

# Measuring fractional exhaled nitric oxide concentration in asthma: NIOXMINO, NIOX VERO and NObreath

Diagnostics guidance

Published: 2 April 2014

[www.nice.org.uk/guidance/dg12](http://www.nice.org.uk/guidance/dg12)

## Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

## Contents

1 Recommendations .....	4
2 The technologies.....	5
3 Clinical need and practice .....	6
The problem addressed .....	6
The condition .....	6
The diagnostic and care pathways .....	7
4 The diagnostic tests.....	10
The interventions.....	10
The comparator .....	11
5 Outcomes .....	12
How outcomes were assessed.....	12
Review of equivalence of FeNO devices.....	12
Diagnostic accuracy of FeNO devices.....	15
Efficacy of FeNO-guided asthma management .....	18
Cost effectiveness .....	23
6 Considerations.....	32
7 Recommendations for further research.....	40
8 Implementation.....	41
9 Diagnostics Advisory Committee members and NICE project team.....	42
Diagnostics Advisory Committee.....	42
NICE project team .....	44
10 Sources of evidence considered by the Committee.....	45
Registered stakeholders .....	45

## 1 Recommendations

- 1.1 FeNO is recommended by NICE to help diagnose asthma; for further details please see NICE's guideline on [asthma: diagnosis, monitoring and chronic asthma management](#).
- 1.2 FeNO measurement is recommended as an option to support asthma management in people who are symptomatic despite using inhaled corticosteroids.

## 2 The technologies

- 2.1 Three devices, NIOX MINO, NIOX VERO and NObreath, used for measuring fractional exhaled nitric oxide (FeNO) concentration in the diagnosis and management of asthma were evaluated. All 3 devices are CE marked. Additional details of the devices are provided in [section 4](#).
- 2.2 The devices and methods in this guidance were identified as being relevant to this assessment. NICE is aware that the devices and methods are evolving, so modifications and new devices are likely to be developed in the future.

### 3 Clinical need and practice

#### *The problem addressed*

- 3.1 Nitric oxide, which is produced in the lungs and is present in exhaled breath, has been implicated in the pathophysiology of lung diseases, including asthma. It has been shown to act as a vasodilator, bronchodilator, neurotransmitter and inflammatory mediator in the lungs and airways. Over the years, fractional exhaled nitric oxide (FeNO) has been proposed as a non-invasive marker of airway inflammation in asthma. FeNO levels are raised in people with asthma and can be lowered by effective treatment with corticosteroids.
- 3.2 The purpose of this evaluation was to evaluate the clinical and cost effectiveness of measuring FeNO in the diagnosis and management of asthma.

#### *The condition*

- 3.3 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 generally characterised by reversible 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 example, pollen, mould and house dust mites).
- 3.4 In people with asthma, cellular inflammation of the airways with eosinophils and neutrophils is considered to be a characteristic feature relevant to the pathogenesis of the disease. Eosinophilic asthma is a distinct phenotype of asthma associated with a rise in nitric oxide in exhaled breath. Eosinophilic asthma may respond to treatment with corticosteroids, while neutrophilic asthma generally does not.
- 3.5 Asthma usually develops in childhood but may start at any age. There is no cure for asthma, although people may have long periods of remission. Poorly controlled asthma can have a significant impact on the quality of life of the

affected person and their family. Because there may be variation in an individual's perception of asthma symptoms, clinical measures such as lung function do not always correlate with quality-of-life scores. However, if asthma is well controlled, near-maximal scores on quality-of-life instruments can be achieved.

## *The diagnostic and care pathways*

- 3.6 Asthma is diagnosed on the basis of symptoms and objective tests of lung function. Spirometry is used to assess lung function by measuring the volume of air that the patient is able to expel from the lungs after a maximal inspiration. Spirometry lung function measurements include peak expiratory flow rate (PEF), forced vital capacity (FVC; the total volume of air that a person can forcibly exhale in 1 breath), forced expiratory volume in the first second (FEV1) and percentage predicted FEV1 (calculated as a percentage of the predicted FEV1 for a person of the same height, sex and age without diagnosed asthma). Variability in PEF and FEV1, either spontaneously or in response to therapy, is a characteristic feature of asthma. The severity of asthma is judged according to symptoms and the amount of medication needed to control them, and is based on the British guideline on the management of asthma (2012) from the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN).
- 3.7 Asthma is diagnosed clinically and there is no standardised definition of the condition. The presence of symptoms (wheezing, breathlessness, chest tightness and cough) and variable airflow obstruction is central to all definitions. 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.
- 3.8 The diagnosis of asthma in children is based on recognising a characteristic pattern of episodic symptoms in the absence of an alternative explanation. If asthma is suspected, an initial clinical assessment should be carried out to estimate the probability of asthma. According to the British guideline on the management of asthma (2012), a child can be classed into 1 of 3 groups based on initial clinical assessment. These groups are:
- high probability – diagnosis of asthma likely

- low probability – diagnosis other than asthma likely
  - intermediate probability – diagnosis uncertain.
- 3.9 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. The response to treatment should be reassessed every 6 months. Those with a poor response to treatment should have more detailed investigations.
- 3.10 In children with an intermediate probability of asthma who can perform spirometry and have no evidence of airway obstruction, tests for atopic status, assessment of bronchodilator reversibility and, if possible, tests for bronchial hyper-responsiveness using methacholine, exercise or mannitol should be considered. In such cases, specialist referral should always be considered.
- 3.11 The diagnosis of asthma in adults is 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. Spirometry is the preferred initial test to assess the presence and severity of airflow obstruction. Adults are also classified as having a high, low or intermediate probability of asthma. Chest X-ray and specialist referral may be considered in any patient presenting atypically or with additional symptoms or signs.
- 3.12 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 from treatment. The British guideline on the management of asthma (2012) recommends a stepwise approach to treatment in both adults and children. 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 achieved. Management options include interventions with or without the use of drugs.
- 3.13 For most children and adults, asthma is monitored in primary care by routine clinical reviews on at least an annual basis. These reviews include (but are not limited to) assessment of the patient's symptom score (using a validated questionnaire), exacerbations, oral corticosteroid use, time off school or work,



growth in children, inhaler technique and, in adults, lung function assessed by spirometry (PEF).

## 4 The diagnostic tests

### *The interventions*

#### **NIOX MINO**

- 4.1 NIOX MINO (Aerocrine) is a diagnostic and monitoring device that analyses a breath sample using an electrochemical sensor to determine exhaled nitric oxide concentration. The technology is designed to help identify people whose airway inflammation is likely to respond to treatment with inhaled corticosteroids. It can also help to predict the onset of asthma symptoms or loss of asthma control, and to monitor compliance with corticosteroid therapy and the effectiveness of treatment.
- 4.2 NIOX MINO determines exhaled nitric oxide concentration in a breath sample. The device is small, hand-held and portable, and can be used by adults and children. It needs a 10-second exhalation of breath at a pressure of 10–20 cm H<sub>2</sub>O to maintain a fixed flow rate of 50±5 ml/s. 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. Clinical cut-off values can be applied to the exhaled nitric oxide values to categorise readings as low, intermediate or high according to the reference ranges for ages less than 12 years and 12 years or more.
- 4.3 NIOX MINO is pre-calibrated and designed to be a service- and calibration-free system. The manufacturer states that the calibrated electrochemical sensors included in the test kit should be replaced every year or once all the tests in the kit have been used. It can be used alone or connected to a computer for monitoring with the NIOX MINO Data Management Program and Electronic Medical Record systems. The device is CE marked.

#### **NIOX VERO**

- 4.4 During the assessment phase, the manufacturer of NIOX MINO (Aerocrine) launched NIOX VERO, a new fractional exhaled nitric oxide (FeNO) device that is intended to replace NIOX MINO. The new device is battery powered and has a longer operational life and extended-test volume life compared with NIOX MINO. NIOX VERO is designed to be service and calibration free. The manufacturer states that the calibrated electrochemical sensors included in the

test kit should be replaced every year or once all the tests in the kit have been used. The device is CE marked.

## NObreath

- 4.5 NObreath (Bedfont Scientific) is a diagnostic monitoring device that measures exhaled nitric oxide produced by airway inflammation. The reading is presented in parts per billion and is claimed to be directly related to the severity of inflammatory disease (for example, asthma). NObreath needs 12 seconds of exhalation of breath in adults and 10 seconds in children. The device is CE marked.

