NICE National Institute for Health and Care Excellence

**DIAGNOSTICS ASSESSMENT PROGRAMME**

**Measuring fractional exhaled nitric oxide concentration in asthma - NIOX MINO, NIOX VERO and NObreath**

**Diagnostics Consultation Document – Comments**

**Diagnostics Advisory Committee date: 11 December 2013**

| Comment number | Name and organisation | Section number | Comment | NICE response |
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| 1. | Consultee 1, NHS Professional | Section 1 | I agree with these recommendations. | Thank you for your comment. |
| 2. | Consultee 2, Royal College of Pathologists | Section 1 | I agree that the measurement of FeNO by one of the listed instruments is potentially a good addition to the current diagnostic toolkit for asthma, especially in directing and monitoring treatment. There needs to be further comparison between the analysers plus any new FeNO measuring hardware that becomes available. | Thank you for your comment. The Committee considered the 3 devices in this assessment to be broadly equivalent based on the available evidence. The committee also agreed that standardisation of FeNO devices should be encouraged. See section 6.2 of the diagnostics guidance document.<br><br>NICE normally reviews guidance 3 years after publication and may update the guidance if significant new evidence becomes available. Please see the Diagnostics Programme Manual for further details. |
| 3. | Consultee 3, Royal College of Physicians | Section 1 | The Royal College of Physicians is grateful for the opportunity to comment. We wish to endorse the comments submitted by the British Thoracic Society (BTS). | Thank you for your comment. |
| 4. | Consultee 4, NHS Professional | Section 1 | I agree that the measurement of FeNO by one of the listed instruments is potentially a good addition to the current diagnostic toolkit for asthma, especially in | Please see response to comment number 2. |

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| | | | directing and monitoring treatment. There needs to be further comparison between the analysers plus any new FeNO measuring hardware that becomes available. | |
| 5. | Consultee 5, NHS Professional | Section 1 | I agree with the first bullet point statement. With respect to the 2nd bullet point statement, bronchodilator reversibility testing is only possible where airways obstruction exists; this is frequently not the case in suspected asthma (which is a variable disease). FENO testing can be performed even when obstruction is not present, as the airways inflammation is persistent, so can be used widely and simply.<br><br>With regard to the statement that asthma can exist with a normal FENO- current evidence suggests that while this may be true in rare cases, it is unlikely to be corticosteroid responsive and so even in this situation, FENO gives important information. | Thank you for your comments.<br><br>In its preliminary recommendations, the Committee recommended the use of FeNO to help with diagnosis in situations where bronchodilator reversibility is intended. This was based on the economic analysis which indicated that this scenario was the most cost effective.<br><br>In response to consultees' comments the Committee reconsidered the recommendation, and in view of the general nature of the economic model and that FeNO testing appeared to be cost effective when used in combination with a range of diagnostic options, the Committee concluded that FeNO testing should be recommended as an option to help with diagnosing asthma where FeNO testing is intended in combination with other diagnostic options according to the British guideline on the management of asthma. Please see section 1.1 of the diagnostics guidance document. |
| 6. | Consultee 6, The British Thoracic Society | Section 1 | The British Thoracic Society supports the provisional recommendations but highlights a number of issues in the responses below.<br><br>Bronchodilator reversibility testing only applies to subjects with airflow obstruction as BTS/SIGN | Thank you for your comments.<br><br>On the issue of bronchodilator reversibility, please see response to comment No.5 above. |

