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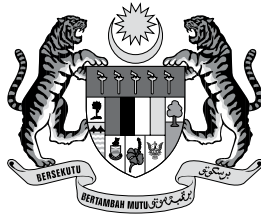MINISTRY OF HEALTH MALAYSIA

EXHALED NITRIC OXIDE MEASUREMENT
USING NIOX OR NIOX MINO

Health Technology Assessment Section (MaHTAS)

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Health Technology Assessment Report

Exhaled Nitric Oxide Measurement Using NIOX or NIOX MINO

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EXECUTIVE SUMMARY

Introduction
Several lung diseases including asthma and chronic obstructive pulmonary disease (COPD) involve chronic inflammation of the airways. Therefore, there is great interest in non-invasive methods assessing airway inflammation. Measurement of bronchial hyper-responsiveness (BHR) and exhaled nitric oxide (NO) are examples of indirect markers for airway inflammation. Nitric oxide (NO) is a molecule produced endogenously in the lungs. Nitric oxide can be generated in the air passages by a synthase which is induced in several cell types by exposure to proinflammatory cytokines. Its induction is blocked by glucocorticoids.

Technical features
Currently, nitric oxide measurement system (NIOX) or a new NIOX MINO are usually used as NO analyzers in many research and clinical use. The NIOX system uses a chemiluminescence gas analyzer that can measure low concentrations of NO. NIOX MINO is a newer, smaller, hand held device for the measurement of airway inflammation based on the established NIOX monitoring system, which detects and measures levels of exhaled nitric oxide. NIOX MINO uses electrochemical sensor technology.

Objective
To assess the safety, effectiveness and cost-effectiveness of exhaled nitric oxide measurement using NIOX or NIOX MINO in the management of respiratory diseases especially asthma.

Methods
Databases such as PubMed, OVID Fulltext, ProQuest, Cochrane databases, Food and Drug Administration (FDA) and HTA databases were searched. Relevant articles were appraised using Critical Appraisal Skills Programme (CASP) and evidence was graded according to Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001).

Results and conclusion
In conclusion, there was evidence to show that FENO measurement is safe and non invasive. There was also good evidence to show that there is good agreement between the FENO values measured with the two devices (NIOX and XIOX MINO). In terms of diagnosis of asthma, FENO measurements provide superior diagnostic accuracy compared to conventional tests. Exhaled nitric oxide measurement can be used as a predictor of steroid response and loss of control (LOC) in asthma following steroid withdrawal. However, there was limited evidence to establish the relationship between exhaled nitric oxide levels and compliance with inhaled corticosteroids and its role in diagnosis and monitoring of other respiratory diseases.

Recommendation
Based on the above review, it is recommended that exhaled nitric oxide measurement can be used in Ministry of Health Facilities with chest physicians (adult and paediatric) particularly for diagnosing and monitoring of asthma. The new NIOX MINO is preferred. More clinical research is warranted for other respiratory diseases such as COPD and bronchiectasis.

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1   INTRODUCTION

Several lung diseases including asthma and chronic obstructive pulmonary disease (COPD) involve chronic inflammation of the airways. Therefore, there is great interest in non-invasive methods assessing airway inflammation. Measurement of bronchial hyper-responsiveness (BHR) and exhaled nitric oxide (NO) are examples of indirect markers for airway inflammation. Additional information about severity of disease, prognosis and possible response to anti-inflammatory treatment with corticosteroids can be gained by these methods.

Nitric oxide (NO) is a molecule produced endogenously in the lungs. It can be detected in exhaled air in animals and humans. Nitric oxide can be generated in the air passages by a synthase which is induced in several cell types by exposure to proinflammatory cytokines. Its induction is blocked by glucocorticoids.[1] The presence of endogenous nitric oxide (NO) in exhaled breath of animals and humans was first described in 1991. Soon after, several publications reported high fractional concentrations of orally exhaled NO (FE_{NO}) in subjects with asthma as compared with unaffected subjects[2,3] which dropped after treatment with corticosteroids.[4] Similar findings have been described in the paediatric age group.[5,6] Atopy seems to be a significant factor associated with raised exhaled NO.[7] Exhaled nitric oxide concentration may be increased also in other diseases, such as chronic obstructive pulmonary disease (COPD), bronchiectasis and some connective tissue diseases (SLE and systemic sclerosis).[8]

There are no non-invasive reliable techniques for the explicit diagnosis of asthma. The British Society guidelines currently recommend that diagnosis be based on a clinical history and lung function (estimated using spirometry and peak expiratory flow). However, this is known to be inaccurate and lead to misdiagnosis, particularly in children where diagnosis is entirely based on clinical history as there is lack of suitable lung function test.[9]

There is also no non-invasive, reliable means for monitoring airway inflammation. The gold-standard technique is bronchoscopy with lavage and biopsy. However, due to cost and invasiveness, routine clinical use is limited. Alternatively, sputum induction (semi invasive) can be undertaken but again cost proves to be a limiting factor for routine monitoring and for alteration of anti-inflammatory dosage. Asthma disease status and response to treatment can be estimated using spirometry and peak expiratory flow, which give an indication of lung function. This is however a crude method of estimating changes in airway inflammation as there is a well documented delay between physiological change in inflammation level and its reflection in lung function tests.[9]

The American Thoracic Society (ATS) and the European Respiratory Society (ERS) issued a joint statement in 2005 to say that NO measurement constitutes a novel way to monitor diseases such as asthma routinely in clinics, provided that a standardised reference data is used. It proposes that exhaled NO may be used as a marker to diagnose asthma, to monitor the response to anti-inflammatory treatment, to check on patient's compliance and to predict upcoming asthma exacerbations.[9]

Most NO analyzers, in research and clinical use, employ the principle of ozone -/NO_{2-} based chemiluminescence to measure NO. However, NO measurement based on alternative technologies including luminal-H_2O_2-based chemiluminescence, tunable diode laser spectrometry, and laser magnetic resonance spectrometry, is currently available or in development. New technologies offer potential advantages regarding increased portability, reduced cost, and autocalibration.[10] Currently, nitric oxide measurement system (NIOX) or a new NIOX MINO are usually use as NO analyzers in many research and clinical use.

This technology review was conducted following a request from the Senior Consultant Chest Physician, who is also the Director of Institute of Respiratory Medicine (IPR)

2   TECHNICAL FEATURES

2.1.   General Principles Regarding Exhaled Nitric Oxide (NO) Measurement

- **Source of exhaled NO.**
  Current thinking is that NO is formed in both the upper and lower respiratory tract and diffuses into the lumen by gaseous diffusion down a concentration gradient, thus conditioning exhaled gas with NO. There may be significant contribution from the oropharynx. Alveolar NO is probably very low because of avid uptake by haemoglobin in the capillary blood. Although gastric NO levels are very high, this does not appear to contaminate exhaled NO.[10]

- **Non-Disease-related Patient Factors Influencing Exhaled NO Values**

  - **Age/sex.**
    In adults, there is no consistent relationship between exhaled NO level and age, but it has been reported that in children FE_{NO} increases with age.[10,11] In adults, there are conflicting reports regarding the effects of sex,[10,12,13] menstrual cycle and pregnancy[10], so these patients' characteristics should be recorded at the time of measurement.

