric oxide as a tool in managing and monitoring difficult-to-treat asthma. *Allergy Asthma Proc* 2011;**32**:185–92	Not a RCT
66	Bukstein DA. Individualized dynamic phenotyping using fractional exhaled nitric oxide levels in children with asthma. *Ann Allergy Asthma Immunol* 2012;**109**:A52	Not a RCT
67	Burnett M, Wegienka G, Havstad S, Ownby D, Cole JC, Zoratti E. The relationship of fractional exhaled nitric oxide levels to allergy and asthma biomarkers in young adults. *J Allergy Clin Immunol* 2011;**127**(2 Suppl. 1):AB58	
68	Bush A. The use of inflammatory markers to guide therapy in children with severe asthma. *ClinicalTrials.gov* 2005	Trial protocol
69	Byrnes CA, Dinarevic S, Busst CA, Shinebourne EA, Bush A. Effect of measurement conditions on measured levels of peak exhaled nitric oxide. *Thorax* 1997;**52**:697–701	No analytical data
70	Cabral AL, Vollmer WM, Barbirotto RM, Martins MA. Exhaled nitric oxide as a predictor of exacerbation in children with moderate-to-severe asthma: a prospective, 5-month study. *Ann Allergy Asthma Immunol* 2009;**103**:206–11	Not a RCT
71	Canady RG, Platts-Mills T, Murphy A, Johannesen R, Gaston B. Vital capacity reservoir and online measurement of childhood nitrosopnea are linearly related. Clinical implications. *Am J Respir Crit Care Med* 1999;**159**:311–14	Online vs. offline

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TABLE 87 Analytical validity review, management review and diagnostic review: table of excluded studies with rationale (*continued*)

Study		Reason for exclusion
72	Cardinale F, De Benedictis FM, Muggeo V, Giordano P, Loffredo MS, Iacoviello G, *et al.* Exhaled nitric oxide, total serum IgE and allergic sensitization in childhood asthma and allergic rhinitis. *Pediatr Allergy Immunol* 2005;**16**:236–42	Wrong flow rate
73	Carlstedt F, Lazowska D, Bornehag CG, Olin AC, Hasselgren M. Exhaled nitric oxide and urinary EPX levels in infants: a pilot study. *Clin Mol Allergy* 2011;**9**:8	No useable diagnostic data
74	Carra S, Gagliardi L, Zanconato S, Scollo M, Azzolin N, Zacchello F, *et al.* Budesonide but not nedocromil sodium reduces exhaled nitric oxide levels in asthmatic children. *Respir Med* 2001;**95**:734–9	Wrong flow rate
75	Carter R, Murphy A, Hargadon B, Agbetile J, Pavord ID, Wardlaw AJ, *et al.* Evaluating the role of triamcinolone in a difficult asthma service. *Thorax* 2010;**65**:A152	Not a RCT
76	Carvalho-Pinto RM, Stelmach R, Angelini L, Santos DO, Dias-Junior S, Cukier A, *et al.* Is there a good tool to measure asthma control on severe asthma patients? *Am J Respir Crit Care Med* 2010;**181**:A2560	Not a RCT
77	Castano R, Miedinger D, Malo JL, Desrosiers M. Nasal and exhaled nitric oxide monitoring during specific inhalation challenge using a portable analyser. *J Allergy Clin Immunol* 2011;**127**(2 Suppl. 1):AB53	No analytical data
78	Castell B, Pike D, Masoli M. Difficult asthma: the Plymouth experience. *Thorax* 2011;**66**:A114	Not a RCT
79	Castro-Rodriguez JA, Sardon O, Perez-Yarza EG, Korta J, Aldasoro A, Corcuera P, *et al.* Young infants with recurrent wheezing and positive asthma predictive index have higher levels of exhaled nitric oxide. *J Asthma* 2013;**50**:162–5	Age < 5 years
80	Caudri D, Wijga AH, Hoekstra MO, Kerkhof M, Koppelman GH, Brunekreef B, *et al.* Prediction of asthma in symptomatic preschool children using exhaled nitric oxide, Rint and specific IgE. *Thorax* 2010;**65**:801–7	Offline
81	Chai J-J, Cai B-Q. The normal value measurement of fractional concentration of exhaled nitric oxide in Chinese adults. *Respirology* 2011;**16**:196–7	No analytical data
82	Chatkin JM, Ansarin K, Silkoff PE, McClean P, Gutierrez C, Zamel N, *et al.* Exhaled nitric oxide as a noninvasive assessment of chronic cough. *Am J Respir Crit Care Med* 1999;**159**:1810–13	Wrong flow rate
83	Chawes BL, Buchvald F, Bischoff AL, Loland L, Hermansen M, Halkjaer LB, *et al.* Elevated exhaled nitric oxide in high-risk neonates precedes transient early but not persistent wheeze. *Am J Respir Crit Care Med* 2010;**182**:138–42	Wrong flow rate
84	Chen E, Strunk RC, Bacharier LB, Chan M, Miller GE. Socioeconomic status associated with exhaled nitric oxide responses to acute stress in children with asthma. *Brain Behav Immunity* 2010;**24**:444–50	Not a RCT
85	Cherot-Kornobis N, Hulo S, Edme JL, de Broucker V, Matran R, Sobaszek A. Analysis of nitrogen oxides (NOx) in the exhaled breath condensate (EBC) of subjects with asthma as a complement to exhaled nitric oxide (FeNO) measurements: a cross-sectional study. *BMC Res Notes* 2011;**4**:202	No useable diagnostic data
86	Chinellato I, Piazza M, Peroni D, Sandri M, Chiorazzo F, Boner AL, *et al.* Bronchial and alveolar nitric oxide in exercise-induced bronchoconstriction in asthmatic children. *Clin Exp Allergy* 2012;**42**:1190–6	Not a RCT
87	Chladkova J, Senkerik M, Havlinova Z, Krcmova I, Chladek J. Alveolar concentration and bronchial flux of nitric oxide: two linear modeling methods evaluated in children and adolescents with allergic rhinitis and atopic asthma. *Pediatr Pulmonol* 2012;**47**:1070–9	Alveolar NO
88	Choi B, Jee H, Park Y, Kim C, Sohn M, Kim K. Relationship between exhaled nitric oxide and allergic inflammation or sensitization in children. *J Allergy Clin Immunol* 2009;**123**(2 Suppl. 1):S207	No useable diagnostic data
89	Choi BS, Kim KW, Lee YJ, Baek J, Park HB, Kim YH, *et al.* Exhaled nitric oxide is associated with allergic inflammation in children. *J Korean Med Sci* 2011;**26**:1265–9	Not FeNO testing for diagnosis

TABLE 87 Analytical validity review, management review and diagnostic review: table of excluded studies with rationale (*continued*)

Study		Reason for exclusion
90	Chow JS, Leung AS, Li WW, Tse TP, Sy HY, Leung TF, *et al.* Airway inflammatory and spirometric measurements in obese children. *Hong Kong Med J* 2009;**15**:346–52	No useable diagnostic data
91	Cibella F, Cuttitta G, La Grutta S, Melis MR, Bucchieri S, Viegi G. A cross-sectional study assessing the relationship between BMI, asthma, atopy, and eNO among schoolchildren. *Ann Allergy Asthma Immunol* 2011;**107**:330–6	No useable diagnostic data
92	Ciprandi G, Tosca MA, Capasso M. Exhaled nitric oxide in children with allergic rhinitis and/or asthma: a relationship with bronchial hyperreactivity. *J Asthma* 2010;**47**:1142-7	Data for both asthma and rhinitis
93	Ciprandi G, Tosca MA, Capasso M. High exhaled nitric oxide levels may predict bronchial reversibility in allergic children with asthma or rhinitis. *J Asthma* 2013;**50**:33–8	Data for both asthma and rhinitis
94	Cirillo I, Ricciardolo FLM, Medusei G, Signori A, Ciprandi G. Exhaled nitric oxide may predict bronchial hyperreactivity in patients with allergic rhinitis. *Int Arch Allergy Immunol* 2013;**160**:322–8	Not diagnosis of asthma
95	Clearie KL, Williamson PA, Vaidyanathan S, Short P, Goudie A, Burns P, *et al.* Disconnect between standardized field-based testing and mannitol challenge in Scottish elite swimmers. *Clin Exp Allergy* 2010;**40**:731–7	Not FeNO for diagnosis
96	Clearie KL, Vaidyanathan S, Williamson PA, Goudie A, Short P, Schembri S, *et al.* Effects of chlorine and exercise on the unified airway in adolescent elite Scottish swimmers. *Allergy* 2010;**65**:269–73	No useable diagnostic data
97	Clearie KL, Jackson CM, Fardon TC, Williamson PA, Vaidyanathan S, Burns P, *et al.* Supervised step-down of inhaled corticosteroids in the community – an observational study. *Respir Med* 2011;**105**:558–65	Not a RCT
98	Cleveland C, Monforte SE, Spahn JD. Establishing normal exhaled nitric oxide (FeNO) values in young children. *J Allergy Clin Immunol* 2013;**131**(2 Suppl. 1):AB195	No useable diagnostic data
99	Cohen J, Douma WR, Ten Hacken NH, Vonk JM, Oudkerk M, Postma DS, *et al.* Ciclesonide improves measures of small airway involvement in asthma. *Eur Respir J* 2008;**31**:1213–20	Alveolar NO
100	Colon-Semidey AJ, Marshik P, Crowley M, Katz R, Kelly HW. Correlation between reversibility of airway obstruction and exhaled nitric oxide levels in children with stable bronchial asthma. *Pediatr Pulmonol* 2000;**30**:385–92	Not a RCT
101	Columbo M, Wong B, Panettieri RA, Rohr AS. Asthma in the elderly: the role of exhaled nitric oxide measurements. *J Allergy Clin Immunol* 2012;**129**(2 Suppl. 1):AB8	No useable diagnostic data
102	Consilvio NP, Di Pillo S, Verini M, de Giorgis T, Cingolani A, Chiavaroli V, *et al.* The reciprocal influences of asthma and obesity on lung function testing, AHR, and airway inflammation in prepubertal children. *Pediatr Pulmonol* 2010;**45**:1103–10	Population obese
103	Consilvio NP, Di Pillo S, de Giorgis T, Cingolani A, Scaparrotta A, Rapino D, *et al.* The reciprocal influences of asthma and obesity on lung function, AHR and bronchial inflammation in prepubertal children. *Paediatr Respir Rev* 2010;**11**:S2–3	No useable diagnostic data
104	Corradi M. What is new in the air? *Monaldi Arch Chest Dis Pulm Ser* 2002;**57**:227-8	Editorial
105	Corradi M, Zinelli C, Caffarelli C. Exhaled breath biomarkers in asthmatic children. *Inflamm Allergy Drug Targets* 2007;**6**:150–9	Review
106	Covar RA, Szefler SJ, Martin RJ, Sundstrom DA, Silkoff PE, Murphy J, *et al.* Relations between exhaled nitric oxide and measures of disease activity among children with mild-to-moderate asthma. *J Pediatr* 2003;**142**:469-75	Not a RCT
107	Cowan DC, Cowan JO, Palmay R, Williamson A, Taylor DR. Effects of steroid therapy on inflammatory cell subtypes in asthma. *Thorax* 2010;**65**:384–90	FeNO testing did not guide step-up/step-down therapy

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TABLE 87 Analytical validity review, management review and diagnostic review: table of excluded studies with rationale (*continued*)

Study		Reason for exclusion
108	Cowan DC, Hewitt RS, Cowan JO, Palmay R, Williamson A, Lucas SJ, *et al.* Exercise-induced wheeze: fraction of exhaled nitric oxide-directed management. *Respirology* 2010;**15**:683–90	Not randomised to FeNO
109	Craig TJ, King TS, Lemanske RF Jr, Wechsler ME, Icitovic N, Zimmerman RR Jr, *et al.* Aeroallergen sensitization correlates with PC(20) and exhaled nitric oxide in subjects with mild-to-moderate asthma. *J Allergy Clin Immunol* 2008;**121**:671–7	FeNO testing did not guide step-up/step-down therapy
110	Crane J, Wickens K, Beasley R, Fitzharris P. Asthma and allergy: a worldwide problem of meanings and management? *Allergy Eur J Allergy Clin Immunol* 2002;**57**:663–72	Review
111	Crane J, Lampshire P, Wickens K, Epton M, Siebers R, Ingham T, *et al.* Asthma, atopy and exhaled nitric oxide in a cohort of 6-yr-old New Zealand children. *Pediatr Allergy Immunol* 2012;**23**:59–64	No useable diagnostic data
112	Crater SE, Peters EJ, Martin ML, Murphy AW, Platts-Mills TAE. Expired nitric oxide and airway obstruction in asthma patients with an acute exacerbation. *Am J Respir Crit Care Med* 1999;**159**:806–11	Wrong flow rate
113	Cristescu SM, Mandon J, Harren FJM, Merilainen P, Hogman M. Methods of NO detection in exhaled breath. *J Breath Res* 2013;**7**:017104	Review
114	Crothall H, Custovic A, Simpson A, Kerry G, Belgrave D, Murray C. The relationship between exhaled nitric oxide, atopy and asthma in school aged children. *Clin Exp Allergy* 2012;**42**:1846	No useable diagnostic data
115	Currie GP, Bates CE, Lee DKC, Jackson CM, Lipworth BJ. Effects of fluticasone plus salmeterol versus twice the dose of fluticasone in asthmatic patients. *Eur J Clin Pharmacol* 2003;**59**:11–15	FeNO testing did not guide step-up/step-down therapy
116	Currie GP, Syme-Grant NJ, McFarlane LC, Carey FA, Lipworth BJ. Effects of low dose fluticasone/salmeterol combination on surrogate inflammatory markers in moderate persistent asthma. *Allergy* 2003;**58**:602–7	Not a RCT
117	Currie GP, Lee DKC, Haggart K, Bates CE, Lipworth BJ. Effects of montelukast on surrogate inflammatory markers in corticosteroid-treated patients with asthma. *Am J Respir Crit Care Med* 2003;**167**:1232–8	Wrong flow rate
118	Dahlen B, Lantz AS, Ihre E, Skedinger M, Henriksson E, Jorgensen L, *et al.* Effect of formoterol with or without budesonide in repeated low-dose allergen challenge. *Eur Respir J* 2009;**33**:747–53	FeNO testing did not guide step-up/step-down therapy
119	Dal Negro R, Micheletto C, Tognella S, Turco P, Rossetti A, Cantini L. Assessment of inhaled BDP-dose dependency of exhaled nitric oxide and local and serum eosinophilic markers in steroids-naive nonatopic asthmatics. *Allergy* 2003;**58**:1018–22	Wrong flow rate
120	Dallinga JW, Robroeks CMHH, van Berkel JJBN, Moonen EJC, Godschalk RWL, Jobsis Q, *et al.* Volatile organic compounds in exhaled breath as a diagnostic tool for asthma in children. *Clin Exp Allergy* 2010;**40**:68–76	No useable diagnostic data
121	de Bot CM, Moed H, Bindels PJ, van Wijk RG, Berger MY, de Groot H, *et al.* Exhaled nitric oxide measures allergy not symptoms in children with allergic rhinitis in primary care: a prospective cross-sectional and longitudinal cohort study. *Prim Care Respir J* 2013;**22**:44–50	No useable diagnostic data
122	de Gouw HW, Hendriks J, Woltman AM, Twiss IM, Sterk PJ. Exhaled nitric oxide (NO) is reduced shortly after bronchoconstriction to direct and indirect stimuli in asthma. *Am J Respir Crit Care Med* 1998;**158**:315–19	FeNO testing did not guide step-up/step-down therapy
123	de Gouw HW, Grunberg K, Schot R, Kroes AC, Dick EC, Sterk PJ, *et al.* Relationship between exhaled nitric oxide and airway hyperresponsiveness following experimental rhinovirus infection in asthmatic subjects. *Eur Respir J* 1998;**11**:126–32	Not RCT study
124	de Gouw HW, Marshall-Partridge SJ, Van der Veen H, Van Den Aardweg JG, Hiemstra PS, Sterk PJ. Role of nitric oxide in the airway response to exercise in healthy and asthmatic subjects. *J Appl Physiol* 2001;**90**:586–92	Wrong flow rate