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| | | | Guidelines so the inference here is that this test will not be used in subjects with normal lung function. This is a a population where this test may have value, because in subjects with airflow obstruction, particularly children and non-smoking adults, the presence of airflow limitation substantially increases the probability of asthma with a compatible history.<br><br>The wording show remove diagnosis of asthma. This test does not diagnose asthma, but identifies a population of patients, who when they present with respiratory symptoms (particularly cough and wheeze) are likely to respond to inhaled steroids. A negative test does NOT exclude asthma and a positive test does NOT diagnose asthma. | Recommendation 1.1 acknowledges that a negative test does not exclude asthma and encourages further investigations. The Committee heard from 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. The recommendation states that FeNO testing is recommended to help with the diagnosis. "Diagnosis", in this case refers to the whole diagnostic pathway and includes all the test and stages included in asthma diagnosis. Please see sections 1.1 and 6.4 of the diagnostics guidance document. |
| 7. | Consultee 7, Astra Zeneca | Section 1 | It may be helpful to include any information that describes how FeNO levels change on ICS therapy to help guide physicians on how cutoffs change on ICS therapy. | Thank you for your comment.<br>Sections 6.6, 6.8 and 6.10 detail the Committees considerations regarding cut off points and use of inhaled corticosteroids.<br>The Committee accepted there is a need for more evidence on stepping-up and stepping-down protocols and recommended further studies in this area. Please see section 7.3 of the diagnostic guidance document. |

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| 8. | Consultee 2, Royal College of Pathologists | Section 1 | No comment. | |
| 9. | Consultee 9, Patient | Section 1 | No comment. | |
| 10. | Consultee 1 ,NHS Professional | Section 2 | The devices are appropriate and reflect practise across most hospitals. | Thank you for your comment. |
| 11. | Consultee 2, Royal College of Pathologists | Section 2 | No comment. | |
| 12. | Consultee 5, NHS Professional | Section 2 | I agree with these statements. | Thank you for your comment. |
| 13. | Consultee 6, The British Thoracic Society | Section 2 | The difficulty of evaluating the technologies in the context of diagnosing asthma should be recognised as this test only examines a single facet of asthma. See comments above on response to inhaled steroid. | Thank you for your comment. Please refer to section 6 of the diagnostic guidance document for more detail on the Committee's consideration of the uncertainties in this assessment. |
| 14. | Consultee 9, Patient | Section 2 | No comment. | |
| 15. | Consultee 1, NHS Professional | Section 3 | 3.3: I would propose to say that asthma "It is characterised by REVERSIBLE airflow obstruction and increased responsiveness. | Thank you for your comment. Section 3.3 has been amended. |
| 16. | Consultee 2, Royal College of Pathologists | Section 3 | Is there any inherent risk in the use of the methacholine or histamine challenge tests or with exercise testing? Might the measurement of FeNO help reduce the need for these dynamic function tests and, hence, any risk from them? | Thank you for your comment. Bronchial challenge tests are considered to be physically demanding for some patients and may also have a risk of bringing about asthma attacks, which is why these tests are done in secondary care. The External Assessment Group considered that FeNO testing may have the ability to prevent expensive secondary care visits if used in |

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| | | | | primary care and the cost effectiveness analysis explored this scenario. |
| 17. | Consultee 4, NHS Professional | Section 3 | Is there any inherent risk in the use of the methacholine or histamine challenge tests or with exercise testing? Might the measurement of FeNO help reduce the need for these dynamic function tests and, hence, any risk from them? | Thank you for your comment. Please see response to comment No. 16. |
| 18. | Consultee 5, NHS Professional | Section 3 | I agree with this summary, but would add some important caveats:<br><br>1: There is growing evidence of widespread mis-diagnosis in asthma, with up to 25% of people in the community labelled and treated for asthma failing to have objective evidence of the condition<br><br>2- Asthma control remains poor in the community; surveys have repeated shown that the majority of people with asthma suffer potentially avoidable symptoms and quality of life impairment<br><br>3- The aims of asthma management are control of current disease impact, and reduction of future risk. The evidence suggests that FENO is a good test in quantifying future risk (ofexacerbation, hospitalisation etc.) | Thank you for your comments.<br><br>The Committee acknowledged the benefits FeNO could have in the diagnosis and management of asthma. Please see section 6.12 of the diagnostic guidance document.<br><br>The Committee also examined the economic evidence for FeNO testing and monitoring which was presented in the External Assessment Group's systematic review of evidence and its economic model. Please see section 5 of the diagnostics guidance document and the External Assessment Group's report for full details of the systematic review of effectiveness of FeNO for management of asthma symptoms. |
| 19. | Consultee 6, The British Thoracic Society | Section 3 | An isolated FeNO is not of value in identifying non-adherence in "difficult asthma", which is often the population where non-adherence is a relevant clinical problem and where an "test" for non-adherence is likely to be applied (McNicholl et al - The utility of fractional exhaled nitric oxide suppression in the identification of non-adherence in difficult asthma. | Thank you for your comment. Section 6.12 of the diagnostic guidance document details the Committee's consideration on the issue of adherence. The Committee heard from patient and clinical experts that FeNO testing could potentially enable patients and doctors to improve treatment concordance in patients who |