- **Respiratory maneuvers.**
  Because spirometric maneuvers have been shown to transiently reduce exhaled NO levels, it is recommended that NO analysis be performed before spirometry. [10]

- **Airway caliber**
  It has been demonstrated that FE_{NO} levels may vary with airway obstruction or after bronchodilatation. It may be prudent to record the time of the last bronchodilator administration and some measure of airway caliber, such as FEV_1.[10]

- **Food and beverages**
  Patients should refrain from eating and drinking before FE_{NO} analysis. An increase in FE_{NO} has been found after ingestion of nitrate-containing foods such as lettuce (with a maximum effect 2 hours after ingestion). Drinking water and ingestion of caffeine may lead to transiently altered FE_{NO} levels. It is prudent when possible to refrain from eating and drinking 1 hour before exhaled NO measurement and to question patients about recent food intake. Alcohol ingestion reduces FE_{NO} in patients with asthma and healthy subjects.[10]

- **Smoking**
  Chronically reduced levels of FE_{NO} have been demonstrated in cigarette smokers in addition to acute effects immediately after smoking.[10,14] Subjects should not smoke in the hour before measurements. Short and long term active and passive smoking history should be recorded. [10]

- **Infection**
  Upper and lower respiratory tract viral infections may lead to increase of exhaled NO in asthma. [10]

- **Circadian rhythm**.
  Where possible to perform serial NO measurements in the same period of the day and to always record the time.[10]

Full detail for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide is contained in current ATS / ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide, 2005.[10]

2.2. Exhaled nitric oxide (NO) analyzers

2.2.1 Nitric oxide measurement system (NIOX)

NIOX is a device that measures the concentration of nitric oxide in exhaled breath (FE_{NO}) as a marker of airway inflammation. It is marketed for use in doctors' offices to monitor patients who have asthma and to assess their response to treatment. It is intended to complement, rather than replace, other clinical tests for asthma.[15]

The NIOX system uses a chemiluminescence gas analyzer that can measure low concentrations of NO. The patient exhales through a mouthpiece that is connected to the analyzer. A flow control system maintains exhalation at 50 ml per second, regardless of patient's skill. A visual display guides the patient in maintaining an appropriate pressure range while exhaling. A NIOX system is sold as a Start Package that includes computer, software, monitor, keyboard, calibration gas, installation and training. It can be used on children over the age of four.[15]

2.2.2 NIOX MINO airway inflammation monitor

NIOX MINO is a newer, smaller, hand held device for the measurement of airway inflammation based on the established NIOX monitoring system, which detects and measures levels of exhaled nitric oxide. NIOX MINO uses electrochemical sensor technology. It claims to have:

- pre-calibrated NO sensor for accurate, repeatable and reproducible results

- easy finger tip navigation - a touch screen for quick and easy navigation and display of results

- unique flow control which keeps exhalation at 50 ml/s regardless of patient skill, unique flow control for filtering of inhaled air which eliminates contamination from elevated ambient NO levels

- disposable single session bacterial and viral filter prevents contamination

- data storage

- printer

- monitor which is sensitive enough to detect as low as 5 particles per billion of exhaled nitric oxide

The manufacturer also claimed that NIOX MINO follows, in all essential aspects, the ATS/ ERS 2005 equipment recommendations for measurement of exhaled NO.[9,16]

The system requires the patient to inhale nitric oxide free air up to total lung capacity and then to slowly exhale via the mouth piece into the analyser. The exhaled NO (FE_{NO}) level is automatically displayed once analysis is complete. Unlike the original NIOX device, there is no requirement for calibration between patients using the device. The company states that it is suitable for use in clinic or at home. It is also suitable for adults and children.[9,16]

Easy-to-follow on-screen instructions

1   Empty lungs.

2   Inhale deeply through disposable filter.

3   Exhale through filter.

4   View results on screen.

3 POLICY QUESTION

Should exhaled nitric oxide measurement using NIOX or NIOX MINO be used in Ministry of Health facilities for respiratory diseases?

4 OBJECTIVE

The objective of this report is to assess the clinical and economic implications of exhaled nitric oxide measurement using NIOX or NIOX MINO. The following research questions were addressed:

i.   The safety aspect of exhaled nitric oxide measurement using NIOX or NIOX MINO

ii.   The accuracy and effectiveness of using exhaled nitric oxide measurement in the management of respiratory diseases especially asthma with regards to diagnosis, monitoring and compliance

iii.   The cost effectiveness of exhaled nitric oxide measurement using NIOX or NIOX MINO when used in the management of asthma

5 METHODOLOGY

5.1 Literature search strategy

Electronic database were searched for published literatures pertaining to exhaled nitric oxide. The searches included PUBMED, OVID, ProQuest, Cochrane databases, Food and Drug Administration (FDA) and HTA databases and related links. Google was used to search for additional web-based information. Additional articles were identified from reviewing the bibliographies of retrieved articles. There was no limitation in the search. The following search terms were used either singly or in combination: exhaled nitric oxide, asthma, respiratory diseases, NIOX, NIOX MINO, safe*, adverse events, side effects, complication, cost, cost effectiveness and cost analysis.

5.2 Selection criteria and method

Studies that were included met the following criteria:

i.   Only studies in human were included

ii.   Study design   :   All study design

iii.   Population group   :   Adults and children with respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), chronic bronchitis and bronchiectasis

iv.   Interventions   :   Exhaled nitric oxide measurement

v.	Comparators	:	Spirometry, airway hyper-responsiveness, induced sputum eosinophils, clinical symptoms
vi.	Outcomes	:	For studies to be included, they were required to have reported on at least one of the following:

- Safety, adverse events or complications

- Diagnostic yield of exhaled nitric oxide – sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), receiver operating characteristic (ROC) and area under receiver operating characteristic curve (AUC) in asthma and respiratory diseases, correlation of FE_{NO} with clinical parameters, induced sputum eosinophils, bronchial hyper-responsiveness

- Asthma monitoring – titration of inhaled corticosteroids, predictor of steroid response and predicting loss of control of asthma

- Cost analysis

5.3   Data extraction

All the relevant articles were retrieved and appraised by two reviewers using Critical Appraisal Skills Programme (CASP) depending on the type of study design.[17] Data was extracted from eligible articles and presented in the Evidence Table Appendix 4 and was discussed with the expert committee before deciding on the eligibility of articles to be included in this report. Only primary studies were included in the results and discussion. Letters to editor, narrative review articles, editorials and commentaries were excluded. All full text articles were classified according to the levels of evidence for assessing diagnosis and intervention using Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001).[18] Appendix 2

6   RESULTS AND DISCUSSION

Search strategies yielded many published articles related to exhaled nitric oxide measurement (FE_{NO}) as a marker of airway inflammation for diagnosis and monitoring of asthma. Few articles were retrieved on other respiratory diseases such as COPD, bronchiectasis and chronic bronchitis. A total of 684 articles were cited and 107 potentially relevant articles were yielded. Out of the 107 potentially relevant articles, 38 articles were presented in the evidence tables for safety, diagnosis, monitoring and cost effectiveness of asthma and other respiratory diseases. The articles included one systematic review by The Cochrane Collaboration, two technology reviews by the National Horizon Scanning Centre, University of Birmingham and Canadian Coordinating Office for Health Technology Assessment and also diagnostic studies.

6.1. SAFETY

Measurement of fractional concentration of exhaled nitric oxide (FE_{NO}) using chemiluminescence gas analyzer such as NIOX or electrochemical sensor technology such as NIOX MINO had been practised in many countries such as New Zealand, Brazil, Hong Kong, United States, Australia, Netherlands, Switzerland, Spain, Greece, France and United Kingdom.

Exhaled Nitric Oxide Measurement System (NIOX)
According to US FDA, NIOX is classified under class 11 (Special Controls). NIOX received a Medical Device Licence from Health Canada in 2004 and US Food and Drug Administration (FDA) marketing approval in 2003.[15] [level 1a]

NIOX MINO airway inflammation monitor
It is CE marked and approved. Launched in UK in 2005.[9] [level 1a] NIOX MINO is 510(k) cleared (K072816) by the U.S. Food and Drug Administration (FDA) for clinical use. NIOX MINO is now approved for use in both adults and children.[19] According to the technology review conducted by the National Horizon Scanning Centre, University of Birmingham, no adverse events have been reported.[9] [level 1a]

6.2. EFFECTIVENESS

6.2.1 Asthma

I. **Studies conducted using chemiluminescence NO analyzer such as NIOX.**

a) Asthma diagnosis
Among the methods of assessment of airway inflammation, the measurement of the expired gases is the most non invasive. Fractional exhaled nitric oxide (FE_{NO}) is a marker of airway inflammation rather than an endogenous modulator of bronchial tone in asthma.[20] [level 1b] FE_{NO} is usually elevated in asthma. Several studies have demonstrated that FE_{NO} measurement might be useful for diagnosis of asthma and its relationship with other markers of asthmatic inflammation.

