

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

FINAL PROTOCOL

HTA Reference No. 1260

5 March 2013

Project Lead: Jon Minton

Health Economics and Decision Science

School of Health and Related Research (SchARR)

The University of Sheffield

Regent Court

30 Regent Street

Sheffield S1 4DA

Tel: (+44) (0)114 222 0836

Fax: (+44) (0)114 272 4095

E-mail: j.minton@sheffield.ac.uk

Address for correspondence

Major documentation should be sent to:

- 1 the project lead (Jon Minton, j.minton@sheffield.ac.uk);
- 2 the project administrator (Andrea Shippam, a.shippam@sheffield.ac.uk);
- 3 and the managing director of SchARR-TAG (Eva Kaltenthaler, e.kaltenthaler@sheffield.ac.uk).

Abbreviations

BTS	British Thoracic Society
CEAC	Cost effectiveness acceptability curve
CEAF	Cost effectiveness acceptability frontier
CRD	Centre for Reviews and Dissemination
DAR	Diagnostic Assessment Group
EAG	Evidence Assessment Group
ENO	Exhaled Nitric Oxide (Assumed synonymous with FENO)
FENO	Fractional Exhaled Nitric Oxide (Assumed synonymous with ENO)
FEV ₁	Forced expiry volume in first second
FN	False Negative
FP	False Positive
HRQoL	Health related quality of life
IAD	Inflammatory Airway Disease
ICER	Incremental cost effectiveness ratio
ICS	Inhaled corticosteroids
LRTS	Lower respiratory tract symptoms
LTRA	leukotriene receptor antagonist
mL/s	millilitres per second
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
OCS	Oral corticosteroids
PEF	Peak expiratory flow
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality adjusted life year
SCM	Specialist committee members
SIGN	Scottish Intercollegiate Guidelines Network
TN	True Negative
TP	True Positive
UK	United Kingdom

Contents

1.	Plain English Summary.....	6
2.	Decision problem.....	6
2.1	Purpose of the decision to be made.....	6
2.2	Clear definition of the intervention.....	7
2.2.1	NIOX MINO	7
2.2.2	NObreath	8
2.3	Populations and relevant subgroups.....	8
2.3.1	Diagnosis.....	8
2.3.2	Management	9
2.4	Place of the intervention in the diagnostic/treatment pathway(s)	9
2.4.1	Diagnosis.....	9
2.4.2	Monitoring and management.....	15
2.5	Relevant comparators	22
2.5.1	Diagnosis.....	22
2.5.2	Management	22
2.5.3	Healthcare setting.....	22
2.5.4	Outcomes.....	22
3	Methods for assessing the outcomes arising from the use of the interventions.....	23
3.1	Diagnostic accuracy review	23
3.1.1	Population	23
3.1.2	Interventions	23
3.1.3	Comparators.....	25

3.1.4	Outcomes	25
3.1.5	Study design	26
3.2	Management review	27
3.2.1	Population	27
3.2.2	Interventions	27
3.2.3	Comparators	28
3.2.4	Study design	28
3.3	Search strategy	28
3.4	Data extraction strategy	29
3.5	Quality assessment strategy	29
3.6	Methods of analysis/synthesis	29
4.	Methods for synthesising evidence of cost effectiveness	31
4.1	Identifying and systematically reviewing published cost-effectiveness studies	31
4.2	Evaluation of costs and cost effectiveness	31
4.3	Development of a health economic model	32
4.3.1	Illustrative short-term diagnostic model	33
4.3.1	Illustrative long-term management model	34
5.	Handling information from the companies	35
	References	36
	Competing interests of authors	38
	Timetable/milestones	38
	Appendices	40
Appendix A	Search Strategy	40
Appendix B:	Additional information that is needed by NETSCC, HTA and NICE	44
Appendix B.1	Details of External Assessment Group	45

1. Plain English Summary

Nitric oxide monitors measure fraction of exhaled (ENO) nitric oxide levels. Two hand-held nitric oxide monitors have been identified: NIOX MINO, developed by Aerocrine Inc; and NObreath, developed by Bedfont Scientific Ltd. High ENO levels in people with symptoms suggestive of asthma, such as coughing and wheezing, may suggest that the patient has a type of asthma that could be treated with inhaled corticosteroids (ICS). In someone already diagnosed with asthma, changes in ENO levels can indicate how well a patient is responding to ICS-based medication, whether medication is being adhered to, and whether the dosage of medication should be increased or decreased (titrated). [1]

The main aim of this assessment is to consider the role of these ENO monitors in (1) the diagnosis of asthma in patients with suspected asthma, and (2) the management and monitoring of patients diagnosed with asthma. The decision problem will be considered separately for adults and children, as the diagnosis and treatment for these patient groups are slightly different. As diagnoses of asthma are routinely made in primary care without extensive testing, the emphasis within the diagnostic part of the decision problem will be on patients whose symptoms are difficult to diagnose.

Systematic reviews will be conducted to find evidence for the diagnostic and management applications of these devices. The evidence produced by these reviews will be combined with other sources of evidence to construct an economic model. This model will be used to examine the expected costs and health outcomes associated with the use of these devices in diagnostic and management settings.

2. Decision problem

2.1 Purpose of the decision to be made

The objective of the evaluation is to assess the clinical and cost-effectiveness of ENO measurement in people with asthma. This can be separated into two distinct questions:

- a) What is the clinical and cost-effectiveness of the nitric oxide monitors included in this evaluation for use in the diagnosis of asthma in adults and children?

- b) What is the clinical and cost-effectiveness of the nitric oxide monitors included in this evaluation for use in the management and monitoring of asthma in adults and children?

As the cut-off values used in diagnostic technologies affect their sensitivity (true positive rate) and specificity (true negative rate) it is also important to determine if an 'optimal' cut-off value can be identified for the use of NIOX MINO/NObreath for either diagnosis or management purposes. Any exploration of test-specific cut-offs will be consistent with the CE-mark instructions of the interventions included in the assessment.

Three key questions emerged from the scoping workshops held in February 2013. One question relates to the diagnostic application of the devices; the other two relate to the management applications:

- **Diagnosis question:** Does ENO concentration help to identify individuals who are most likely to respond to corticosteroid therapy?
- **Management question 1:** Does ENO concentration help to optimise (i.e. lead to appropriate increases or decreases in) 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?
- **Management question 2:** Does ENO concentration help to identify individuals who are not complying with corticosteroid therapy and can compliance be improved?

2.2 Clear definition of the intervention

2.2.1 NIOX MINO

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 H₂O 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 a stand-alone device or connected to a PC for monitoring with the NIOX MINO Data Management Program and for use with Electronic Medical Record systems.

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).

2.2.2 NObreath

NObreath (Bedfont Scientific Ltd.) is a 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.