TABLE 87 Analytical validity review, management review and diagnostic review: table of excluded studies with rationale (*continued*)

Study		Reason for exclusion
125	de Groot EP, Nijkamp A, Duiverman EJ, Brand PL. Allergic rhinitis is associated with poor asthma control in children with asthma. *Thorax* 2012;**67**:582–7	Not a RCT
126	de Jongste JC, Carraro S, Hop WC, CHARISM Study Group, Baraldi E. Daily telemonitoring of exhaled nitric oxide and symptoms in the treatment of childhood asthma. *Am J Respir Crit Care Med* 2009;**179**:93–7	Daily monitoring
127	de Meer G, van Amsterdam JGC, Janssen NAH, Meijer E, Steerenberg PA, Brunekreef B. Exhaled nitric oxide predicts airway hyper-responsiveness to hypertonic saline in children that wheeze. *Allergy* 2005;**60**:1499–504	Offline
128	de Winter-de Groot K, van der Ent CK. Measurement of nasal nitric oxide: evaluation of six different sampling methods. *Eur J Clin Invest* 2009;**39**:72–7	Nasal NO
129	de Kluijver J, Evertse CE, Schrumpf JA, van der Veen H, Zwinderman AH, Hiemstra PS, *et al.* Asymptomatic worsening of airway inflammation during low-dose allergen exposure in asthma: protection by inhaled steroids. *Am J Respir Crit Care Med* 2002;**166**:294–300	FeNO testing did not guide step-up/step-down therapy
130	Debley JS, Stamey DC, Cochrane ES, Gama KL, Redding GJ. Exhaled nitric oxide, lung function, and exacerbations in wheezy infants and toddlers. *J Allergy Clin Immunol* 2010;**125**:1228–34	Infants aged < 2 years
131	Debley J, Stamey D, Cochrane E, Elliot M, Redding G. Exhaled nitric oxide predicts persistence of wheezing, exacerbations, and decline in lung function in wheezy infants and toddlers. *Am J Respir Crit Care Med* 2011;**183**:A1033	Infants
132	Debley JS, Cochrane ES, Redding GJ, Carter ER. Lung function and biomarkers of airway inflammation during and after hospitalization for acute exacerbations of childhood asthma associated with viral respiratory symptoms. *Ann Allergy Asthma Immunol* 2012;**109**:114–20	Not a RCT
133	Decimo F, Capristo C, Amelio R, Maiello N, Capristo AF, Miraglia Del GM, *et al.* Evaluation of bronchial hyperreactivity with mannitol dry powder challenge test in a paediatric population with intermittent allergic asthma or allergic rhinitis. *Int J Immunopathol Pharmacol* 2011;**24**:1069–74	No useable diagnostic data
134	del Giudice MM, Brunese FP, Piacentini GL, Pedulla M, Capristo C, Decimo F, *et al.* Fractional exhaled nitric oxide (FENO), lung function and airway hyperresponsiveness in naive atopic asthmatic children. *J Asthma* 2004;**41**:759–65	Unselected population
135	Delclaux C, Mahut B, Zerah-Lancner F, Delacourt C, Laoud S, Cherqui D, *et al.* Increased nitric oxide output from alveolar origin during liver cirrhosis versus bronchial source during asthma. *Am J Respir Crit Care Med* 2002;**165**:332–7	Case–control study
136	Delclaux C, Sembach N, Claessens YE, Dolbeau G, Chevalier-Bidaud B, Renaud B, *et al.* Offline exhaled nitric oxide in emergency department and subsequent acute asthma control. *J Asthma* 2008;**45**:867–73	Offline
137	Delgado-Corcoran C, Kissoon N, Murphy SP, Duckworth LJ. Exhaled nitric oxide reflects asthma severity and asthma control. *Pediatr Crit Care Med* 2004;**5**:48–52	Not a RCT
138	Demange V, Bohadana A, Massin N, Wild P. Exhaled nitric oxide and airway hyperresponsiveness in workers: a preliminary study in lifeguards. *BMC Pulm Med* 2009;**9**:53	Unselected population
139	Demange V, Wild P, Zmirou-Navier D, Tossa P, Bohadana A, Barbaud A, *et al.* Associations of airway inflammation and responsiveness markers in non asthmatic subjects at start of apprenticeship. *BMC Pulm Med* 2010;**10**:37	Unselected population
140	Dente FL, Melosini L, Novelli F, Bacci E, Cianchetti S, Di Franco A, *et al.* Asthma control test (ACT) score is related to PEF variability and markers of airway inflammation in corticosteroids naives asthmatics. *Am J Respir Crit Care Med* 2010;**181**:A2738	No useable diagnostic data

continued

TABLE 87 Analytical validity review, management review and diagnostic review: table of excluded studies with rationale (*continued*)

Study		Reason for exclusion
141	Deykin A, Massaro AF, Drazen JM, Israel E. Exhaled nitric oxide as a diagnostic test for asthma: online versus offline techniques and effect of flow rate. *Am J Respir Crit Care Med* 2002;**165**:1597–601	Wrong flow rate
142	Deykin A, Lazarus SC, Fahy JV, Wechsler ME, Boushey HA, Chinchilli VM, *et al.* Sputum eosinophil counts predict asthma control after discontinuation of inhaled corticosteroids. *J Allergy Clin Immunol* 2005;**115**:720–7	Offline
143	Diaconu R, Diaconu C, Bica C, Bulucea D. Bronchial responsiveness and airway inflammation in various sports. *Allergy* 2010;**65**:195	No useable diagnostic data
144	Diamant Z, Kuperus J, Baan R, Nietzmann K, Millet S, Mendes P, *et al.* Effect of a very late antigen-4 receptor antagonist on allergen-induced airway responses and inflammation in asthma. *Clin Exp Allergy* 2005;**35**:1080–7	FeNO testing did not guide step-up/step-down therapy
145	Dichiaro CA, Baptist AP. Exhaled nitric oxide levels in African American children. *Ann Allergy Asthma Immunol* 2009;**103**(5 Suppl. 3):A71	No useable diagnostic data
146	Dichiaro CA, Joiner TA, Hudson SA, Baptist AP. Factors influencing asthma control and quality of life in African American children. *J Allergy Clin Immunol* 2010;**125**(2 Suppl. 1):AB138	No useable diagnostic data
147	Divjan A, Rosa M, Just AC, Sheares BJ, Perera FP, Miller RL, *et al.* IgE and symptoms by age 2 years predict FENO at age 5-7 years in a low-income urban New York City population. *J Allergy Clin Immunol* 2009;**123**(2 Suppl. 1):S19	No useable diagnostic data
148	Divjan A, Rosa M, Reyes M, Hoepner L, Sheares BJ, Zhang H, *et al.* Exhaled NO at age 7–11 years is elevated with early life but not recent onset of allergic sensitization. *Am J Respir Crit Care Med* 2011;**183**:A4472	No useable diagnostic data
149	Domingo C, Moreno A, Amengual MJ, Monton C, Suarez D, Pomares X. Omalizumab in the management of oral corticosteroid-dependent IGE-mediated asthma patients. *Curr Med Res Opin* 2011;**27**:45–53	Not a RCT
150	Donohue KM, Miller RL, Perzanowski MS, Just AC, Hoepner LA, Arunajadai S, *et al.* Prenatal and postnatal bisphenol A exposure and asthma development among inner-city children. *J Allergy Clin Immunol* 2013;**131**:736–42	Not FeNO testing for diagnosis
151	Dressel H, Gross C, de la Motte D, Sultz J, Jorres RA, Nowak D. Educational intervention decreases exhaled nitric oxide in farmers with occupational asthma. *Eur Respir J* 2007;**30**:545–8	Not a RCT
152	Dressel H, Gross C, de la Motte D, Sultz J, Jorres RA, Nowak D, *et al.* Educational intervention in farmers with occupational asthma: long-term effect on exhaled nitric oxide. *J Invest Allergol Clin Immunol* 2009;**19**:49–53	Not a RCT
153	Dupont LJ, Demedts MG, Verleden GM. Prospective evaluation of the validity of exhaled nitric oxide for the diagnosis of asthma. *Chest* 2003;**123**:751–6	Wrong flow rate
154	Dweik RA, Sorkness RL, Wenzel S, Hammel J, Curran-Everett D, Comhair SA, *et al.* Use of exhaled nitric oxide measurement to identify a reactive, at-risk phenotype among patients with asthma. *Am J Respir Crit Care Med* 2010;**181**:1033–41	Not a RCT
155	Ekerljung L, Bossios A, Lotvall J, Olin AC, Ronmark E, Wennergren G, *et al.* Multi-symptom asthma as an indication of disease severity in epidemiology. *Eur Respir J* 2011;**38**:825–32	No useable diagnostic data
156	Fernandez-Nieto M, Sastre B, Sastre J, Lahoz C, Quirce S, Madero M, *et al.* Changes in sputum eicosanoids and inflammatory markers after inhalation challenges with occupational agents. *Chest* 2009;**136**:1308–15	No data on FeNO testing for diagnosis
157	Fireman E, Toledano B, Soferman R, Moshe S, Sivan Y, Kivity S, *et al.* Airways eosiniphilic inflammation in the airways of astmatic children is correlated to particulate matter in induced sputum. *Am J Respir Crit Care Med* 2010;**181**:A1156	No useable diagnostic data
158	Fortuna A, Feixas T, Gonzalez M, Casan P. Portable equipment (NIOX MINO, aerocrine) for determination of NO in respiratory air (FENO). *Arch Bronconeumol* 2006;**42**:420	Foreign language

TABLE 87 Analytical validity review, management review and diagnostic review: table of excluded studies with rationale (*continued*)

Study		Reason for exclusion
159	Franklin PJ, Turner SW, Le Souef PN, Stick SM. Exhaled nitric oxide and asthma: complex interactions between atopy, airway responsiveness, and symptoms in a community population of children. *Thorax* 2003;**58**:1048–52	Wrong flow rate
160	Fuchs O, Latzin P, Singer F, Petrus N, Proietti E, Kieninger E, *et al.* Comparison of online single-breath vs. online multiple-breath exhaled nitric oxide in school-age children. *Pediatr Res* 2012;**71**:605–11	Single breath vs. multiple breaths
161	Fujimura M, Ohkura N, Abo M, Furusho S, Waseda Y, Ichikawa Y, *et al.* Exhaled nitric oxide levels in patients with atopic cough and cough variant asthma. *Respirology* 2008;**13**:359–64	Case–control study
162	Gill M, Graff GR, Adler AJ, Dweik RA. Validation study of fractional exhaled nitric oxide measurements using a handheld monitoring device. *J Asthma* 2006;**43**:731–4	Inter-reliability
163	Grzelewski T, Grzelewska A, Majak P, Stelmach W, Kowalska A, Stelmach R, *et al.* Fractional exhaled nitric oxide (FeNO) may predict exercise-induced bronchoconstriction (EIB) in schoolchildren with atopic asthma. *Nitric Oxide Biol Chem* 2012;**27**:82–7	Diagnosing EIB in asthmatics, i.e. not diagnostic of asthma
164	Hafkamp-de-Groen E, Mohangoo AD, de Jongste JC, van der Wouden JC, Moll HA, Jaddoe VW, *et al.* Early detection and counselling intervention of asthma symptoms in preschool children: study design of a cluster randomised controlled trial. *BMC Public Health* 2010;**10**:555	Study design only
165	Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, *et al.* Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;**178**:218–24	Not a RCT
166	Hardaker K, Downie S, Kermode J, Farah C, Berend N, King G, *et al.* The predictors of airway hyperresponsiveness are different in younger and older asthmatics. *Respirology* 2010;**15**:A37	No useable diagnostic data
167	Hardaker KM, Downie SR, Kermode JA, Farah CS, Brown NJ, Berend N, *et al.* Predictors of airway hyperresponsiveness differ between old and young patients with asthma. *Chest* 2011;**139**:1395–401	No useable diagnostic data
168	Hemmingsson T, Horn A, Linnarsson D. Measuring exhaled nitric oxide at high altitude. *Respir Physiol Neurobiol* 2009;**67**:292–8	Not in humans
169	Högman M, Malinovschi A, Norbäck D, Janson C. Added value with extended NO analysis in atopy and asthma. *Clin Physiol Funct Imaging* 2011;**31**:294–9	No useable diagnostic data
170	Honkoop PJ, Loymans RJ, Termeer EH, Snoeck-Stroband JB, Bakker MJ, Assendelft WJ, *et al.* Asthma control cost–utility randomized trial evaluation (ACCURATE): the goals of asthma treatment. *BMC Pulm Med* 2011;**11**:53	Ongoing study
171	Huang J, Yao T, Yeh K. Exhaled nitric oxide discriminates children with and without allergic sensitisation in a population-based study. Allergy 2011;**66**:198	Unselected population
172	Hur G-Y, Oh JY, Choi J-H, Sim J-K, Min KH, Lee S-Y, *et al.* Mannitol challenge test, sputum eosinophils and exhaled nitric oxide (FENO) for diagnosis of asthma. *J Allergy Clin Immunol* 2013;**131**(2 Suppl. 1):AB64	No useable diagnostic data
173	Imaoka M, Tanahashi T, Kishikawa R, Shimoda T, Iwanaga T. Gender-specific effect of overweight and obesity on airway inflammation in adults with asthma. *J Allergy Clin Immunol* 2011;**127**(2 Suppl. 1):AB98	No useable diagnostic data
174	Imaoka M, Tanahashi T, Kishikawa R, Shimoda T, Iwanaga T. Overweight and obesity reduce exhaled nitric oxide levels in Japanese women with asthma. *Allergy* 2011;**66**:515	No useable diagnostic data
175	Inoue H, Niimi A, Takeda T, Matsumoto H, Ito I, Otsuka K, *et al.* Pathophysiological characteristics of asthma in the elderly. *Am J Respir Crit Care Med* 2010;**181**:A5096	No useable diagnostic data

continued

TABLE 87 Analytical validity review, management review and diagnostic review: table of excluded studies with rationale (*continued*)