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| | | | Am J Respir Crit Care Med. 2012 Dec 1;186(11):1102-8)<br><br>The use of FeNO as a test on non-adherence needs to be more rigorously tested in a milder asthmatic population and in children and importantly at an individual patient level<br><br>Assessment of adherence is complex and prescription filling, and other surrogate measures, which should be simple and are already recommended in the Guidelines are poorly utilised it is very important that the message that measuring this test is a simple test to identify non-adherence is removed.<br><br>The paediatric expertise in the Asthma SAG expressed some queries about the utility in children. | are on medications for asthma. |
| 20. | Consultee 7, Astra Zeneca | Section 3 | Section 3.4 Not all patients with eosinophilic asthma respond to steroids.<br>Suggest modifying the wording as follows:<br>”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. Some patients with eosinophilic asthma may respond to treatment with corticosteroids, while patients with neutrophilic asthma generally do not. “<br>It is important to note that not all patients with eosinophilic asthma will respond to treatment with | Thank you for your comment. Section 3.4 has been changed to indicate that eosinophilic asthma does not always respond to treatment with corticosteroids. |

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| | | | corticosteroids. | |
| 21. h | Consultee 9, Patient | Section 3 | Agree these are the most appropriate evidence based test for diagnosing and managing asthma. | Thank you for your comment. |
| 22. | Consultee 1, NHS Professional | Section 4 | I would put in a sentence to say that children 6 years and under are rarely able to perform the test. (Essentially the test is more difficult than spirometry). | Thank you for your comment. The Committee heard from both manufacturers that the minimum recommended age for using FeNO monitors 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 make recommendations for children younger than 5 years. Please see section 6.3 of the diagnostic guidance document. |
| 23. | Consultee 2, Royal College of Pathologists | Section 4 | There may be an issue with evaluating the NIOX MINO if it is to be superseded to the VERO model and comparison work needs to be done against the new model and the commercial data from NIOX made available in the public domain if possible. There is also need to have side by side comparison studies done between these models (plus any other that come to the market in the interim). Finally, there ought to be some discussion on the way results are produced (eg electronically or as paper print-outs) and how these will be included in the patient's records, especially if the result is part of a diagnostic workup which defines the patient as having a lifelong condition like asthma. | Thank you for your comment. Section 6.2 details the committee's consideration on the equivalence of the devices. The committee was aware of the uncertainty of the available evidence. The Committee concluded that the devices can be considered to be broadly equivalent but thought that standardisation should be encouraged. |
| 24. | Consultee 4, NHS Professional | Section 4 | There may be an issue with evaluating the NIOX MINO if it is to be superseded to the VERO model and comparison work needs to be done against the | Thank you for your comment. Please see response to comment 23. |