2.3 *Populations and relevant subgroups*

2.3.1 Diagnosis

The population of interest is people with clinical characteristics suggestive of asthma.

Subgroups:

- Scoping workshop attendees considered that exhaled nitric oxide measurement had the greatest potential to benefit people who are difficult to diagnose.
- 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.

2.3.2 Management

The population of interest is patients diagnosed with asthma. There are two subgroups of particular interest:

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

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.

2.4 Place of the intervention in the diagnostic/treatment pathway(s)

Scoping workshop attendees considered that the interventions should be assessed when added to current practice.

2.4.1 Diagnosis

Asthma is diagnosed on the basis of symptoms and objective tests of lung function (such as peak expiratory flow [PEF] rate and 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 of 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 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).[2]

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.

2.4.1.1 Diagnosis of asthma in children

2.4.1.1.1 Current pathway

A flow chart of the diagnostic pathway for asthma in children is given in Figure 1 with locations for the use of ENO measurements. Diagnosis 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,[2] 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.[2] 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. These tests are performed in secondary care. 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 atopy by skin test or blood eosinophilia or by chest x-ray.

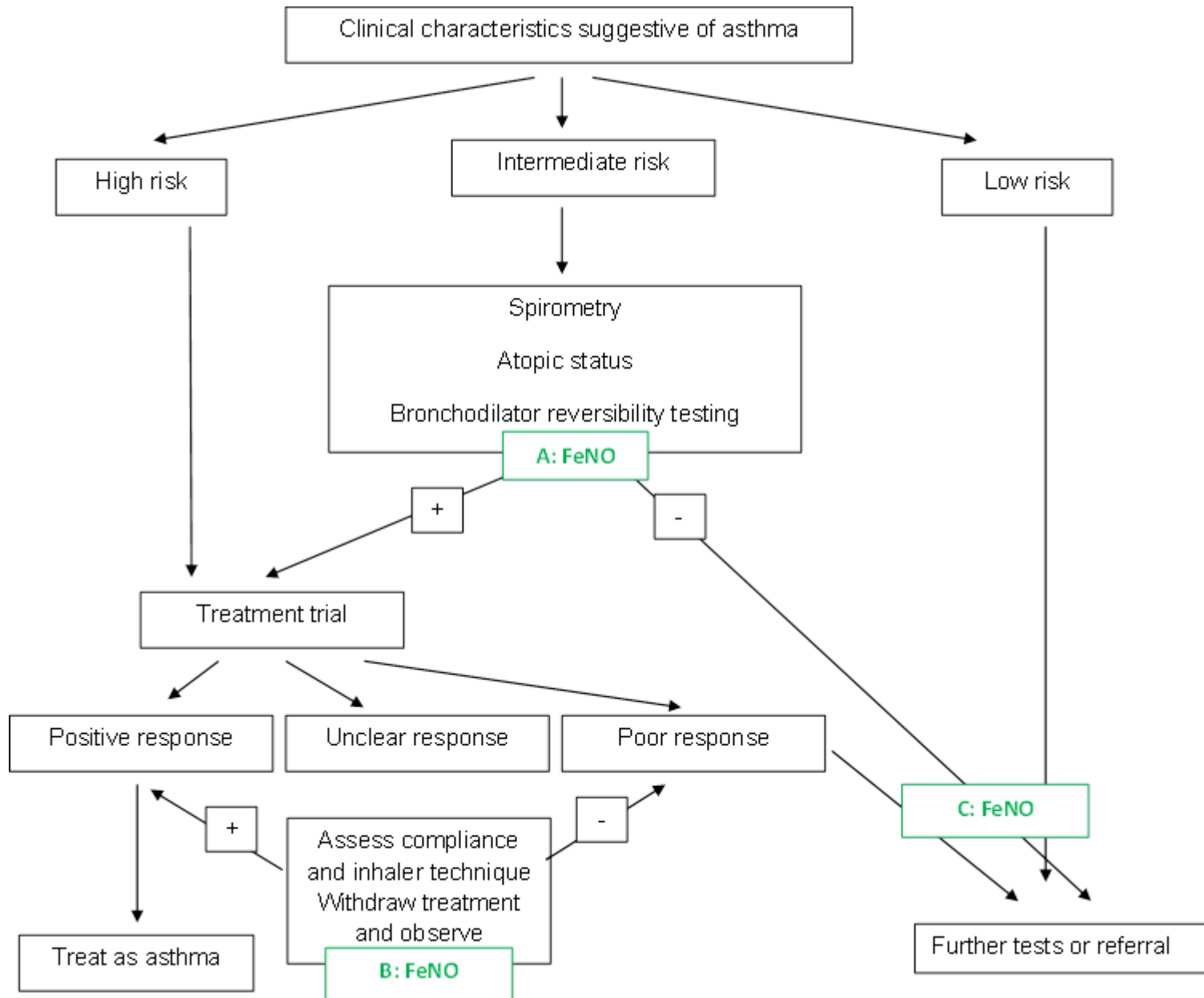
2.4.1.1.2 *Position of ENO in the pathway*

ENO is thought to be of most use in positions A, B and C as shown in Figure 1. This equates to patients who are difficult to diagnose. In primary care, ENO measurement may help to reduce the number of individuals who are subjected to a trial of treatment with inhaled corticosteroids and may reduce the number of referrals to secondary care. 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 a trial of treatment with inhaled corticosteroids. During the scoping workshop, 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.

Position B can also be considered as a management strategy (see Section 2.4.2), but as patients undergoing a trial of treatment may not yet have been diagnosed as asthmatic, it

may be necessary to assess this use as both a diagnostic strategy and a management strategy. The availability of evidence may dictate how this position is assessed.

Figure 1. Flow chart for the diagnosis of asthma in children as described in the British Guidelines on the Management of Asthma,[2] with possible positions for the addition of ENO testing.



2.4.1.2 Diagnosis of asthma in adults

2.4.1.2.1 *Current pathway*

A flow chart of the diagnostic pathway for asthma in adults is presented in Figure 2. Diagnosis in adults is also 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. Unlike in children, spirometry is tested initially to assess the presence and severity of airflow obstruction.