	Study	Reason for exclusion
176	Ishizuka T, Matsuzaki S, Aoki H, Yatomi M, Kamide Y, Hisada T, *et al.* Prevalence of asthma symptoms based on the European Community Respiratory Health Survey questionnaire and FENO in university students: gender differences in symptoms and FENO. *Allergy Asthma Clin Immunol* 2011;**7**:15	No useable diagnostic data
177	Ito Y, Adachi Y, Itazawa T, Okabe Y, Adachi YS, Katsumuma T, *et al.* Comparison of exhalation time methods (6 sec vs. 10 sec) of a hand-held exhaled nitric oxide analyzer. *Pediatr Pulmonol* 2010;**45**:1005–8	Measurement not in accordance with ATS 2005 guidelines[35]
178	Jackson DJ, Virnig CM, Gangnon RE, Evans MD, Roberg KA, Anderson EL, *et al.* Fractional exhaled nitric oxide measurements are most closely associated with allergic sensitization in school-age children. *J Allergy Clin Immunol* 2009;**124**:949–53	No useable diagnostic data
179	Jobsis Q, Raatgeep HC, Hop WC, Jongste JC. Controlled low flow off line sampling of exhaled nitric oxide in children. *Thorax* 2001;**56**:285–9	Offline
180	Jobsis Q, Schellekens SL, Kroesbergen A, Hop WCJ, de Jongste JC. Off-line sampling of exhaled air for nitric oxide measurement in children: methodological aspects. *Eur Respir J* 2001;**17**:898–903	Offline
181	Jung A, Summermatter S, Geidel C, Moller A, Menz G, Lauener R. Diagnostic value of nasal NO measurement using the NIOX MINO device. *Atemwegs Lungenkr* 2012;**38**:57–8	Nasal NO
182	Jung M, Korn S, Taube C, Buhl R. Short-term reproducibility of non-invasive clinical and inflammatory parameters in asthma. *Am J Respir Crit Care Med* 2011;**183**:A4481	No analytical data
183	Kelso JM. Titrating steroids on exhaled nitric oxide in children with asthma: a randomized, controlled trial: commentary. *Pediatrics* 2006;**118**(Suppl. 1):S33	Commentary
184	Kharitonov SA, Donnelly LE, Montuschi P, Corradi M, Collins JV, Barnes PJ, *et al.* Dose-dependent onset and cessation of action of inhaled budesonide on exhaled nitric oxide and symptoms in mild asthma. *Thorax* 2002;**57**:889–96	FeNO testing did not guide step-up/step-down therapy
185	Khurana S, Larj M, Saatian B, Lerner LB, Smith S, Pietropaoli A, *et al.* Correlation of bronchodilator reversibility with exhaled nitric oxide levels and asthma severity. *Am J Respir Crit Care Med* 2011;**183**:A4474	No useable diagnostic data
186	Kim S, Kim T, Sohn J, Yoon H, Shin D, Park S. Measurement of the exhaled nitric oxide in the assessment of chronic cough. *J Allergy Clin Immunol* 2009;**123**(2 Suppl. 1):S6	No useable diagnostic data
187	Kim S-H, Kim TH, Sohn JW, Yoon HJ, Shin DH, Park SS. Measurement of exhaled and nasal nitric oxide in the diagnosis of chronic cough. *Respirology* 2009;**14**:A160	No useable diagnostic data
188	Kim YH, Kim KW, Baek J, Park HB, Kim H, Song K-J, *et al.* Usefulness of impulse oscillometry and fractional exhaled nitric oxide in children with eosinophilic bronchitis. *Pediatr Pulmonol* 2013;**48**:221–8	No useable diagnostic data
189	Klaassen EM, van de Kant KD, Jobsis Q, Hovig ST, van Schayck CP, Rijkers GT, *et al.* Symptoms, but not a biomarker response to inhaled corticosteroids, predict asthma in preschool children with recurrent wheeze. *Mediators Inflamm* 2012;**2012**:162571	No useable diagnostic data
190	Konstantinou G, Xepapadaki P, Manousakis E, Makrinioti C, Kouloufakou-Gratsia K, Chatziioannou A, *et al.* Non-invasive evaluation of airway inflammation during virus-induced asthma exacerbations in atopic and non-atopic preschool-children. *Allergy* 2009;**64**:432–3	FeNO testing in exacerbations
191	Konstantinou GN, Xepapadaki P, Manousakis E, Makrinioti H, Kouloufakou-Gratsia K, Saxoni-Papageorgiou P, *et al.* Assessment of airflow limitation, airway inflammation, and symptoms during virus-induced wheezing episodes in 4- to 6-year-old children. *J Allergy Clin Immunol* 2013;**131**:87–93	No useable diagnostic data
192	Koopman M, Arets HG, Uiterwaal CS, van der Ent CK. Comparing 6 and 10 sec exhalation time in exhaled nitric oxide measurements in children. *Pediatr Pulmonol* 2009;**44**:340–4	Measurement not in accordance with ATS 2005 guidelines[35]

TABLE 87 Analytical validity review, management review and diagnostic review: table of excluded studies with rationale (*continued*)

Study		Reason for exclusion
193	Kotaniemi-Syrjanen A, Malmberg LP, Malmstrom K, Pelkonen AS, Makela MJ. Factors associated with elevated exhaled nitric oxide fraction in infants with recurrent respiratory symptoms. *Eur Respir J* 2013;**41**:189–94	Infants aged < 3 years
194	Krcmova I, Novosad J, Kralickova P, Kleiberova M, Chladkova J, Melicharova J. Asthma control test, FeNO, functional parameters, ECP and their correlation. *Allergy* 2009;**64**:301–2	Not a RCT
195	Kumor M, Przybylowski T, Maskey-Warzechowska M, Hildebrand K, Fangrat A, Bielicki P, *et al.* [Reproducibility of exhaled nitric oxide (FENO) measurements in healthy subjects]. *Pneumonol Alergol Pol* 2004;**72**:395–9	Foreign language
196	Larj MJ, Khurana S, Lerner LB, Smith SM, Aung T, Pietropaoli A, *et al.* Alveolar and airway nitric oxide correlations in asthma. *Am J Respir Crit Care Med* 2010;**181**:A4282	Alveolar NO
197	Larson JL, Zeidler MR, Kleerup EC, Kim HJG, Tashkin DP. Correlation of alveolar nitric oxide with methacholine responsiveness in asthmatic subjects following a naturalistic cat challenge. *Am J Respir Crit Care Med* 2011;**183**:A4471	Alveolar NO
198	Larson JL, Zeidler M, Kleerup E, Tashkin D. Evaluation of exhaled nitric oxide as a surrogate for airways hyperresponsiveness. *J Invest Med* 2011;**59**:214	No useable diagnostic data
199	Latzin P, Kuehni CE, Baldwin DN, Roiha HL, Casaulta C, Frey U. Elevated exhaled nitric oxide in newborns of atopic mothers precedes respiratory symptoms. *Am J Respir Crit Care Med* 2006;**174**:1292–8	No useable diagnostic data
200	Lee J, Lee BH, Lee S-H. Repeatability of successive measurements with a portable nitric oxide analyser in healthy Koreans. *Chest* 2011;**140**:213A	Repeatability
201	Lehtimaki L, Turjanmaa V, Kankaanranta H, Saarelainen S, Hahtola P, Moilanen E. Increased bronchial nitric oxide production in patients with asthma measured with a novel method of different exhalation flow rates. *Ann Med* 2000;**32**:417–23	Device not in scope
202	Lemiere C, D'Alpaos V, Chaboillez S, Cesar M, Wattiez M, Chiry S, *et al.* Investigation of occupational asthma: sputum cell counts or exhaled nitric oxide? *Chest* 2010;**137**:617–22	Offline
203	Lemiere C, Tremblay C, Bohadana A, Chaboillez S. Prognosis of the workers with non-eosinophilic occupational asthma. *Am J Respir Crit Care Med* 2011;**183**:A1172	Not FeNO testing
204	Lex C, Dymek S, Heying R, Kovacevic A, Kramm CM, Schuster A. Value of surrogate tests to predict exercise-induced bronchoconstriction in atopic childhood asthma. *Pediatr Pulmonol* 2007;**42**:225–30	Diagnosis of EIB not asthma
205	Li S, Lou XS, Ma Y, Han SL, Liu CH, Chen YZ, *et al.* [Exhaled nitric oxide levels in school children of Beijing]. *Zhonghua Erke Zazhi* 2010;**48**:148–52	Foreign language
206	Linkosalo L, Lehtimaki L, Holm K, Kaila M, Moilanen E. Increased bronchial nitric oxide output is associated with exercise-induced bronchoconstriction in atopic children. *Allergy* 2009;**64**:72–3	No useable diagnostic data
207	Linn WS, Rappaport EB, Berhane KT, Bastain TM, Avol EL, Gilliland FD. Exhaled nitric oxide in a population-based study of southern California schoolchildren. *Respir Res* 2009;**10**:28	Wrong device
208	Linn WS, Rappaport EB, Berhane KT, Bastain TM, Salam MT, Gilliland FD, *et al.* Extended exhaled nitric oxide analysis in field surveys of schoolchildren: a pilot test. *Pediatr Pulmonol* 2009;**44**:1033–42	No useable diagnostic data
209	Linn WS, Berhane KT, Rappaport EB, Bastain TM, Avol EL, Gilliland FD. Relationships of online exhaled, offline exhaled, and ambient nitric oxide in an epidemiologic survey of schoolchildren. *J Expo Sci Environ Epidemiol* 2009;**19**:674–81	No useable diagnostic data
210	Little SA, Chalmers GW, MacLeod KJ, McSharry C, Thomson NC. Non-invasive markers of airway inflammation as predictors of oral steroid responsiveness in asthma. *Thorax* 2000;**55**:232–4	Wrong flow rate

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TABLE 87 Analytical validity review, management review and diagnostic review: table of excluded studies with rationale (*continued*)

Study		Reason for exclusion
211	Lonnkvist K, Anderson M, Hedlin G, Svartengren M. Exhaled NO and eosinophil markers in blood, nasal lavage and sputum in children with asthma after withdrawal of budesonide. *Pediatr Allergy Immunol* 2004;**15**:351–8	FeNO testing did not guide step-up/step-down therapy
212	Lund TK. Asthma in elite athletes: how do we manage asthma-like symptoms and asthma in elite athletes? *Clin Respir J* 2009;**3**:123	Case–control study
213	Magori E, Hiltawsky K, Fleischer M, Simon E, Pohle R, von Sicard O, *et al.* Fractional exhaled nitric oxide measurement with a handheld device. *J Breath Res* 2011;**5**:027104	Device not in scope
214	Mahut B, Peyrard S, Delclaux C. Exhaled nitric oxide and clinical phenotypes of childhood asthma. *Respir Res* 2011;**12**:65	No useable diagnostic data
215	Malby Schoos AM, Chawes BL, Bonnelykke K, Bisgaard H. Fraction of exhaled nitric oxide and bronchial responsiveness are associated and continuous traits in young children independent of asthma. *Chest* 2012;**142**:1562–8	No useable diagnostic data
216	Malik G, Turner SW. Deselecting the instant flow option on the NIOX© analyser increases the number of successful FENO measurements without altering the results. *Eur Respir J* 2005;**26**:Abstract 3907	No comparison between devices
217	Malik G, Turner S. Is the 'instant flow' option on the NIOX analyser needed? *Med Eng Physics* 2007;**29**:72–5	Wrong device
218	Malinovschi A, Janson C, Hogman M, Rolla G, Toren K, Norback D, *et al.* Both allergic and nonallergic asthma are associated with increased FE(NO) levels, but only in never-smokers. *Allergy* 2009;**64**:55–61	No useable diagnostic data
219	Malinovschi A, Backer V, Harving H, Porsbjerg C. The value of exhaled nitric oxide to identify asthma in smoking patients with asthma-like symptoms. *Respir Med* 2012;**106**:794–801	Incorrect reference standard
220	Malka-Rais J, Krawiec ME, Spahn JD. Are there differences in levels of impairment, risk, and biomarkers of inflammation in children vs. adults with severe persistent asthma? *J Allergy Clin Immunol* 2010;**125**(2 Suppl. 1):AB6	No useable diagnostic data
221	Malka-Rais J, Davidson J, Krawiec ME, Spahn JD. Which parameters are useful in the determining asthma severity in childhood? *Am J Respir Crit Care Med* 2010;**181**:A2556	No useable diagnostic data
222	Malmberg LP, Pelkonen AS, Mattila PS, Hammaren-Malmi S, Makela MJ. Exhaled nitric oxide and exercise-induced bronchoconstriction in young wheezy children – interactions with atopy. *Pediatr Allergy Immunol* 2009;**20**:673–8	Age 3–7 years
223	Malmberg LP, Laatikainen T, von Hertzen L, Makela MJ, Vartiainen E, Haahtela T, *et al.* Exhaled nitric oxide in contrasting population samples of Finnish and Russian Karelia. *Eur Respir J* 2010;**35**:1416–18	No useable diagnostic data
224	Maniscalco M, Lundberg JO. Hand-held nitric oxide sensor NIOX MINO for the monitoring of respiratory disorders. *Expert Rev Respir Med* 2010;**4**:715–21	Review
225	Martin N, Lindley MR, Hargadon B, Monteiro W, Pavord ID. Airway dysfunction and inflammation in pool and non-pool based elite endurance athletes. *Thorax* 2010;**65**:A60–1	No useable diagnostic data
226	Martin N, Lindley MR, Hargadon B, Monteiro W, Pavord ID. Airway dysfunction and inflammation in pool and non-pool based elite international athletes with symptoms suggesting exercise-induced asthma. *Am J Respir Crit Care Med* 2010;**181**:A3970	No useable diagnostic data
227	Martin N, Lindley MR, Hargadon B, Monteiro W, Pavord ID. Airways dysfunction and eosinophilic inflammation in elite athletes with symptoms suggesting exercise-induced asthma. *Thorax* 2009;**64**:A72	No useable diagnostic data
228	Martin N, Lindley MR, Hargadon B, Monteiro WR, Pavord ID. Airway dysfunction and inflammation in pool- and non-pool-based elite athletes. *Med Sci Sports Exerc* 2012;**44**:1433–9	No useable diagnostic data

TABLE 87 Analytical validity review, management review and diagnostic review: table of excluded studies with rationale (*continued*)

Study		Reason for exclusion
229	Martin RJ, Szefler SJ, King TS, Kraft M, Boushey HA, Chinchilli VM, *et al.* The Predicting Response to Inhaled Corticosteroid Efficacy (PRICE) trial. *J Allergy Clin Immunol* 2007;**119**:73–80	No useable diagnostic data
230	Martins P, Caires I, Pinto JR, da Mata PL, Torres S, Valente J, *et al.* The clinical use of exhaled nitric oxide in wheezing children. *Rev Port Pneumol* 2008;**14**:195–218	Population not self-presenting for assessment
231	Matsunaga K, Hirano T, Akamatsu K, Koarai A, Sugiura H, Minakata Y, *et al.* Exhaled nitric oxide cutoff values for asthma diagnosis according to rhinitis and smoking status in Japanese subjects. *Allergol Int* 2011;**60**:331–7	Case–control study
232	McCurdy MR, Bakhirkin YA, Tittel FK. Quantum cascade laser-based integrated cavity output spectroscopy of exhaled nitric oxide. *Appl Physics B Lasers Optics* 2006;**85**:445–52	Laser spectroscopy
233	McCurdy MR, Bakhirkin Y, Wysocki G, Tittel FK. Performance of an exhaled nitric oxide and carbon dioxide sensor using quantum cascade laser-based integrated cavity output spectroscopy. *J Biomed Optics* 2007;**12**:034034	Laser spectroscopy
234	McKinlay L, Williamson PA, Short PM, Fardon TC, Lipworth BJ. Proof of concept study to evaluate step-down therapy with inhaled corticosteroid alone or additive therapy on surrogate inflammatory markers in asthma. *Br J Clin Pharmacol* 2011;**71**:128–31	FeNO testing did not guide step-up/step-down therapy
235	Menzies D, Jackson C, Mistry C, Houston R, Lipworth BJ. Symptoms, spirometry, exhaled nitric oxide, and asthma exacerbations in clinical practice. *Ann Allergy Asthma Immunol* 2008;**101**:248–55	FeNO testing did not guide step-up/step-down therapy
236	Meyts I, Proesmans M, Van Gerven V, Hoppenbrouwers K, De Boeck K. Tidal off-line exhaled nitric oxide measurements in a pre-school population. *Eur J Pediatr* 2003;**162**:506–10	No useable diagnostic data
237	Mgaloblishvili N, Gotua M, Rukhadze M, Dolidze N, Lomidze N, Abramidze T, *et al.* Exhaled nitric oxide and respiratory symptoms in the diagnosis of atopic asthma. *Allergy* 2009;**64**:179–80	No useable diagnostic data
238	Mgaloblishvili N, Gotua M, Gamkrelidze A. Exhaled nitric oxide and asthma severity in georgian population. *Allergy* 2010;**65**:549	No useable diagnostic data
239	Mi Q, Balzar S, Wenzel SE. Distinguishing the features of severe asthma: feature selection in the asthma dataset using linear support vector machines (SVM) approach. *Am J Respir Crit Care Med* 2011;**183**:A4301	No useable diagnostic data
240	Miedinger D, Chhajed PN, Tamm M, Stolz D, Surber C, Leuppi JD. Diagnostic tests for asthma in firefighters. *Chest* 2007;**131**:1760–7	Unselected population
241	Monforte S, Malka-Rais J, Spahn JD. The use of exhaled nitric oxide (FeNO) in the outpatient management of children with asthma. *J Allergy Clin Immunol* 2009;**123**:727	No useable diagnostic data
242	Monforte S, Malka-Rais J, Spahn JD. The association of exhaled nitric oxide (FeNO) with asthma control and severity in children. *J Allergy Clin Immunol* 2010;**125**(2 Suppl. 1):AB186	Not RCT study
243	Montella S, Alving K, Maniscalco M, Sofia M, De Stefano S, Raia V, *et al.* Measurement of nasal nitric oxide by hand-held and stationary devices. *Eur J Clin Invest* 2011;**41**:1063–70	Nasal NO
244	Motomura C, Odajima H, Tezuka J, Murakami Y, Moriyasu Y, Kando N, *et al.* Effect of age on relationship between exhaled nitric oxide and airway hyperresponsiveness in asthmatic children. *Chest* 2009;**136**:519–25	No useable diagnostic data
245	Motomura C, Odajima H, Tezuka J, Kodama T, Amimoto Y, Murakami Y, *et al.* Exhaled nitric oxide predicts bronchial responsiveness according to age in asthmatic children. *Am J Respir Crit Care Med* 2010;**181**:A3294	No useable diagnostic data

continued

TABLE 87 Analytical validity review, management review and diagnostic review: table of excluded studies with rationale (*continued*)