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| | | | new model and the commercial data from NIOX made available in the public domain if possible. There is also need to be side by side comparison studies done between these models (plus any other that come to the market in the interim). Finally, there ought to be some discussion on the way results are produced (eg electronically, as paper print-outs) and how these will be included in the patient's records, especially if the result is part of a diagnostic workup which defines the patient as having a lifelong condition like asthma. | |
| 25. | Consultee 5, NHS Professional | Section 4 | I agree with this summary, but it is worth pointing out that access to BHR testing does not exist for GPs. It is a labour intensive test that can only be done in a hospital setting at present. FENO is a simple test that can be safely performed in the community. | Thank you for your comment. |
| 26. | Consultee 6, The British Thoracic Society | Section 4 | We note that the diagnostic section seems to miss the core issue that this is not so much about diagnosing asthma but abut identifying an airway signal in a patient with respiratory symptoms, which is likely to responsive to inhaled steroids.<br><br>We agree that FeNO is useful in helping make decisions on INITAITION of inhaled steroid treatment but heterogeneity in cut-off values may cause problems.<br><br>We note that the monitoring section seems to over-interpret the available evidence and does not make a distinction between different severities of asthma. We accept that in some of the prior negative clinical trials using FeNO to titrate inhaled steroids, one of | Thank you for your comments. Section 4.1 of the diagnostic guidance document states that FeNO testing has the aim of identifying people whose airway inflammation is likely to respond to treatment with inhaled corticosteroids. Section 6 details the Committees consideration on the uncertainties relating to asthma diagnosis, exacerbation rates and secondary outcomes. The Committee also 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. |

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| | | | the issues may have been thresholds used but the evidence that FeNO can be used to titrate inhaled steroid treatment is not currently in existence - a meta-analysis concluded (Petsky HL et al. A systematic review and meta-analysis (Tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils. Thorax. 2012 Mar;67(3):199-208) FeNO studies delivered no exacerbation benefit and no consistent benefit on secondary outcomes. | |
| 27. | Consultee 8, Aerocrine | Section 4 | In addition, NIOX MINO follows ERS/ATS recommendations with internal quality control that disqualify measurements that are not within the quality assured limits.<br><br>NIOX VERO is also service and calibration free for its 5 year life.<br><br>As per the official user manual the NOBreath device requires annual service and calibration by the manufacturer along with an additional monthly calibration/zeroing and does not follow the ERS/ATS recommendations from 2005 of a 10 second exhalation in adults. | Thank you for your comments. Section 4 of the diagnostic guidance document has been amended to reflect NIOX VERO is service-free and calibration-free. |
| 28. | Consultee 9, Patient | Section 4 | No comment. | |
| 29. | Consultee 2, Royal College of Pathologists | Section 5 | How big are the studies mentioned in the reviews where FeNO cut-off levels are quoted? It seems there is a dearth of good quality evidence to firmly support the use of FeNO in diagnosis and treatment of asthma. | Thank you for your comment. The diagnostics guidance document is only intended to give a brief overview of the studies identified by the External Assessment Group. For further details, please see the Diagnostics Assessment Report which is available on the NICE website. The |

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| | | | | Committee's consideration of uncertainty relating to the use of FeNO in diagnosis has been detailed in section 6 of the diagnostics guidance document. |
| 30. | Consultee 4, NHS Professional | Section 5 | How big are the studies mentioned in the reviews where FeNO cut-off levels are quoted? It seems there is a dearth of good quality evidence to firmly support the use of FeNO in diagnosis and treatment of asthma. | Please see response to comment 29. |
| 31. | Consultee 5, NHS Professional | Section 5 | 5.18: In my experience FENO is a good 'rule-out' test; a reading of below 20 in a patient with respiratory symptoms indicates to me that this person is most unlikely indeed to have corticosteroid responsive airways disease.<br><br>Even if the patient does have physiological evidence of asthma, it is likely to be a particular phenotype of asthma ('neutrophilic' asthma) unresponsive to steroids. The issue of phenotyping is important.<br><br>5.42- a good summary. When assessing outcomes, it is important also to assess steroid load- ie is the beneficial effect related just to more steroids or to better use and targeting of steroids. For me the evidence points to the latter but more and better studies are needed. The best algorythm and cut-offs are still being defined, but the Gibson study of pregnant women in the Lancet provides the best current model for operationalising the information. | Thank you for your comments. The recommendation in section 1.1 does not stipulate whether FeNO should be used as a rule-in or rule-out test. However in its deliberation, 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 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. Please see section 6.6 of the diagnostics guidance document.<br><br>The External Assessment Group's systematic review of diagnostic accuracy contains further details of the accuracy across the studies. Please see Table 83 of the diagnostics assessment report available on the NICE |