Two key studies have prospectively evaluated the diagnostic utility of FE_{NO} in patients with undiagnosed symptoms.[21, 22] The accuracy of exhaled nitric oxide levels for the diagnosis of asthma was evaluated by Dupont LJ, Demedts MG and Verleden GM. Two hundred and forty consecutive non smoking, steroid naive adult patients suggestive of

obstructive airway disease, were investigated. Asthma was diagnosed in 160 patients on the basis of the presence of significant airways reversibility (FEV_1 > 12% predicted) and/or airways hyper-responsiveness (provocative concentration of histamine causing a 20% fall in FEV_1 d" 8 mg/mL). The mean exhaled NO level was significantly higher in patients with asthma than in non asthmatics [(25 parts per billion (ppb), 95% CI = 23 to 28 ppb) versus (11 ppb, 95% CI = 10 to12 ppb), p < 0.001]. The measurement of exhaled NO in the study population showed, at a cut off level of 16 ppb, with 90% specificity for the diagnosis of asthma and > 90% positive predictive value (PPV).[21] [level 1b]

In another study, Smith et al. compared the diagnostic utility of FE_{NO} measurements and induced sputum eosinophils to the conventional tests such as peak flow measurements and spirometry in diagnosing asthma. His study involved 47 consecutive patients with symptoms suggestive of asthma. The sensitivity for each of the conventional tests varies from 0% to 47%. However, this was found to be lower than FE_{NO50} at >20 ppb, with sensitivity of 88% and; sputum eosinophils at >3%, with sensitivity of 86%. The specificity, PPV and NPV for FE_{NO50} at >20 ppb, was 79%, 70% and 92% respectively. The specificity, PPV and NPV for sputum eosinophils at >3%, was 88%, 80% and 92% respectively. Diagnostic accuracy for conventional tests was found to be also lower compared to $FE_{NO\ 50}$ and sputum eosinophils. AUC for $FE_{NO\ 50}$ was 0.864 and AUC for sputum eosinophils was 0.861. There was a significant positive correlation between $FE_{NO\ 50}$ and sputum eosinophils (r=0.67, p <0.01).[22] [level 1b]

The ability of exhaled nitric oxide (eNO) to diagnose asthma in patients with non-specific respiratory symptoms compared to bronchial provocation tests such as exercise, methacoline (MCH), and adenosine-5'-monosphosphate (AMP) challenges was studied by Berkman et al. Patients were considered asthmatic based on clinical follow up 24 months after testing. Forty patients were considered asthmatic and 45 were not. The AUC under ROC showed values of 0.896 for eNO, 0.781 for exercise, 0.924 for MCH, and 0.939 for AMP. A comparison of AUC for eNO with other tests showed that there was a significant difference for eNO versus exercise and eNO versus AMP (p = 0.033 and 0.085 respectively). A cut off value of NO > 7 ppb at a flow rate of 250 ml/s best differentiates between asthmatic and non-asthmatics (sensitivity 82.5%, specificity 88.9%). The authors concluded that measurement of eNO can be used as safe, simple and rapid test for diagnosis of asthma and is as good as bronchial provocation tests.[23] [level 1b]

Balboa et al. in his study involving 105 healthy children aged 6-14 years and 79 asthmatic children aged 6-14 years demonstrated that children with asthma of various degrees of severity have a significantly higher expired NO than healthy children (15.02 ppb versus 5.40 ppb, p<0.01).[5]

A study involving younger children (age 3.8-7.5 years), was conducted by Malmberg et al. to compare the value of exhaled nitric oxide (FE_{NO}), baseline lung function and bronchodilator responsiveness in identifying children with newly detectable probable asthma. The analysis of ROC showed that FE_{NO} provided the best power for discriminating between children with probable asthma and healthy controls (AUC = 0.91, 95% CI 0.64-0.96). The optimal cut off level for FE_{NO} was 1.5 SD, corresponding approximately to a value of 9.7 ppb giving a sensitivity of 86% and specificity of 92%. In comparison, AUC for lung function was 0.77 and AUC for bronchodilator responsiveness measured using impulse oscillometry (IOS) was 0.76. [24 level 1b]

In another study, Zietkowski et al. compared exhaled nitric oxide measurement with conventional tests used in diagnosis of asthma in 101 steroid-naive asthmatics. [25 level 1b] Compared to the healthy volunteers, FE_{NO} was elevated in both groups of allergic and non allergic asthmatics. In allergic and non allergic asthmatics, FE_{NO} was found to be significantly correlated with:

- bronchial hyper-responsiveness to histamine (allergic asthma, r = - 0.62, p < 0.0002 and non allergic asthma, r = - 0.41, p < 0.01)

- reversibility of airway obstruction after $\hat{a}_2$ agonist inhalation (allergic asthma, r = 0.51, p < 0.02 and non allergic asthma, r = 0.47, p < 0.03)

- serum eosinophil cationic protein (ECP) levels (allergic asthma, r = 0.57, p < 0.0005 and non allergic asthma, r = 0.47, p < 0.01)

- blood eosinophil count (allergic asthma, r = 0.69, p < 0.0002 and non allergic asthma, r = 0.64, p < 0.0001)

  There was no correlation between FE_{NO} with baseline FEV_1 in neither group of asthmatics. In 31% of non allergic and 9% of allergic patients, FE_{NO} was less than 20 ppb.[25 level 1b]

The correlation of FE_{NO} with other inflammatory markers such as sputum eosinophil count is further demonstrated by Berry et al. and Payne et al.[26,27] Berry et al. demonstrated that there was a significant positive relationship between exhaled NO and sputum eosinophil count ($R^2 = 0.26$, P <0.001) which was best described using non-linear model. In non-smokers, an exhaled NO concentration of >8.3 ppb at 250 mL/s gave 71% sensitivity and 72% specificity for identifying a sputum eosinophil of >3%.[26 level 1b]

Payne et al. demonstrated the relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma, after treatment with oral prednisolone. There was a correlation between FE_{NO} and eosinophil score (r = 0.54, p = 0.03). The relationship was strongest in patients with persistent symptoms after prednisolone, in whom the FE_{NO} > 7ppb was associated with a raised eosinophil score. For all patients, FE_{NO} < 7 ppb was associated with an eosinophil score within the non asthmatic range, regardless of symptoms.[27] [level 1b]

In another study, Fortuna et al. demonstrated that combined used of FE_{NO} measurement and induced sputum eosinophil count to diagnose asthma in clinical practice is more accurate than spirometry or FE_{NO} assessment alone. Twenty-two of the 50 patients presenting with asthma symptoms were diagnosed as asthma. The sensitivity and diagnostic accuracy were higher for FE_{NO} measurement (77%; AUC = 0.8) than for spirometry (22%; AUC = 0.63). The sensitivity, specificity and AUC for induced sputum eosinophil count were 40%, 82% and 0.58 respectively. When FE_{NO} and sputum eosinophil count were used together specificity increased to 76%.[28]

b) **Asthma monitoring**

The original NIOX system has been shown to yield reproducible measurements (without day to day variation) and easy to use and non-invasive test for monitoring asthma status. Kharitonov et al. in a study involving 59 subjects (40 children aged 7-13 years and 19 adults aged 18-60 years) both healthy (n = 30) and with mild asthma (n = 29) showed that the coefficient of reproducibility expressed as the mean pooled standard deviation (n = 59, 675 estimations) was 2.1 ± 1.25 parts per billion and interclass correlation coefficient was 0.99 in both children and adults. The repeatability of the FE_{NO} measurements as measured by the Bland-Altman limits of agreement was ± 2.92 ppb. FE_{NO} was significantly higher in asthma subjects (32.3 ppb) than in healthy subjects (16.36 ppb). There was no diurnal or day to day variation or learning effects.[29] [level 1b]

