National Institute for Health and Clinical Excellence

Diagnostics Assessment Programme

Measurement of exhaled nitric oxide concentration in asthma; NIOX MINO and NObreath

Final scope

February 2013

1. Introduction

The Medical Technologies Advisory Committee identified NIOX MINO (Aerocrine Ltd.) as potentially suitable for evaluation by the Diagnostics Assessment Programme (DAP) on the basis of a briefing note. The technology measures levels of exhaled nitric oxide (ENO) with the aim to assist in the diagnosis, management and monitoring of asthma. The scope has been extended to include another similar test (the NObreath test, Bedfont Scientific Ltd.), and outlines the approach for assessing the clinical and cost effectiveness components for exhaled nitric oxide concentration in asthma in both primary and secondary care.

The scope has been compiled using a variety of sources, including the briefing note, information provided by manufacturers, a scoping literature review, the opinions of experts and attendees at the scoping workshop held on 7 February 2013 and input from assessment subgroup members. NICE has not carried out an independent evaluation of this information. Assumptions made in the scope will be verified in the assessment.

2. Description of the technology

This section describes the properties of the diagnostic technology based on Aerocrine's notification to NICE.

2.1. Purpose of the notified medical technology

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 that is associated pathologically by a thickening of the basement membrane zone.

The symptoms of eosinophilic asthma can be controlled with corticosteroids. In contrast, neutrophilic asthma generally does not respond to treatment with corticosteroids (Fahy, 2009). In humans, 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 (Dweik *et al,* 2011). Over the years, ENO has been proposed as a non-invasive marker of eosinophilic airway inflammation in asthma. ENO has been shown to be elevated in patients with eosinophilic asthma and effective treatment with corticosteroids reduces the level of ENO (Payne *et al,* 2001).

NIOX MINO 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 aid in the identification of patients whose airway inflammation will respond to treatment with inhaled corticosteroids. It can also be used to predict the onset of asthma symptoms or loss of asthma control and also to monitor compliance to corticosteroid therapy and the effectiveness of treatment.

2.2. Product properties

NIOX MINO determines ENO concentration in a breath sample. The device is small, hand-held and portable, and it can be used by both adults and children. It requires a 10 second exhalation of breath by the patient, at an exhalation pressure of 10 - 20 cm H_2O to maintain a fixed flow rate of 50±5 mL/s. The last 3 seconds of the 10 second exhalation is analysed by a calibrated electrochemical sensor, to give a definitive result in parts per billion. Clinical cut-off values can be applied to the ENO values to categorise readings as low, intermediate or high according to the reference ranges for age less than 12 years and 12 years or more (Aerocrine. ‘Guide to Interpretation of eNO Values’).

NIOX MINO is pre-calibrated and designed to ensure a service and calibration free system. It can be used as stand-alone or connected to a PC for monitoring with the NIOX MINO Data Management Program and for use with Electronic Medical Record systems.

NIOX MINO is CE-marked and was launched in the UK in November 2004. It is currently available in 8 GP surgeries and used in more than 90 hospitals across the UK.

The manufacturer claims that NIOX MINO is indicated for use as follows:

- To diagnose the specific type of airway inflammation to guide treatment
- To predict the onset of asthma symptoms or loss of asthma controls due to eosinophilic airway inflammation
- To monitor compliance to corticosteroid therapy and effectiveness of treatment (frequency of exacerbations)

2.3. Alternative technologies

NObreath (Bedfont Scientific Ltd.) is diagnostic monitoring device that measures ENO 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 requires 12 seconds of exhalation of breath in adults and 10 seconds in children.

NObreath weighs approximately 400g (including batteries). It has a battery life that lasts up to 120 tests. The device is CE marked.

3. Target conditions/indications

Scoping workshop attendees (including manufacturers and clinicians) suggested that exhaled nitric oxide has a potentially important role to play in the diagnosis, management and monitoring of people with asthma. Also, much of the data for exhaled nitric oxide has been generated in this disease area.

3.1. Asthma

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

Asthma usually develops in childhood but may start at any age. There is no cure for asthma, although people may experience long periods of remission. Poorly controlled asthma can have a significant impact on the quality of life of the affected person and their family. However, there may be variation in an individual's perception of the symptoms and how he or she adapts to the condition over time. Clinical measures such as lung function may not correlate with an individual's quality of life scores, but if asthma is well controlled, near-maximal scores on quality of life instruments can be achieved.