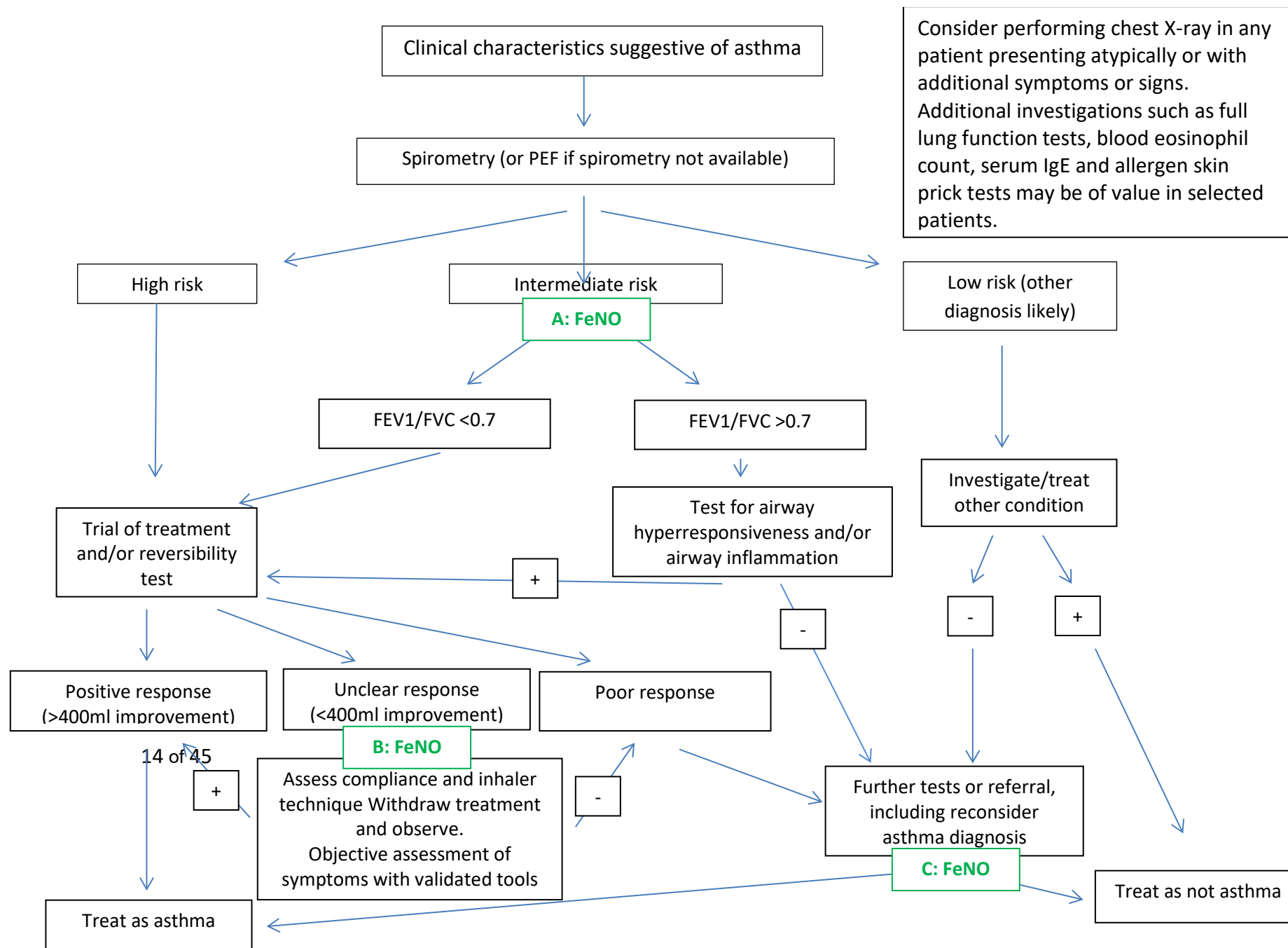
As in the diagnosis of children, adults are also classified as having a high, low or intermediate probability of asthma. Chest x-ray and specialist referral may be considered in any patient presenting atypically or with additional symptoms or signs.

2.4.1.2.2 *Position of ENO in the pathway*

ENO is thought to be of most use in positions A, B and C as shown in Figure 2. This equates to patients who are difficult to diagnose. In primary care, ENO measurement may help to reduce the number of individuals who are subjected to a trial of treatment with inhaled corticosteroids and may reduce the number of referrals to secondary care. 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 a trial of treatment with inhaled corticosteroids. During the scoping workshop, 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.

Position B can also be considered as a management strategy (see Section 2.4.2), but as patients undergoing a trial of treatment may not yet be diagnosed as asthmatic, it may be necessary to assess this use as both a diagnostic strategy and a management strategy. The availability of evidence may dictate how this position is assessed.

Figure 2, Flow chart for the diagnosis of asthma in adults as described in the British Guidelines on the Management of Asthma,¹ with positions for the addition of ENO testing.



2.4.2 Monitoring and management

For both children and adults, asthma is monitored and managed 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 or peak expiratory flow. Patients are managed in a stepwise manner, with escalation of medication until control is reached. This approach to pharmacological management for children and adults is represented in Tables 1 and 2 respectively (taken from the British guidelines).[2] Patients are started on the step that most closely matches the severity of their symptoms.

2.4.2.1 *Monitoring asthma in children*

The British Guideline on the Management of Asthma[2] 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".

2.4.2.2 Monitoring asthma in adults

According to the guideline,[2] 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

2.4.2.3 Management in adults and children

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).

2.4.2.4 Position of ENO in the management pathway

Experts suggested that ENO measurement may be helpful in individuals diagnosed with asthma to facilitate titration of corticosteroid therapy, to check for compliance with medication, and ultimately to lead to better asthma control. It is likely that management decisions would be based on a combination of the monitoring information collected at

review and ENO measurements. Possible contingencies based on this information will be elicited from clinicians during the course of the assessment.

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

Table 1: Asthma in children. - Summary of stepwise management (from British Thoracic Society/SIGN Guidelines for the Management of Asthma).[2]

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
<p>Inhaled short acting B₂-agonist</p> <p>Prescribe inhalers only after the patient has received training in the use of the device and has demonstrated satisfactory technique</p>	<p>Add inhaled corticosteroid (ICS) 200-800mcg/day (BDP or equivalent)</p> <p>Start dose of inhaled corticosteroid appropriate to severity of disease. 400mcg/day (BDP or equivalent) is an appropriate dose for most patients</p>	<p>1. Add inhaled long-acting B₂-agonist (LABA) and assess control of asthma: Good response to LABA Continue LABA</p> <p>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</p> <p>2. If control still inadequate, Institute trial of other therapies, leukotriene antagonist or SR theophylline receptor</p>	<p>Consider trials of:</p> <p>Increased dose of inhaled corticosteroid up to 2000mcg/day (BDP or equivalent)</p> <p>Consider adding a fourth drug eg leukotriene receptor antagonist, SR theophylline or B₂-agonist tablet</p>	<p>Use daily steroid tablet in lowest dose to provide adequate control</p> <p>Maintain high dose inhaled corticosteroids at 2000mcg/day (BDP or equivalent)</p> <p>Consider other treatments to minimise the use of oral steroids</p> <p>Refer patient for specialist care</p>
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).[2]

2.5 Relevant comparators

The relevant comparators are diagnosis or management according to the current UK guideline,[2] as described in sections 2.4.1.2.1 and 2.4.1.1.1.