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| | | | 5.58: I'm not sure I agree with the estimate that a false positive diagnosis will be revised after 18 months- the current data suggest that it may never be revised for many, and result in ongoing misdiagnosis and inappropriate, ineffective treatment.<br><br>5.63: The modelling involves many assumptions, but is OK for me. | website for a summary of the results. :<br><br>The External Assessment Group considered the assumptions regarding time it takes to resolve false-negative and false-positive diagnoses to be highly uncertain and tested them in sensitivity analyses. Please see the diagnostics assessment report for further details.<br><br>Thank you for comment. |
| 32. | Consultee 6, The British Thoracic Society | Section 5 | We agree with the points made in relation to challenge testing vs inflammometry and we would place more utility in a negative challenge test than a normal FeNO value in the exclusion of a diagnosis of asthma (see comments in section 1 above) .The negative predictive value of a negative challenge test in the exclusion of asthma has been better characterised and evaluated over many years. | Thank you for your comment. 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 noted that a higher cut-off was needed to optimise the specificity of the devices. Please see section 6.6 of the diagnostics guidance document.<br>The recommendation encourages the use of FeNO testing in conjunction with other diagnostic options according to the British guideline on the management of asthma |
| 33. | Consultee 8, Aerocrine | Section 5 | FeNO measurement in stationary chemiluminescence devices does not guarantee a correct value, since it will be dependent on the calibration procedure performed on site. NIOX/NIOX Flex is the only chemiluminscence device where the whole system, including the calibration procedure, is CE-marked. Only one additional device has CE | Thank you for your comments. The External Assessment Group undertook a review of equivalence to ascertain whether existing diagnostic and management studies performed using chemiluminescent devices could be used to inform the appraisal. Any equivalence study relating to devices used in management and |

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| | | | marked components (Eco Medics) but the CE mark does not cover the overall system specification. Therefore, comparison with chemiluminescence devices other than NIOX/NIOX Flex, several of them no longer on the market, should be considered with caution. Overall, the DAC considers many old studies of instrument comparison that should be considered obsolete due to the rapid technical development in the field.<br><br>Most of the differences demonstrated by the studies analysed are within the specifications for the devices. Even if the data for some parts are statistical significant, the difference is within the specified accuracy of the device.<br><br>The optimal cut-off is not interesting to know for biomarkers, since this cut-off will rarely be useful for "rule-in" or "rule-out" purposes. Rather, separate cut-offs with high sensitivity and high specificity, respectively, should be sought for. Such cut-offs show more narrow ranges for sensitivity and specificity, respectively. | diagnostic studies was deemed relevant, regardless of age and current availability. There were also diagnostic and management studies where it is unclear which device was used. The inclusion of all chemiluminescent devices in the review is therefore valid to account for this.<br><br>The Committee noted that that some differences were observed in the test results, however there was generally a good correlation with results from other chemiluminescence devices. The Committee noted apparent poorer equivalence between devices in some circumstances and this varied between studies. However, the Committee was mindful there is no commonly accepted definition of clinically acceptable differences in FeNO measurements and concluded that the 3 devices could, on balance, be considered to be broadly equivalent.<br><br>Please see section 6 6 for the Committee's consideration of cut-off values. The recommendation in section 1.1 does not stipulate whether FeNO should be used as a rule-in or rule-out test. However in its deliberation, 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 noted that a higher cut- |