3.2. Prevalence and benefitting population

In 2011 it was reported that 5.4 million people in the UK were receiving treatment for asthma. Of these, 1.1 million were children (1 in 11) and 4.3 million were adults (1 in 12). The UK has among the highest prevalence rates of asthma symptoms in children worldwide; on average there are two children with asthma in every classroom. Occupational asthma, for instance due to allergens from animals, flour or grain, may afflict up to 20% of the workforce exposed to the sensitiser (*NHS Choices, GP notebook, 2012).*

Asthma most commonly starts in childhood. It runs in some families, but many people with asthma have no other family members affected. In adults, asthma is more common in women than in men (*NHS Choices, Patient UK May 2012).*

3.3. Classification

Asthma can be divided into extrinsic (external cause) and intrinsic (when no causative agent can be found).

Extrinsic asthma is triggered by allergens. Hence, it is also termed as allergic asthma. In extrinsic asthma, the immune system reacts to substances such as pollen and produces antibodies. This results in symptoms like hay fever, rhinitis and asthma. In case of asthma, the allergic reaction is observed in lungs which results in production of huge amounts of mucus that obstructs the air passage. Extrinsic asthma is commonly seen in children. About ninety percent of childhood asthma cases are due to allergens. Individuals with a family history of allergens are at more risk for extrinsic asthma.

Intrinsic asthma is a non-seasonal, non-allergic form of asthma, which usually first occurs later in life than allergic asthma and tends to be chronic and persistent rather than episodic. Intrinsic asthma is not allergy-related and may be caused by inhalation of chemicals such as cigarette smoke or cleaning agents, non-steroidal anti-inflammatory drugs, a chest infection, emotion, exercise, cold air, food preservatives or various other factors. Intrinsic asthma

is separated into such categories as exercise-induced asthma and occupational (chemical- induced) asthma.

The inflammatory response of the airways is the same in extrinsic and intrinsic asthma.

3.4. Symptoms and impact

The principal symptoms of asthma are wheezing attacks and episodic shortness of breath. Coughing, which worsens at night, may also be a symptom.

Asthma attacks tend to vary considerably in terms of frequency and duration. Some people experience one or two attacks per year lasting for a few hours, whilst others have attacks lasting for weeks. Attacks may be precipitated by a wide range of triggers.

Asthma is a major cause of impaired quality of life with impact on work, recreational as well as physical activities and emotions.

4. Current diagnostic and care pathways

4.1. Diagnostic and care pathway information

The diagnostic and care pathways have been extracted from the British Guideline on the Management of Asthma (2012) available from the British Thoracic Society (BTS) and the Scottish Intercollegiate Guidelines Network (SIGN).

Guidelines may be supplemented with clinical expert input as appropriate.

4.2. Diagnosis of Asthma

Asthma is diagnosed on the basis of symptoms and objective tests of lung function (such as peak expiratory flow rate [PEF] and forced expiratory volume in the first second [FEV_1]) and percentage predicted FEV_1 (calculated as a percentage of the predicted FEV_1 for a person of the same height, sex and age without diagnosed asthma). Variability of PEF and FEV_1, 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 required to control the symptoms, and is based on British Guidelines for the Management of Asthma from the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN).

The diagnosis of asthma is a clinical one and there is no standardised definition of the condition. Central to all definitions is the presence of symptoms (wheezing, breathlessness, chest tightness, and cough) and of variable airflow obstruction. 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.

4.2.1. Children

The diagnosis of asthma in children is clinically-based on recognising a characteristic pattern of episodic symptoms in the absence of an alternative explanation.

Clinical features that increase the probability of asthma include:

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

If asthma is suspected, an initial clinical assessment should be carried out to estimate the probability of asthma. According to the British Guidelines on the Management of Asthma, based on initial clinical assessment, an individual child can be classed into one of three groups:

High probability – diagnosis of asthma likely

Low probability – diagnosis other than asthma likely

Intermediate probability – diagnosis uncertain

For children identified as having a low probability of asthma, a more detailed investigation and specialist referral should be considered. For children with a high probability of asthma, a trial of treatment should be started immediately.

The response to treatment should be reassessed every 6 months. Those with a poor response to treatment should undergo more detailed investigations.

According to the British Guidelines on the Management of Asthma, there is insufficient evidence at first consultation to make a firm diagnosis of asthma in some children, particularly those below the age of 4 to 5 years. For these children who can perform spirometry and for whom airway obstruction is evident, change in forced expiratory flow volume or peak expiratory flow monitoring should be assessed in response to an inhaled bronchodilator and/or the response to a trial of treatment for a specified period.