## *The comparator*

- 4.6 Scoping workshop attendees indicated that following the British guideline on the management of asthma (2012) from the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) is an appropriate comparator for people with asthma.

## 5 Outcomes

The Diagnostics Advisory Committee ([section 9](#)) considered evidence from several sources ([section 10](#)).

### *How outcomes were assessed*

- 5.1 The assessment was performed by an External Assessment Group and consisted of a systematic review and development of a decision analytical model.
- 5.2 The systematic review was carried out to identify evidence on the equivalence of fractional exhaled nitric oxide (FeNO) devices (analytical validity), evidence of the diagnostic accuracy of FeNO testing for asthma diagnosis and evidence of the efficacy of FeNO-guided asthma management.
- 5.3 A decision analytical model and a Markov model were developed to assess the cost effectiveness of measuring FeNO in the diagnosis and management of asthma.

### *Review of equivalence of FeNO devices*

- 5.4 The External Assessment Group undertook this review to establish whether FeNO devices could be considered to be equivalent to one another in their measurements, and so whether studies that used other devices could helpfully inform this appraisal. Because there was insufficient evidence from primary research studies that used the mobile, hand-held FeNO electrochemical devices (NIOX MINO, NIOX VERO and NObreath), a review of equivalence to the precursory large, stationary FeNO chemiluminescent devices (including Niox, also made by Aerocrine) was conducted.
- 5.5 The review identified 27 studies that compared NIOX MINO, NIOX VERO and NObreath with other devices. The External Assessment Group undertook 3 main comparisons for this purpose. The first included comparisons of means, which compare the reported mean FeNO values as measured by each device in the same cohort. The second compared correlation coefficients, which show whether measurements by 2 devices are correlated but not whether the actual values produced are the same. The third compared the result of Bland–Altman analyses, which produce statistics that assess agreement between devices

rather than just correlation.

## NIOX MINO

- 5.6 Eight studies compared NIOX MINO with Niox in adults. Of these studies, 5 were exclusively in adults and 3 were in adults and other age groups. There was variability in correlation between the devices among the studies. While 5 studies showed largely similar mean values between NIOX MINO and Niox, 3 studies showed higher FeNO readings with NIOX MINO (ranging from 0.5 to 9 parts per billion [ppb]). Small (non-significant) differences in the mean FeNO readings were observed between the devices when the cohort mean FeNO values were below 30 ppb (as measured by Niox). When the mean FeNO values were above 35 ppb, the differences in cohort means were larger and statistically significant. Correlation coefficients ranged from 0.73 to 0.998. The results of 1 study suggested that there may also be some variation between NIOX MINO devices themselves, although a second study showed good agreement. Across the 8 studies, Bland–Altman analyses were not reported in a consistent way. Limits of agreement were 10 ppb above and below the mean in some cases, and the studies with the largest mean differences did not report Bland–Altman statistics.
- 5.7 Three studies comparing NIOX MINO with Niox included children. Of these, 2 studies reported statistically significantly higher mean FeNO values with NIOX MINO, while 1 study reported statistically significantly lower values. This study had low mean values (below 10 ppb). All studies reported good correlation between the devices, while Bland–Altman statistics reported in 2 studies showed that NIOX MINO gave higher readings (by 1.1 ppb [limits of agreement –4.4 to 6.7] and 3.9 ppb [limits of agreement –1.1 to 8.9] respectively).
- 5.8 Twelve studies compared NIOX MINO with stationary chemiluminescent devices other than Niox in adults and children. Of these, 6 studies were in adults, 3 in an unspecified group and 3 in children. The chemiluminescence devices used in each of the 12 studies were different. In the adults and the unspecified age group, correlation coefficients ranged from 0.876 to 0.96, indicating good correlation between devices. However, the mean FeNO levels and Bland–Altman statistics did not suggest such good correlation. In 4 studies, NIOX MINO gave higher readings than the comparator device, while 2 studies reported lower readings and 2 studies showed the devices to be comparable.

Bland–Altman statistics, reported in 4 studies, suggested that mean differences were small, but the limits of agreement were much greater.

- 5.9 In children, correlation coefficients between NIOX MINO and other chemiluminescent devices ranged from 0.69 to 0.98, indicating variable correlation. The study with the poorer correlation reported higher mean FeNO levels, suggesting that poorer correlation is due to greater variability at higher FeNO values. However, the authors stated that correlation improved at higher values. One study noted that the direction of disagreement was different in children aged over and under 12 years. The back-transformed Bland–Altman statistics and range of ratios reported showed a wide range of agreement, suggesting that the devices are not interchangeable.
- 5.10 The External Assessment Group stated that the comparability of NIOX MINO to chemiluminescent devices appears to be influenced by several factors. These include variability between NIOX MINO devices themselves, a lack of comparability between other chemiluminescent devices (which leads to heterogeneity in estimates of comparability between these devices and NIOX MINO) and poorer equivalence between the devices at higher FeNO levels.

## NIOX VERO

- 5.11 The manufacturer of NIOX MINO and NIOX VERO provided details of a study (commercial in confidence) that compared the technical performance and accuracy of the 2 technologies.

## NObreath

- 5.12 Four studies compared NObreath with 3 chemiluminescent devices other than Niox. Bland–Altman analysis done in 1 study in a healthy cohort with low FeNO values showed a mean difference of –3.95 ppb in comparison with the chemiluminescent device. Limits of agreement in this study were wide (–10.98 to 4.08). Another study reported an absolute mean difference in FeNO measurements of –3.81 ppb. Comparisons with the third type of chemiluminescent device showed small differences between mean FeNO values for the cohort, with NObreath giving lower values in some cohorts.
- 5.13 Two studies that compared NObreath with NIOX MINO in adults found that NIOX MINO provided lower mean FeNO values than NObreath in most

analyses. This contradicts the available evidence for comparisons of NIOX MINO with Niox and NObreath with Niox, which suggested that NIOX MINO should provide higher readings than NObreath. The 2 direct comparisons of NObreath and NIOX MINO included small numbers of patients, and only 1 included patients with asthma, but did not provide a Bland–Altman analysis to assess agreement.

- 5.14 The External Assessment Group stated that, based on available evidence, any differences in absolute values between results from NObreath and other devices are relatively small, although derived cut-offs and maximum sensitivity and specificity may differ.

### *Diagnostic accuracy of FeNO devices*

- 5.15 No end-to-end studies were identified, and no cohort study compared use of FeNO testing within a sequence of tests with a suitable reference standard of the same sequence of tests without FeNO testing. The review identified 24 studies that met the inclusion criteria; 20 included adults of all ages and 4 included children. The studies were classified according to the position of the patients' asthma in the UK care pathway and the reference standards used.

### **FeNo testing in adults with asthma symptoms compared with most of, or all, the UK care pathway**

- 5.16 The review identified 4 studies in this group. Cut-offs for the highest sum of sensitivity and specificity ranged from 20 ppb to 47 ppb in the 4 studies in this group. Sensitivities ranged from 32% to 88%, and specificities from 75% to 93%. Because of the heterogeneity in the results, study designs and the devices used, the External Assessment Group concluded that it is difficult to identify the optimal cut-off for sensitivity and specificity.
- 5.17 Cut-offs yielding the highest sensitivity ranged from 9 ppb to 15 ppb, with sensitivities ranging from 85% to 96% and specificities from 13% to 48%. Cut-offs yielding the highest specificity ranged from 47 ppb to 76 ppb, with sensitivities ranging from 13% to 56% and specificity from 88% to 100%.
- 5.18 Estimates of specificity consistently had a smaller range and higher values than estimates of sensitivity reported, suggesting that FeNO may be more reliable as

a 'rule-in' test than as a 'rule-out' test. A rule-in test implies that patients whose test is positive are assumed to have asthma and those testing negative go on to have further tests. However, the cost effectiveness of this balance will depend on the clinical and cost consequences of the correct or incorrect classification of patients.