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| | | | | 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. Please see section 6.6 of the diagnostics guidance document. |
| | | | The NICE DAC suggests that FeNO may be more reliable as a "rule-in" than a "rule-out" test. This is in conflict with what has been suggested by international experts in the field (Dweik et al Am J Respir Crit Care Med 2011, Taylor J Breath Res 2012). The key issue here is the choice of reference standard. FeNO is a marker of Th2-driven, corticosteroid-sensitive inflammation, but an asthma diagnosis can be made based on a positive bronchodilator response test or methacholine challenge test. The latter tests may be positive also in e g COPD. Maybe it should be reconsidered what is important for the patient, namely what treatment will be effective and not just giving the patient a diagnostic label. When corticosteroid response (or indirect challenges such as mannitol) are used as reference standard, FeNO measurement generally show high sensitivity as well. Hence, FeNO is also a useful test for identifying patients who would not benefit from ICS treatment, thus avoiding unnecessary treatment. | Please see response to comment 31 on the issue of using FeNO as a rule-in or rule-out test. With regard to the studies you referred to, the external assessment group responded as follows:<br>• *Dweik et al Am J Respir Crit Care Med 2011 recommends >50ppb for ruling-in and <25ppb for ruling-out eosinophilic inflammation and likelihood of ICS responsiveness, based on a moderate quality of evidence. This does not relate to a diagnosis of asthma, and does in fact incorporate both a rule-in and rule-out scenario at the upper and lower ends of the FeNO spectrum respectively. Taylor 2012 recommends a rule-out scenario. However, this study is not a systematic review, and the recommendation is based on a very limited set of studies which have been selected without a systematic search, or pre-set inclusion criteria. In this sense, our assessment is more robust. We have included over 20 cohort studies, identified through systematic methods. Taylor includes* |

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| | | | | *10 studies, 3 of which are included in our review (Smith et al 2004, Smith et al 2005, Hahn et al 2007). The remaining seven were excluded from our review for the following reasons:*<br>• *Kowal et al 2009 – case control design*<br>• *Chatkin et al 1999 case-control design and wrong flow rate*<br>• *Oh 2008 - is listed as an asthma study in Taylor 2012, but in fact diagnoses non-asthmatic eosinophilic bronchitis;*<br>• *Dummer et al 2009 - diagnoses COPD*<br>• *Akamatsu et al 2011 - diagnoses COPD*<br>• *Perez de Llano et al 2010 - recruited patients who were already diagnosed with asthma*<br>• *Neurohr et al 2011 - diagnoses bronchiolitis obliterans Syndrome not asthma* |
| | | | This conclusion is based on one abstract. Two recent original articles show that FeNO can be used in elderly patients and correlate with asthma control, airway hyperresponsiveness and sputum eosinophil count, just as in younger patients (Porsbjerg et al Respirol 2013, Hsu et al Allergy Asthma Proc 2013).<br><br>The study of Syk et al is indicated to be of highest risk of bias. This is, according to the authors, not a fair judgement. Regarding "Attrition bias": The dropout rate was low also in Syk et al, and the dropouts were thoroughly described (see Fig. 1, Table E2 and Table E3). Since differences between last and first visits were analysed, imputation could not be done. The rationale for this is thoroughly | The guidance does not indicate a maximum age for FeNO testing in older people. Please see section 1.1 of the diagnostic guidance document.<br><br>The External Assessment Group confirmed that the **attrition bias** has been scored poorly as there appears to be patient data missing from some time points in some analyses, and these |

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| | | | described and explained in the article. Regarding "Reporting bias": Severe exacerbations are presented, both in Fig. E4 (Time to first exacerbation) and Table 5 (proportion of patients with at least one severe exacerbation).<br><br>Syk et al did not report higher rates of oral corticosteroids (severe exacerbations) in the intervention arm as claimed by the External Assessment Group. Both the analyses presented in the article (see comment 9) were far from being statistically significant. The rate of severe exacerbations was not presented in the article but the authors judged that a third presentation, which was also far from being significant (p=0.601), would not add anything to the article. The rate of moderate exacerbations was reduced in the intervention arm, and this was highly significant (p=0.003). The External Assessment Group has had access to all these data.<br><br>The small difference in short-acting beta-2 agonist use seen in Syk et al was non-significant and no trend was indicated (see Results section). This means that all p-values were >0.10.<br><br>The report does not consider Peirsman et al Ped Pulm 2013 that was made available to the NICE as | are not described or corrected for. The External Assessment Group could not find any explanation of why imputation could not be done in the study, and cannot see why imputation could not have been performed, given there were multiple time points of measurement within the study. **Reporting bias** was scored poorly because a key outcome, severe exacerbations, has not been reported in full. This constitutes reporting bias, according to the Cochrane risk of bias scoring: "One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis"<br><br>The External Assessment Group were clear that this was not statistically significant – see page 166 of the diagnostics assessment report. Moderate exacerbations were also considered in the assessment report. The External Assessment Group could not find the P value 0.003 either in the manuscript draft or in the clarifications provided by Aerocrine. Severe exacerbations are a key modelling input, as it is these exacerbations that are associated with the greatest costs and health losses for patients, so their inclusion in the study report was key to the assessment.<br><br>The wording in section 5.42 of the diagnostic guidance document has been amended. |