c) **Response to inhaled corticosteroid**

The use of exhaled nitric oxide as a predictor of steroid response was evaluated by Smith et al. involving 60 consecutive patients referred for investigation for persistent undiagnosed respiratory symptoms. Subjects with baseline FE_{NO} levels in the highest tertile (> 47 ppb) had significantly lower FEV_1 percent predicted and FEV_1/FVC ratio. Significantly greater improvement in FEV_1 with bronchodilator compared to the other two tertiles was also demonstrated. They also had a significantly greater response to inhaled fluticasone for all four categories of "Steroid response" (increase in FEV_1, increase in mean morning peak flows, improved respiratory

symptoms, and reduction in air-way hyper-responsiveness to provocative concentration of AMP resulting in 20% reduction in $FEV_{1)}$. The predictive values for FE_{NO} were significantly greater than for almost all other baseline predictors (peak flow variation, provocative dose of metacholine resulting in 20% reduction in FEV1, FEV_1% predicted, FEV_1 bronchodilator response) with optimum cut-off point of 47 ppb.[30] [1evel 1b]

d) Tailoring asthma interventions based on exhaled nitric oxide.

A systematic review was conducted by Cochrane Collaboration to assess the efficacy of tailoring asthma interventions based on exhaled nitric oxide in comparison to clinical symptoms (with or without spirometry / peak flow) for asthma related outcomes in adults and children. [31] [level 1a] The review included four studies. Two studies were conducted in children by Fritsch et al. and Pijnenburg et al. One study was conducted in adult patients by Shaw et al.. The other study was conducted by Smith et al. combining children and adults. This systematic review has limitations due to these studies differed in a variety of ways including definition of asthma exacerbations, FE_{NO} cut-off levels and duration of study. Of the 356 participants randomised, 324 completed the trials. In the meta-analysis, there was no difference between groups for the primary outcome of asthma exacerbations or for other outcomes (clinical symptoms, FE_{NO} level and spirometry). In post-hoc analysis, a significant reduction in mean final daily dose inhaled corticosteroid (ICS) per adult was found where treatment was based on FE_{NO} in comparisons to clinical symptoms; [Weighted Mean Difference (WMD) fixed = -282.42 (95% CI= -421.81 to -143.03)]. There was no difference in ICS dose between the groups in the overall daily dose in the adult studies or in the paediatric studies.[31] [level 1a]

e) Predicting loss of control of asthma

The usefulness of exhaled nitric oxide (eNO) for diagnosing and predicting loss of control (LOC) in asthma following steroid withdrawal was evaluated by Jones et al. There were highly significant correlations between the changes in eNO that occurred between visits 1 and F (final visit) and, the changes in symptoms, FEV_1, sputum eosinophils and dose of saline causing 15% fall in FEV_1 (saline $PD_{15)}$. Correlation between eNO and symptoms, $p < 0.0001$, eNO and $FEV_{1,}$ $p < 0.002$, eNO and sputum eosinophils, $p < 0.0002$ and eNO and saline $PD_{15,}$ $p < 0.0001$. There were significant differences between LOC and no LOC groups. Both single measurements and changes of eNO (10 ppb, 15 ppb, or an increase of > 60% over baseline) had positive predictive values that ranged from 80% to 90% for predicting and diagnosing LOC. The authors concluded that eNO measurements are as useful as induced sputum analysis and airway hyper-responsiveness (AHR). [32] [level 1b]

Prieto et al. evaluated the utility of the determination of airway responsiveness to inhaled 5'-monophosphate (AMP) and exhaled nitric oxide (eNO) levels as markers for safely reducing the dose of inhaled corticosteroids (ICS) in patients with asthma who were well controlled with a moderately high ICS dose. Using a Kaplan-Meier survival analysis, the significant predictors of a failure of ICS reduction were having both bronchconstriction in response to AMP and eNO levels i.e e" 15 ppb at baseline (p= 0.006), as well as having both bronchconstriction in response to AMP and eNO levels e" 20 ppb at baseline i.e (p= 0.033).[33 level 1b]

The use of exhaled nitric oxide to predict success or failure of reduction of inhaled steroids among children was evaluated by Zacharasiewicz et al. Forty children with stable asthma eligible for inhaled steroids reduction were reviewed every 8 weeks, and their inhaled steroid dose was halved if clinically indicated. Exhaled nitric oxide (eNO), sputum induction combined with bronchial hyper-reactivity testing, and exhaled breath condensate collection were performed at each visit to predict success or failure of reduction of inhaled steroids. Treatment reduction was successful in all children who had no eosinophils in induced sputum before the attempted reduction. Using multiple logistic regression, increased eNO [eNO e" 22 ppb (OR, 6.3; 95% CI = 3.75-10.58)] and percentage of sputum eosinophils (OR = 1.38; 95% CI = 1.06 – 1.81) were significant predictors of failed reduction. [34 level 1b]

In contrast, Lueppi JD et al. in his study involving 50 subjects age (18-69 years) with well controlled asthma demonstrated the significant predictors of a failure of inhaled corticosteroid (ICS) reduction. These were: i) being hyper-responsiveness to both histamine and mannitol at baseline (p=0.039), ii) being hyper-responsive to mannitol during the dose-reduction phase of the study (p=0.02). Subjects older than 40 year of age tended to be at greater risk of ICS reduction failure (p=0.059). Response to mannitol and percentage sputum eosinophils were significantly greater before a failed ICS reduction than before the last successful ICS reduction, whereas there were no significant differences in symptoms, spirometry, or eNO.[35 level 1b]

f) Predictor of exercise induced bronchoconstriction

Exercise induced bronchoconstriction (EIB) is of a particular important in children with asthma. It is an important measure of asthma control and should be monitored by exercise testing. However, an exercise test requires complex equipment with a treadmill, dry air supply, and pulse monitoring. The value of FE_{NO} as a predictor of EIB in asthmatic children is studied by Buchvald F et al. FF_{NO} and response to a standardized submaximal exercise

test on the treadmill were measured in 111 school children with asthma. EIB can be excluded with the probability of 90% in asthmatic children with FE_{NO} levels < 20 ppb without current inhaled corticosteroid treatment, and < 12 ppb in children with current inhaled corticosteroid treatment. The authors concluded FE_{NO} measurement is a cost-saving procedure that can be used in paediatric asthma management as a rapid and feasible screening tool to assess the need for exercise testing in children with asthma .[36 level 1b]

g) Compliance with inhaled corticosteroid

Katsara M et al. demonstrated the relationship between eNO levels and compliance with inhaled corticosteroids in twenty asthmatic children. There was a weak but non-significant correlation between eNO and both, day (r = 0.055, p = 0.67) as well as dose (r = 0.153, p = 0.23). [37 level 1b]

II. Studies conducted using NIOX MINO as exhaled nitric oxide analyzer

a) Asthma diagnosis

Studies comparing exhaled nitric oxide measurements from the original NIOX system with the new NIOX MINO device showed there was agreement between the two devices.[38,39,40,41,42,43,44] Alving et al. in his study involving 71 subjects showed that the success rate was high (e" 84%) in both devices for adults and children. The subjects included were having an FE_{NO} range of 8-147 ppb. The Bland-Altman plot shows agreement between the NIOX and NIOX MINO when comparing the mean of three valid nitric oxide measurements. The median of the intra-subject FE_{NO} difference was -1.2ppb, thus NIOX MINO gave FE_{NO} readings that were generally slightly higher than the FE_{NO} measurements obtained using NIOX. The 95% limit of agreement was -9.8 and 8.0 ppb. The same degree of agreement was obtained when comparing the mean of the three approved exhaled measurements in the NIOX and the first approved measurement in NIOX MINO. The median of the intra-subject FE_{NO} difference was -2.0. The 95% limit of agreement was -13.2 and 1.2 ppb. Repeatability was similar in the NIOX and the NIOX NINO. The median repeatability for NIOX and NIOX NINO was 1.1 and 1.2 respectively.[38 level 1b]