Study		Reason for exclusion
246	Motomura C, Odajima H, Higashi N, Tezuka J, Honjo S, Okada K, *et al.* Exercise-induced bronchoconstriction in children with asthma: is there an association with urinary leukotriene E4 or exhaled nitric oxide. *Pediatr Allergy Immunol Pulmonol* 2012;**25**:208–12	No useable diagnostic data
247	Muller KC, Jorres RA, Magnussen H, Holz O. Comparison of exhaled nitric oxide analysers. *Respir Med* 2005;**99**:631–7	Wrong device
248	Munnik P, van der Lee I, Fijn J, van Eijsden LJ, Lammers JW, Zanen P. Comparison of eNO and histamine hyperresponsiveness in diagnosing asthma in new referrals. *Respir Med* 2010;**104**:801–7	Not comparing relevant devices
249	Murata A, Kida K, Hasunuma H, Kanegae H, Ishimaru Y, Motegi T, *et al.* Environmental influence on the measurement of exhaled nitric oxide concentration in school children: special reference to methodology. *J Nippon Med School* 2007;**74**:30–6	No useable diagnostic data
250	Musk AWB, Knuiman M, Hunter M, Hui J, Palmer L, Beilby J, *et al.* Patterns of airway disease and the clinical diagnosis of asthma in the Busselton population. *Respirology* 2010;**15**:A46	No useable diagnostic data
251	Musk AW, Knuiman M, Hunter M, Hui J, Palmer LJ, Beilby J, *et al.* Patterns of airway disease and the clinical diagnosis of asthma in the Busselton population. *Eur Respir J* 2011;**38**:1053–9	No useable diagnostic data
252	Nagase H, Toda T, Kamiyama A, Nakase Y, Sugimoto N, Yoshihara H, *et al.* Usefulness of measuring fractional exhaled nitric oxide (FeNO) in various respiratory diseases. *J Allergy Clin Immunol* 2011;**127**(2 Suppl. 1):AB7	Unclear how patients recruited
253	Nakajima N, Mochizuki H, Muramatsu R, Hagiwara S, Mizuno T, Arakawa H, *et al.* Relationship between exhaled nitric oxide and small airway lung function in normal and asthmatic children. *Allergol Int* 2011;**60**:53–9	No useable diagnostic data
254	Narang I, Ersu R, Wilson NM, Bush A. Nitric oxide in chronic airway inflammation in children: diagnostic use and pathophysiological significance. *Thorax* 2002;**57**:586–9	Case–control study
255	Nelson BV, Sears S, Woods J, Ling CY, Hunt J, Clapper LM, *et al.* Expired nitric oxide as a marker for childhood asthma. *J Pediatr* 1997;**130**:423–7	Case–control study
256	Nikasinovic L, Rouffai L, Dassonville C, Momas I, Just J. Nasal lavage fluid IL8 and fractional exhaled nitric oxide (FeNO) association in untreated asthmatic children. *Allergy* 2011;**66**:643–4	No useable diagnostic data
257	Nishio K, Odajima H, Motomura C, Nakao F, Nishima S, Nishio K, *et al.* Exhaled nitric oxide and exercise-induced bronchospasm assessed by FEV_1, FEF25–75% in childhood asthma. *J Asthma* 2007;**44**:475–8	No useable diagnostic data
258	Obata H, Dittrick M, Chan H, Chan-Yeung. Sputum eosinophils and exhaled nitric oxide during late asthmatic reaction in patients with western red cedar asthma. *Eur Respir J* 1999;**3**:489–95	Wrong flow rate
259	Olaguibel JM, Parra A, Alvarez MJ, Quirce S, Lopez R. Measurements of fractional exhaled nitric oxide with 2 portable electrochemical sensors: a comparative study. *J Invest Allergol Clin Immunol* 2011;**21**:322–3	Healthy volunteers
260	Oros M, Codleanu C, Calapod L, Bogdan R, Bulacu E, Momarla C, *et al.* Is FENO of some help for pediatric outpatients with asthma? *Am J Respir Crit Care Med* 2010;**181**:A3301	No useable diagnostic data
261	Oshikata C, Tsuburai T, Tsurikisawa N, Ono E, Higashi A, Fukutomi Y, *et al.* Cutoff point of the fraction of exhaled nitric oxide (FeNO) with the off-line method for diagnosing asthma and the effect of smoking on FeNO. *Nihon Kokyuki Gakkai Zasshi* 2008;**46**:356–62	Foreign language
262	Perez-de-Llano LA, Carballada F, Castro AO, Pizarro M, Golpe R, Baloira A, *et al.* Exhaled nitric oxide predicts control in patients with difficult-to-treat asthma. *Eur Respir J* 2010;**35**:1221–7	FeNO testing did not guide step-up/step-down therapy

TABLE 87 Analytical validity review, management review and diagnostic review: table of excluded studies with rationale (*continued*)

Study		Reason for exclusion
263	Perzanowski MS, Divjan A, Mellins RB, Canfield SM, Rosa MJ, Chew GL, *et al.* Exhaled NO among 7-year-old children who attended Head Start in New York City. *J Allergy Clin Immunol* 2009;**123**(2 Suppl. 1):S171	No useable diagnostic data
264	Perzanowski MS, Divjan A, Mellins RB, Canfield SM, Rosa MJ, Chew GL, *et al.* Exhaled NO among inner-city children in New York City. *J Asthma* 2010;**47**:1015–21	No useable diagnostic data
265	Pijnenburg MW, Lissenberg ET, Hofhuis W, Ghiro L, Ho WC, Holland WP, *et al.* Exhaled nitric oxide measurements with dynamic flow restriction in children aged 4–8 yrs. *Eur Respir J* 2002;**20**:919–24	Online vs. offline
266	Porsbjerg C, Brannan JD, Anderson SD, Backer V. Relationship between airway responsiveness to mannitol and to methacholine and markers of airway inflammation, peak flow variability and quality of life in asthma patients. *Clin Exp Allergy* 2008;**38**:43–50	Diagnosis of airway hyper-responsiveness
267	Porsbjerg C, Lund TK, Pedersen L, Backer V. Inflammatory subtypes in asthma are related to airway hyperresponsiveness to mannitol and exhaled NO. *J Asthma* 2009;**46**:606–12	Population all asthmatics
268	Porsbjerg C, Sverrild A, Thomsen SF, Backer V. The association between AHR to mannitol and to methacholine and exhaled NO in a random sample population. *Respirology* 2010;**15**:A47	Unselected population
269	Prasad A, Langford B, Stradling JR, Ho LP. Exhaled nitric oxide as a screening tool for asthma in school children. *Respir Med* 2006;**100**:167–73	No useable diagnostic data
270	Profita M, Montuschi P, Bonanno A, Riccobono L, Montalbano AM, Ciabattoni G, *et al.* Nasobronchial markers of oxidative stress and inflammation in atopic airway diseases. *Pediatr Allergy Immunol* 2009;**20**:58	No useable diagnostic data
271	Puckett JL, Galant SP, Taylor RWE, Cirson LC, Warren JL, Guijon OL, *et al.* Bronchodilator response and airway nitric oxide flux correlate in a pediatric asthma population. *J Allergy Clin Immunol* 2009;**123**(2 Suppl. 1):S78	No useable diagnostic data
272	Raulf-Heimsoth M, van Kampen V, Sucker K, Heinze E, Eliakopoulos C, Bruning T, *et al.* Application of non-invasive methods to assess current airway inflammation in health care workers 10 years after the latex ban in Germany. *Allergy* 2010;**65**:56	No useable diagnostic data
273	Raulf-Heimsoth M, van Kampen V, Heinze E, Bernard S, Borowitzki G, Freundt S, *et al.* Comparison of different non-invasive methods for detection of allergic asthma. *Adv Exp Med Biol* 2013;**755**:55–63	No useable diagnostic data
274	Rees PJ. Using exhaled NO concentrations to adjust inhaled corticosteroid dose maintained asthma control and reduced the dose. *Evid Based Med* 2006;**11**:20	Commentary
275	Reyes RL, Tordera MP, Gisbert VM. Relationship between values for exhaled nitric oxide at a flow rate of 250 ml/s and levels obtained from a linear regression equation. *Am J Respir Crit Care Med* 2011;**183**:A4374	Wrong flow rate
276	Robroeks CM, van de Kant KD, Jobsis Q, Hendriks HJ, van Gent R, Wouters EF, *et al.* Exhaled nitric oxide and biomarkers in exhaled breath condensate indicate the presence, severity and control of childhood asthma. *Clin Exp Allergy* 2007;**37**:1303–11	Case–control study
277	Rosa M, Divjan A, Johnson A, Hoepner L, Sheares B, Perera FP, *et al.* Flow-dependent and independent parameters of exhaled nitric oxide in 9 year-old children living in low-income NYC communities. *J Allergy Clin Immunol* 2009;**123**(2 Suppl. 1):S5	No useable diagnostic data
278	Rosa MJ, Divjan A, Hoepner L, Sheares BJ, Diaz D, Gauvey-Kern K, *et al.* Fractional exhaled nitric oxide exchange parameters among 9-year-old inner-city children. *Pediatr Pulmonol* 2011;**46**:83–91	Offline measurement
279	Rutgers SR, Meijer RJ, Kerstjens HA, van der Mark TW, Koeter GH, Postma DS, *et al.* Nitric oxide measured with single-breath and tidal-breathing methods in asthma and COPD. *Eur Respir J* 1998;**12**:816–19	Case–control study

continued

TABLE 87 Analytical validity review, management review and diagnostic review: table of excluded studies with rationale (*continued*)

Study		Reason for exclusion
280	Ryan D, Thomas MD, Dorinsky PM, Burden A, Von Ziegenweidt J, Hutton C, *et al.* The role of exhaled nitric oxide in guiding asthma. *J Allergy Clin Immunol* 2013;**131**(2 Suppl. 1):AB205	Not diagnostic study
281	Sachs-Olsen C, Lodrup Carlsen KC, Mowinckel P, Haland G, Devulapalli CS, Munthe-Kaas MC, *et al.* Diagnostic value of exhaled nitric oxide in childhood asthma and allergy. *Pediatric Allergy Immunol* 2010;**21**:e213–21	Unselected population
282	Saito J, Fukuhara A, Sato Y, Sato S, Saito K, Nakagawa N, *et al.* [Differences of fractional exhaled nitric oxide (FeNO) levels performed using two different analyzers]. *Nihon Kokyuki Gakkai Zasshi* 2010;**48**:17–22	Foreign language
283	Sakai T, Sugiyama N, Hirai K, Muramatsu R, Hagiwara S, Oh Y, *et al.* Consistently high levels of exhaled nitric oxide in children with asthma. *Pediatr Int* 2010;**52**:801–5	No useable diagnostic data
284	Sanchez-Vidaurre S, Cruz MJ, Gomez-Olles S, Morell F, Munoz X. Diagnostic utility of exhaled breath condensate analysis in conjunction with specific inhalation challenge in individuals with suspected work-related asthma. *Ann Allergy Asthma Immunol* 2012;**108**:151–6	No data on FeNO testing
285	Sardon PO, Aldasoro RA, Korta MJ, Mintegui AJ, Emparanza Knorr JI, Perez-Yarza EG, *et al.* [Agreement between two devices for measuring exhaled nitric oxide]. *An Pediatr* 2007;**67**:572–7	Foreign language
286	Sardon PO, Perez-Yarza EG, Aldasoro RA, Korta MJ, Mintegui AJ, Emparanza Knorr JI, *et al.* [Fractional exhaled nitric oxide: validation of a 6 second exhalation time with two different analysers]. *An Pediatr* 2008;**69**:221–6	Foreign language
287	Schleich FN, Seidel L, Sele J, Manise M, Quaedvlieg V, Michils A, *et al.* Exhaled nitric oxide thresholds associated with a sputum eosinophil count ≥ 3% in a cohort of unselected patients with asthma. *Thorax* 2010;**65**:1039–44	Population all asthmatic
288	Scollo M, Zanconato S, Ongaro R, Zaramella C, Zacchello F, Baraldi E, *et al.* Exhaled nitric oxide and exercise-induced bronchoconstriction in asthmatic children. *Am J Respir Crit Care Med* 2000;**161**:1047–50	Case–control study
289	Selby A, Clayton B, Grundy J, Pike K, Drew K, Raza A, *et al.* Are exhaled nitric oxide measurements using the portable NIOX MINO repeatable? *Respir Res* 2010;**11**:43	Repeatability
290	Silkoff PE, Lent AM, Busacker AA, Katial RK, Balzar S, Strand M, *et al.* Exhaled nitric oxide identifies the persistent eosinophilic phenotype in severe refractory asthma. *J Allergy Clin Immunol* 2005;**116**:1249–55	Diagnosis of Eosinophilic airway inflammation + phenotype
291	Simpson JL, McDonald VM, Gibson PG. Exhaled nitric oxide is not a marker of eosinophilic inflammation in older Australians. *Respirology* 2010;**15**:A53	No useable diagnostic data
292	Smith AM, Villareal M, Bernstein DI, Swikert DJ. Asthma in the elderly: risk factors and impact on physical function. *Ann Allergy Asthma Immunol* 2012;**108**:305–10	No useable diagnostic data
293	Sobrevia M, Segura N, Ferrer L, Lezaun A, Cubero J, Sierra J, *et al.* Influence of positive skin prick tests in FeNO measurement. *Allergy* 2010;**65**:675	No useable diagnostic data
294	Sordillo J, Milton DK, Platts-Mills TA, Gold DR. Asthma symptoms, sensitization, and allergen exposure as predictors of exhaled NO. *J Allergy Clin Immunol* 2009;**123**(2 Suppl. 1):S22	No useable diagnostic data
295	Sordillo JE, Webb T, Kwan D, Kamel J, Hoffman E, Milton DK, *et al.* Allergen exposure modifies the relation of sensitization to fraction of exhaled nitric oxide levels in children at risk for allergy and asthma. *J Allergy Clin Immunol* 2011;**127**:1165–72	FeNO testing did not guide step-up/step-down therapy
296	Stahl MC, Arora R, Tucker M, Johnson T, Calabria C. A prospective evaluation of the fraction of exhaled nitric oxide and the subsequent diagnosis of asthma in military basic trainees. *Ann Allergy Asthma Immunol* 2009;**103**(5 Suppl. 3):A72	Unselected population
297	Sverrild A, Porsbjerg C, Thomsen SF, Backer V. Airway hyperresponsiveness to mannitol and methacholine and exhaled nitric oxide: a random-sample population study. *J Allergy Clin Immunol* 2010;**126**:952–8	Unselected population