### **FeNO testing in patients with difficult-to-diagnose asthma compared with airway hyper-responsiveness**

- 5.19 Three studies used some form of airway hyper-responsiveness as the sole reference standard. Estimates of sensitivity and specificity appeared comparable to those in the studies of patients presenting in primary care with symptoms of asthma. One study included a set of patients whose methacholine challenge tests were negative and compared FeNO with an adenosine challenge test. This study produced 100% sensitivity (29% specificity) at a cut-off of 30 ppb, making it likely to operate well as a rule-out test.
- 5.20 The other 2 studies used methacholine challenge tests in people who had been found not to have asthma in previous tests. Cut-offs for the highest sum of sensitivity and specificity ranged from 34 ppb to 40 ppb when compared with a methacholine challenge test as a gold standard. Sensitivities ranged from 24% to 74%, and specificities from 73% to 99%, which is a similar range to the broader cohort. A range of cut-offs was not reported in these studies.

### **FeNO testing in patients with difficult-to-diagnose asthma with chronic cough compared with response to a trial of inhaled corticosteroids**

- 5.21 Three studies included patients with chronic cough who had tested negative for other causes. All 3 studies used response to a trial of treatment with inhaled corticosteroids as a reference standard. Cut-offs for the highest sum of sensitivity and specificity were similar in all 3 studies. Accuracy was somewhat better in 2 studies at 90–95% sensitivity and 76–85% specificity.

### **FeNO testing in children with asthma symptoms compared with various reference standards**

- 5.22 Four studies were identified that included children, and these had patients with a similar severity of asthma and similar reference standards as the adult cohorts, while the cut-offs derived were generally lower but with similar ranges



of estimates of sensitivity and specificity. There was a high degree of agreement between studies in terms of 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. Estimates of sensitivity at these cut-off points were also wide-ranging and of a similar range to those in the studies in adults (49% to 86%).

- 5.23 When selecting the cut-off with the highest sensitivity, results were similar to those for adult cohorts. Cut-offs ranged from 5 ppb to 20 ppb, sensitivities from 89% to 94% and specificities from 14% to 70%. When selecting the cut-off with the highest specificity, results were also similar to adult cohorts. Cut-offs were a little lower again, and ranged from 30 ppb to 50 ppb. Sensitivities ranged from 20% to 50% and specificities from 92% to 100%.
- 5.24 The External Assessment Group did not conduct a meta-analysis in any group because of the high heterogeneity between studies. Estimates of cut-off points, sensitivity and specificity were not consistent within groups and ranged widely when used as a rule-in or rule-out test and when considering the highest sum of sensitivity and specificity. Because of this, the External Assessment Group found it difficult to estimate the relative diagnostic accuracy of FeNO testing in any situation and at any given cut-off point. However, there did not appear to be a difference in the relative diagnostic accuracy of FeNO testing in the 2 settings (primary and secondary care), either in comparison with the standard UK care pathway (entire or parts) or in comparison with airway hyper-responsiveness in patients whose asthma was difficult to diagnose. But the large variation in estimates within groups may obscure any true underlying differences in the accuracy of FeNO testing between groups and between different reference standards.

## FeNO testing in population subgroups included in the scope

- 5.25 No cohort studies were found that provided evidence relating to the subgroups of pregnant women, older people, people who smoke or people exposed to environmental tobacco, and therefore lower levels of evidence were consulted.
- 5.26 FeNO testing appeared to be able to distinguish people with asthma from people without asthma with similar accuracy in people who smoke and people who do not smoke or used to smoke. It seems likely that FeNO levels are

generally lower in people who smoke, and it may be useful to consider a person's smoking status when interpreting results, or to select lower cut-off points for people who smoke. Limited data in children support the same conclusion as for adults.

- 5.27 There is limited and conflicting evidence for the benefit of FeNO testing in older people and, therefore, uncertainty as to whether FeNO testing is useful for diagnosing asthma in the older population.
- 5.28 A cross-sectional study suggested that pregnancy does not alter FeNO levels in women with or without asthma, and that FeNO testing can distinguish between healthy, pregnant women with asthma or without asthma.

### *Efficacy of FeNO-guided asthma management*

- 5.29 The External Assessment Group reviewed evidence relating to outcomes in adults, children and subgroups of people as defined in the scope for this assessment. The outcomes included exacerbations, inhaled corticosteroid use and health-related quality of life.

### **FeNO-guided asthma management in adults**

- 5.30 Four studies (based in the UK, New Zealand, Sweden and the USA) were included in this review. The quality of the 4 studies was assessed according to the Cochrane Library and Centre for Reviews and Dissemination (CRD) handbook. The External Assessment Group indicated that the study with the highest risk of bias was the study by Syk et al. (2013); this was because of the lack of blinding, incomplete outcome data and selective reporting.
- 5.31 All 4 studies were randomised controlled trials; 2 were single blind (Smith et al. 2005 and Shaw et al. 2007), 1 was open label (Syk et al. 2013) and 1 was described as 'multiply blinded' (Calhoun et al. 2013). There was a high degree of heterogeneity in all aspects of study design across the 4 studies. Three studies did not clearly report which device was used to measure FeNO levels.
- 5.32 The inclusion criteria, trial protocols and treatment doses varied across the studies. Only 1 study reported using the British guideline on the management of asthma (2012), hereafter referred to as the 'British guideline', in the comparator

- arm. The number of patients in the trials ranged from 94 to 229, and they were recruited from primary care in 3 studies. For 1 study, it was unclear what setting people were recruited from.
- 5.33 Exacerbations were reported in all 4 studies, although definitions varied and results were not always consistent across the studies. However, all 4 studies reported a fall in exacerbation rates per person year, although it appeared that this was mostly driven by mild and moderate exacerbations.
- 5.34 For severe exacerbations, the Syk et al. (2013) study reported higher rates of oral corticosteroid use in the intervention arm (although the difference was not statistically significant), while the composite outcome of moderate or severe exacerbations favoured the intervention arm. In the other studies, the difference in direction of effect between the outcome for oral corticosteroid use and the composite outcomes that included less severe exacerbations was not evident. Oral corticosteroid use and the composite outcomes of severe and less severe exacerbations decreased in intervention arms, although there was still an apparently greater effect in the composite outcomes. Rate ratios calculated by the External Assessment Group for major/severe exacerbations ranged from 0.79 (95% confidence interval [CI] 0.44 to 1.41) to 1.29 (95% CI 0.51 to 3.30), while rate ratios calculated by the External Assessment Group for composite outcomes of all severity of exacerbation ranged from 0.52 (95% CI 0.30 to 0.91) to 0.63 (95% CI 0.40 to 0.98).
- 5.35 Despite the high level of between-study heterogeneity, an exploratory meta-analysis of the rates of major and severe exacerbations using fixed effects methods was conducted. The result showed no heterogeneity, with an  $I^2$  statistic of 0%. The pooled estimate was 0.87 (95% CI 0.64 to 1.19,  $p=0.38$ ). This indicates that there were fewer major exacerbations in the intervention arm, but the difference did not reach statistical significance.
- 5.36 A sensitivity analysis was done using the results of studies that reported the number of exacerbations resulting in oral corticosteroid use. The pooled risk ratio was 0.90 (95% CI 0.56 to 1.45), indicating a statistically non-significant difference for asthma management with FeNO measurement. However, the External Assessment Group noted that there were only 2 studies in this analysis. Both studies reported non-significant differences, but with risk ratios on opposite sides of the line of no effect. This could suggest that differences in

study design, step-up and step-down protocols, and patient characteristics may account for differences in direction of effect.

- 5.37 When considering the composite outcome of all exacerbations and failure rates, 3 studies reported composite outcomes that the External Assessment Group considered to be broadly similar and to represent 'treatment failure'. In 2 studies, FeNO-guided management groups showed numerically, but not statistically significant, lower rates of failure. In the Syk et al. (2013) study, the improvement was statistically significant, with a rate of 0.22 in the intervention arm compared with 0.41 in the control arm ( $p=0.024$ ). The rate ratio calculated by the External Assessment Group was 0.52 (95% CI 0.30 to 0.91). A meta-analysis of these rates was conducted despite the high level of heterogeneity between study characteristics. The result showed a statistically significant effect, with a rate ratio of 0.58 (95% CI 0.43 to 0.77). This represents a statistically significant effect in favour of using FeNO-guided management in people with asthma for the composite outcome of all exacerbations and treatment failure rates.
- 5.38 An additional study (Honkoop et al. 2013) was identified by the External Assessment Group. The study was a randomised controlled trial with a 12-month follow-up period and dose titration at baseline and every 3 months thereafter. The number of people in the study was larger than in the other 4 studies and they were recruited from primary care. Outcome data were limited because this study was only reported in a conference abstract; however, a non-significant trend towards a reduction in courses of oral prednisolone was reported for the FeNO measurement group compared with the comparator arms. The External Assessment Group performed an additional meta-analysis that included the Honkoop et al. study, calculating the rate ratio for exacerbation as 0.69. Errors could not be calculated for this meta-analysis because the exact numbers of people and events were not reported. Results of the meta-analysis ranged from significant to non-significant in favour of FeNO measurement, depending on the error rate imputed.
- 5.39 All studies reported some data on inhaled corticosteroid use. Two studies reported inhaled corticosteroid use as a mean per day at the end of the study, with mean differences of -270 micrograms per day (95% CI -112 to -430,  $p=0.003$ ) and -338 micrograms per day (95% CI -640 to -37 micrograms,  $p=0.028$ ) respectively, in favour of FeNO-guided management. The Syk et al.