In another study by Menzies D, Nair A and Lipworth BJ involving 101 asthmatic patients and healthy volunteers showed that there was good correlation between the measurements obtained using NIOX and NIOX MINO in asthmatics patients (r = 0.94; p < 0.001) as well as healthy volunteers (r = 0.96; p < 0.001). Altman-Bland plots confirmed this agreement. Receiver operating characteristics curves indicated a sensitivity of 83.2% for identifying asthmatic patients from healthy volunteers using a cut off of 13 ppb for NIOX and 12.5 ppb for NIOX MINO device.[39 level 1b]

Agreement with the existing 'gold standard' FE_{NO} measurement technique, were further emphasised by Hemingsson T et al. [40 level 1b] Khaili B et al. in his study showed that there was a very strong correlation between FE_{NO} measurements by NIOX and NIOX MINO (r = 0.98, p < 0.0001). [41] Similarly Sojivari et al. showed that there was linear interdevice correlation coefficient for FE_{NO} 0.992 (p < 0.0001). [42] Similar findings was noted by Torre et al. The inter-device (NIOX versus NOX MINO) correlation coefficient was 0.99 (p < 0.0001). The repeatability coefficient (CoR) was 7.7%. [43.] In another study Sardon et al. concluded that there was good agreement between the FE_{NO} values measured with the two devices (Cohen's Kappa statistic = 0.78).[44]

McGill C, Malik G and Turner SW showed that intraclass correlation co-efficient for mean FE_{NO} values obtained from NIOX and NIOX MINO was 0.986 (95 % CI = 0.972 to 0.993). Paired mean FE_{NO} values were obtained from 34 children and the values were higher for the NIOX (mean difference 3.9 ppb limits of agreement -1.1 to 8.9). The differences between analysers became greater at higher FE_{NO} values. The mean first acceptable FE_{NO} value using the NIOX MINO was 24 ppb and the mean of all FE_{NO} values using the MINO was 27 ppb (difference was not significant). Exhaled NO values were comparable between the two analysers although there was greater consistency at lower values. [45]

The ability of exhaled nitric oxide (FE_{NO}) measurements to improve management and confidence in patients presenting with non-specific respiratory symptoms was evaluated by Hewitt et al. In his observational study based in a large primary care practice (15,500 patients, 14 GPs), showed that in 94% (48/51) of cases, FE_{NO} was considered significant in formulating a diagnosis. Spirometry was deemed helpful in (54%) 27/51. The authors concluded that FE_{NO} measurements improved diagnostic confidence when assessing non-specific respiratory symptoms.[46 level 3b]

b) Asthma monitoring

The feasibility of exhaled nitric oxide monitoring in allergic asthmatic children who were exposed to relevant allergens in their homes was studied by Bodini et al.[47] Significant differences were seen between the mite-free baseline FE_{NO} level (26.4 ppb with a range of 19.3 ppb to 36.3 ppb) and FE_{NO} levels measured during natural mite exposure (37.3 ppb with a range of 27.3 ppb to 51 ppb) and after natural mite exposure (34.9 ppb with a range of 25.2 ppb to 48.2 ppb). Six children reported asthma symptoms during mite exposure, and an increased in FE_{NO} in each case (p <0.031). Peak

expiratory flow (PEF) values showed no significant differences in all the environments. He concluded that there was a possible role of frequent determinations of FE_{NO} in order to promptly assess changes in level of airway inflammation in asthmatic children. [47] Similarly, Vahlkist S et al. demonstrated that daily FE_{NO} (NIOX MINO) increased significantly (p < 0.01) with increasing pollen count. FE_{NO} (NIOX MINO) and FE_{NO} (NIOX) exhibited a correlation coefficient of 0.98, but FE_{NO} (NIOX MINO) was significantly higher than FE_{NO} (NIOX) (p <0.01). Peak expiratory flow rate (PEFR) and FEV_1 remained unchanged.[48]

Pijnenburg et al. assessed the feasibility and analyzed the variability of daily exhaled NO (FE_{NO}) home measurement using a new hand-held NO-analyzer. Twenty-one asthmatics (mean age 14.5 yr; range 8-25 yr) participated. Nineteen used stable dose of inhaled corticosteroid and all are in stable condition. FE_{NO} was measured twice daily for 14 consecutive days. Measurements and symptoms score were recorded on a smart card in the analyzer. Measurements showed a success rate of 93%. The authors found significant diurnal variation in FE_{NO} with geometric mean morning levels 14% higher than evening levels (95% CI = 4% to 25%; p = 0.013). Individual subjects showed fluctuation of FE_{NO} . The mean intrasubject coefficient of variation of FE_{NO} was 40% for morning and 36% for evening values. The difference in coefficient of variation for morning and evening values was not significant (p = 0.35). FE_{NO} and cumulative symptom scores did not correlate. The authors concluded that home FE_{NO} measurements are feasible, and offer the possibility to assess airway inflammation on a daily basis.[49] level 3b

6.2.2 Other respiratory diseases (chronic obstructive pulmonary disease (COPD), chronic bronchitis and bronchiectasis)

The possibility of using exhaled NO to differentiate airway inflammation in patients with fixed airflow obstruction due to asthma or COPD was evaluated by Fabbri et al. Forty six consecutive outpatients presenting with fixed airflow obstruction due to either COPD (n=27) or asthma (n=19) were studied. Subjects with a history of COPD and asthma had similar degree of fixed flow obstruction (FEV_1: 56 ± 2% versus 56 ± 3% predicted) and airway hyper-responsiveness ($PC_{20}FEV_1$, mean 2.81[SD= 3.1] versus mean 1.17 [SD= 3.3]). However, exhaled NO and sputum eosinophils were most reliable measurements to distinguish asthma and COPD. Subjects with asthma had a significantly higher eosinophils and exhaled nitric oxide (37.5 ± 9.2 ppb versus 11.1 ppb; p < 0.01). For sputum eosinophils the best cut off point was 4.6% (with a sensitivity of 0.96 and a specificity of 0.74). This indicated that values higher than or equal to 4.6% predicted history of asthma, whereas values lower than 4.6% predicted a history of COPD. For exhaled nitric oxide, the best cut off point was 16 ppb, which had a sensitivity of 0.91 and a specificity of 0.77. Values higher than 16 ppb predicted history of asthma, whereas values lower than 16 ppb predicted a history of COPD.[50] level 1b

Liu et al. in a cross sectional study involving 96 COPD patients and 80 normal subjects, demonstrated that exhaled nitric oxide levels in COPD patients were significantly higher than those of normal subjects (9.8 ± 0.7 ppb versus 5.5 ± 0.4 ppb, p < 0.005). Nitrite/nitrates (NOx) levels in exhaled breath condensate (EBC) were weakly correlated with eNO levels (pearson r = 0.20, p = 0.03).[51 level 1b]

In contrast, Delen et al. in his study involving 179 consecutive patients referred for routine pulmonary function testing with two control groups namely patients control subjects (n= 18), and outside control subjects, (n=20), showed that among non smokers, the levels of exhaled NO were significantly higher in patients with chronic bronchitis (17 ± 1.1 ppb; p = 0.035) and asthma (16.4 ± 1.3 ppb; p = 0.05) when compared to either control groups (patient control subjects, 11.1 ± 1.6 ppb; outside control subjects, 11.5 ± 1.5 ppb). In contrast, exhaled nitric oxide was not significantly increased in 59 nonsmoking patients with COPD (14.7 ± 1.0 ppb).[52 level 1b]