TABLE 87 Analytical validity review, management review and diagnostic review: table of excluded studies with rationale (*continued*)

Study		Reason for exclusion
298	Sverrild A, Malinovschi A, Porsbjerg C, Backer V, Alving K. Predicting airway hyperreactivity to mannitol using exhaled nitric oxide in an unselected sample of adolescents and young adults. *Respir Med* 2013;**107**:150–2	Unselected population
299	Syed A, Rehman A, Akram M, Bukhari R. Role of FeNO in predicting asthma relapse and clinical relevance in children on inhaled corticosteroid. *J Allergy Clin Immunol* 2011;**127**(2 Suppl. 1):AB158	No relevant outcomes
300	Tanaka H, Kitada J, Fujii M, Takahashi H. Diagnostic strategy for chorinic cough using FENO and impulse oscillometry. *Am J Respir Crit Care Med* 2011;**183**:A4386	No useable diagnostic data
301	Tatyana S, Mitrova R, Ganeva M, Boyadjieva L, Markova R. Fractional exhaled nitric oxide and bronchodilator responsiveness in preschool children with asthma. *Allergy* 2011;**66**:197	Age < 5 years
302	Taylor DR, Palmay R, Cowan JO, Herbison GP. Long term performance characteristics of an electrochemical nitric oxide analyser. *Respir Med* 2011;**105**:211–17	Reproducibility and long-term performance in NIOX MINO only
303	Taylor DR, de la Barra SL, Herbison GP, Cowan JO, Smith AD. Predicted versus absolute values in the interpretation of exhaled nitric oxide measurements. *Am J Respir Crit Care Med* 2011;**183**:A4476	No usable diagnostic data
304	Taylor ES, Smith AD, Cowan JO, Herbison GP, Taylor DR. Effect of caffeine ingestion on exhaled nitric oxide measurements in patients with asthma. *Am J Respir Crit Care Med* 2004;**169**:1019–21	FeNO testing did not guide step-up/step-down therapy
305	Terada A, Fujisawa T, Iguchi K, Astuta J, Togari H. [Exhaled nitric oxide of childhood asthma]. *Arerugi* 1999;**48**:466–71	Foreign language
306	Thijs W, Middeldorp S, Hiemstra PS, Rosendaal FR, Rabe KF. Reproducibility of exhaled NO measurements in overweight subjects. *Am J Respir Crit Care Med* 2010;**181**:A2530	No comparison between devices
307	Thomas PS, Gibson PG, Wang H, Shah S, Henry RL. The relationship of exhaled nitric oxide to airway inflammation and responsiveness in children. *J Asthma* 2005;**42**:291–5	Unselected population
308	Tossa P, Bohadana A, Demange V, Wild P, Michaely JP, Hannhart B, *et al.* Early markers of airways inflammation and occupational asthma: rationale, study design and follow-up rates among bakery, pastry and hairdressing apprentices. *BMC Public Health* 2009;**9**:113	Study design only
309	Travers J, Marsh S, Aldington S, Williams M, Shirtcliffe P, Pritchard A, *et al.* Reference ranges for exhaled nitric oxide derived from a random community survey of adults. *Am J Respir Crit Care Med* 2007;**176**:238–42	Unselected population
310	Tseliou E, Bessa V, Hillas G, Delimpoura V, Papadaki G, Roussos C, *et al.* Exhaled nitric oxide and exhaled breath condensate pH in severe refractory asthma. *Chest* 2010;**138**:107–13	Population – severe refractory asthma
311	Tsuburai T, Tsurikisawa N, Higashi N, Tatsuno S, Fukutomi Y, Tanimoto H, *et al.* [Differences in fraction of exhaled nitric oxide values measured by two offline methods or NIOXmino in adult Japanese asthmatics]. *Arerugi* 2010;**59**:956–64	Offline
312	Tsuburai T, Tsurikisawa N, Higashi N, Tatsuno S, Fukutomi Y, Tanimoto H, *et al.* The difference of the fraction of exhaled nitric oxide (FeNO) levels measured by off-line methods or NIOXmino in adult Japanese asthmatics. *Nitric Oxide Biol Chem* 2010;**22**:S93	Foreign language
313	Turner SW, McSweeny C, Malik G. Comparisons of exhaled nitric oxide measurements using the NIOX and MINO analysers in children. *Proc Am Thorac Soc* 2006;A484	Unable to obtain

continued

TABLE 87 Analytical validity review, management review and diagnostic review: table of excluded studies with rationale (*continued*)

Study		Reason for exclusion
314	Tworek D, Bochenska-Marciniak M, Kupczyk M, Kuprys-Lipinska I, Kuna P. [Lack of correlation between exhaled nitric oxide (eNO) and clinical indicators of the disease activity and quality of life in mild and moderate asthmatics]. *Pneumonol Alergol Pol* 2006;**74**:391–5	Foreign language
315	van Amsterdam JGC, Zanen P, Somer S, van Loveren H, Opperhuizen A, Steerenberg PA. Flow dependency and off-line measurement of exhaled NO in children. *Pediatr Allergy Immunol* 2003;**14**:266–71	Wrong flow rate
316	van de Kant KD, Koers K, Rijkers GT, Lima Passos V, Klaassen EMM, Mommers M, *et al.* Can exhaled inflammatory markers predict the response to inhaled corticosteroids in wheezing preschool children? *Am J Respir Crit Care Med* 2011;**183**:A4465	Age < 5 years
317	van der Valk RJ, Caudri D, Savenije O, Koppelman GH, Smit HA, Wijga AH, *et al.* Childhood wheezing phenotypes and FeNO in atopic children at age 8. *Clin Exp Allergy* 2012;**42**:1329–36	No useable diagnostic data
318	van Wonderen KE, van der Mark LB, Mohrs J, Geskus RB, van der Wal WM, van Aalderen WM, *et al.* Prediction and treatment of asthma in preschool children at risk: study design and baseline data of a prospective cohort study in general practice (ARCADE). *BMC Pulm Med* 2009;**9**:13	Study design only
319	Vieira T, Fonseca J, Cruz L, Silva R, Ferreira A, Leblanc A, *et al.* Results of a school-based asthma assessment from the upKids questionnaire validation study. *Allergy* 2009;**64**:441–2	No useable diagnostic data
320	Vieira T, Fonseca JA, Silva R, Cruz L, Ferreira AR, Leblanc A, *et al.* Validity of a questionnaire in a school-based allergic asthma screening- comparison with exhaled nitric oxide fraction and skin prick tests. *Rev Port Imunoalergologia* 2011;**19**:215–21	Population – children with positive skin prick test
321	Vitruba J, Cap P. [Fractional exhaled nitric oxide and its correlation with bioptic results in chronic cough patients]. *Cas Lek Cesk* 2009;**148**:429–33	Foreign language
322	Vitruba J, Cap P, Statsny B. Fractional exhaled nitric oxide and its correlation with biopsy results in chronic cough patients. *Allergy* 2011;**66**:575	Not valid reference standard (biopsy results)
323	Wang C-C, Wang C-Y, Hsu J-Y. Evaluation the causes of chronic cough of unknown origin by a protocol based on result of fractional exhaled nitric oxide. *Respirology* 2009;**14**:A132	No useable diagnostic data
324	Wanich NH, Kaplan MS. 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. *Pediatrics* 2009;**124**(Suppl. 2):S147	Commentary
325	Warke TJ, Fitch PS, Brown V, Taylor R, Lyons JD, Ennis M, *et al.* Exhaled nitric oxide correlates with airway eosinophils in childhood asthma. *Thorax* 2002;**57**:383–7	Population is mix of asthmatics and healthy people
326	Wedes SH, Khatri SB, Zhang R, Wu W, Comhair SA, Wenzel S, *et al.* Noninvasive markers of airway inflammation in asthma. *Clin Transl Sci* 2009;**2**:112–17	Case–control study
327	Wildhaber JH, Hall GL, Stick SM. Measurements of exhaled nitric oxide with the single-breath technique and positive expiratory pressure in infants. *Am J Respir Crit Care Med* 1999;**159**:74–8	No useable diagnostic data
328	Wildhaber JH, Moller A, Hall GL, Sennhauser FH, Stick S. Levels of exhaled nitric oxide in recurrently wheezy infants are decreased following inhaled steroid therapy. *Schweiz Med Wochenschr* 2000;**130**:529–34	No useable diagnostic data
329	Yang CL, Simons E, Foty RG, To T, Dell SD. Parental report of asthma diagnosis superior to exhaled nitric oxide for measuring childhood asthma prevalence. *Am J Respir Crit Care Med* 2011;**183**:A6361	Not FeNO
330	Yang CL, Simons E, Foty RG, Marshall L, Nelligan K, To T, *et al.* Questionnaire diagnosis of asthma leads to misclassification compared to guideline-based diagnosis. *Am J Respir Crit Care Med* 2011;**183**:A5466	Case–control

TABLE 87 Analytical validity review, management review and diagnostic review: table of excluded studies with rationale (*continued*)

Study		Reason for exclusion
331	Yao TC, Ou LS, Lee WI, Yeh KW, Chen LC, Huang JL, *et al.* Exhaled nitric oxide discriminates children with and without allergic sensitization in a population-based study. *Clin Exp Allergy* 2011;**41**:556–64	Unselected population
332	Yawn B, Rickard K, Herje N, Dorinsky PM. Clinical outcomes of subjects with non-specific respiratory symptoms and high FENO who were not diagnosed with asthma: a retrospective review of outcomes 6 months following the initial evaluation. *J Allergy Clin Immunol* 2013;**131**(2 Suppl. 1):AB64	Non-specific respiratory symptoms
333	Yoo Y, Bauer S, La KS, Seo HS, Seo SC, Song DJ, *et al.* Relationships between airway hyperresponsiveness to methacholine, blood eosinophil markers and FENO in asthmatic children. *J Allergy Clin Immunol* 2012;**129**(2 Suppl. 1):AB211	No useable diagnostic data
334	Yoo Y, Bauer S, Harmin S, Seo S, Yoon W, Choung JT. Relationships between exhaled nitric oxide and atopy profiles (mono-sensitization/poly-sensitization) in children with asthma. *J Allergy Clin Immunol* 2013;**131**(2 Suppl. 1):AB62	No useable diagnostic data
335	Zhang Y-M, Lin J-T, Su N, Chen X, Liu G-L, Yu H-X, *et al.* Values of fractional exhaled nitric oxide in the diagnosis of chronic cough. *Nat Med J China* 2011;**91**:1254–8	Foreign language
336	Zhang YM, Lin JT. [The values of fractional exhaled nitric oxide in the diagnosis and treatment of chronic cough]. *Chung-Hua Chieh Ho Ho Hu Hsi Tsa Chih* 2011;**34**:504–8	Foreign language
337	Zietkowski Z, Skiepko R, Tomasiak-Lozowska MM, Mroczko B, Szmitkowski M, Bodzenta-Lukaszyk A, *et al.* RANTES in exhaled breath condensate of allergic asthma patients with exercise-induced bronchoconstriction. *Respiration* 2010;**80**:463–71	Case–control study
338	Zietkowski Z, Skiepko R, Tomasiak-Lozowska M, Bodzenta-Lukaszyk A. RANTES in exhaled breath condensate of allergic asthma patients with exercise-induced bronchoconstriction. *Allergy* 2010;**65**:148	No useable diagnostic data

TABLE 88 Studies excluded from the update search

	Study	Reason for exclusion
1	Adachi Y. [Biomarkers in childhood asthma]. *Arerugi* 2013;**62**:124–30	Not English language
2	Bozek A, Filipowski M, Fischer A, Jarzab J. Characteristics of atopic bronchial asthma in seniors over 80 years of age. *Biomed Res Int* 2013;**2013**:689782	Not a diagnostic accuracy study – included in subgroup review of elderly
3	Columbo M, Wong B, Panettieri RA Jr, Rohr AS. Asthma in the elderly: the role of exhaled nitric oxide measurements. *Respir Med* 2013;**107**:785–7	Not a diagnostic accuracy study – included in subgroup review of elderly
4	Gregoriano C, Abu HN, Maier S, Zogg S, Margelli HD, Miedinger D, *et al.* Predictive value of exhaled nitric oxide to predict exercise induced bronchoconstriction. *Respiration* 2013;**85**:605	Unselected population
5	Grzelewski T, Witkowski K, Makandjou-Ola E, Grzelewska A, Majak P, Jerzynska J, *et al.* Diagnostic value of lung function parameters and FeNO for asthma in schoolchildren in large, real-life population. *Pediatr Pulmonol* 2014;**49**:632–40	Unable to extract reliable data
6	Hsu JY, Wang CY, Cheng YW, Chou MC. Optimal value of fractional exhaled nitric oxide in inhaled corticosteroid treatment for patients with chronic cough of unknown cause. *J Chin Med Assoc* 2013;**76**:15–19	Already included
7	Hur G-Y, Oh JY, Choi J-H, Sim J-K, Min KH, Lee S-Y, *et al.* Mannitol challenge test, sputum eosinophils and exhaled nitric oxide (FENO) for diagnosis of asthma. *J Allergy Clin Immunol* 2013;**131**(2 Suppl. 1):AB64	Not enough information to data extract
8	Raulf-Heimsoth M, van Kampen V, Heinze E, Bernard S, Borowitzki G, Freundt S, *et al.* Comparison of different non-invasive methods for detection of allergic asthma. *Adv Exp Med Biol* 2013;**755**:55–63	Wrong patient cohort – not symptoms of asthma
9	Ryan D, Thomas MD, Dorinsky PM, Burden A, Von Ziegenweidt J, Hutton C, *et al.* The role of exhaled nitric oxide in guiding asthma. *J Allergy Clin Immunol* 2013;**131**(2 Suppl. 1):AB205	Not enough information to data extract
10	Schneider A, Schwarzbach J, Faderl B, Welker L, Karsch-Volk M, Jorres RA. FENO measurement and sputum analysis for diagnosing asthma in clinical practice. *Respir Med* 2013;**107**:209–16	Already included
11	Voorend-van Bergen S, Vaessen-Verberne A, Landstra A, Brackel H, van den Berg N, de Jongste J, *et al.* FeNO and web-based monitoring in paediatric asthma managemant; the BATMAN study. *Eur Respir J* 2013;**42**(Suppl. 57):3014	Not enough information to data extract

Appendix 6 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[193] flow diagram (adapted) of lower levels of evidence identified during database interrogation for the subgroups relating to the elderly, smokers and pregnant women