(2013) study showed a small (non-significant) increase in inhaled corticosteroid use in the intervention arm (586 micrograms, standard error [SE] 454; compared with 540 micrograms, SE 317, in the control arm). One study reported means per month, although it is unclear if this was an average over the whole course of the study, or the means for the final month of the study. The means were very similar at 1617 micrograms per month in the intervention arm and 1610 micrograms per month in the control arm.

- 5.40 A meta-analysis used standardised mean difference analysis because outcomes were not reported in a standardised way. This showed an overall effect of  $-0.24$  standard deviations in favour of FeNO-guided management, although this narrowly missed significance (95% CI  $-0.56$  to  $0.07$ ,  $p=0.13$ ).
- 5.41 Two studies used versions of the Asthma Quality of Life Questionnaire (AQLQ) to measure quality of life. Both showed no effect in the global score, but 1 investigated domains and found a statistically significant difference in the symptoms score. A meta-analysis of the overall scores showed no effect on quality of life, with a standardised mean of  $0.00$  (95% CI  $-0.20$  to  $0.20$ ).
- 5.42 All 4 original studies (excluding Honkoop et al. 2013) reported data for asthma control. In 3 studies, asthma control did not change but in the Syk et al. (2013) study there was a statistically significant increase in asthma control between the 2 trial arms. Two studies (Smith et al. 2005 and Calhoun et al. 2012) reported no significant difference between groups for bronchodilator use. Syk et al. did not report the significance of the difference between the 2 arms, reporting a median of  $1.56$  (interquartile range [IQR]  $0.06$  to  $5.18$ ) uses per week in the intervention arm, and a median of  $0.94$  (IQR  $0.03$  to  $2.81$ ) in the control arm. No asthma-related adverse events or deaths were reported.

## FeNO-guided asthma management in children

- 5.43 Five studies (based in Austria, the USA, Italy, the Netherlands and Australia) that included children (plus adolescents and young adults) and compared FeNO-guided management with non-FeNO-guided management were identified. The quality of the studies was assessed according to criteria proposed in the Cochrane Handbook and CRD Handbook. The study quality varied; no single study scored well in every item, and no item scored well in every study.

- 5.44 There was a high degree of heterogeneity in all aspects of study design across 4 studies. No study reported using the British guideline in the comparator arm. Two studies included patients who appeared to be poorly controlled. One study included patients who had mild to moderate persistent asthma and 1 study included patients who had received a stable dose of inhaled corticosteroids for the previous 3 months, suggesting that their asthma was reasonably well controlled.
- 5.45 All 5 studies reported some data on asthma exacerbations, although the definition of exacerbation was unclear in some cases. Two studies reported severe exacerbations in a way that allowed calculation of rates per person year. Both had lower rates in the intervention arm. In patients with uncontrolled asthma, the rate was 0.746 in the intervention arm and 0.950 in the control arm. In patients who had been on a stable dose of inhaled corticosteroids for 3 months, the rate was 0.21 in the intervention arm and 0.39 in the control arm. Both rates were calculated by the External Assessment Group and the statistical significance is unclear.
- 5.46 For all definitions of exacerbations, 4 studies reported outcomes that were not defined as either major or minor and had different definitions to each another. All the studies showed a trend in favour of fewer exacerbations in the intervention arm. The only study to report a significant between-group difference was a conference abstract, which showed that exacerbations (not clearly defined) occurred in 6 of the 31 patients in the intervention group (19.4%) and 15 of 32 in the control group (46.9%,  $p=0.021$ ).
- 5.47 Overall, results showed that inhaled corticosteroid use increased in the intervention group compared with the comparator group, although there was variability between the studies. These differences could be attributed to the specifics of the step-up and step-down protocols or the characteristics of the patients selected. The 2 studies that included children whose asthma was hard-to-treat or uncontrolled (Szeffler et al. 2009 and Fritsch et al. 2006) saw an increase in inhaled corticosteroid use, while the studies that did not include children with these characteristics saw no significant increase.
- 5.48 Health-related quality of life was only reported in 1 study in abstract form and using an unknown tool. The External Assessment Group was not able to draw a definite conclusion from these data. Four studies provided some data on asthma

control, none of which demonstrated any statistically significant effects favouring either intervention or control. With respect to additional medication use, 3 studies provided data, but there did not appear to be a clear direction of effect within the data.

- 5.49 One study reported no difference in adverse events between groups and there were no deaths reported. The adverse events listed included gastrointestinal disorders, haematological disorders, infections, musculoskeletal symptoms and skin symptoms.

### *Cost effectiveness*

- 5.50 The economic analysis done by the External Assessment Group compared the cost effectiveness of measuring FeNO using NIOX MINO, NIOX VERO and NObreath with current standard tests for diagnosing and managing asthma in England and Wales.

### **Review of existing economic analyses**

- 5.51 The External Assessment Group did a review to identify existing economic analyses of FeNO testing and measurement (using NIOX MINO, NIOX VERO or NObreath) for diagnosing and managing asthma respectively. The review also sought to identify existing models and potentially relevant evidence sources to inform parameter values within the de novo economic models developed by the External Assessment Group.
- 5.52 Only 1 published UK cost-effectiveness model was identified for asthma diagnosis, and 1 for asthma management. Modified versions of these models were provided to NICE by the manufacturer of NIOX MINO and NIOX VERO. The wider review identified several economic analyses that the External Assessment Group described as including various methodological problems, questionable assumptions and weak evidence.

### **De novo cost-effectiveness model**

- 5.53 The External Assessment Group developed 2 de novo models: 1 to assess the expected cost effectiveness of measuring FeNO in addition to, or in place of, standard tests for diagnosing asthma (the diagnostic model) and 1 to assess the expected cost effectiveness of FeNO plus the British guideline compared with

the British guideline alone for managing people with diagnosed asthma (the management model). The 2 models, although distinct, shared several parameter values and assumptions.

- 5.54 The diagnostic model was structured in the form of a decision tree. The decision tree model was used to estimate the probability that a person with asthma will be correctly diagnosed (true positive) or incorrectly diagnosed (false negative); and the probability that a person without asthma will be correctly diagnosed (true negative) or incorrectly diagnosed (false positive) and the expected health outcomes and costs arising from this. The management model was in the form of a simple Markov model with 2 states: alive with diagnosed asthma and dead.
- 5.55 Estimates of test accuracy for measuring FeNO were drawn from several separate studies based on the results of the systematic review for clinical effectiveness, while estimates of test accuracy for comparator tests were drawn from best available evidence. The economic analyses included estimates of the sensitivity and specificity of individual tests as well as combinations of FeNO devices plus other standard tests. One study (Schneider et al. 2013) that used the NIOX MINO device was used to inform estimates of the sensitivity and specificity of FeNO alone. The true pre-test probability of asthma in undiagnosed patients was estimated as a weighted mean of several cases of asthma and non-asthma in the studies used, to inform the diagnostic test accuracy parameters. Across the included studies, 412 of 881 patients were diagnosed with asthma ( $p=0.47$ ).
- 5.56 Health-related quality of life values for people without asthma were estimated using a general population EQ-5D regression model. The values were common to all diagnostic comparator groups and did not therefore have any effect on the estimates of incremental health gain for the diagnostic tests included in the economic analysis. The disutility associated with asthma, estimated to be  $-0.0463$ , was taken from the catalogue of EQ-5D values reported by Sullivan et al. (2011). It was noted that this disutility was applied to all patients with asthma and to those who tested false positive (until their misdiagnosis was corrected). This disutility is unlikely to fully reflect health losses associated with the delayed diagnosis of more serious pathology, such as cancer or tuberculosis. The disutility associated with poor asthma control was derived from a study (McTaggart-Cowan et al. 2008) that reported EQ-5D estimates for 4 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'.