2.5.1 Diagnosis

This comprises following the established diagnostic pathway without the use of ENO measurements (See Figures 1 & 2 for children and adults respectively).

2.5.2 Management

This comprises following the established diagnostic pathway without the use of ENO measurements (See Tables 1 & 2 for children and adults respectively).

2.5.3 Healthcare setting

Primary care and secondary care.

2.5.4 Outcomes

2.5.4.1 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 professionals, visit to accident and emergency departments or hospitalisations.
- 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

2.5.4.1 Cost considerations

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

3 Methods for assessing the outcomes arising from the use of the interventions

A systematic review will be conducted to identify evidence relevant to the decision problem.

There will be two main reviews, each reporting results for adults and children separately.

The two main reviews are:

1. A review of diagnostic accuracy
2. A review of the efficacy of monitoring and management strategies

The inclusion and exclusion criteria are detailed for each review separately here.

3.1 Diagnostic accuracy review

3.1.1 Population

The primary population is patients presenting with clinical characteristics suggestive of asthma. The main relevant subgroups within this population are:

- Those presenting with clinical characteristics suggestive of asthma and who are difficult to diagnose. This patient group roughly equates to the “intermediate” group in the patient pathway (position A in Figures 1 and 2), and those in positions D and E
- Women during pregnancy
- Older people
- Smokers (whose ENO levels may be affected by smoking)

Studies will be included if they recruited a wider population but report *a priori* subgroup analyses for the populations of relevance to this review.

3.1.2 Interventions

Studies will be included if they report results relating to the clinical validity or clinical utility of NIOX MINO or NObreath.

If data are not available for the clinical validity and clinical utility of the interventions, studies will be included if they report clinical validity or clinical utility of ENO measured by chemiluminescence (the gold standard in ENO measurement) and supporting evidence of the analytic validity of NIOX MINO and NObreath compared to chemiluminescence will be presented. A full systematic review of analytic validity may not be necessary if a recent (2010 onwards), good quality systematic review of this evidence is found. Otherwise, a full systematic review of analytic validity of NIOX MINO and NObreath will be conducted.

Studies will be included if they utilise the standard cut-off rates defined in the ATS guidelines,[3] and as recommended by the manufacturers of NIOX MINO[4] (Bedfont do not provide an interpretation guide). These are as follows:

- ENO less than 25 ppb (< 20 ppb in children) indicates that eosinophilic inflammation and responsiveness to corticosteroids are less likely
- ENO greater than 50 ppb (>35 ppb in children) indicates that eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids are likely
- ENO values between 25 ppb and 50 ppb (20–35 ppb in children) should be interpreted cautiously and with reference to the clinical context

Where evidence is available, and subject to the approval of NICE, studies using other cut-off points will also be included to allow modelling of the optimum values for cost effectiveness.

Expiratory flow rate and exhalation time are important factors that can affect measurements. The standard methodology defined in the ATS/BTS guidelines recommends

- Expiratory flow rate of 50mL per second, though other flow rates can be used in certain situations if desired or to measure flow-independent parameters.
- An exhalation time of 10 seconds may be necessary to establish a stable plateau in ENO for evaluation over a 3 second window.[5]

These guidelines will be interpreted, based on clinical advice given at the scoping workshop and the design specifications of the two interventions, as:

- Expiratory flow rate of 50mL per second (0.05L/sec)
- An exhalation time of at least 10 seconds.

Studies of ENO measurement by NIOX MINO, NObreath or chemiluminescence will only be included if they comply with these parameters.

3.1.3 Comparators

Studies of clinical validity and utility will be included if the comparator for the diagnosis of asthma comprises any combination of the tests and clinical characteristics described in the UK guideline. [2]

Studies will be excluded if the comparator uses tests to diagnose asthma that are not used as standard in the UK or if the comparator includes the use of ENO measurement. If studies are identified which compare different locations of ENO testing head-to-head, within a diagnostic pathway comparable to clinical practice in the UK, and these do not include a comparator arm without ENO, these could be presented separately as additional evidence for consideration by the assessment committee.

Studies of analytic validity will be included if they compare the intervention devices to ENO values measured by chemiluminescence at the flow rate and exhalation time stated for the interventions. If no studies at this flow rate and exhalation time are found, any flow rate or exhalation time will be included.

3.1.4 Outcomes

Studies of clinical utility will be included if they report any of the following outcomes at any time point:

- Incidence of acute exacerbations, including those requiring unscheduled contact with healthcare professionals, visits to accident and emergency departments or hospitalisations. As patients can experience more than one exacerbation within the timeframe of follow-up, the rate of exacerbations is the preferred outcome measurement. Other measures (time-to-event data; numbers of patients experiencing an exacerbation) will only be considered if insufficient data are available for the rate of exacerbations. Any definition of exacerbation will be acceptable.
- Asthma control which includes asthma symptoms, either reported individually or by use of a standardised patient outcome measure or symptom score.
- Clinical complications associated with acute exacerbations
- Levels of inhaled corticosteroids
- Use of oral corticosteroids

- Adverse effects of treatments (including bronchodilators and steroids)
- Health-related quality of life
- Mortality
- Test failure rate

Studies of clinical validity will be included if they report data that allow the extraction of the numbers of patients who are true positive, true negative, false positive and false negative against the reference standard. Studies which report test failure rates will also be included.

Studies of analytic validity will be included if they report the ability of the test to measure ENO accurately, as compared to chemiluminescence in humans.

3.1.5 Study design

There are three types of evidence that may inform reviews of diagnostic accuracy: clinical utility, clinical validity and analytic validity.[6] This review will include the highest level of evidence, namely clinical utility studies, which follow patients from diagnostic test to clinical outcomes (also known as end-to-end studies and which demonstrate the ability of the test to improve patient outcomes). If no evidence is found at this level, clinical validity studies (which compare the diagnosis of patients by the intervention with a reference standard diagnostic; this is influenced by both calibration of the test and its ability to differentiate between patients with and without disease) will be included. If there is no evidence at this level, studies of analytic validity linked to studies of the clinical utility (or if no utility studies are available, clinical validity) of ENO will be included. The inclusion criteria for each level are given below.

For the review of clinical utility, RCTs will be included where available. If sufficient high quality evidence is not available from RCTs, the next best level of evidence will be included, according to the well-established hierarchy of evidence.[7] It may be preferable, however, to draw conclusions from well-designed studies of clinical validity rather than poor quality studies of clinical utility.

For the review of clinical validity, studies are likely to be prospective cohort studies, cross sectional studies or retrospective cohort studies. If studies of these designs are not located, other study designs will be considered (e.g. case control studies). Both studies deriving cut-off values for diagnosis and studies validating existing cut-off values for diagnosis will be included.