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| | | | AIC.(now published online).<br><br>The cost analysis does not consider the fact that a reversibility test takes at least 15-20 min and must be performed by experienced nurses, while a FeNO measurement takes less than 5 min and can easily be performed by any trained healthcare professional, e. g the doctor during consultation time.<br>When comparing NIOX MINO/VERO with the NOBreath device, please bear in mind that NOBreath requires service and calibration which causes disrupted service and additional costs.<br><br>The expectation that the methacholine challenge test would produce the greatest QALY gain seems to be based on one small study only (Hunter et al Chest 2002). This is questionable since, in this study, asthmatics had been diagnosed by e g the methacholine challenge test. Instead, most QALY gain is expected to lie in the ability of a test to detect corticosteroid-responsive disease, and not only to set a diagnostic label, and the methacholine challenge test will suffer from false positives in this respect. Further, the risk and discomfort posed to the patient by this test is not considered, and the test is difficult to perform in children.<br><br>The full cost of the NOBreath test process has not been fully assessed as it is documented that to get a suitable test result from the NOBreath 3 acceptable consecutive tests need to be taken (minimum of 2 | Peirsman et al (2013) was included in the addendum produced by the EAG in response to the Stakeholder comments and was considered by the Committee. Please refer to the addendum documentation.<br><br>The costing assumptions were based on expert opinion. These assumptions were also peer reviewed by the specialist committee members. Maintenance costs are provided free of charge. The External Assessment Group felt that it is reasonable to assume a zero cost for disruption.<br><br>The scope relates to the diagnosis of asthma, and this is what the External Assessment Group has compared FeNO testing with. The Price model uses this same study.<br><br>The Committee was informed that a NObreath |

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| | | | minutes between test) and an average of the 3 calculated. The NIOX VERO and NIOX MINO require only one test for a quality assured reading. | mouthpiece could be used 3 times, and NObreath does not require maintenance after a certain number of tests. The true marginal per-test cost is an area of uncertainty. Different scenarios in which different costs are assumed were examined in the assessment report. |
| 34. | Consultee 9, Patient | Section 5 | In 5.60 how many routine visits to GP are included? Cost of managing exacerbations. Was there any literature on self-management? If I feel I am having an exacerbation I can ring the surgery, the GP who knows my condition will ring back, go through symptoms and leave a prescription for oral steroids, presumably cheaper than £43 quoted.<br>Results in adults 5.65. Using feno with British Guidelines seems staggeringly more expensive than just using the latter, even taking into account the possible benefits of fewer exacerbations and better control with feno + ICS The longer the regime the better the results in adults but 40 years seems a long time. Not sure with children whether cost effectiveness better if ICS and feno used for short time, or just considerably worse if used for a long time. | Thank you for your comment. The External Assessment Group assumed 4 FeNO visits per year. All other management costs are assumed to be the same for FeNO vs guidelines. The costs of managing exacerbations were based on assumptions from previous HTA reports and routine NHS costing sources. |
| 35. | Consultee 2, Royal College of Pathologists | Section 6 | The subject of heterogeneity of the available evidence is discussed extensively in this section which is something I feel, as representing the RCPath, to be the major obstacle to be overcome before FeNO measuring technology is integrated into any sort of pathway or guideline. | Thank you for your comment. |
| 36. | Consultee 4, NHS Professional | Section 6 | The subject of heterogeneity of the available evidence is discussed extensively in this section which is something I feel, as representing the | Thank you for your comment. |