- 5.57 The External Assessment Group assumed that the health loss associated with poor control because of a false-negative diagnosis related to the difference between the 'well-controlled' state and the 'not-controlled' state (mean disutility of  $-0.04$ ). This disutility was applied to all false-negatives until the misdiagnosis was corrected.
- 5.58 Because of the lack of empirical evidence relating to the time needed to resolve incorrect diagnoses, the External Assessment Group attempted to elicit these values from clinical specialists. Based on the response received, the External Assessment Group assumed that the time to resolve a false-negative diagnosis has a mean of 8 months (95% CI 4 to 12 months) and the time to resolve a false-positive diagnosis has a mean of 18 months (95% CI 12 to 24 months). The External Assessment Group considered these estimates to be highly uncertain and tested them in sensitivity analyses.
- 5.59 The following costs were used to inform the diagnostic and management models:
- Test costs: the marginal per-test costs for all 3 devices were calculated based on information provided by the manufacturers. The calculation was complicated by the fact that the devices each have different lifetimes, and that test kits and mouthpieces for each device are available at lower marginal costs if higher volumes of kits are purchased. These marginal per-test costs do not include any costs associated with education and training for NHS staff to use the devices.
  - Maintenance costs: the External Assessment Group assumed that the manufacturer provides the maintenance of NObreath free of charge to the NHS. The External Assessment Group assumed zero maintenance costs for NIOX MINO and NIOX VERO.
  - Primary care costs: the External Assessment Group assumed that spirometry, reversibility testing and measuring FeNO can be done in primary care and would need 2 GP visits and 1 nurse visit. The unit cost of a GP visit was based on published economic analyses that used an estimate of £43 (based on an appointment of 11.7 minutes, and including direct staff costs and qualifications). The cost of a GP practice nurse visit was assumed to be £13.69 (based on a visit of 15.5 minutes). For the management model, the External Assessment Group assumed that measuring

- FeNO would be done during routine GP visits and would need an additional nurse visit once every 3 months. The marginal cost of measuring FeNO was applied as the per-test cost plus the cost of a primary care nurse appointment.
- Secondary care costs: the External Assessment Group assumed that sputum induction and airway hyper-responsiveness (methacholine challenge test) would be done in secondary care and would need 2 secondary care visits, 1 laboratory visit and an initial GP visit for referral. Secondary care attendance costs were based on the Healthcare Resource Group for respiratory medicine attendances (£204.29). The cost of a laboratory visit was based on the Healthcare Resource Group for simple bronchodilator studies (£203.29). The External Assessment Group assumed the standard errors around these estimates were normally distributed, with a standard error equal to 15% of the mean.
- Costs of asthma management: estimates of the annual cost of combined inhalers were derived from 2 previous health technology assessment reports. For children, the least expensive annual cost for combined inhalers was estimated to be £201. For adults, the least expensive annual cost of the inhalers was estimated to be £231.
- Costs associated with resolving misdiagnoses: the assumption was made that 1 additional primary care attendance, 2 additional secondary care attendances and 1 laboratory visit would be needed to correctly diagnose false-positive and false-negative results. This same assumption was made in previously published models.
- Costs associated with loss of control for false-negatives: the External Assessment Group assumed that people who were falsely diagnosed as not having asthma would experience 1 exacerbation in each year they remain misdiagnosed. The model assumed that a proportion of these exacerbations would need hospitalisation.

5.60 The following costs were used to inform the management model alone:

- Additional costs of FeNO measurement: The External Assessment Group assumed that FeNO measurement would be done during routine GP visits and would require 1 additional nurse visit every 3 months.
- Costs of managing exacerbations: the External Assessment Group assumed that a proportion of exacerbations would need hospitalisation while the remainder could be managed in primary care. It also assumed that severe exacerbations that do not need hospitalisation would need 1 GP attendance (£43.00) plus oral corticosteroids for 5 days (£1.73) based on an earlier health technology assessment report. The cost of

- asthma hospitalisation was derived from current NHS Reference Costs (£1266.72).

## Base-case results

- 5.61 The base-case model was evaluated probabilistically using Monte Carlo sampling techniques. Deterministic one-way sensitivity analyses were also performed to account for different modelling assumptions. Central estimates of cost effectiveness were presented as incremental cost-effectiveness ratios (ICERs). Uncertainty surrounding the cost-effectiveness estimates was presented using cost-effectiveness planes and cost-effectiveness acceptability curves.
- 5.62 The base-case results of the diagnostic model in children and adults suggested that, across the 17 diagnostic options included in the economic analysis, the expected difference in quality-adjusted life years (QALYs) is likely to be small (4.2686–4.2834). They also suggested that airway hyper-responsiveness (methacholine challenge test) is expected to produce the greatest QALY gain (4.2834), followed by FeNO testing (either NObreath, NIOX VERO or NIOX MINO) plus bronchodilator reversibility, with a QALY of 4.2829. The difference between the QALYs produced by the methacholine challenge test and FeNO testing plus a bronchodilator was very small (0.0005 QALYs). Other diagnostic test options, either with or without FeNO testing, resulted in increasingly lower QALYS, with spirometry (forced expiratory volume in the first second divided by the total volume of air that a person can forcibly exhale in one breath) producing the lowest QALY gain of 4.2686.
- 5.63 The External Assessment Group presented an incremental cost-effectiveness analysis, in which the diagnostic options were ranked in decreasing order of QALY. The ICER for airway hyper-responsiveness (methacholine challenge test) compared with the next best option in terms of QALY (NObreath plus bronchodilator reversibility) was approximately £1.125 million per QALY gained. Following methacholine challenge, the option producing the next best QALY (FeNO testing plus bronchodilator reversibility) yielded 4.2829 QALYs, but the cost associated with the individual tests varied (£686.08 for NObreath, £687.61 for NIOX VERO and £688.33 for NIOX MINO). FeNO testing plus bronchodilator reversibility is therefore cost saving compared with methacholine challenge, but is estimated to produce marginally fewer QALYs (see section 5.62). All further options, with or without FeNO testing, were dominated because they were both more expensive and produced fewer QALYs.

The External Assessment Group considered these results to be very uncertain.

### **Results in children**

5.64 The base-case results for asthma management in children suggested that the British guideline plus FeNO measurement produces a small health benefit (0.05 QALYs) compared with the British guideline alone. The British guideline plus FeNO measurement was also more costly (£8148.59 for the British guideline plus NObreath, £8314.30 for the British guideline plus NIOX VERO and £8391.53 for the British guideline plus NIOX MINO) than the British guideline alone (£5860.06) because of projected inhaled corticosteroid use for the FeNO measurement groups. The resulting ICER for NObreath plus the British guideline compared with the British guideline alone was £45,213 per QALY gained. NIOX VERO and NIOX MINO were expected to be dominated by NObreath because of their higher marginal per-test costs.

### **Results in adults**

5.65 The base-case results for asthma management in adults showed that the British guideline plus FeNO measurement is expected to produce a small health benefit (0.04 QALYs) compared with the British guideline alone. The British guideline plus FeNO measurement was also more costly in adults (£7377.61 for the British guideline plus NObreath, £7535.43 for the British guideline plus NIOX VERO and £7608.99 for the British guideline plus NIOX MINO) than the British guideline alone (£7296.30) because of increased inhaled corticosteroid use in the FeNO measurement groups during the first 12 months of monitoring. Similarly to the children's model for asthma management, the model assumed that all 3 FeNO devices produce the same health benefits. NIOX MINO and NIOX VERO were dominated by NObreath because of their higher marginal per-test costs. The ICER of the British guideline plus NObreath compared with the British guideline alone was approximately £2146 per QALY gained. If dominance was ignored, the ICERs for the British guideline plus the NIOX devices, compared with the British guideline alone, were £6310 per QALY gained for NIOX VERO and £8250 per QALY gained for NIOX MINO.