For the review of analytic validity, the most recent or comprehensive good quality systematic review will be included where available. If this has been conducted recently

(2010 onwards), no further evidence will be included. However, if no good quality recent reviews are identified, studies of analytic validity will be included if they have been conducted in humans. Studies performed *in vitro* on gas samples will not be included unless no test evidence is found in humans. Studies of inter-rater reliability or inter-subject repeatability will be excluded.

In all three reviews, studies with the following characteristics will be excluded:

- studies not meeting the inclusion criteria
- animal models
- preclinical and biological studies
- editorials and opinion pieces
- studies only published in languages other than English
- reports published as meeting abstracts will only be included where comparable data do not exist in full published studies and where sufficient methodological details are reported to allow critical appraisal of study quality.

3.2 Management review

An existing Cochrane review [8] will be updated with searches from 2009. Additional data for exacerbation rates will be included as reported in an update and reanalysis of the same review provided by Aerocrine.[9]

3.2.1 Population

The population of interest is patients diagnosed with asthma. There are two subgroups of particular interest:

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

And three further subgroups within each of these categories:

- Women during pregnancy
- Older people
- Smokers (whose ENO levels may be affected by smoking)

Studies will be included if they recruit whole asthma populations or if they recruit patients exclusively from any of the subgroups.

3.2.2 Interventions

Studies using NIOX MINO or NObreath will be included if they comply with the flow rate specifications listed in Section 3.1.2.

If studies using NIOX MINO or NObreath are not located, studies using chemiluminescence to measure ENO at the flow rate and specification listed in Section 3.1.2 will be included.

Only studies using ENO measurements in:

- routine annual monitoring
- dose titration indicated during routine monitoring
- assessment of compliance

will be included in the review. Studies where ENO is measured on a regular basis (ie not during routine annual review), with the intention of predicting exacerbations or loss of control, will be excluded.

Any protocols and cut-off values for management decisions or compliance monitoring will be included.

3.2.3 Comparators

Studies comparing the interventions to any other management strategy that does not utilise ENO measurements will be included. Studies using management strategies that closely match all or part of UK practice as described in the UK guidelines[2] will be included. If no studies which closely match UK practice are found, studies using other management strategies will be included.

3.2.4 Study design

Randomised controlled trials will be included. If insufficient RCT evidence is identified, other study designs will be included according to the hierarchy of evidence for efficacy trials.[7]

3.3 *Search strategy*

The search strategy will comprise the following main elements:

- Searching of electronic databases, clinical trial registers and websites
- Reference tracking of retrieved papers
- Citation searching
- Contact with experts in the field

The electronic databases and websites to be searched will include the following:

- MEDLINE and Medline in Process

- EMBASE
- The Cochrane Library (including Cochrane Database of Systematic Reviews, and the Cochrane Controlled Trials Register)
- Web of Knowledge Science Citation Index Expanded
- Conference Proceedings Citation Index – Science
- Clinicaltrials.gov
- metaRegister of Controlled Trials
- Manufacturer and User Facility Device (MAUDE)
- EuroScan International Network

A comprehensive Medline search strategy for the diagnostic review is provided in Appendix A. During the course of the review, two iterative approaches will be considered upon further discussion with the DAR review team:

- Application of study design filters (RCTs, SRs, diagnostic) to the strategy (Appendix A) to identify an initial collection of relevant papers which will then be used to inform smaller searches for similar papers.
- Key papers provided by NICE and the manufacturers and those identified by the review team will be used to inform and design iterative searches for similar papers that were not retrieved in the search above.

No language restrictions will be applied.

3.4 Data extraction strategy

Data will be extracted by one reviewer using a standardised data extraction form and checked by another. Any discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary. Data will be extracted from the existing Cochrane review[8] and manufacturer's meta-analysis [9] where possible. Any discrepancies between sources will be checked against the original journal articles. If time allows, attempts will be made to contact authors for any missing data. Data from multiple publications of the same study will be extracted and quality assessed as a single study.

3.5 Quality assessment strategy

This review is likely to draw on evidence provided by several different study designs. Each study design will be assessed according to the principles outlined in the CRD handbook and the Cochrane handbook.[10,11] RCT studies will be assessed according to the Cochrane risk of bias tool, with additional questions taken from the CRD guidelines if relevant. Diagnostic

accuracy studies will be assessed using QUADAS II.[12] Other study designs will be assessed using tools or adapted tools specific to the study design.

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

3.6 Methods of analysis/synthesis

Studies will be tabulated and discussed in a narrative review in the following groups and population subgroups:

Diagnostic review

- Adults with clinical characteristics of asthma
 - Patients who are difficult to diagnose
 - Pregnant women
 - Older age adults
 - Smokers
- Children with clinical signs of asthma
 - Patients who are difficult to diagnose

Management review

- Adults with clinical signs of asthma
 - Pregnant women
 - Older age adults
 - Smokers
- Children with clinical signs of asthma

If sufficient clinically and statistically homogenous data are available, data will be pooled using appropriate meta-analytic techniques to estimate a summary measure of effect on relevant outcomes. The following subgroup analyses will be considered:

- Studies with similar comparators; studies conducted in the UK or with a comparator with a high degree of similarity to UK guidelines in terms of diagnostic pathway and management pathway
- Studies using different cut of values for interpretation
- Location of care (primary or secondary care)

Clinical, methodological and statistical heterogeneity will be investigated in sensitivity analyses. Sources of heterogeneity that may be investigated include (list not exhaustive)

- Duration of study (treatment and measurement of outcomes)
- Definition of asthma
- Definition of exacerbation
- Study quality

4. Methods for synthesising evidence of cost effectiveness

4.1 Identifying and systematically reviewing published cost-effectiveness studies

A systematic review of existing models of NIOX MINO/NObreath in either diagnosis or management of asthma will be conducted. Because the estimated clinical and cost-effectiveness of ENO monitors depends on patient management pathways, it is important that existing models of patient management for patients with asthma are reviewed. Due to finite resources, a full systematic review of this broader asthma will not be conducted, although a thorough search of existing asthma management models will be conducted.

The primary outcome from the model will be an estimate of the incremental cost per additional quality-adjusted life year (QALY) gained associated with the use of the devices as compared against current UK guidelines. Secondary outcomes (the health benefits listed above) will also be presented. The economic analysis will adopt an NHS and Personal Social Services (PSS) perspective. Costs and health outcomes will be discounted at an annual rate of 3.5%. Modelling assumptions will be drawn from expert clinical expert opinion where required. Health-related quality of life (HRQoL) data will be reviewed and used to generate the quality adjustment weights required to estimate QALYs. Costs will be derived from national sources (e.g. NHS reference costs, national unit costs, British National Formulary)[13,14] and data provided by the manufacturers.