Tsang et al. conducted a study to determine the levels of exhaled and sputum nitric oxide in 109 patients with stable bronchiectasis and 78 control subjects by using automatic chemiluminescence analyzer. He demonstrated that there was no significant difference in exhaled nitric oxide between patients with bronchiectasis and control subjects (p = 0.11). Bronchiectasis patients with *Pseudomonas aeruginosa* infection in their sputum had a significantly lower exhaled nitric oxide levels when compared to their counterparts and control subjects (p = 0.04 and p = 0.009, respectively).[53 level 1b]

6.3   COST EFFECTIVENESS

6.3.1 NIOX

There was no retrievable evidence on the cost effectiveness of measurement of fractional concentration of exhaled nitric oxide (FE_{NO}) using NIOX for diagnosis and monitoring of asthma. However, a NIOX system is sold as a Start Package that includes computer, software, monitor, keyboard, calibration gas, installation and training. The US price is US$43,000. The operational costincludes US$94 every 6 months to replace the NO scrubber (the filter that provides the instrument and the patient with NO-free air) and US$1,400 every 12 months for calibration gas. The NIOX system should be serviced every 18 months (US$3,000). There is a per test cost of US$4 for each disposable mouth piece filter.[15 level 1a]

6.3.2   NIOX MINO

The procurement cost of NIOX MINO device is £2,100 (an estimated £5 per test).[9 level 1a] Berg J and Lindgren P conducted an economic evaluation of FE_{NO} measurement in diagnosis and 1-year management of asthma in Germany. Two decision trees were constructed to capture the different alternatives and consequences in asthma diagnosis and management, comparing FE_{NO} measurement against standard diagnostics and treatment guidelines. A German payer perspective was chosen. Effectiveness was measured in quality-adjusted life-years. The impact of asthma management with FE_{NO} measurement on resource use and health outcomes was evaluated over a 1-year timeframe. Asthma diagnosis based on FE_{NO} measurement results in a cost of 38 per patient compared with 26 for standard diagnostics. In mild to severe patients, asthma management with FE_{NO} measurement instead of standard guidelines results in cost-savings of 30 per patient. In a more severe population, management with FE_{NO} measurement would save costs of 160 per patient. The use of FE_{NO} measurement in treatment decisions is less costly than asthma management based on standard guidelines which provides similar health benefits.[54]

6.4   SETTING AND TRAINING

All studies were conducted in University Hospitals, or Hospitals with Respiratory Departments / Units with exception of one study which was conducted in a general practitioner setting. Training on the measurement techniques and interpretation of FE_{NO} values is essential.

7   CONCLUSION

7.1   Safety

There was evidence to show that FE_{NO} measurement is safe and non invasive.

7.2   Effectiveness

7.2.1 Asthma

The advent of FE_{NO} measurement is a major advance in lung function assessment, providing relevant information about airway inflammation in patients with asthma. There was good evidence to show that:

- Compared to conventional tests, FE_{NO} measurement provides superior diagnostic accuracy in the diagnosis of asthma

- Good correlation for the FE_{NO} values measured with the two devices (Original NIOX system with the new NIOX MINO)

- There was a significant correlation between FE_{NO} and sputum eosinophils but there was no correlation between FE_{NO} and baseline FEV_1

- Exhaled nitric oxide measurement can be used as a predictor of steroid response and loss of control (LOC) in asthma following steroid withdrawal

  However, there was limited evidence to establish the relationship between exhaled nitric oxide levels and compliance with inhaled corticosteroids.

7.2.2 Other respiratory diseases

The role and clinical use of exhaled nitric oxide measurements have not been fully established in COPD since studies report conflicting results. More clinical data is needed for the use of exhaled nitric oxide measurement in chronic bronchitis and bronchiectasis.

7.3   Cost effectiveness

There was evidence to show that the use of FE_{NO} measurement in treatment decisions is less costly than asthma management based on standard guidelines and provides similar health benefits.

8   RECOMMENDATION

i.   Based on the above review, it is recommended that exhaled nitric oxide measurement can be used in Ministry of Health facilities with chest physicians (adult and paediatric) particularly for diagnosing and monitoring of asthma.

ii.   The new NIOX MINO is preferred because it is smaller, portable and costs a fraction of the original NIOX system. It does not require regular calibration and has been shown to be equally reliable and repeatable as the original system.

iii.   More clinical research is warranted for other respiratory diseases such as COPD and bronchiectasis.

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APPENDIX 1

Definition of abbreviations.

NO	Nitric oxide
eNO	Exhaled nitric oxide also ENO
FENO	Fractional concentration of orally exhaled nitric oxide also FENO , FE(NO), FENO
BHR	Bronchial hyper-responsiveness
FEV$_1$	Forced expiratory volume in 1 second
FVC	Forced vital capacity
PER	Peak expiratory flow
PEFR	Peak expiratory flow rate
MHC	Metacholine
AMP	Adenosine -5'-monophosphate
PD$_{15}$	Dose of saline causing 15% fall in FEV$_1$
ICS	Inhaled corticosteroids
COPD	Chronic obstructive pulmonary disease
ATS/ERS	American Thoracic Society / European Respiratory Society
PPV	Positive Predictive Value
NPV	Negative Predictive Value
ROC	Receiver operating characteristic
AUC	Area under receiver operating characteristic curve

Levels of Evidence Scale   - Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)

Level	Therapy/Prevention, Aetiology/Harm	Prognosis	Diagnosis	Differential diagnosis/ symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval‡)	Individual inception cohort study with > 80% follow-up; CDR† validated in a single population	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts††	All or none case-series	Absolute better-value or worse-value analyses ††††
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† or validated on split-sample§§§ only	Exploratory** cohort study with good†††reference standards; CDR† after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998.

Notes : Users can add a minus-sign "-" to denote the level of that fails to provide a conclusive answer because of:
- EITHER a single result with a wide Confidence Interval (such that, for example, an ARR in an RCT is not statistically significant but whose confidence intervals fail to exclude clinically important benefit or harm)
- OR a Systematic Review with troublesome (and statistically significant) heterogeneity.
- Such evidence is inconclusive, and therefore can only generate Grade D recommendations.

*	By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
†	Clinical Decision Rule. (These are algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category.)
‡	See note #2 for advice on how to understand, rate and use trials or other studies with wide confidence intervals.
§	Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
§§	By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.
§§§	Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
††	An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.
‡‡	Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.
†††	Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.
††††	Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.
**	Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.
***	By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.
****	Good follow-up in a differential diagnosis study is > 80%, with adequate time for alternative diagnoses to emerge (eg 1-6 months acute, 1-5 years chronic)

Grades of Recommendation

A	consistent level 1 studies
B	consistent level 2 or 3 studies or extrapolations from level 1 studies
C	level 4 studies or extrapolations from level 2 or 3 studies
D	level 5 evidence or troublingly inconsistent or inconclusive studies of any leve

"Extrapolations" are where data is used in a situation which has potentially clinically important differences than the original study situation.

APPENDIX 3

HEALTH TECHNOLOGY ASSESSMENT (HTA) PROTOCOL
EXHALED NITRIC OXIDE MEASUREMENT USING NIOX OR NIOX MINO

1   BACKGROUND INFORMATION

Several lung diseases including asthma and chronic obstructive pulmonary disease (COPD) involve chronic inflammation of the airways. Therefore there is great interest in non-invasive methods assessing airway inflammation. Measurement of bronchial hyper-responsiveness (BHR) and exhaled nitric oxide (NO) are such indirect markers of airway inflammation. Additional information about severity of disease, prognosis and possible response to anti-inflammatory treatment with corticosteroids can be gained by these methods.