### **Sensitivity analysis results**

5.66 The External Assessment Group carried out several deterministic sensitivity analyses for the diagnostic and management models.

### ***Diagnostic model***

- 5.67 For the diagnostic model, results of the deterministic sensitivity analyses indicated that the cost-effectiveness frontier presented in the base-case analysis was maintained across most scenarios. In most scenarios, most options were expected to be ruled out because of simple dominance. The results based on the point estimates of parameters were similar to the results of the probabilistic analysis, and discounting did not have a substantial effect on the cost effectiveness of the non-dominated diagnostic options.
- 5.68 Other indications from the results of the sensitivity analysis showed that the costs of the various FeNO devices influenced which options were dominated, but had only a negligible impact on the cost-effectiveness results for non-dominated options. Longer misdiagnosis correction times substantially improved the cost effectiveness of airway hyper-responsiveness (methacholine challenge test) compared with FeNO testing plus bronchodilator reversibility, with the lowest ICER being £126,982 per QALY gained when time to correct diagnosis was extended 10-fold.
- 5.69 In terms of diagnostic accuracy, the results of the sensitivity analyses showed that the use of other sources for the operating characteristics of FeNO testing and standard tests did not impact on the cost effectiveness of non-dominated options. Also, the use of a rule-out decision approach may have improved the comparative effectiveness and cost effectiveness of FeNO testing alone.

### ***Management model***

- 5.70 For the management model in children, the results of the sensitivity analyses indicated that NIOX MINO and NIOX VERO were expected to be consistently dominated by NObreath because of their higher marginal per-test cost. In addition, while the marginal per-test cost influenced which device would be preferred, it did not have a substantial impact on the overall cost effectiveness of the British guideline plus FeNO measurement compared with the British guideline alone.
- 5.71 The results of the sensitivity analyses indicated that the length of time FeNO measurement was assumed to impact on exacerbations and inhaled corticosteroid use was a key source of uncertainty within the children's model. Shorter impact times improved the cost effectiveness of FeNO measurement.

The British guideline plus FeNO measurement dominated the British guideline alone when it was assumed that the impact of FeNO-guided management on exacerbations and inhaled corticosteroid use was reduced to 1–4 years, whereas assumptions for 5 years and 10 years produced ICERs of £7598 and £27,660 per QALY gained respectively.

- 5.72 When alternative sources of exacerbation rates and inhaled corticosteroid use for children were explored, the ICERs for managing children changed considerably. The sensitivity analysis used values from the Pijnenburg et al. (2005) study, rather than the Szeffler et al. (2008) study used in the base case, in which exacerbation rates were 0.18 for the British guideline plus FeNO measurement and 0.39 for the British guideline alone, and relative corticosteroid dose intensity beyond the first year was 1.23 for the British guideline plus FeNO measurement and 1.22 for the British guideline alone. The analysis based on Pijnenburg et al. suggested a considerably more favourable ICER for the British guideline plus FeNO measurement compared with the British guideline alone in children (£18,963 per QALY gained). The External Assessment Group noted that the Szeffler et al. study included patients with uncontrolled asthma 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 inhaled corticosteroid use was higher for the British guideline plus FeNO measurement than for the British guideline alone.
- 5.73 The results of the sensitivity analyses for managing children also indicated that the model was sensitive to the rate of exacerbations and the associated health loss. When exacerbation rates were doubled, the ICER for the British guideline plus FeNO measurement compared with the British guideline alone was £19,891 per QALY gained. When exacerbation rates were halved, the ICER was £95,632 per QALY gained. When the exacerbation disutility was doubled the ICER was £31,479 per QALY gained and £52,844 per QALY gained when halved.
- 5.74 Results for the deterministic sensitivity analyses for the management model in adults showed that the model was highly sensitive to the exacerbation rates used. Exacerbation rates from Syk et al. (2013) increased the ICER to £184,000 per QALY gained for the British guideline plus FeNO measurement compared with the British guideline alone. When exacerbation rates from Syk et al. were used, the British guideline alone dominated the British guideline plus FeNO measurement. In addition, NIOX MINO and NIOX VERO were expected to be

consistently dominated by NObreath because of their higher marginal per-test cost. However, while the marginal per-test cost influenced which device would be preferred, it did not have a substantial impact on the overall cost effectiveness of FeNO measurement compared with the British guideline.

- 5.75 Another observation from the sensitivity analyses of the management in the adult model was that the length of time that FeNO measurement was assumed to impact on exacerbations and the use of inhaled corticosteroids was a key driver of cost effectiveness. In the adult model, the cost effectiveness improved when the duration of impact of FeNO measurement was extended (£885,451 per QALY gained when 1 years' duration was assumed, to £8898 per QALY gained when 40 years' duration was assumed). The opposite was true in the children's model in which cost effectiveness worsened when the duration of effect on exacerbations and inhaled corticosteroid use was increased (see section 5.71). The External Assessment Group stated that this was driven entirely by the observed differences in relative inhaled corticosteroid use at the last observed time point in the trials.

## 6 Considerations

- 6.1 The Diagnostics Advisory Committee reviewed the evidence available on the clinical and cost effectiveness of measuring fractional exhaled nitric oxide (FeNO) to inform the diagnosis and management of asthma in children and adults. The Committee considered the report produced by the External Assessment Group and statements from patient experts on the Committee and from clinical specialists who acted as specialist Committee members on this assessment.
- 6.2 The Committee considered whether NIOX MINO, NIOX VERO and NObreath could be considered equivalent for the purpose of this assessment. It noted the review by the External Assessment Group, which indicated that, although some differences were observed in test results, there was generally a good correlation with results from other chemiluminescence devices. The Committee noted that there appeared to be poorer equivalence between devices in some circumstances, such as at higher FeNO levels, and that the direction of disagreement varied between studies and devices. However, the Committee acknowledged that there is no commonly accepted definition of clinically acceptable differences in FeNO measurements. The Committee concluded that, based on the available evidence, the 3 devices could, on balance, be considered to be broadly equivalent. The Committee also thought that standardisation of FeNO devices should be encouraged.
- 6.3 The Committee considered whether very young children would be able to perform the test. It heard from both manufacturers that the minimum recommended age for using FeNO monitoring devices is 5 years. The Committee also noted that the External Assessment Group's systematic review only included studies of children 5 years and older, in line with the review protocol. The Committee concluded that there was insufficient evidence to determine the suitability of FeNO testing for children younger than 5 years.
- 6.4 The Committee discussed the lack of gold standard for asthma diagnosis. It heard from the clinical specialists that there is no single clinical definition of asthma and that the diagnosis is based on multiple factors, including the presence of symptoms and evidence of airway obstruction. It heard that high FeNO levels in people with symptoms suggestive of asthma, such as coughing and wheezing, may indicate that the patient has eosinophilic asthma, which may



be treated with inhaled corticosteroids. However, FeNO levels are not raised in all patients with asthma and, conversely, not all people with raised FeNO levels have asthma. The Committee further heard from a clinical specialist that, although it is generally accepted that FeNO levels correlate with eosinophilic airway inflammation, this effect may be stronger in some groups of patients than others and that there are other causes of inflammation. The Committee also heard that clinical practice varies and so the use of standard clinical practice as a reference standard is problematic. The Committee therefore concluded that the lack of gold standard for diagnosis, the complexity of diagnosis and the variation in clinical practice introduced an increased uncertainty in the assessment of the clinical validity of FeNO devices.