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, bronchial hyper-responsiveness using methacholine, exercise or mannitol should be considered. In such cases, specialist referral should always be considered.

Other investigations to diagnose asthma in children include tests of eosinophilic airway inflammation using induced sputum or exhaled nitric oxide concentrations, tests of atophy by skin test or blood eosinophilia or by chest x-ray.

4.2.2. Adults

The diagnosis of asthma in adults is based on the 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.

For both 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 patient’s symptom score (using a validated questionnaire), exacerbations, oral corticosteroid use, time off school or work, growth, inhaler technique and in adults, lung function assessed by spirometry of peak expiratory flow.

4.3. Monitoring

4.3.1. Monitoring asthma in children

The British Guideline on the Management of Asthma states that asthma in children is best monitored in primary care by routine clinical review on at least an annual basis. The factors that should be monitored and recorded include:

- Symptom score, for instance Children's Asthma Control test or Asthma Control Questionnaire
- Exacerbations, oral corticosteroid use and time off school/nursery due to asthma since last assessment
- Inhaler technique
- Adherence to treatment, which can be assessed by reviewing prescription refill frequency
- Possession of and use of self management plan/personalised asthma action plan
- Exposure to tobacco smoke
- Growth (height and weight centile)

The guideline is indistinct about the use of biomarkers in monitoring asthma. It states: "*a better understanding of the natural variability of biomarkers independent of asthma is required and studies are needed to establish whether subgroups of patients can be identified in which biomarker guided management is effective*".

4.3.2. Monitoring asthma in adults

According to the guideline, symptom-based monitoring is adequate in the majority of adults with asthma. Those with poor lung function and with a history of exacerbations in the previous year may be at a greater risk of future exacerbations for a given level of symptoms.

Asthma in adults is best monitored in primary care by routine clinical review on at least an annual basis. The factors that should be monitored and recorded include:

- Symptomatic asthma control: best assessed using directive questions such as the Asthma Control Questionnaire or Asthma Control Test
- Lung function, assessed by spirometry or by PEF
- Exacerbations, oral corticosteroid use and time off work or school since last assessment

- Inhaler technique
- Adherence to treatment, which can be assessed by reviewing prescription refill frequency
- Bronchodilator reliance, which can be assessed by prescription refill frequency
- Possession of and use of self management plan/personal action plan

4.4. Management

Asthma management aims to control symptoms (including nocturnal symptoms and exercise-induced asthma), prevent exacerbations and achieve the best possible lung function, with minimal side effects of treatment. The British Guideline on the Management of Asthma 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 good (see tables 1 and 2).

4.4.1. Nondrug treatment

Primary prophylaxis

According to the guideline, there is evidence that suggests reducing parental smoking and encouraging breast-feeding may both reduce the chance of developing asthma. In addition, allergen avoidance, dietary manipulations and modified infant milk formulae have all shown inconsistent effects.

Secondary prophylaxis

- Smoking cessation: clear personalised advice should be given to stop smoking and help provided with nicotine replacement therapy, etc. where appropriate.
- Weight reduction in obese people improves asthma symptoms and should be encouraged.
- Allergen avoidance: there is little evidence that reducing allergen exposure reduces morbidity from asthma and it does not appear to be a cost-effective treatment for asthma.
- Immunotherapy: this may be considered where there is a clinically significant and identified allergen that cannot be avoided. Patients need to

be aware of the risk of anaphylaxis and treatment should only take place within specialist settings.

- Dietary modifications: (use of probiotics, antioxidants, fish oils/lipid supplements, magnesium) are not currently supported by the guidelines.

4.4.2. Drug treatment

Adults and children over 12 years

Mild intermittent asthma (step 1) is treated with inhaled short-acting beta2 agonists, as required. The introduction of regular preventer therapy with inhaled corticosteroids (step 2) should be considered when a person has had exacerbations of asthma in the previous 2 years, is using inhaled short-acting beta2 agonists three times a week or more, is symptomatic three times a week or more, or is waking at night once a week because of asthma. Add-on therapy (step 3) involves the introduction of an additional therapy, the first choice of which is an inhaled long-acting beta2 agonist. Alternatives include orally administered leukotriene receptor antagonists, theophyllines and slow-release beta-2 agonist tablets, or increasing the dose of inhaled corticosteroids. At step 4, further interventions may be considered if control remains inadequate on a dose of inhaled corticosteroids that is equivalent to 800 micrograms per day of beclometasone dipropionate in combination with a long-acting beta2 agonist, or following an unsuccessful trial of a long-acting beta2 agonists. Options include increasing the dose of the inhaled corticosteroids to 2000 micrograms beclometasone dipropionate equivalent per day or adding a leukotriene antagonist, a theophylline or a slow-release beta2 agonist tablet. At step 5, continuous or frequent courses of oral corticosteroids are introduced. The majority of people with asthma are treated at steps 1, 2 or 3.