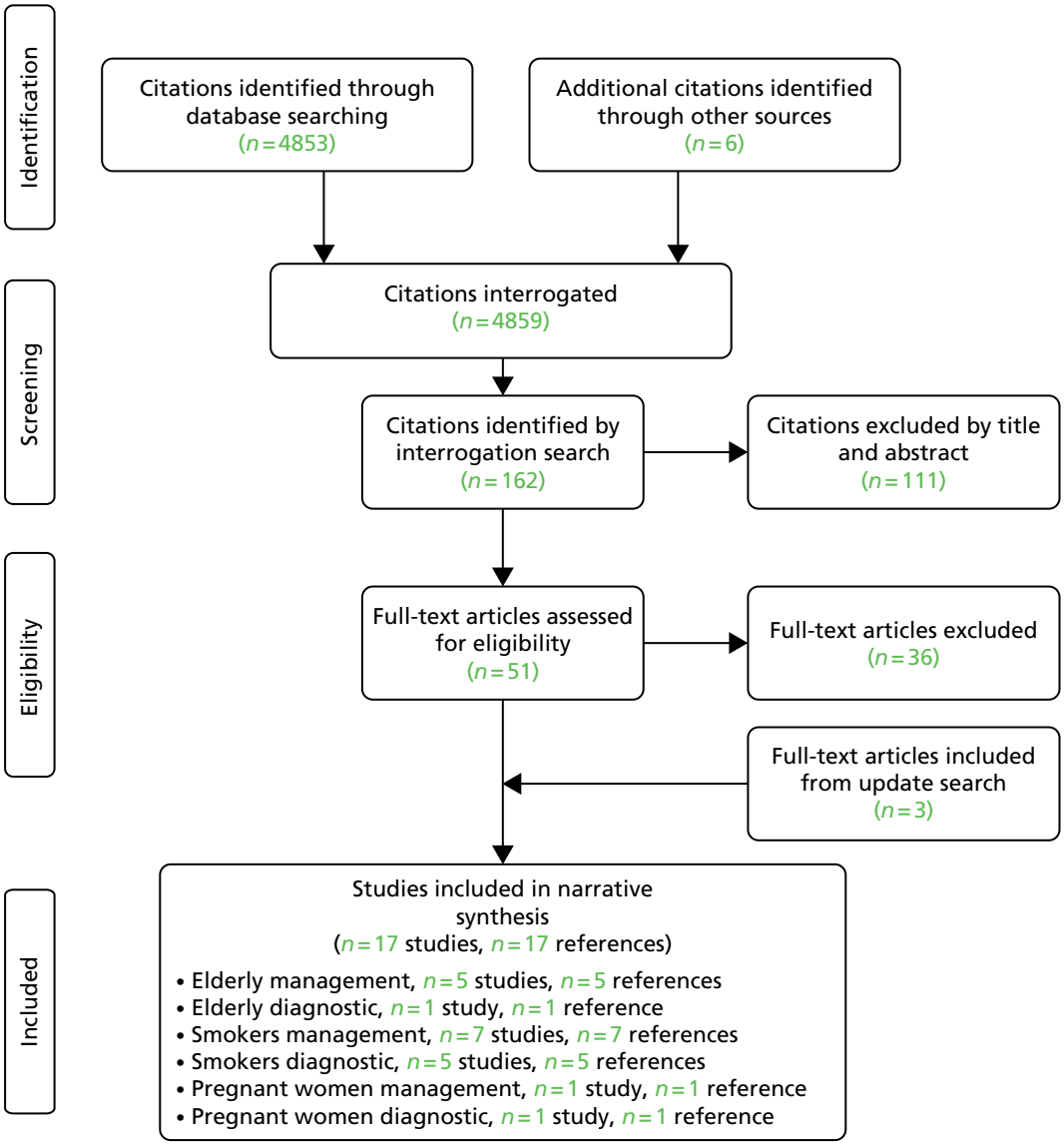

TABLE 89 Smokers management review, elderly management and diagnostic review and pregnancy diagnostic review: table of excluded studies with rationale

	Study	Reason for exclusion
1	Baur X, Barbinova L. Latex allergen exposure increases exhaled nitric oxide in symptomatic healthcare workers. *Eur Respir J* 2005;**25**:309–316	Non-asthmatics
2	Berry MA, Shaw DE, Green RH, Brightling CE, Wardlaw AJ, Pavord ID, *et al.* The use of exhaled nitric oxide concentration to identify eosinophilic airway inflammation: an observational study in adults with asthma. *Clin Exp Allergy* 2005;**35**:1175–9	Wrong flow rate
3	Bivins J, Ownby D, Waller J, Tingen M. Exhaled nitric oxide level and school absenteeism in rural high school students with current asthma. *J Allergy Clin Immunol* 2013;**131**(2 Suppl. 1):AB64	No data for smokers vs. non-smokers
4	Bohadana AB, Hannhart B, Ghezzo H, Teculescu D, Zmirou-Navier D. Exhaled nitric oxide and spirometry in respiratory health surveillance. *Occup Med (Oxford)* 2011;**61**:108–14	Not all asthmatics
5	Bommarito L, Migliore E, Bugiani M, Heffler E, Guida G, Bucca C, *et al.* Exhaled nitric oxide in a population sample of adults. *Respiration* 2008;**75**:386–92	Diagnostic – not all asthmatic
6	Bozek A, Krajewska J, Jarzab J. Nasal nitric oxide and other diagnostic procedures in seasonal allergic rhinitis: elderly vs juvenile patients. *Am J Otolaryngol* 2011;**32**:105–8	Population not asthmatic
7	de la Barra SL, Smith AD, Cowan JO, Herbison GP, Taylor DR. Predicted versus absolute values in the application of exhaled nitric oxide measurements. *Respir Med* 2011;**105**:1629–34	No data for smokers vs. non-smokers
8	Dinakar C, Lapuente M, Barnes C, Garg U. Real-life environmental tobacco exposure does not affect exhaled nitric oxide levels in asthmatic children. *J Asthma* 2005;**42**:113–18	Offline
9	Gaku I, Risako S, Hiroyoshi W, Nene K, Mayuko T, Masanori W, *et al.* Smoking exacerbates airway inflammation in patients with asthma. *Respirology* 2010;**15**:61	Mean FeNO levels only
10	Gemicioglu B, Guven K, Dogan I. FeNO in different asthma phenotypes. *Allergy* 2009;**64**:560	Mean FeNO levels only
11	Gibson PG, Powell H, Giles W, Clifton V, Hensley M, Taylor DR, *et al.* Asthma exacerbations during pregnancy are reduced by inflammometry (FENO) guided asthma management: a randomised controlled trial. *Am J Respir Crit Care Med* 2011;**183**:A6414	Management study
12	Gouvis-Echraghi R, Nikasinovic L, Bernard A, Herr-Breget M, Momas I, Just J. Passive smoke exposure lowers the fraction of exhaled nitric oxide in preschool children with recurrent wheeze. *Allergy* 2012;**67**:479	Preschool
13	Hardaker K, Downie S, Kermode J, Farah C, Berend N, King G, *et al.* The predictors of airway hyperresponsiveness are different in younger and older asthmatics. *Respirology* 2010;**15**:A37	Wrong flow rate
14	Hardaker KM, Downie SR, Kermode JA, Farah CS, Brown NJ, Berend N, *et al.* Predictors of airway hyperresponsiveness differ between old and young patients with asthma. *Chest* 2011;**139**:1395–1401	Wrong flow rate
15	Hillas G, Kostikas K, Mantzouranis K, Bessa V, Kontogianni K, Papadaki G, *et al.* Exhaled nitric oxide and exhaled breath condensate pH as predictors of sputum cell counts in optimally treated asthmatic smokers. *Respirology* 2011;**16**:811–18	Mean FeNO levels only
16	Jung A, Summermatter S, Geidel C, Moller A, Menz G, Lauener R. Diagnostic value of nasal NO measurement using the NIOX MINO device. *Atemwegs Lungenkr* 2012;**38**:57–8	Nasal NO
17	Kostikas K, Papaioannou AI, Tanou K, Koutsokera A, Papala M, Gourgoulianis KI, *et al.* Portable exhaled nitric oxide as a screening tool for asthma in young adults during pollen season. *Chest* 2008;**133**:906–13	Diagnostic AUCs reported for smokers vs. non-smokers

TABLE 89 Smokers management review, elderly management and diagnostic review and pregnancy diagnostic review: table of excluded studies with rationale (*continued*)

Study		Reason for exclusion
18	Leblanc A, Castro E, Castel-Branco M. Evolution and asthma control in pregnant women followed in an allergy Division. *Allergy* 2009;**64**:194–5	Not diagnostic study
19	Lehtimaki L, Turjanmaa V, Kankaanranta H, Saarelainen S, Hahtola P, Moilanen E. Increased bronchial nitric oxide production in patients with asthma measured with a novel method of different exhalation flow rates. *Ann Med* 2000;**32**:417–23	Wrong flow rate
20	Mahut B, Trinquart L, Le Bourgeois M, Becquemin MH, Beydon N, Aubourg F, *et al.* Multicentre trial evaluating alveolar NO fraction as a marker of asthma control and severity. *Allergy* 2010;**65**:636–44	Adults mean FeNO levels only
21	Malinovschi A, Janson C, Hogman M, Rolla G, Toren K, Norback D, *et al.* Both allergic and nonallergic asthma are associated with increased FE(NO) levels, but only in never-smokers. *Allergy* 2009;**64**:55–61	Diagnostic adults
22	Matsunaga K, Hirano T, Akamatsu K, Koarai A, Sugiura H, Minakata Y, *et al.* Differences in cutoff values of exhaled nitric oxide for asthma diagnosis according to rhinitis and smoking status. *Am J Respir Crit Care Med* 2011;**183**:A4480	Diagnostic adults
23	Matsunaga K, Hirano T, Akamatsu K, Koarai A, Sugiura H, Minakata Y, *et al.* Exhaled nitric oxide cutoff values for asthma diagnosis according to rhinitis and smoking status in Japanese subjects. *Allergol Int* 2011;**60**:331–7	Diagnostic adults
24	McCallister JW. Asthma in pregnancy: management strategies. *Curr Opin Pulm Med* 2013;**19**:13–17	Review
25	Munnik P, van der Lee I, Fijn J, van Eijsden LJ, Lammers JW, Zanen P, *et al.* Comparison of eNO and histamine hyperresponsiveness in diagnosing asthma in new referrals. *Respir Med* 2010;**104**:801–7	Diagnostic in adults, correction for smoking only
26	Nadif R, Matran R, Maccario J, Bechet M, Le Mouai N, Scheinmann P, *et al.* Passive and active smoking and exhaled nitric oxide levels according to asthma and atopy in adults. *Ann Allergy Asthma Immunol* 2010;**104**:385–93. [Erratum published in *Ann Allergy Asthma Immunol* 2010;**105**:97–8]	Mean FeNO levels only
27	Nadif R, Matran R, Maccario J, Bechet M, Le Moual N, Scheinmann P, *et al*. Passive and active smoking and exhaled nitric oxide levels according to asthma and atopy in adults. *Ann Allergy Asthma Immunol* 2010;**105**:97–8	Mean FeNO levels only
28	Oshikata C, Tsuburai T, Tsurikisawa N, Ono E, Higashi A, Fukutomi Y, *et al.* Cutoff point of the fraction of exhaled nitric oxide (FeNO) with the off-line method for diagnosing asthma and the effect of smoking on FeNO. *Nihon Kokyuki Gakkai Zasshi* 2008;**46**:356–62	Diagnostic adults
29	Persson MG, Zetterstrom O, Agrenius V, Ihre E, Gustafsson LE. Single-breath nitric oxide measurements in asthmatic patients and smokers. *Lancet* 1994;**343**:146–7	Healthy only
30	Perzanowski MS, Divjan A, Mellins RB, Canfield SM, Rosa MJ, Chew GL, *et al.* Exhaled NO among inner-city children in New York City. *J Asthma* 2010;**47**:1015–21	Wheeze not asthma
31	Powell H, Murphy VE, Taylor DR, Hensley MJ, McCaffery K, Giles W, *et al.* Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial. *Lancet* 2011;**378**:983–90	Management study
32	Rouhos A, Ekroos H, Karjalainen J, Sarna S, Haahtela T, Sovijarvi AR, *et al.* Smoking attenuates increase in exhaled nitric oxide in atopic but not in nonatopic young adults with asthma. *Int Arch Allergy Immunol* 2010;**152**:226–32	Mean FeNO levels only

continued

TABLE 89 Smokers management review, elderly management and diagnostic review and pregnancy diagnostic review: table of excluded studies with rationale (*continued*)

Study		Reason for exclusion
33	Rutgers SR, Meijer RJ, Kerstjens HA, van der Mark TW, Koeter GH, Postma DS, *et al.* Nitric oxide measured with single-breath and tidal-breathing methods in asthma and COPD. *Eur Respir J* 1998;**12**:816–19	Mean FeNO levels only
34	Shimoda T, Obase Y, Imaoka M, Kishikawa RT, Iwanaga T. Influence of cigarette smoking on airway inflammation and inhaled corticosteroid treatment in asthmatic patients. *J Allergy Clin Immunol* 2013;**131**(2 Suppl. 1):AB52	Mean FeNO levels only
35	Spears M, Weir CJ, Smith AD, McSharry C, Chaudhuri R, Johnson M, *et al.* Bronchial nitric oxide flux (J'aw) is sensitive to oral corticosteroids in smokers with asthma. *Respir Med* 2011;**105**:1823–30	Wrong flow rate
36	Taylor DR, de la Barra SL, Herbison GP, Cowan JO, Smith AD. Predicted versus absolute values in the interpretation of exhaled nitric oxide measurements. *Am J Respir Crit Care Med* 2011;**183**:A4476	No data for smokers vs. non-smokers

Appendix 7 Table of study characteristics for non-relevant adult diagnostics

Author, year	Study design, funding	Country, setting, recruitment dates	Population	Device	Reference standard	*n* analysed/*N* recruited, reasons for withdrawals	Mean age (years)	Sex male , *n*/*N* (%)	Severity: FEV_1% or FEV_1/FVC	Mean FeNO (ppb)	Smokers	Atopic
Arora 2006[79]	Design: prospective Funding: US Air Force Surgeon General's Office	USA Specialist care Dates NR	Adult (military recruits) with symptoms suggestive of asthma (position A)	Niox	Included both a consistent history with recurrent respiratory symptoms of non-productive cough, shortness of breath, chest tightness or wheezing with exertion or at rest and positive histamine bronchoprovocation [20% fall in FEV_1 (PC_{20}) of ≤ 8 mg/ml of histamine]	172/172	Asthmatic: 20 ± 2.7; non-asthmatic: 21 ± 2.7	85 (49.4)	FEV_1% Asthmatic: mean 98 ± 13 (range 69–133); non-asthmatic: mean 107 ± 14 (range 89–135)	Asthmatic: 30 ± 31; non-asthmatic: 19 ± 11	0/138 (0%)	NR
Fortuna 2007[70]	Design: prospective, consecutive Funding NR	Spain Secondary care (outpatient clinic) Dates: October 2004–November 2005	Symptoms suggestive of asthma (position A)	N-6008	Lung function tests (spirometry and bronchodilator response) and MCT following GINA guidelines[112]	50/57 *n* = 7 receiving OCS treatment at the time of study	Asthmatic: 37 (range 18–68); non-asthmatic: 38 (range 18–64)	21/50 (42)	FEV_1% Asthmatic: mean 94 ± 19; non-asthmatic: mean 99 ± 10	Asthmatic: 40 ± 31; non-asthmatic: 18 ± 23	Asthmatic: *n* = 3 smokers, *n* = 4 ex-smokers; non-asthmatic: *n* = 4 smokers, *n* = 3 ex-smokers	NR
Fukuhara 2011[54]	Design: prospective Funding NR; authors reported no conflict of interests	Japan Secondary care Dates: May 2007–June 2007	Symptoms suggestive of asthma (position A)	NA623	(1) At least one of the subjective symptoms of recurrent cough, wheezing or dyspnoea; (2) at least two of the three criteria of induced sputum eosinophilia, airway hyper-responsiveness and reversible airway obstruction; (3) exclusion of other lung diseases	61/97 *n* = 36 unable to complete all tests	55.6 (range 17–81)	31/61 (50.8)	96.1% (95% CI 90.1% to 102.0%)	74.5 (95% CI 56.2 to 92.8)	*n* = 6 current smokers; *n* = 13 ex-smokers; *n* = 42 non-smokers	14/61 (23%)
Mathew 2011,[91] Sato 2008[75]	Design: prospective Funding NR	UK Secondary care Dates NR	Difficult to diagnose (position B)	NR	MCT	84/84	NR	36/84 (42.9)	NR	NR	NR	NR
Pizzimenti 2009[90]	Design: prospective, consecutive Funding NR	Italy Secondary care (outpatient clinic) Dates NR	Patients with chronic cough (position A)	NIOX MINO	MCT (PD20 FEV_1 < 800 µ)	156/156	NR	64/156 (41.0)	NR	34.1 (95% CI 28.5 to 39.5)	14/156 (9%)	74/156 (47.4%)
Zhang 2011[89]	Design: prospective Funding NR	China Secondary care October 2009–September 2010	Chronic cough with normal chest radiographs (position A)	NIOX MINO	Diagnosis of cough variant asthma, eosinophilic bronchitis and other based on sputum cell counts, pulmonary function test, bronchial hyper-responsiveness, 24-hour oesophageal pH monitoring, skin prick test and serum IgE	106/106	NR	NR	NR	NR	NR	NR

IgE, immunoglobulin E; NR, not reported; PD20, dose of methacholine needed to cause a 20% fall from baseline in FEV_1.