- 6.5 The Committee considered the diagnostic accuracy of FeNO testing. The Committee noted that the External Assessment Group had presented accuracy data for both children and adults against various reference standards and in different positions in the diagnostic pathway. It acknowledged that, because of the clinical heterogeneity of the data, a meta-analysis had not been performed and that estimates of specificity and sensitivity varied between studies. Overall, the Committee accepted the External Assessment Group's observation that the ranges of specificity were generally narrower than those for sensitivity, and that FeNO testing appeared to have a higher specificity than sensitivity. It heard from the clinical specialists that higher specificity would indicate that testing would be of greater use as a rule-in test; that is, patients testing positive are assumed to have asthma and patients testing negative have further tests for asthma. The Committee considered that the absence of a meta-analysis of accuracy meant that there was a greater uncertainty about the accuracy of FeNO devices in this assessment. Nevertheless, it was satisfied that the specificity of the devices was acceptable if they are used in a rule-in scenario.
- 6.6 The Committee considered FeNO cut-off values for guiding diagnosis of asthma in adults and children. The Committee heard from the External Assessment Group that cut-offs were generally not interchangeable between the FeNO devices, and that there appeared to be a high degree of heterogeneity between the studies. The Committee also heard from a clinical specialist that, in their experience, the devices generally produce different readings when used by the same patient. However, the differences appeared to be consistent. The Committee noted that the highest sum of sensitivity and specificity was obtained when the cut-offs ranged from 19–21 parts per billion (ppb) in children

and the highest sum of sensitivity and specificity was wider for adults (20–47 ppb). The Committee further noted that a higher cut-off was needed to optimise the specificity of the devices; a cut-off between 47 ppb and 76 ppb resulted in specificity of 88–100% in adults and a cut-off range of 30 ppb to 50 ppb resulted in specificity of 92–100% in children. The Committee was informed by clinical experts that cut-off values in the higher range would be preferred to reduce the rate of indeterminate results, and that the test could be used to rule in a diagnosis of asthma in people whose test is positive. The Committee concluded that cut-off values in the higher ranges should generally be used, and that cut-off values should be lower in children than adults.

- 6.7 The Committee considered the generalisability of the clinical evidence to the whole population both for diagnosing and managing asthma. The Committee acknowledged that the clinical evidence was heterogeneous in terms of clinical characteristics and results, and that studies were identified based on their similarity to UK practice and similarity to the subgroups of interest as defined in the protocol (that is, in people in whom the condition is difficult to diagnose, or the wider population of people presenting with symptoms of asthma). As such, no single study can be generalised to the whole population. The Committee therefore concluded that both the variation in UK clinical practice and the heterogeneity of studies included in the assessment would increase the uncertainty around the clinical benefits of measuring FeNO.
- 6.8 The Committee discussed the clinical evidence on the use of FeNO to guide asthma management in adults. The Committee noted that there was a statistically significant reduction in the meta-analysis for the composite outcome of any severity of exacerbations when FeNO measurement was used to guide management compared with treatment without FeNO measurement during the first 12 months of management. However, it acknowledged that the results from the individual studies were heterogeneous and that the meta-analysis did indicate a non-significant trend towards reduction in severe exacerbation rates. The Committee noted that the meta-analysis also showed a non-significant trend towards decreased inhaled corticosteroid use and considered that the effects of FeNO measurement on inhaled corticosteroid use were uncertain. It further noted that step-up and step-down protocols for inhaled corticosteroid use varied between studies and the effect of this on the outcomes was not known. The Committee concluded that FeNO-guided management was likely to reduce exacerbation rates in adults, but the extent

and duration of this effect was uncertain.

- 6.9 The Committee discussed the additional meta-analysis, performed by the External Assessment Group, which incorporated the more recent Honkoop et al. study (2013). It recognised that the addition of this study provided some further support that severe exacerbations could be reduced when FeNO measurement was added to asthma management. However, because the External Assessment Group had been unable to calculate accurate error rates for outcomes, the Committee was still uncertain whether this effect was statistically significant. The Committee therefore concluded that the Honkoop et al. study appeared to lend weight to the assumption that FeNO-guided management was effective, but was unable to establish whether this was statistically significant.
- 6.10 The Committee then discussed the clinical results for FeNO-guided management in children with asthma. As with the studies in adults, those in children appeared to have variations in design, including in the step-up and step-down protocols, medications and inclusion criteria. The Committee noted that all studies reported a decrease in exacerbations in the intervention arm, but only 1 reported a statistically significant reduction. It also noted that there was a greater uncertainty around whether inhaled corticosteroid use went up or down when FeNO measurement was added to asthma management. On balance, the Committee concluded that FeNO-guided management in children is likely to result in reduced exacerbation rates, but that the extent and duration of this effect is still uncertain. The Committee further concluded that the effect of FeNO-guided management on inhaled corticosteroid use is uncertain and recommended that further evidence is generated to establish its benefits.
- 6.11 The Committee discussed the role of measuring FeNO in diagnosing and managing asthma in children and adults. It heard from the clinical specialists that diagnosis of asthma needs consideration of many different elements, including symptoms, response to treatment and physiological testing. Given the complexities of diagnosis, the Committee considered that FeNO testing would not be able to replace current practice for diagnosis. The Committee concluded that measuring FeNO had not been shown to be able to reliably replace other tests and clinical observations, and therefore should be used as an add-on to current clinical diagnosis and management in people with asthma.
- 6.12 The Committee discussed the additional benefits of measuring FeNO in the

diagnosis and management of asthma. It heard from a patient expert that an accurate diagnosis of asthma can sometimes take many years, resulting in less than optimal treatment, which can have a direct impact on health. The Committee also heard from a patient expert that FeNO-guided management could result in patients better understanding their own condition and disease progression, which could reduce hospitalisations and improve patient experience. The Committee also considered the effect that measuring FeNO could have on adherence to medication. The Committee was informed by a clinical specialist that approximately 30% of people do not take their medication as prescribed. The clinical specialist indicated that studies have shown that FeNO is a useful marker for medicine adherence and that FeNO devices could be a useful tool for doctors to improve concordance, by which the patient and clinicians make decisions together about the treatment. The Committee concluded that FeNO testing could potentially enable patients and doctors to improve treatment concordance in patients who are on medications for asthma.

- 6.13 The Committee considered the areas of uncertainty in the economic models produced by the External Assessment Group for diagnosing and managing asthma. The Committee noted that the diagnostic models were sensitive to: assumptions about the length of time needed to resolve misdiagnoses; assumptions about health losses incurred by patients who have false-negative results; the costs of asthma management; and the use of rule-in and rule-out diagnostic decision rules. The Committee considered the assumptions made in the management model, in which it noted that the results in both the children and adult subgroups were particularly sensitive to: assumptions about changes in inhaled corticosteroid use over time; the annual number of nurse visits for FeNO measurement; and the length of time FeNO measurement was assumed to impact on exacerbation rates and inhaled corticosteroid use. The Committee concluded that both models for diagnosis and management were subject to considerable uncertainty, and therefore the results should be interpreted with caution.
- 6.14 The Committee discussed the results from the base-case analysis for the use of FeNO testing in diagnosis. It noted that, although the methacholine challenge test produced the most quality-adjusted life years (QALYs), the incremental cost-effectiveness ratio (ICER) was very high at £1.25 million per QALY gained when compared with FeNO testing plus bronchodilator reversibility. The Committee also noted that the difference in the health benefit for methacholine

challenge test compared with FeNO testing plus bronchodilator reversibility was estimated to be very small (0.0005 QALYs) and that costs were considerably lower for FeNO testing plus bronchodilator reversibility. Given that FeNO testing plus bronchodilator reversibility dominated the other tests, the Committee concluded that FeNO testing plus bronchodilator reversibility testing in adults and children delivered equal or greater QALYs at a lower ICER than other tests. Moreover, the Committee noted that the use of FeNO testing in conjunction with existing tests is more cost-effective than when the existing tests are used alone. The Committee therefore recommended FeNO testing as an option to help diagnose asthma in adults and children who, after initial clinical examination, are considered to have an intermediate probability of having asthma and where FeNO testing is intended to be done in combination with other diagnostic options according to the British guideline on the management of asthma (2012).

- 6.15 The Committee then discussed the results from the base-case analysis for asthma management in children. It noted that, for base-case results, the External Assessment Group had used 2 studies, Szeffler et al. (2008) and Pijnenburg et al. (2005), to inform the clinical effectiveness, and the ICER was £45,200 per QALY gained. The Committee then discussed the sensitivity analyses for management in children and noted that, when the analysis was based on Pijnenburg et al., a more favourable ICER of £19,000 per QALY gained was obtained. It also noted that, when it was assumed that FeNO measurement impacts for a shorter length of time on exacerbations and inhaled corticosteroid use, FeNO measurement plus management as recommended in the British guideline on the management of asthma (2012), hereafter referred to as the 'British guideline', dominated management by the British guideline use alone for up to 4 years. It also noted that the ICER was £7600 per QALY gained for 5 years and £27,700 per QALY gained for 10 years. The Committee assumed that shorter duration of up to 10 years, rather than lifetime duration, was a more reasonable assumption, given that children would not be expected to remain in the child-model for the rest of their lifetime. Moreover, the Committee heard from the External Assessment Group that the Szeffler et al. study included patients with uncontrolled asthma, and the study protocol did not allow therapy to be stepped down on the basis of low FeNO levels. The Committee considered that, in clinical practice, it was unlikely that the assumption of higher inhaled corticosteroid use throughout the time horizon with FeNO measurement would be seen, and therefore preferred the sensitivity

analysis based on the Pijnenburg et al. study over the base-case analysis.