4.2 Evaluation of costs and cost effectiveness

The economic analysis will follow the NICE Reference Case. [6]

The costs of the treatment will include both the costs of performing the diagnostic tests, and downstream costs which result from using the information made available by the test. These downstream costs could be much larger than the test costs. Correctly estimating these downstream costs requires that the long-term consequences of a diagnostic test result are

known. Sufficiently realistic modelling of the patient management pathways of those patients categorised as ICS responsive or ICS non-responsive will thus be required.

4.3 Development of a health economic model

If a review of existing economic models, does not identify a suitable model, a *de novo* model will be developed. This model will be based around the UK asthma diagnostic and care management pathway. The model will involve two components: a diagnostic component, and a management component. Both components could involve the use of NIOX MINO/NObreath. This means it is expected there will be at least three interventions to compare against the reference case of routine diagnosis and management:

- **Reference case:** NIOX MINO/NObreath used for neither diagnosis nor management;
- **Comparator 1:** NIOX MINO/NObreath used for diagnosis but not for management;
- **Comparator 2:** NIOX MINO/NObreath used for management but not diagnosis;
- **Comparator 3:** NIOX MINO/NObreath used for both management and diagnosis.

A model has already been identified, but if it is not suitable the development of a *de novo* model is likely to be an iterative process. [15] A conceptual model will be developed in conjunction with clinical experts to capture the current pathway of care for the diagnosis and management asthma and how the new tests would change the pathway if routinely available in the NHS. The conceptual model will indicate the data requirements which will be sought both from the published literature and within commercial-in-confidence data held by the manufacturers. The model is likely to evolve following discussions with project stakeholders and the specialist committee members (SCMs), and according to the availability of evidence. It is anticipated that there may be limited evidence for some of the parameters that will be included in the economic model. Therefore, the uncertainty around the parameter estimates will be modelled to take this into account. A range of scenarios will be presented varying main model assumptions to identify parameters that impact the most the ICER and to represent the uncertainty in parameter estimates. Furthermore, probabilistic sensitivity analysis (PSA) will also be undertaken using standard Monte Carlo simulation methods. The uncertainty in each parameter will be characterised using a probability distribution. The decision uncertainty will be presented as the probability that each intervention is the most cost-effective for a given cost-effectiveness threshold. Decision uncertainty will be represented using cost-effectiveness acceptability curves (CEACs) and cost-effectiveness acceptability frontiers (CEAFs).

The methods and approaches described in the NICE Decision Support Unit Technical Support Document 13 will be used in structuring and parameterising the model. [16]

The next two subsections of this report will provide illustrative conceptual models of the short-term and long-term components of the economic models. However, the final model or models used may differ substantially from these.

4.3.1 Illustrative short-term diagnostic model

An illustrative decision tree describing the diagnostic component of the economic model is shown in Figure 1 below.

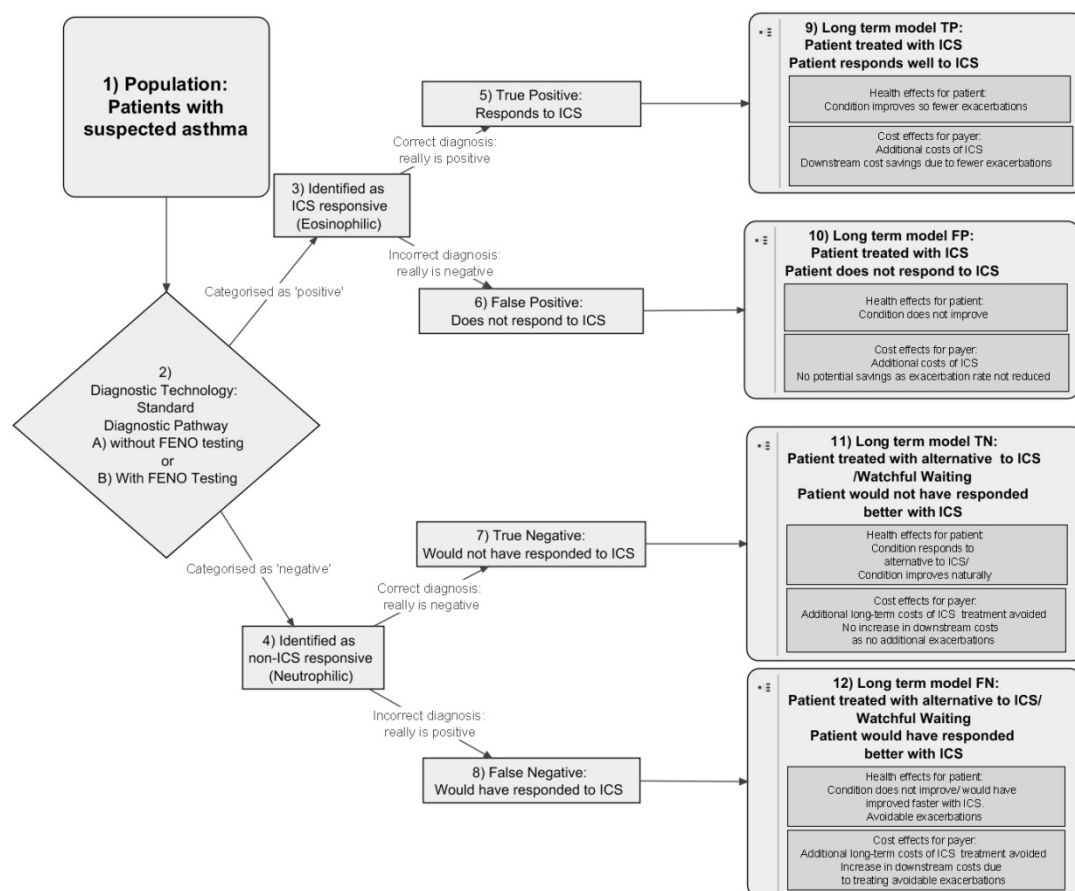


Figure 1 Illustrative short term diagnostic model

The different end states of the diagnostic part of the model are four separate nodes. These nodes correspond to the expected patient care pathways and clinical outcomes for true positives (TPs), false positives (FPs), true negatives (TNs) and false negatives (FNs). Both TPs and FPs will receive the same patient management, although in the model only the true positives will see a significant improvement in their symptoms as a result. Similarly, both TNs and FNs will receive the same patient management, but the health consequences will be better for TNs than FNs. The best clinical outcomes are achieved if all patients are correctly

diagnosed - i.e. all patients are either true positives or true negatives. However misclassification errors mean that some proportion of patients will either be FPs or FNs. The marginal clinical utility of a better diagnostic test results from how the test results lead to increases in the proportion of patients receiving appropriate outcomes, and a reduction in the proportion receiving inappropriate outcomes. However, as the cost and health consequences of TPs, FPs, TNs and FNs are not necessarily equal, the most clinically or cost effective outcomes may not result from a strategy with the lowest rate of misclassification.