Appendix 8 Table of the highest sum of sensitivity and specificity, highest sensitivity and highest specificity for non-relevant studies

Author, year	Population	Device	Reference standard	Highest sum of sensitivity and specificity					Rule-out sensitivity					Rule-in specificity				
				Cut-off (ppb)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Cut-off (ppb)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Cut-off (ppb)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Position A vs. whole pathway																		
Arora 2006[79]	Adults Position A	Niox	Included both a consistent history with recurrent respiratory symptoms of non-productive cough, shortness of breath, chest tightness or wheezing with exertion or at rest and positive histamine bronchoprovocation [20% fall in FEV_1 (PC_{20}) of ≤8 mg/ml of histamine]	>17	63	58.8	86.14	28.17	>6	96.4	0	79.64	0.00	>46	16.7	100	100	22.81
Fortuna 2007[70]	Adults Position A	N-6008	Lung function tests (spirometry and bronchodilator response) and MCT following GINA guidelines[112]	≥20	77	64	62.96	78.26	–	–	–	–	–	–	–	–	–	–
Fukuhara 2011[54]	Adults Position A	NA623	(1) At least one of the subjective symptoms of recurrent cough, wheezing or dyspnoea; (2) at least two of the three criteria of induced sputum eosinophilia, airway hyper-responsiveness and reversible airway obstruction; (3) exclusion of other lung diseases	40	78.6	89.5	94.28	65.38	–	–	–	–	–	–	–	–	–	–
Pizzimenti 2009[90]	Unspecified age group Position A	NIOX MINO	MCT (PD20 FEV_1 <800 µ)	55	10	67.2	39.28	97.66	–	–	–	–	–	–	–	–	–	–
Zhang 2011[89]	Unspecified age group Position A	NIOX MINO	Diagnosis of cough variant asthma, eosinophilic bronchitis and other based on sputum cell counts, pulmonary function test, bronchial hyper-responsiveness, 24-hour oesophageal pH monitoring, skin prick test and serum IgE	40	75	86	76.31	85.29	–	–	–	–	–	–	–	–	–	–
Position B																		
Mathew 2011[91] Sato 2008[75]	Unspecified age group Position B	NR	Airway reversibility, positive response to ICS, airway hyper-responsiveness (MCT)	NR	NR	NR	8.7	70.49	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

IgE, immunoglobulin E; PD20, dose of methacholine needed to cause a 20% fall from baseline in FEV_1.

Appendix 9 Table detailing the reference standards used in relevant adult diagnostic studies

Author, year	Details of reference standard	Summarised as
Position A vs. whole pathway		
Schneider 2009[71,72]	• $FEV_1/FVC < 0.7$ or $FEV_1\% < 80\%$ plus positive bronchodilator response = asthma • $FEV_1/FVC > 0.7$ or $FEV_1\% > 80\%$ plus positive MCT = asthma	FEV_1, FEV_1/FVC, airway reversibility, airway hyper-responsiveness (MCT)
Schneider 2013[69]	If $FEV_1 < 80\%$ predicted, patient received salbutamol plus whole-body plethysmography 20 minutes later. Obstructive airway disease diagnosed if FEV_1/FVC was ≤ 0.70. Classified as asthma according to clinical symptoms and history plus change in $FEV_1 \geq 12\%$ compared with baseline and ≥ 200 ml and if lung function increased to predicted normal range. Classified as incomplete bronchodilator response if response was $\leq 12\%$ compared with baseline and ≥ 200 ml and lung volumes remained below predicted. Classified as COPD according to clinical symptoms and history plus FEV_1 after salbutamol $< 12\%$ compared with baseline and < 200 ml. If $FEV_1 \geq 80\%$ predicted, bronchial provocation performed to determine bronchial hyper-responsiveness to methacholine according to the 1-concentration–4-step dosimeter protocol. Asthma diagnosed if 20% fall in FEV_1 from baseline after inhaling methacholine stepwise until the maximum concentration (16 mg/ml) *or* doubling of airway resistance (Raw) and its increase to ≥ 2.0 kPa/second. The pneumologist was blinded to the FeNO results and made diagnostic decisions on basis of medical history, physical examination, spirometry, whole-body plethysmography and bronchial provocation results	FEV_1, FEV_1/FVC, airway reversibility, hyper-responsiveness (MCT)
Smith 2004[86]	Relevant symptom history (ATS 1987 guidelines[113]) *and* a positive test for bronchial hyper-responsiveness (provocative dose of hypertonic saline resulting in a 15% fall in FEV_1 of < 20 ml) *and/or* a positive response to bronchodilator (increase in FEV_1 of $\geq 12\%$ from baseline 15 minutes after inhaled albuterol)	Airway reversibility, positive response to ICS, airway hyper-responsiveness (MCT)
Smith 2005[83]	ATS 1987[113] diagnostic criteria plus one or more of: 1. positive response to bronchodilator (increase in FEV_1 of $\geq 12\%$ from baseline 15 minutes after inhaled albuterol) 2. positive response to ICS (increase in FEV_1 of $\geq 12\%$ or an increase in mean morning peak flow over previous 7 days of $\geq 15\%$) 3. positive test for airway hyper-responsiveness (defined as a provocative dose of methacholine, resulting in a 20% reduction in FEV_1 of < 8 µmol)	Airway reversibility, positive response to ICS, airway hyper-responsiveness (MCT)
Position A vs. airway reversibility		
de la Barra 2011[84]	Positive response to bronchodilator (increase in FEV_1 of $\geq 12\%$ from baseline 15 minutes after inhaled albuterol)	Airway reversibility

Author, year	Details of reference standard	Summarised as
Subset of Position A vs. airway reversibility or airway hyper-responsiveness		
Cordeiro 2011[87]	History of typical respiratory symptoms and FEV_1% improvement of > 12% and > 200 ml or PC_{20} histamine of ≤ 8 mg/ml, according to GINA guidelines[129]	Airway reversibility, airway hyper-responsiveness (histamine)
Heffler 2006[82]	Asthma confirmed based on typical symptoms and > 12% improvement in FEV_1 in response to salbutamol or a dose of methacholine needed to cause a 20% fall from baseline in FEV_1 (PD20) of < 800 µg	Airway hyper-responsiveness (MCT) or airway reversibility
Difficult to diagnose vs. airway hyper-responsiveness		
Bobolea 2012[88]	Adenosine challenge test (PC20 < 400 mg/ml)	Adenosine challenge test
Katsoulis 2013[81]	Dose of methacholine needed to cause a 20% fall from baseline in FEV_1 (PD_{20}) according to ATS guidelines[133]	Airway hyper-responsiveness (MCT)
Pedrosa 2010[85]	Consistent symptoms and a positive methacholine bronchial challenge. Patients stopped asthma medication before the test. The test was performed according to ATS 1999 guidelines[133] and was considered positive when a decrease in FEV_1 from baseline of ≥ 20% or higher was obtained after methacholine inhalation	Airway hyper-responsiveness (MCT)
Schleich 2012[77]	Asthma diagnosed based on airway hyper-responsiveness (MCT) provoking a 20% fall in FEV_1 of < 16 mg/ml. Subjects were characterised as atopic if they had at least one positive skin prick test (wheal > 3 mm compared with negative control) or specific IgE (> 0.35 kU/l) for at least one common aeroallergen (cat, dog, house dust mites, grass pollen, tree pollen and a mixture of moulds)	Airway hyper-responsiveness (MCT)
Suspected EIB vs. exercise challenge test		
El Halawani 2003[78]	Exercise challenge test was performed on a treadmill with an incremental work rate (up to 14 minutes of symptom-limited exercise). Treadmill speed began at 2 miles/hour and increased by 1 mile/hour every 2 minutes. Treadmill grade began at 10%, increasing to 15% after 8 minutes. The targeted heart rate was 85% predicted maximum and maintained for 2 minutes. Spirometry was performed every 5 minutes after exercise for a total of 30 minutes. Pulmonary functioning discontinued when a fall in FEV_1 of 15% from baseline was demonstrated	Exercise challenge
Position F with chronic cough vs. ICS responsiveness		
Hahn 2007[74]	ICS responsiveness assessed 1–16 months after diagnostic tests	ICS responsiveness
Hsu 2013[73]	Complete improvement of cough on ICS treatment with 250 µg twice per day for at least 2 weeks	ICS responsiveness
Prieto 2009[76]	Responsiveness to FP was identified by a reduction of > 50% in the mean daily cough symptom scores during the 4 weeks of the fluticasone propionate trial compared with the baseline period	ICS responsiveness

IgE, immunoglobulin E; PC_{20}, provocative concentration that cause a positive reaction; PD_{20}, dose of methacholine needed to cause a 20% fall from baseline in FEV_1.

Appendix 10 Table detailing the inclusion and exclusion criteria of the studies considered of most relevance to the review

Author, year	Details of inclusion and exclusion criteria	Categorised as
Position A vs. whole pathway		
Schneider 2009[71,72]	Patients presenting to their GP for the first time with complaints suggestive of obstructive airway disease; presentation of symptoms such as dyspnoea, coughing or expectoration for > 2 months, thus leading to clinical suspicion of obstructive or restrictive airway disease as most important differential diagnoses ('indicated population'). GPs were advised to exclude patients with respiratory tract infections preceding the evaluation by 6 weeks. Patients with a previously established diagnosis of obstructive airway disease were excluded. Other exclusion criteria related to well-known contraindications for bronchodilator reversibility testing or bronchial provocation, namely untreated hyperthyreosis, unstable coronary artery disease and cardiac arrhythmia. Pregnancy also led to exclusion	Position A
Schneider 2013[69]	Patients presenting for the first time with symptoms such as dyspnoea, cough or phlegm for > 2 months, leading to the clinical suspicion of obstructive or restrictive airway disease ('indicated population'). Patients were advised not to smoke on the day of investigation and not to use inhaler medication for 12 hours before lung function testing. Exclusions: patients with respiratory tract infections within the last 6 weeks; previously established diagnosis of chronic obstructive airway disease; known contraindications for bronchodilator reversibility testing or bronchial provocation, namely untreated hyperthyreosis, unstable coronary artery disease and cardiac arrhythmia; pregnancy	Position A
Smith 2004[86]	Patients referred by their GP for investigation of possible bronchial asthma with symptoms for a minimum of 6 weeks. No patient had been referred for specialist consultation. Exclusions: those who used oral or inhaled corticosteroids in the previous 4 weeks and those with a respiratory tract infection in the previous 6 weeks	Position A
Smith 2005[83]	Patients referred by their GP for investigation of persistent, undiagnosed respiratory symptoms lasting for at least 6 weeks. Exclusions: use of ICSs or OCSs in the previous 4 weeks, respiratory tract infection in the previous 6 weeks, other established respiratory diagnosis or significant comorbidity; smokers were not excluded	Position A
Position A vs. airway reversibility		
de la Barra 2011[84]	New undiagnosed symptoms of cough, wheeze or dyspnoea of ≥ 6 weeks in duration	Position A
Subset of Position A vs. airway reversibility or airway hyper-responsiveness		
Cordeiro 2011[87]	All new patients who were referred to a general outpatient allergy clinic from January 2007 to September 2007. Patients using ICSs or oral corticosteroids within 6 weeks of the first visit were excluded from data analysis	Position A
Heffler 2006[82]	Nasal symptoms for > 4 days per week over > 8 weeks; asthma-like symptoms during the past 2 months. Exclusions: use of steroids or any other anti-inflammatory drugs in the last 2 months, current smoker (within the past 12 months), previous diagnosis of asthma, respiratory infection within the past 6 weeks	Position A

Author, year	Details of inclusion and exclusion criteria	Categorised as
Difficult to diagnose vs. airway hyper-responsiveness		
Bobolea 2012[88]	Patients with suspected asthma who had normal spirometry, a negative bronchodilator test, a negative methacholine challenge [provocative concentration inducing a 20% fall in FEV_1 (PC_{20}) > 16 mg/ml)]	Difficult to diagnose
Katsoulis 2013[81]	Patients with one positive answer for respiratory symptoms. Exclusions: pre-existing asthma diagnosis, treatment with asthma-related medication, 12% reversibility after bronchodilation and 200 ml FEV_1, respiratory infection within the last 8 weeks, recent ex-smokers	Difficult to diagnose
Pedrosa 2010[85]	Those reporting persistent symptoms consistent with asthma (shortness of breath, wheezing and/or cough) regardless of atopic status who showed normal spirometry and who had a negative bronchodilator test. Exclusions: as per ATS 1999 guidelines[133] for bronchial challenge test	Difficult to diagnose
Schleich 2012[77]	Patients were referred to a respiratory physician for a methacholine challenge to detect asthma. Subjects referred to methacholine challenge were those in whom the bronchodilating test failed to demonstrate reversible airways obstruction or those in whom baseline spirometric values were normal giving a low probability for a bronchodilating test to be significant. Patients had either (1) baseline $FEV_1 \geq 80\%$ predicted and a FEV_1/FVC ratio $\geq 70\%$ or (2) baseline $FEV_1 < 80\%$ predicted and a FEV_1/FVC ratio $< 70\%$ plus bronchodilation $< 12\%$ from baseline and 200 ml after 400 µg inhaled salbutamol Exclusions: patients already receiving ICSs	Difficult to diagnose
Suspected EIB vs. exercise challenge test		
El Halawani 2003[78]	Patients with suspected asthma who had normal spirometry, a negative bronchodilator test, negative methacholine challenge [provocative concentration inducing a 20% fall in FEV_1 (PC_{20}) > 16 mg/ml]	EIB
Position F with chronic cough vs. ICS responsiveness		
Hahn 2007[74]	Age > 18 years, uncontrolled chronic cough (> 8 weeks), normal/non-localising chest radiograph, documented MCT results and measurement of NO levels within 1 day of each other. Only patients who had started ICS therapy or who had their current ICS doses altered were included. Exclusions: current smokers and users of angiotensin-converting enzyme inhibitors	Difficult to diagnose with chronic cough
Hsu 2013[73]	Patients with a history of chronic cough of > 8 weeks' duration and who did not stop coughing after treatment for upper airway cough syndrome or gastro-oesophageal reflux disease. Exclusions: obvious chest radiograph abnormalities, current smokers/smoking history of > 10 pack-years	Difficult to diagnose with chronic cough
Prieto 2009[76]	Chronic cough of at least 8 weeks' duration with no evidence of any other lung disease, non-smokers, not currently being treated with angiotensin-converting enzyme inhibitors or beta-blockers, not previously received treatment with ICSs or OCSs or not experienced a respiratory tract infection in the previous 4 weeks. Each subject required to have a FEV_1 of at least 80% predicted	Difficult to diagnose with chronic cough