Nitric oxide (NO) is a molecule produced endogenously in the lungs. It can be detected in exhaled air in animals and humans. Nitric oxide can be generated in the air passages by a synthase which is induced in several cell types by exposure to proinflammatory cytokines. Its induction is blocked by glucocorticoids. The presence of endogenous nitric oxide (NO) in exhaled breath of animals and humans was first described in 1991. Soon after, several publications reported high fractional concentrations of orally exhaled NO (FE_{NO}) in subjects with asthma as compared with unaffected subjects and fall after treatment with corticosteroids.   Similar findings have been described in the paediatric age group. Atopy seems to be a significant factor associated with raised exhaled NO. Exhaled nitric oxide concentration may be increased also in other diseases, such as chronic obstructive airway diseases (COPD), bronchiectasis and some connective tissue diseases (SLE and systemic sclerosis).

The American Thoracic Society and the European Respiratory Society issued a joint statement in 2005 to say that NO measurement constitutes a novel way to monitor diseases such as asthma routinely in clinics, provided that a standardised reference data used. The statement proposes that exhaled NO may be used as a marker to diagnose asthma, to monitor the response to anti-inflammatory treatment, to check on patient compliance and to predict upcoming asthma exacerbations.

Most NO analyzers in research and clinical use employ the principle of ozone -/NO_2-based chemiluminescence to measure NO. However, NO measurement based on alternative technologies including luminal-H2O2-based chemiluminescence, tunable diode laser spectrometry, and laser magnetic resonance spectrometry, is currently available or in development. New technologies offer potential advantages regarding increased portability, reduced cost, and autocalibration. Currently, nitric oxide measurement system (NIOX) or a new NIOX MINO are usually use as NO analyzers in many research and clinical use.

2   POLICY QUESTION

Should exhaled nitric oxide measurement using NIOX or NIOX MINO be introduced in Ministry of Health facilities?

3   OBJECTIVE

To determine the:

i.   The safety aspect of exhaled nitric oxide measurement using NIOX or NIOX MINO

ii.   The accuracy and effectiveness of using exhaled nitric oxide measurement in the management of respiratory diseases especially asthma with regards to diagnosis, monitoring and compliance

iii. The cost effectiveness of exhaled nitric oxide measurement using NIOX or NIOX MINO when used in the management of asthma

4   SCOPE

The scope of this report is regarding the use of exhaled nitric oxide measurement in management of respiratory diseases especially asthma with regard to diagnosis, monitoring and compliance in comparison to competing technologies for similar application

4.1   INCLUSION CRITERIA

4.1.1 Subject criteria: human, all age

4.1.2 Literature: no limit

4.1.3 Technology: exhaled nitric oxide measurement using NIOX or NIOX MINO

4.1.4 Application: for diagnosis, monitoring of asthma and other respiratory diseases

4.1.5 Competing technologies for similar application

4.2   EXCLUSION CRITERIA

Use of exhaled nitric oxide in animal studies

5   ASPECT TO BE CONSIDERED
5.1   SAFETY

The safety aspect of exhaled nitric oxide measurement using NIOX or NIOX MINO

5.2   EFFECTIVENESS

The accuracy and effectiveness of using exhaled nitric oxide measurement in the management of respiratory diseases especially asthma with regards to diagnosis, monitoring and compliance

5.3   COST EEFFECTIVENESS

The cost effectiveness of exhaled nitric oxide measurement using NIOX or NIOX MINO when used in the management of asthma

6   STRATEGY

Adopt or adapt other HTA

New HTA

7   METHODOLOGY

Review existing HTA
Retrieval of evidence
Analysis of evidence
HTA writing
Feedback on draft report and preparation for final report
Presentation of report to HTA TAC
Presentation of report to HTA & CPG Council
Implementation of HTA report

APPENDIX 4

Evidence Table : Safety
Question   : Is exhaled nitric oxide measurement system (NIOX) safe ?

Bibliographic Citation	Emerging Technology List. Nitric oxide measurement system (NIOX) for monitoring response to asthma treatment. Canadian Coordinating Office for Health Technology Assessment. July 2004 No. 22
Study Type / Methodology	Systematic review (5 studies)
LE	1a
Number of patients and patient characteristics	65 asthmatic patients- adults and children Conducted at 9 medical centres in US
Intervention	Tested using NIOX system before they began drug treatment and two weeks later.
Comparison	
Length of follow up (if applicable)	
Outcome measures/ Effect size	FDA approval was based on results from clinical studies (adults and children aged four years and older) with confirmed diagnosis of asthma. Most patients had a 30% to 70% decrease in NO levels two weeks of treatment of inhaled steroids. Exhaled NO levels above 30 parts ppb correlated with severe asthma. Can be used by children over the age of four. Received a Medical Device Licence from Health Canada in 2004 and US Food and Drug Administration (FDA) marketing approval in 2003
General Comments	

Evidence Table : Safety
Question   : Is NIOX MINO airway inflammation monitor for the diagnosis and monitoring asthma safe?

Bibliographic Citation	New and Emerging Technology Briefing. NIOX MINO airway inflammation monitor for the diagnosis and monitoring of asthma. National Horizon Sacnning Centre. The University of Birmingham. July 2005
Study Type / Methodology	Systematic review
LE	1a
Number of patients and patient characteristics	
Intervention	
Comparison	
Length of follow up (if applicable)	
Outcome measures/ Effect size	It is CE marked and approved. Launched in UK in 2005. No adverse events have been reported.
General Comments	

29

Evidence Table : **Effectiveness of FENO measurement using chemiluminescence NO analyzer such as NIOX**

Question : **Is it effective in asthma diagnosis?**

No.1

Bibliographic Citation	Garnier P, Fajac I, Dessanges JF, Dall'Ava-Santucci J, Lochhart A, Dinh-Xuan AT. Exhaled nitric oxide during acute changes of airways caliber in asthma. Eur Respir J. 1996; 9: 1134-1138
Study Type / Methodology	Cross sectional study Lung function parameters (FEV_1) and NO in exhaled air were measured in all subjects at baseline. In 7 of the steroid free asthmatic subjects whose FEV_1 was normal, NO in exhaled air was measured 2,5, 10 and 20 minutes: after methacholine challenge and NO in exhaled air was measured again 10 min after inhalation of salbutamol (400ug).
LE	1b
Number of patients and patient characteristics	43 patients 22 asthmatic patients 10 males, 12 females • mean age 41±4 yrs. • History of mild atopic asthma. • Non smokers • 14 steroid free asthmatics received either no regular treatment or inhaled 2- agonists alone. $FEV_1 = 92.4\pm4$ % • 8 asthmatics were treated with inhaledsteroids (beclomethasone dipropionate or budesonide) on a regular basis.$FEV_1=73\pm7\%$ 21 non atopic controls (healthy subjects) 11 males and 10 females • mean age 34±3 years. • Non smokers • No history of respiratory or CVD or receiving long term medication. $FEV_1= 95\pm2\%$
Intervention	Lung function parameters (FEV_1) and NO in exhaled air.
Comparison	Nil
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	Nitric oxide (NO) concentration and NO output in exhaled air and FEV_1. NO concentration and NO output in exhaled air were sig. higher in steroid- free asthmatic patients (15.6±1.5ppb) and (6.3±0.7 nmol min^{-1})as compared with : • control (8.9±1.0ppb) and (3.5 ±0.3 nmol min^{-1}) [p< 0.001] • steroid treated asthmatic patients (11.3 ±3.3 ppb) and (3.7 ±0.9 nmol min^{-1}) [p< 0.05] Neither NO concentration nor NO output of steroid-treated patients differed from those of control subjects. Neither methacholine induced bronchial constriction nor salbutamol induced bronchial dilatation caused a significant change in exhaled NO **Conclusion:** NO production is : • higher in steroid-free than in steroid – treated asthmatics and in control subjects. • not affected by acute pharmacologically-induced changes of airways caliber in asthmatic subjects. a marker of airways inflammation rather than an endogenous modulator of bronchial tone in asthma.
General Comments	