4.3.1 Illustrative long-term management model

An illustrative conceptual model describing the management component of the economic model is shown in Figure 2 below.

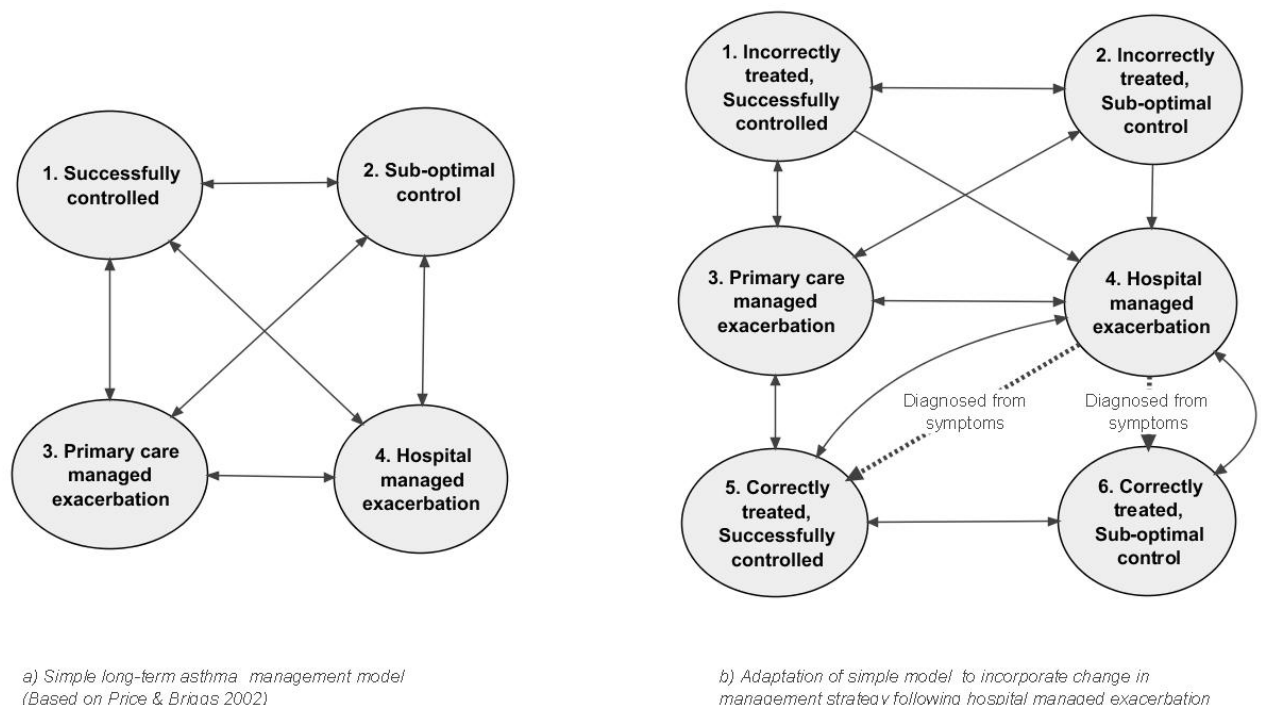


Figure 2 Illustrative long-term management model

The conceptual model shown in Figure 2a is based on an existing asthma management model. [17] It is flexible enough that the four long-term nodes in the diagnostic model could all, in principle, be represented by different parameterisations of the same model structure. It could also be adapted structurally to incorporate a range of alternative scenarios, such as that shown in Figure 2b. In this figure it is assumed that, if a patient who has been receiving suboptimal treatment due to an incorrect diagnosis experiences a severe exacerbation which leads to hospitalisation, then as a result more comprehensive tests are conducted in secondary care, leading to a correct diagnosis, and so improved condition management

afterwards. Similar structural adaptations could be produced following expert clinical guidance. Models featuring more states will require more model parameters to be populated, and where good quality data are not available to do this may mean stronger assumptions will be required in their construction.

A wide range of scenarios and sensitivity analyses will be conducted to evaluate the influence of a range of types of uncertainty on estimated outcomes and decision uncertainty.

5. Handling information from the companies

All relevant data submitted by the manufacturers/sponsors will be considered if received by the TAR team no later than 1 May 2013. Data arriving after this date are unlikely to be considered, except for data specifically requested by the EAG. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any economic evaluations included in company submissions, provided that they comply with NICE's advice on presentation, will be assessed for clinical relevance, reasonableness of assumptions and appropriateness of the data used in the economic model. If the EAG judge that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or developing a *de novo* model.

Any 'commercial in confidence' data taken from a company submission, and specified as confidential in the check list, will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant company name e.g. in brackets). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

References

1. Payne DN, Adcock IM, Wilson NM, Oates T, Scallan M, Bush A (2001) Relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma, after treatment with prednisalone. *Am J Respir Crit Care Med* 164: 1376-1381.
2. British Thoracic Society and Scottish Intercollegiate Guidelines Network. (2012) British Guideline on the Management of Asthma: a national clinical guideline.
3. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, Olin AC, Plummer AL, Taylor DR (2011) An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med* 184: 602-615. 184/5/602 [pii];10.1164/rccm.9120-11ST [doi].
4. Aerocrine. (2012) Guide to Interpretation of eNO Values.
5. 2005) ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 171: 912-930. 171/8/912 [pii];10.1164/rccm.200406-710ST [doi].
6. NICE (2008) Guide to the methods of technology appraisal.
7. National Institute for Health and Clinical Excellence (2012) Clinical guideline development methods.
8. Petsky HL, Cates CJ, Li A, Kynaston JA, Turner C, Chang AB (2009) Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults (Review).
9. Aerocrine (2013) Meta Analysis of Asthma Exacerbation Rates with FeNO Guided Asthma Management.
10. [Anonymous] (2011) Cochrane Handbook for systematic reviews of interventions Version 5.1.0.
11. Centre for Reviews and Dissemination (2009) Systematic reviews. CRD's guidance for undertaking reviews in healthcare.
12. Whiting PF RAWMMSDJRJLMSJaBP (2011) QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. *Ann Intern Med* 155: 529-536.
13. Curtis L (2010) Unit Costs of Health and Social Care 2010.
14. DoH (2011) NHS Reference Costs 2009-2010. 2012.
15. Price D, Berg J, Lindgren P (2009) An economic evaluation of NIOX MINO airway inflammation monitor in the United Kingdom. *Allergy* 64: 431-438.