Considering the combined shorter duration of impact of FeNO measurement and analysis based on the Pijnenburg et al. study, the Committee concluded that the most plausible ICER for management in children was likely to be lower than £19,000 per QALY gained.

6.16 The Committee discussed the results from the base-case analysis for asthma management in adults. It noted that the ICER for FeNO measurement plus the British guideline compared with the British guideline alone was £2100 per QALY gained. The Committee considered that, although there were uncertainties relating to this estimate, this ICER was low and therefore the use of FeNO measurement for asthma management in adults was likely to be cost effective. The Committee therefore accepted the base-case results for adults.

6.17 The Committee then discussed its recommendation for the use of FeNO measurement in asthma management in children and adults. The Committee heard from clinical specialists that there was considerable uncertainty around the use of stepping-up and stepping-down protocols for inhaled corticosteroid use, and that the External Assessment Groups' review had not conclusively demonstrated that FeNO measurement would be effective and safe for guiding the stepping down of inhaled corticosteroids. The Committee expressed concerns about using FeNO measurement as a basis for stepping-down treatment and was not satisfied that the evidence was robust enough to show that the benefits out-weighed the potential harms of under treatment. The Committee therefore concluded that FeNO measurement should not be recommended to help with stepping down inhaled corticosteroid use in adults or children whose asthma is well managed. However, it considered FeNO measurement to be cost and clinically effective when used as an option to support symptomatic asthma management in people using inhaled corticosteroids.

6.18 The Committee discussed the evidence in the subgroups defined in the scope for this assessment, (pregnant women, older people, people who smoke and those who have been exposed to tobacco smoke). The Committee heard from the External Assessment Group that there is little robust evidence for most of these groups (study designs were generally of lower quality), which could lead to biased results. It noted that randomised controlled trial evidence shows that measuring FeNO is at least as useful during pregnancy as it is for the general

population, but it appears likely that FeNO is a less reliable indicator of airway inflammation in older people. The Committee therefore concluded that, in view of the limited evidence, it was unable to provide any specific recommendations for the subgroups defined in the scope.

## 7 Recommendations for further research

- 7.1 The Committee discussed the potential for future research. The Committee accepted that there is a need to further establish the accuracy of current practice in diagnosing asthma and the incremental accuracy associated with the addition of FeNO testing.
- 7.2 The Committee also considered the role of FeNO measurement in asthma management. It accepted that currently available evidence on the use of FeNO measurement in asthma management is unclear on whether benefits of treatment are maintained long-term. The Committee concluded that long-term studies following patients for several years could address this gap.
- 7.3 The Committee also considered the role of FeNO in guiding inhaled corticosteroid dosing through stepping-up and stepping-down protocols. It accepted there is a need for more evidence on which protocols offer the safest and most optimal asthma management when used in UK clinical practice. Therefore, further studies are recommended, with consideration for the different protocols and cut-off points that may be necessary in different populations.



## 8 Implementation

- 8.1 NICE has developed [tools](#), in association with relevant stakeholders, to help organisations put this guidance into practice.
- 8.2 NICE will support this guidance with a range of activities to promote the recommendations for further research. This will include incorporating the research recommendations in [section 7](#) into the [NICE guidance research recommendations database](#) and highlighting these recommendations to public research bodies. The research proposed will also be put forward to NICE's Medical Technologies Evaluation Programme research facilitation team for consideration of the development of specific research protocols.

## 9 Diagnostics Advisory Committee members and NICE project team

### *Diagnostics Advisory Committee*

The Diagnostics Advisory Committee is an independent committee consisting of 22 standing members and additional specialist members. A list of the Committee members who participated in this assessment appears below.

#### **Standing Committee members**

##### **Professor Ron Akehurst**

Professor in Health Economics, School of Health and Related Research (SchARR), University of Sheffield

##### **Dr Trevor Cole**

Consultant Clinical and Cancer Geneticist, Birmingham Women's Hospital

##### **Professor Paul Collinson**

Consultant Chemical Pathologist and Professor of Cardiovascular Biomarkers, St George's Hospital

##### **Dr Sue Crawford**

General Practitioner (GP) Principal, Chillington Health Centre

##### **Professor Ian A Cree**

Senior Clinical Advisor, NIHR Evaluation Trials and Studies Coordinating Centre, University of Southampton

##### **Professor Erika Denton**

National Clinical Director for Imaging, NHS England, Honorary Professor of Radiology, University of East Anglia and Norfolk and Norwich University Hospital

##### **Dr Steve Edwards**

Head of Health Technology Assessment, BMJ Evidence Centre

##### **Mr David Evans**

Lay member, Safety Engineer and Occupational Hygienist

##### **Dr Simon Fleming**

Consultant in Clinical Biochemistry and Metabolic Medicine, Royal Cornwall Hospital

**Professor Chris Hyde**

Professor of Public Health and Clinical Epidemiology, Peninsula Technology Assessment Group (PenTAG)

**Professor Noor Kalsheker**

Professor of Clinical Chemistry, University of Nottingham

**Dr Mark Kroese**

Vice Chair, Diagnostics Advisory Committee and Consultant in Public Health Medicine, PHG Foundation, Cambridge and UK Genetic Testing Network

**Dr Peter Naylor**

General Practitioner (GP), Chair Wirral Health Commissioning Consortia

**Professor Adrian Newland**

Chair, Diagnostics Advisory Committee

**Dr Richard Nicholas**

Consultant Neurologist; Honorary Senior Lecturer, Heatherwood and Wexham Park Hospitals

**Dr Gail Norbury**

Consultant Clinical Scientist, Guys Hospital

**Dr Diego Ossa**

Director of Market Access Europe, Novartis Molecular Diagnostics

**Mr Stuart Saw**

Director of Finance, North East London and the City PCTs

**Professor Mark Sculpher**

Professor of Health Economics at the Centre for Health Economics, University of York

**Dr Steve Thomas**

Consultant Vascular and Cardiac Radiologist at Sheffield Teaching Hospitals Foundation Trust

**Mr Paul Weinberger**

CEO, DiaSolve Ltd, London

**Mr Christopher Wiltsher**

Lay member

### **Specialist Committee members**

**Professor Hasan Arshad**

Professor of Allergy and Clinical Immunology and Consultant Physician, Southampton General Hospital

**Dr Clifford Godley**

General Practitioner (GP), Strathaven Health Centre

**Dr John White**

Consultant Physician, Respirator Medicine, York General Hospital

**Mrs Kim Price**

Lay member

### ***NICE project team***

Each diagnostics assessment is assigned to a team consisting of a Technical Analyst (who acts as the topic lead), a Technical Adviser and a Project Manager.

**Farouk Saeed**

Topic Lead

**Dr Pall Jonsson**

Technical Adviser

**Robert Fernley**

Project Manager

## 10 Sources of evidence considered by the Committee

The diagnostics assessment report for this assessment was prepared by the School of Health and Related Research (SchARR), University of Sheffield:

- Harnan S, Tappenden P, Essat M et al. Measurement of exhaled nitric oxide concentration in asthma: NIOX MINO, NIOX VERO and NObreath. August 2013

### *Registered stakeholders*

The following organisations accepted the invitation to participate in this assessment as stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report and the diagnostics consultation document.

### **Manufacturers/sponsors:**

- Aerocrine Ltd
- Bedfont Scientific Ltd
- Intermedical UK Ltd

### **Professional/specialist and patient/carer groups:**

- Association of Respiratory Nurse Specialists (ARNS)
- Asthma UK
- Department of Health
- Healthcare Improvement Scotland
- National Clinical Guidelines Centre
- NHS Lanarkshire
- NHS England
- Primary Care Respiratory Society
- Research in Real Life Ltd
- Royal Aberdeen Children's Hospital

- Royal College of Nursing
- Royal College of Pathologists
- Welsh Government

ISBN: 978-1-4731-0533-1

## *Accreditation*