Expert input on diagnosis and management/monitoring : during scoping, clinical specialists suggested that ENO measurement is likely to be most beneficial when used in addition to current tools in individuals who are difficult to diagnose. Clinical specialists highlighted positions in the diagnostic pathway (in the BTS guidelines) where the use of ENO measurement is most likely to be of benefit in both adults and children (please refer to the protocol available on the NICE website). In primary care, ENO measurement may help to reduce the number of individuals who are subjected to trial of treatment with inhaled corticosteroids and may reduce the number of referrals. In secondary care, ENO measurement may help to reduce the use of more expensive diagnostics (for example, tests of airway hyperresponsiveness) and reduce the number of individuals who are subjected to trial of treatment with inhaled corticosteroids. Clinical specialists suggested that individuals who have had

their ENO measured in primary care, but have been referred to secondary care, will have their ENO level measured again. In terms of management and monitoring, experts suggested that ENO measurement may be helpful in individuals diagnosed with asthma to facilitate titration of corticosteroid therapy and ultimately lead to better asthma control.

Step 1: Mild intermittent asthma	Step 2: Regular preventer therapy	Step 3: Initial add-on therapy	Step 4: Persistent poor control	Step 5: Continuous or frequent use of oral steroids
Inhaled short acting B_2-agonist Prescribe inhalers only after the patient has received training in the use of the device and has demonstrated satisfactory technique **0-5 years pMDI and spacer are preferred delivery system.**	Add inhaled corticosteroid (ICS) 200-400mcg/day (BDP or equivalent) Start dose of inhaled corticosteroid appropriate to severity of disease. 200mcg/day is an appropriate dose for most children **Special instructions for under 5 years** Use a leukotriene receptor antagonist (LTRA) if inhaled corticosteroid cannot be used	**Special instructions for under 5 years** In the under 5 years and those already taking inhaled corticosteroids consider adding LTRA. In those already taking LTRA consider adding ICS 200-400mcg/day (BDP or equivalent).	**Special instructions for under 5 years** Refer to paediatrician	
		Special instructions for 5-12 years Add inhaled long-acting B2-agonist (LABA) and assess response. **If response good** - continue. Consider combination inhalers in those for whom LABA are effective at controlling symptoms. **If response poor** discontinue and increase ICS to 400mcg/day (BDP or equivalent). **If response still poor**, add other therapies.	**Special instructions for 5-12 years** Increase inhaled corticosteroid up to 800mcg/day (BDP or equivalent) Consider referral to paediatrician	**Special instructions for 5-12 years** Use daily steroid tablet in lowest dose to provide adequate control Maintain high-dose ICS at 800mcg (BDP or equivalent) per day Refer to paediatrician

Table 1: Asthma in children. - Summary of stepwise management (from British Thoracic Society/SIGN Guidelines for the Management of Asthma).

Step 1: Mild intermittent asthma	Step 2: Regular preventer therapy	Step 3: Initial add-on therapy	Step 4: Persistent poor control	Step 5: Continuous or frequent use of oral steroids
Inhaled short acting B_2-agonist Prescribe inhalers only after the patient has received training in the use of the device and has demonstrated satisfactory technique	Add inhaled corticosteroid (ICS) 200-800mcg/day (BDP or equivalent) Start dose of inhaled corticosteroid appropriate to severity of disease. 400mcg/day (BDP or equivalent) is an appropriate dose for most patients	**1.** Add inhaled long-acting B_2-agonist (LABA) and assess control of asthma: **Good response to LABA** Continue LABA Combination inhalers should be considered in those for whom LABA are effective at controlling symptoms. **Benefit from LABA but control still inadequate** Continue LABA and increase inhaled steroid dose to 800 mcg/day BDP or equivalent (if not already on this dose) **No response to LABA** Stop LABA and increase inhaled steroid to 800mcg/ day. BDP or equivalent **2. If control still inadequate**, Institute trial of other therapies, leukotriene antagonist or SR theophylline receptor	Consider trials of: Increased dose of inhaled corticosteroid up to 2000mcg/day (BDP or equivalent) Consider adding a fourth drug eg leukotriene receptor antagonist, SR theophylline or B_2-agonist tablet	Use daily steroid tablet in lowest dose to provide adequate control Maintain high dose inhaled corticosteroids at 2000mcg/day (BDP or equivalent) Consider other treatments to minimise the use of oral steroids Refer patient for specialist care
Regular review of patients as treatment is stepped down is important. Patients should be maintained at the lowest possible dose of inhaled corticosteroid. Any reduction in inhaled steroids should be undertaken slowly, every three months, as patients deteriorate at different rates. Inhaled corticosteroid reduction in severe asthma should be reduced by 25% only, 50% for more stable patients				
In selected patients at Step 3 who are poorly controlled, or in selected patients at step 2 who are poorly controlled, the use of budesonide/formoterol in a single inhaler as rescue medication and maintenance therapy can be an effective treatment option.				