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| | | | RCPath, to be the major obstacle to be overcome before FeNO measuring technology is integrated into any sort of pathway or guideline. | |
| 37. | Consultee 5, NHS Professional | Section 6 | 6.3 I agree with this assessment, and the lack of a 'gold standard'. The future 'stratified medicine' approach in asthma is likely to involve using biomarkers to define groups for particular therapeutic interventions- FENO fits well here, as it is better at defining steroid responsiveness than 'asthma'; the best treatment for asthma without raised feno is uncertain but almost certainly does not involve the current ICS-based treatment strategies in the guidelines.<br><br>6.11: the issue of FENO monitoring as a guide to non-adherence is important and under-researched; if a patient on ICS has a persising raised FENO, the explanations are either non-adherence (common) or steroid resistance (rare) | Thank you for your comment<br><br>The issue of non-adherence was considered by the Committee. Please see section 6.12 of the diagnostic guidance document. |
| 38. | Consultee 6, The British Thoracic Society | Section 6 | There seems little in the documentation recommending how and when to use the test. Multiple vs single measures? Where - Clinic / GP surgery vs physiology lab etc? | Thank you for your comment. NIC E will develop implementation tools, in association with relevant stakeholders, to help organisations put this guidance into practice. |
| 39. | Consultee 7, Astra Zeneca | Section 6 | Section 6.3. Suggest modifying the sentence to: ? wheezing, may indicate that the patient has eosinophilic asthma which may be treated with inhaled corticosteroids. | Thank you for your comment. The sentence has been modified. Please see section 6.4 of the diagnostic guidance document. |
| 40. | Consultee 9, Patient | Section 6 | 6.3 I agree with the Committee that the evidence would seem to suggest that there is uncertainty about measuring the validity of individual clinical devices. | Thank you for your comments.<br><br>The Committee deemed the evidence relating to |

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| | | | The evidence would also seem to suggest that the test are more useful for ruling in asthma, and that even if someone tested negatively for FeNO in diagnosing, this should only be an indicator to move onto other tests.<br>The case is made strongly to reach the conclusion in 6.6. That the variability in practice and the heterogeneity of studies would increase the uncertainty of the benefits of measuring Feno.<br>The evidence presented in 6.7 that although the use of FeNO in managing exacerbations in the first 12 months does suggest a reduction is not held up to be statistically significant. However from a patient point of view the comments in 6.11 should not be underestimated. Neither should those of the specialist who talked about non adherence to medication. If using FeNO in measuring and highlighting none adherence and that helps the physician and patient to sit down and talk together about concordance or lack of it, then it could save exacerbations, admissions to unscheduled care and morbidity, although admittedly there is a lack of research in this area<br>The evidence seems quite clear that using FeNO as a guide for stepping down ICS is not to be recommended. | stepping down inhaled corticosteroids on the basis of FeNO alone to be inconclusive. The Committee considered this to be a potential area for further research (see section 7.3 of the diagnostic guidance document). |
| 41. | Consultee 2, Royal College of Pathologists | Section 7 | No comment. | |
| 42. | Consultee 5, NHS Professional | Section 7 | I'd agree with these research needs. Pragmatic 'real-world' studies evaluation FENO-enhanced diagnostic strategies are needed, and are being worked up. | Thank you for your comment. |

| Comment number | Name and organisation | Section number | Comment | NICE response |
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| 43. | Consultee 9, Patient | Section 7 | No comment. | |
| 44. | Consultee 2, Royal College of Pathologists | Section 8 | No comment. | |
| 45. | Consultee 5, NHS Professional | Section 8 | It is vital that community/primary care based groups are involved in this, eg PCRS-UK. | Thank you for your comment. |
| 46. | Consultee 2, Royal College of Pathologists | Section 9 | No comment. | |