Appendix 11 Table of results for all diagnostic studies in adults

Author, year	Prevalence of positive result by reference standard, *n/N* (%)	FeNO cut-off (ppb)	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)	Sensitivity asthma (95% CI) (%)	Specificity asthma (95% CI) (%)
Position A								
de la Barra 2011[84]	NR	25	10	17	2	23	83.3	57.5
		40	9	12	3	28	75	70
		50	7	8	5	32	58.3	80
		70	5	5	7	35	41.7	87.5
		90	5	3	7	37	41.7	92.5
		110	3	2	9	38	25	95
		130	2	2	10	38	16.7	95
		150	2	2	10	38	16.7	95
Fortuna 2007[70]	Induced sputum (Eos%) 16/50 (32.0); bronchodilator test 13/50 (26.0); FEV_1 < 80% 5/50 (10.0)	≥ 20 ppb	17	10	5	18	77	64
Fukuhara 2011[54]	42/61 (68.9)	40	33	2	9	17	78.6	89.5
Schneider 2009[71,72]	75/160 (46.9)	> 20	48	36	27	49	64 (53 to 74)	58 (47 to 77)
		> 12	64	65	11	20	85 (76 to 92)	24 (16 to 34)
		> 16	52	40	23	45	69 (58 to 79)	53 (42 to 63)
		> 35	24	14	51	71	32 (25 to 42)	84 (74 to 90)
		> 46	24	6	51	79	32 (23 to 43)	93 (85 to 97)
		> 76	10	0	65	85	13 (7 to 23)	100 (96 to 100)
Schneider 2013[69]	154/393 (39.2)	> 9	146	209	7	31	96 (91 to 98)	13 (9 to 18)
		> 12	135	167	23	68	85 (79 to 90)	29 (23 to 35)
		> 16	105	128	46	114	70 (62 to 76)	47 (41 to 54)
		> 20	91	89	62	151	60 (52 to 67)	63 (57 to 69)
		> 25	75	59	79	180	49 (41 to 57)	75 (69 to 80)
		> 35	50	29	104	210	33 (26 to 40)	88 (83 to 91)
		> 41	42	20	112	219	27 (21 to 35)	92 (87 to 94)
		> 42	40	20	114	219	26 (20 to 33)	92 (87 to 94)
		> 43	39	19	115	220	25 (19 to 32)	92 (88 to 95)
		> 44	39	19	115	220	25 (19 to 32)	92 (88 to 95)
		> 45	38	19	116	220	23 (17 to 31)	92 (88 to 95)
		> 46	38	17	116	222	27 (21 to 35)	92 (87 to 94)
		> 71	27	7	127	232	18 (12 to 24)	97 (94 to 99)

Author, year	Prevalence of positive result by reference standard, *n*/*N* (%)	FeNO cut-off (ppb)	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)	Sensitivity asthma (95% CI) (%)	Specificity asthma (95% CI) (%)
Smith 2004[86]	17/47 (36.2)	> 20	14	6	2	22	88	79
Smith 2005[83]	27/52 (51.9)	≥ 15	22	13	5	12	81.5	48
		> 47	15	2	12	23	55.6	92
		< 15	5	12	22	13	18.5	52
Subset of Position A								
Cordeiro 2011[87]	42/114 (36.8)	27	33	6	9	66	78	92
Heffler 2006[82]	18/48 (37.5)	> 10	18	29	0	1	100	3.3
		> 15	18	26	0	4	100	13.3
		> 20	18	20	0	10	100	33.3
		> 25	18	16	0	14	100	46.7
		> 30	14	15	4	15	77.8	50
		> 34	14	14	4	16	77.8	53.3
		> 36	14	12	4	18	77.8	60
		> 40	11	11	7	19	61.1	63.3
		> 45	11	8	7	22	61.1	73.3
		> 50	10	7	8	23	55.6	76.7
		> 55	9	6	9	24	50	80
		> 60	9	4	9	26	50	86.7
		> 65	8	4	10	26	44.4	86.7
		> 75	8	3	10	27	44.4	90
		> 80	7	1	11	29	38.9	96.7
		> 85	5	1	13	29	27.8	96.7
		> 100	5	0	13	30	27.8	100
Pizzimenti 2009[90]	14/156 (9.0)	55	11	17	3	125	78	88
Difficult to diagnose								
Bobolea 2012[88]	6/30 (20.0)	> 30	6	17	0	7	100	29.2
Katsoulis 2013[81]	48/112 (42.9)	> 30	24	12	24	52	49 (34 to 64)	82 (71 to 90)
		> 25	24	16	24	48	51 (36 to 66)	75 (63 to 85)
		> 20	31	26	17	38	64 (49 to 78)	60 (47 to 72)
		> 15	35	33	13	31	73 (58 to 85)	49 (37 to 62)
		> 10	39	39	9	25	81 (64 to 91)	39 (29 to 50)
Mathew 2011[91]	20/84 (23.8)	NR	2	21	18	43	10	67.2
Pedrosa 2010[85]	35/114 (30.7)	40	26	22	9	57	74.3	72.5
Schleich 2012[77]	82/174 (47.1)	34	29	4	53	88	35.4	95.4
Schneider 2009[71,72]	Subjects with unsuspicious spirometric results: 49/101 (48.5)	> 46	17	5	32	47	35 (23 to 49)	90 (79 to 96)
		> 15	38	29	11	23	78 (63 to 89)	45 (34 to 57)

Author, year	Prevalence of positive result by reference standard, *n*/*N* (%)	FeNO cut-off (ppb)	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)	Sensitivity asthma (95% CI) (%)	Specificity asthma (95% CI) (%)
Difficult to diagnose with chronic cough								
[a]Hahn 2007[74]	38/64 (59.4)	35	36	5	2	21	95 (83 to 99)	80 (62 to 92)
		38	34	4	4	22	90 (76 to 96)	85 (76 to 96)
[a]Hsu 2013[73]	38/81 (46.9)	33.9	36	9	2	34	94.7	76.3
		30	37	14	1	29	97.4	65.8
Prieto 2009[76]	19/43 (44.2)	20	10	9	9	15	53	63
Sato 2008[75]	48/71 (67.6)	38.8	38	2	10	21	79.2	91.3
Zhang 2011[89]	39/106 (36.8)	40	29	9	10	58	75	86
		36[a]	32	5	7	62	82	93
EIB								
El Halawani 2003[78]	7/49 (14.3)[b]	< 12	7	29	0	13	100	31
Other								
Arora 2006[79]	138/172 (80.2)	> 6	133	34	5	0	96.4	0
		> 7	131	33	7	1	94.6	2.9
		> 8	130	31	8	3	94.2	8.8
		> 9	127	30	11	4	92	11.8
		> 10	119	28	19	6	86.2	17.6
		> 11	115	26	23	8	83.3	23.5
		> 12	113	25	25	9	81.9	26.5
		> 13	110	21	28	13	79.7	38.2
		> 14	102	19	36	15	73.9	44.1
		> 15	98	19	40	15	71	44.1
		> 16	92	17	46	17	66.7	50
		> 17	87	14	51	20	63	58.8
		> 18	83	14	55	20	60.1	58.8
		> 19	78	13	60	21	56.5	61.8
		> 20	73	11	65	23	52.9	67.6
		> 25	56	7	82	27	40.6	79.4
		> 30	45	7	93	27	32.6	79.4
		> 40	32	3	106	31	23.2	91.2
		> 46	23	0	115	34	16.7	100
Brannan 2013[92]	76/401 (19.0)	47	23	12	44	322	30.2	96.3
Chancafe-Morgan 2013[80]	12/30 (40.0)	35	9	3	3	15	75	83.3

Eos%, eosinophil count expressed as a percentage.
a Data are for ICS responsiveness.
b Test for EIB.

Appendix 12 Table of results for all diagnostic studies in children

Author, year	Prevalence of positive result by reference standard, *n*/*N* (%)	FeNO cut-off (ppb)	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)	Sensitivity asthma (%)	Specificity asthma (%)
Linkosalo 2012[93]	18/30 (60.0)	10	16	8	2	4	89	33
		20	13	2	5	10	72	83
		30	9	1	9	11	50	92
		40	7	1	11	11	39	92
		50	2	1	16	11	11	92
Ramser 2008[94]	105/169 (62.1)	10	75	24	45	25	76	36
		20	49	50	17	53	49	76
		30	33	66	12	58	33	83
		40	23	76	7	63	23	90
		50	20	79	5	65	20	93
Sivan 2009[95]	106/150 (70.7)	15	62	13	7	31	90	70
		18	87	7	19	37	82	84
		19	59	5	10	39	86	89
		25	52	5	17	39	75	89
		> 20 or < 15	58	4	7	32	89	88
Woo 2012[96]	167/245 (68.2)	> 50	24	0	143	78	14.4	100
		> 45	29	0	138	78	17.4	100
		> 41	39	0	128	78	23.4	100
		> 40	41	1	126	77	24.6	98.7
		> 35	54	1	113	77	32.3	98.7
		> 30	71	4	96	74	42.5	94.9
		> 25	83	6	84	72	49.7	92.3
		> 24	84	7	83	71	50.3	91
		> 23	86	7	81	71	51.5	91
		> 22	90	10	68	68	53.9	87.2
		> 21	95	10	68	68	56.9	87.2
		> 20	101	15	63	63	60.5	80.8
		> 15	120	26	52	52	71.9	66.7
		> 10	134	43	35	35	80.2	44.9
		> 5	157	67	11	11	94	14.1
		22	93	9	51	51	72.1	85

Appendix 13 MEDLINE search strategies for the economic review

Use of NIOX MINO/NObreath for either the diagnosis or the management of asthma (30 May 2013)

1. niox mino.mp.
2. aerocrine.mp.
3. (niox adj5 (monitor$ or chemiluminescence or analyser$ or sensor or device$ or desktop)).mp.
4. nobreath.mp.
5. bedfont.mp.
6. or/1-5
7. exp "Costs and Cost Analysis"/
8. Economics/
9. exp Economics, Hospital/
10. exp Economics, Medical/
11. Economics, Nursing/
12. exp models, economic/
13. Economics, Pharmaceutical/
14. exp "Fees and Charges"/
15. exp Budgets/
16. budget$.tw.
17. ec.fs.
18. cost$.ti.
19. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.
20. (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti.
21. (price$ or pricing$).tw.
22. (financial or finance or finances or financed).tw.
23. (fee or fees).tw.
24. (value adj2 (money or monetary)).tw.
25. quality-adjusted life years/
26. (qaly or qalys).af.
27. (quality adjusted life year or quality adjusted life years).af.
28. or/7-28
29. 6 and 28

Models of asthma and FENO testing (30 May 2013)

1. niox mino.mp.
2. aerocrine.mp.
3. (niox adj5 (monitor$ or chemiluminescence or analyser$ or sensor or device$ or desktop)).mp.
4. nobreath.mp.
5. bedfont.mp.
6. or/1-5
7. exp cough/
8. cough$.mp.
9. phlegm.mp.
10. sputum.mp.
11. mucus.mp.

12. wheez$.mp.
13. chest pain/
14. chest pain$.mp.
15. (chest adj5 tight$).tw.
16. ((lower respiratory or lrt) adj5 symptom$).tw.
17. (lower airway adj5 symptom$).tw.
18. ((trache$ or wind pipe or lung$ or bronch$) adj3 symptom$).tw.
19. exp lung/ or trachea/
20. symptom$.tw.
21. 19 and 20
22. or/7-18,21
23. exp asthma/
24. asthma$.mp.
25. exp respiratory hypersensitivity/
26. exp bronchial hyperreactivity/
27. bronchial spasm/
28. bronchospas$.mp.
29. exp Bronchoconstriction/
30. bronchoconstric$.mp.
31. (bronch$ adj3 constrict$).mp.
32. (bronch$ adj5 spas$).mp.
33. (airway$ adj5 (obstruct$ or inflammation$)).mp.
34. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
35. or/23-34
36. Nitric Oxide/
37. nitric oxide.mp.
38. 36 or 37
39. (exhal$ or expir$ or alveolar or fractional).mp.
40. 38 and 39
41. exhaled NO.mp.
42. eno.mp.
43. fe?no$.mp.
44. (fractional adj2 NO).mp.
45. or/40-44
46. 22 and 45
47. 35 and 45
48. 6 or 46 or 47
49. exp "Costs and Cost Analysis"/
50. Economics/
51. exp Economics, Hospital/
52. exp Economics, Medical/
53. Economics, Nursing/
54. exp models, economic/
55. Economics, Pharmaceutical/
56. exp "Fees and Charges"/
57. exp Budgets/
58. budget$.tw.
59. ec.fs.
60. cost$.ti.
61. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.
62. (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti.
63. (price$ or pricing$).tw.

64. (financial or finance or finances or financed).tw.
65. (fee or fees).tw.
66. (value adj2 (money or monetary)).tw.
67. quality-adjusted life years/
68. (qaly or qalys).af.
69. (quality adjusted life year or quality adjusted life years).af.
70. or/49-69
71. 48 and 70

Asthma management models (3 June 2013)

1. exp asthma/
2. asthma$.mp.
3. exp respiratory hypersensitivity/
4. exp bronchial hyperreactivity/
5. bronchial spasm/
6. bronchospas$.mp.
7. exp Bronchoconstriction/
8. bronchoconstric$.mp.
9. (bronch$ adj5 spas$).mp.
10. (airway$ adj5 (obstruct$ or inflammation$)).mp.
11. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
12. exp models, economic/
13. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ti.
14. ((cost$ or economic) adj5 model$).ti.
15. or/1-11
16. or/12-14
17. 15 and 16

Asthma diagnostic models (7 June 2013)

1. exp asthma/
2. asthma$.mp.
3. exp respiratory hypersensitivity/
4. exp bronchial hyperreactivity/
5. bronchial spasm/
6. bronchospas$.mp.
7. exp Bronchoconstriction/
8. bronchoconstric$.mp.
9. (bronch$ adj3 constrict$).mp.
10. (bronch$ adj5 spas$).mp.
11. (airway$ adj5 (obstruct$ or inflammation$)).mp.
12. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
13. or/1-12
14. exp "Costs and Cost Analysis"/
15. Economics/
16. exp Economics, Hospital/
17. exp Economics, Medical/
18. Economics, Nursing/

19. exp models, economic/
20. Economics, Pharmaceutical/
21. exp "Fees and Charges"/
22. exp Budgets/
23. budget$.tw.
24. ec.fs.
25. cost$.ti.
26. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.
27. (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti.
28. (price$ or pricing$).tw.
29. (financial or finance or finances or financed).tw.
30. (fee or fees).tw.
31. (value adj2 (money or monetary)).tw.
32. quality-adjusted life years/
33. (qaly or qalys).af.
34. (quality adjusted life year or quality adjusted life years).af.
35. or/14-34
36. exp "Sensitivity and Specificity"/
37. sensitivity.tw.
38. specificity.tw.
39. ((pre-test or pretest) adj probability).tw.
40. post-test probability.tw.
41. predictive value$.tw.
42. likelihood ratio$.tw.
43. diagnostic$.ti,ab.
44. or/36-43
45. 13 and 35 and 44

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HS&DR
HTA
PGfAR
PHR

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