Table 2: Asthma in adults. - Summary of stepwise management (from British Thoracic Society/SIGN Guidelines for the Management of Asthma).

5. Objectives of the evaluation

The objective of the evaluation is to assess the clinical and cost-effectiveness of ENO measurement in people with asthma. After speaking to a range of stakeholders (including manufacturers and clinicians) the following questions need to be taken into account in guiding this evaluation:

- What is the clinical and cost-effectiveness of the nitric oxide monitors included in this evaluation for:

  a) use in diagnosis of asthma in adults and children?

  b) use in management and monitoring of asthma in adults and children?

- Do cut-off values used to interpret the results of nitric oxide concentration affect the cost-effectiveness of nitric oxide monitors? What are the optimal cut-offs for use in primary and secondary care? What are the optimal cut-offs for use in diagnosis compared with cut-offs for management and monitoring? Any exploration of test-specific cut-offs should be consistent with the CE-mark instructions of the interventions included in the assessment.

The results of the evaluation will contribute to identifying the optimal diagnostic strategies/service delivery frameworks for exhaled nitric oxide measurement in primary and secondary care.

Scoping workshop attendees considered that although the objectives stated above are important, the key factor driving the use of ENO measurement in clinical management is to identify individuals most likely to respond to corticosteroid therapy. In this regard, three important questions arise that should be addressed by the assessment:

1. Does exhaled nitric oxide concentration help to identify individuals most likely to respond to corticosteroid therapy?

2. Does exhaled nitric oxide concentration help to optimise corticosteroid therapy doses during patient management? In particular, can exhaled nitric oxide concentration be used to safely reduce the dose of corticosteroid therapy when appropriate?

3. Does exhaled nitric oxide concentration help to identify individuals who are not complying with corticosteroid therapy and can compliance be improved?

6. Scope of the evaluation

6.1. Population

Diagnosis: people with clinical characteristics suggestive of asthma

Management: people diagnosed with asthma

Scoping workshop attendees considered that exhaled nitric oxide measurement had the greatest potential to benefit people who are difficult to diagnose. Attendees also considered that as well as assessing the impact of ENO on the entire patient pathway, the impact of ENO on diagnosis and management (including monitoring) should be assessed separately.

Subgroups: certain groups of patients may experience different outcomes from the use of ENO when compared to the main population under assessment (for example, ENO levels tend to be lower in smokers than non-smokers). Such groups should be assessed separately if evidence allows.

6.2. Interventions

- NIOX MINO (Aerocrine)
- NObreath (Bedfont)

Scoping workshop attendees considered that these technologies should be assessed when added to current practice.

Reference/Gold standard: chemiluminescence systems

6.3. Comparators

Current NHS practice

Scoping workshop attendees indicated that the SIGN and British Thoracic Society's British Guideline on the Management of Asthma are considered an appropriate comparator for people with asthma.

6.4. Healthcare setting

Primary care and secondary care

6.5. Outcomes

6.5.1. Clinical considerations

The intermediate measures for consideration include:

- Diagnostic test accuracy
- Test failure rate

The clinical outcomes for consideration include:

- Asthma control which includes asthma symptoms
- Exacerbation rate. Including frequency of exacerbations requiring unscheduled contact with healthcare professional, visit to accident and emergency department or hospitalisation.
- Clinical complications associated with acute exacerbations
- Levels of inhaled corticosteroids
- Use of oral corticosteroids
- Adverse effects of treatments (including bronchodilators and steroids)
- Health-related quality of life
- Mortality

6.5.2. Cost considerations

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

The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.