16. Kaltenthaler E, Tappenden P, Paisley S, Squires H (2011) NICE DSU Technical Support Document 13: Identify and reviewing evidence to inform the conceptualisation and population of cost-effectiveness models.
17. Price MJ, Briggs AH (2002) Development of an economic model to assess the cost effectiveness of asthma management strategies. *Pharmacoeconomics* 20: 183-194.

Competing interests of authors

None

Timetable/milestones

Milestone	Date to be completed
TAR Centre meets with the assessment subgroup to discuss the draft scope and the draft protocol	19-Feb-13
Final protocol prepared by TAR Centre and sent to NICE cc NETSCC, HTA.	05-Mar-13
Progress report to NETSCC, HTA (stripped version forwarded to NICE for info)	05-Jun-13
Draft version of DAR and executable economic model from TAR Centre to NICE	31-Jul-13
TAR Centre deliver final DAR simultaneously to NICE and NETSCC, HTA including executable (or redacted if applicable) economic model	29-Aug-13
NICE circulate stripped DAR and executable or redacted economic model to registered stakeholders	05-Sep-13
Registered stakeholder comments on DAR and economic model sent to TAR Centre	23-Sep-13
TAR Centre responds verbally or submits a written response to relevant stakeholder comments for inclusion in DAC meeting papers	01-Oct-13
4 week public consultation on the DCD	27-Nov-13

Consultation comments on DCD forwarded from NICE to AG for optional response	02-Dec-13
NICE receives AG's responses (written or verbal) to DCD consultation comments	05-Dec-13
Second Diagnostics Advisory Committee meeting (to consider final recommendations)	11-Dec-13

Appendices

Appendix A Search Strategy

1. niox mino.mp.
2. aerocrine.mp.
3. (niox adj5 (monitor\$ or chemiluminescence or analyser\$ or sensor or device\$ or desktop)).mp.
4. nobreath.mp.
5. bedfont.mp.
6. or/1-5
7. exp cough/
8. cough\$.mp.
9. phlegm.mp.
10. sputum.mp.
11. mucus.mp.
12. wheez\$.mp.
13. chest pain/
14. chest pain\$.mp.
15. (chest adj5 tight\$.tw.
16. ((lower respiratory or lrt) adj5 symptom\$.tw.
17. (lower airway adj5 symptom\$.tw.
18. ((trache\$ or wind pipe or lung\$ or bronch\$) adj3 symptom\$.tw.
19. exp lung/ or trachea/
20. symptom\$.tw.
21. 19 and 20
22. or/7-18,21
23. exp asthma/
24. asthma\$.mp.
25. exp respiratory hypersensitivity/
26. exp bronchial hyperreactivity/
27. bronchial spasm/
28. bronchospas\$.mp.
29. exp Bronchoconstriction/
30. bronchoconstric\$.mp.

31. (bronch\$ adj3 constrict\$).mp.
32. (bronch\$ adj5 spas\$).mp.
33. (airway\$ adj5 (obstruct\$ or inflammation\$)).mp.
34. ((bronchial\$ or respiratory or airway\$ or lung\$) adj3 (hypersensitiv\$ or hyperreactiv\$ or allerg\$ or insufficiency)).mp.
35. or/23-34
36. Nitric Oxide/
37. nitric oxide.mp.
38. 36 or 37
39. (exhal\$ or expir\$ or alveolar).mp.
40. 38 and 39
41. exhaled NO.mp.
42. eno.mp.
43. fe?no\$.mp.
44. (fractional adj2 NO).mp.
45. or/40-44
46. 22 and 45

Where applicable, the following filters could be applied:

RCT filter

1. Randomized controlled trials as Topic/
2. Randomized controlled trial/
3. Random allocation/
4. randomized controlled trial.pt.
5. Double blind method/
6. Single blind method/
7. Clinical trial/
8. exp Clinical Trials as Topic/
9. controlled clinical trial.pt.
10. or/1-9
11. (clinic\$ adj25 trial\$).ti,ab.
12. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$ or mask\$)).tw.
13. Placebos/
14. Placebo\$.tw.

15. (allocated adj2 random).tw.
16. or/11-15
17. 10 or 16
18. Case report.tw.
19. Letter/
20. Historical article/
21. 18 or 19 or 20
22. exp Animals/
23. Humans/
24. 22 not (22 and 23)
25. 21 or 24
26. 17 not 25

Systematic review filter

1. meta-analysis as topic/
2. (meta analy\$ or metaanaly\$).tw.
3. Meta-Analysis/
4. (systematic adj (review\$1 or overview\$1)).tw.
5. "Review Literature as Topic"/
6. or/1-5
7. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or bids or cancerlit).ab.
8. ((reference adj list\$) or bibliograph\$ or hand-search\$ or (relevant adj journals) or (manual adj search\$)).ab.
9. ((selection adj criteria) or (data adj extraction)).ab.
10. "review"/
11. 9 and 10
12. comment/ or editorial/ or letter/
13. Animals/
14. Humans/
15. 13 not (13 and 14)
16. 12 or 15
17. 6 or 7 or 8 or 11
18. 17 not 16

Diagnostic filter

1. exp "sensitivity and specificity"/
2. sensitivity.tw.
3. specificity.tw.
4. ((pre-test or pretest) adj probability).tw.
5. post-test probability.tw.
6. predictive value\$.tw.
7. likelihood ratio\$.tw.
8. *Diagnostic Accuracy/
9. or/1-9

***Appendix B: Additional information that is needed by NETSCC,
HTA and NICE.***

Appendix B.1 Details of External Assessment Group

Jon Minton

Research Associate

Health Economics and Decision Science

School of Health and Related Research

The University of Sheffield

Regent Court, 30 Regent Street

Sheffield, S1 4DA

Tel: +44 (0) 114 222 0836

E-mail: j.minton@sheffield.ac.uk

Susan Harnan

Research Fellow

Health Economics and Decision Science

School of Health and Related Research

The University of Sheffield

Regent Court, 30 Regent Street

Sheffield, S1 4DA

Tel: (+44) (0)114 222 0869

E-mail: s.harnan@sheffield.ac.uk

Munira Essat

Research Associate

Health Economics and Decision Science

School of Health and Related Research

The University of Sheffield

Regent Court, 30 Regent Street

Sheffield, S1 4DA

Tel: (+44) (0)114 222 0860

E-mail: m.essat@sheffield.ac.uk

Ruth Wong
Information Specialist
Health Economics and Decision Science
School of Health and Related Research
The University of Sheffield
Regent Court, 30 Regent Street
Sheffield, S1 4DA
Tel: (+44) (0)114 222 0797
E-mail: ruth.wong@sheffield.ac.uk

Paul Tappenden
Reader
Health Economics and Decision Science
School of Health and Related Research
The University of Sheffield
Regent Court, 30 Regent Street
Sheffield, S1 4DA
Tel: (+44) (0)114 222 0855
E-mail: p.tappenden@sheffield.ac.uk