Time horizon should be long enough to allow reasonable estimation of expected costs (including adverse events if applicable) and benefits.

Costs will be considered from an NHS and Personal Social Services perspective.

7. Modelling approach

7.1. Existing models

Very few models assessing the use of exhaled nitric oxide monitors have been identified. An economic analysis of NIOX MINO airway inflammation monitor was carried out in the UK (Price *et al,* 2009).The objective of this study was to determine the cost-effectiveness of FENO measurement using a NIOX MINO for asthma diagnosis and management in the UK.

7.2. Model structure

As no end-to-end studies were identified during the scoping phase, it is likely that a linked evidence approach will need to be used in the modelling.

The model will estimate the likely impact of the new technologies in terms of health outcomes, costs and cost-effectiveness, when compared with the comparator.

8. Equality issues

The National Institute for Health and Clinical Excellence (NICE) is committed to promoting equality and eliminating unlawful discrimination. We aim to comply fully with all legal obligations to:

- promote race and disability equality and equality of opportunity between men and women, and
- eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, pregnancy and maternity (women post delivery are covered), sexual orientation, and religion or belief, in the way we produce our guidance. (Note that these are protected characteristics under the Equalities Act 2010).

Asthma is more common in boys than girls, pre-puberty. The risk of persistent asthma is higher for girls in the transition from childhood to adulthood. Some people with severe asthma may be covered by equalities legislation, for example, where this affects activities of daily living. Scoping workshop attendees indicated that the characteristics of asthma may be different in groups also protected by equalities legislation. ie women during pregnancy and older people.

9. Implementation

Support tools are developed by the implementation team at NICE. The implementation team does not get involved in developing the guidance recommendations but works alongside the guidance-producing programme, the communications team and field based teams to, amongst other things, ensure intelligent dissemination of NICE guidance to the appropriate target audiences.

Commissioners will need to know whether there are significant non-recurrent set-up costs associated with the introduction of the interventions, particularly where these are likely to influence the location of services or the size of population they would need to serve. They are also likely to be interested in implementation advice that describes and supports the optimal diagnostic strategies/service delivery frameworks emerging from the evaluation.

Appendix A Related NICE guidance

Published guidance

- Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over. TA138. 2008 www.nice.org.uk/guidance/TA138 Review date: November 2012
- Inhaled corticosteroids for the treatment of chronic asthma in children under the age of 12 years. TA131. 2007 www.nice.org.uk/guidance/TA131 Review date: November 2012

Appendix B References

Aerocrine. Guide to Interpretation of eNO Values. http://www.aerocrine.com/Global/pdf/Interpretation_guide.pdf. Accessed 1 February 2013.

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Payne et al. (2001). Relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma, after treatment with prednisolone. *American journal of respiratory and critical care medicine*. 164 (8), 1376-1381.

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Appendix C Equality impact assessment

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Diagnostics Assessment Programme

Equality impact assessment – Scoping

Measurement of exhaled nitric oxide concentration in asthma; NIOX MINO and NObreath

The impact on equality has been assessed during this assessment according to the principles of the NICE Equality scheme.

1.	Have any potential equality issues been identified during the scoping process (scoping workshop discussion, assessment subgroup discussion), and, if so, what are they?
Yes. The following has been listed in section 8 of the scope: Asthma is more common in boys than girls, pre-puberty. The risk of persistent asthma is higher for girls in the transition from childhood to adulthood. Some people with severe asthma may be covered by the equalities legislation. Additionally, scoping workshop attendees indicated that the characteristics of asthma may be different in groups also protected by equalities legislation. ie women during pregnancy and older people.	

2.	What is the preliminary view as to what extent these potential equality issues need addressing by the Committee?
Subgroups of patients may experience different outcomes from the use of ENO when compared to the main population under assessment. The assessment will aim to consider the clinical and cost effectiveness of ENO	

testing in these subgroups separately where possible.

When formulating its recommendations, the Committee should be mindful of any equality issues raised, and ensure its guidance does not have a disproportional adverse impact on any of the groups of people protected under the equality and diversity legislation.

3.	Has any change to the draft scope been agreed to highlight potential equality issues?
Section 8 of the scope was updated to reflect the discussion of equality issues during scoping.	

4.	Have any additional stakeholders related to potential equality issues been identified during the scoping process, and, if so, have changes to the stakeholder list been made?
None identified.	

Approved by Associate Director (name): …Nick Crabb……..

Date: 26/02/2013