NO. 2

Bibliographic Citation	Smith A D, Cowan JO, Filsell S, McLachlan C, Monti- Sheehan G, Jackson P, Taylor RD. Diagnosing Asthma Comparisons between Exhaled Nitric Oxide measurements and Conventional Tests. *Am J Respir Crit Care Med*. 2004; 169: 473-478
Study Type / Methodology	Cross sectional study Patients attended on three separate occasions at 2-week intervals. Short acting -agonist and anticholinergic inhalers were permitted during the study, but withheld minimum of 6 hours. Questionare –providing details of respiratory symptoms, affixed diagnostic investigations was performed at each of the study visits. FE_{NO} measurement at 50 ml/second and 250 ml/second flow rate
LE	1b
Number of patients and patient characteristics	47 consecutive patients aged 8–75 years referred by their family practitioner to the Dunedin Hospital (Dunedin, New Zealand).
Intervention	FE_{NO} measurement at 50 ml/second and 250 ml/second flow rate
Comparison	Skin allergy test Spirometry and peak flow recording Bronchodilator reversibility after inhaling 400 µg,of albuterol Bronchial hyper-responsiveness to hypertonic saline challenge Sputum induction, sputum eosinophil Trial of oral prednisone.
Length of follow up (if applicable)	
Outcome measures/ Effect size	FE_{NO} the optimum cut point for diagnosis asthma, based on calculating the predictive accuracy for a range of different FE_{NO} levels, (20 ppb). In contrast conventional lung function tests (spirometry and peak flow recordings) provided substantially lower degrees of diagnosis accuracy. Bronchodilator reversibility and bronchial hyper responsiveness (BHR) were used to define the diagnosis of asthma, similar comparisons could not be made for these tests. Significant bronchodilator reversibility was present in only 7 of 17 patients with asthma (41%) (poorly sensitive). There were significant correlation between FE_{NO} and sputum eosinophils (r=0.67,p<0.001) and PD_{15} (r= -0.56,p<0.001) (Diagnostic test for asthma) -FE_{NO50}.>20ppb- Sensitivity 88%, Specificity -79% ,positive predictive value 70% and negative predictive value=92% Sputum eosinophil s= Sensitivity 86%, specificity 88%,positive predictive value 80% and negative predictive value is 92%. AUC - FE_{NO50} = 0.864 AUC - Sputum Eosinophils= 0.861
General Comments	

NO. 3

Bibliographic Citation	Berkman N, Avital A, Breuer R, Bardach E, Springer C, Godfrey S. Exhaled nitric oxide in the diagnosis of asthma: comparison with bronchial provocation tests. *Thorax* .2005; 60: 383-388
Study Type / Methodology	Cross sectional study Subjects underwent intial measurement of eNO followed by bronchial challenges using metacholine (MCH), exercise, and adenosine-5'-monophosphate (AMP). Provocation tests were performed in random order and in blinded fashion. A minimum of 4 hours washout time was observed between each challenge. Patients were assessed by the investigating physicians 24 months after performing provocation test. A final diagnosis of asthma was made n the blinded fashion.
LE	1b
Number of patients and patient characteristics	Patients with non-specific respiratory symptoms of at least 3 months duration referred to the outpatient pulmonary clinic of Hadasah University hospital for diagnostic evaluation and in whom the consulting respiratory physician considered the possibility of a diagnosis of asthma were included in the study.
Intervention	Exhaled nitric oxide was measured using a chemiluminescence analyser (LR 2000, Logan Research, Rochester UK. 250 ml/second flow rate
Comparison	Spirometric tests were performed using a pnuemotachograph based system. Bronchial challenges for MCH, AMP and exercise were performed according to recommended guidelines.
Length of follow up (if applicable)	24 months
Outcome measures/ Effect size	Forty patients were considered asthmatic and 45 were not. The area under receiver operating characteristic curves gave values of 0.896 for eNO, 0.781 for exercise, o.924 for MCH, and 0.939 for AMP. P = 0.033 for eNO versus evercise, p=0.575 for eNO versus MCH and p=0.085 for eNO versus AMP. A cut off value of NO > 7 ppb at a flow rate of 250 ml/s best differentiates between asthmatic and non-asthmatics (sensitivity 82.5%, specificity 88.9%). Optimal cut off value for other tests were exercise: FEV1≥10% (sensitivity 57.9%, specificity 100%), PC_{20}-MCH:≤ 3mg/ml (sensitivity 87.5%, specificity 86.7%), and PC_{20}-MCH:≤ 150mg/ml (sensitivity 89.5%, specificity 95.6%). **Conclusion** Measurement of eNO can be used as safe, simple and rapid test for diagnosis of asthma and is as good as bronchial provocation tests.
General Comments	

NO. 4

Bibliographic Citation	Balboa De Paz F, Rueda Esteban S, Aleo Lujan E, Rodriguez tauriz G.Exhaled nitric oxide in healthy and asthmatic chidren. *An Esp Pediatr*. 2002; 57 (1) : 12-7
Study Type / Methodology	Cross sectional study in a tertiary hospital The concentration of exhaled nitric oxide was analyzed by chemiluminescence using T technique of exhaling against expiratory resistance with positive mouthpiece pressure in 2 different study groups. Control=105 healthy children Asthma = 97 children
LE	
Number of patients and patient characteristics	105 healthy children aged 6-14 and 79 asthmatic children undergoing asthmatic treatment for at least the previous 2 months, depending on the severity of their disease.
Intervention	Exhaled nitric oxide was measured using a chemiluminescence analyser
Comparison	
Length of follow up (if applicable)	
Outcome measures/ Effect size	Expired NO was significantly higher in the asthma group (15.02 ppb) than in the control group (5.40 ppb0 (p<0.01). No significant differences were found among the asthmatic children in asthma severity. Children with atopic dermatitis showed higher expired NO concentrations (23.07 ppb) than those without atopic dermatitis (11.68 ppb) (p<0.01)
General Comments	Abstract

NO. 5

Bibliographic Citation	Dupont LJ, Demedts MG, Verleden GM. Prospective evaluation of validity of exhaled nitric oxide for diagnosis of asthma. *Chest* .2003; 123: 751-756
Study Type / Methodology	Cross sectional study In each patient, exhaled NO was measured prior to pulmonary function tests and histamine challenge by an operator who was blinded to the patient history and diagnosis. Exhaled NO was measured by means of an Eco Physics CLD 700 AL MED chemiluminescence analyzer, according to the European Respiratory Society and American Thoracic Society Guidelines. Clinical diagnosis was made by an experienced respiratory physician who was unaware of the exhaled NO level, based on the history and the results of pulmonary function and provocation tests and other tests when indicated. The patients were subdivided for further analysis into two subgroups: asthmatics and non asthmatics.
LE	1b
Number of patients and patient characteristics	240 consecutive, non smoking steroid naïve adult patients, with symptoms suggestive of obstructive airway disease (eg. cough, wheezing, episodic dyspnea) who were consecutively referred to the asthma outpatient clinic of the university hospital Gasthuisberg, Leuven, Belgium, for diagnostic evaluation.
Intervention	Exhaled NO was measured by means of an Eco Physics CLD 700 AL MED chemiluminescence analyzer
Comparison	Conventional diagnostic tools. Spirometry was measured both before and 15 min after inhalation of salbutamol, 400 ug, according to American Thoracic Society guidelines. Histamine challenge test was performed according to the method of Cockcroft at al. The provocative concentration of histamine causing a 20% fall in FEV_1 (PC_{20}) was calculated by linear interpolation.
Length of follow up (if applicable)	
Outcome measures/ Effect size	Asthma was diagnosed in 160 patients on the basis of the presence of significant airways reversibility (FEV1 > 12% predicted) and /or airway hyper-responsiveness (provocative concentration of histamine causing a 20% fall in $FEV_1 \leq$ 8mg/mL) The mean exhaled NO level was significantly higher in patients with asthma than in non asthmatics (25 parts per billion (ppb) 95CI -23 to 28 ppb) versus (11 ppb 95 CI -10 -12 ppb) p < 0.001. The specificity of the measurement of exhaled NO for the diagnosis of asthma was maximal at cut off levels of exhaled NO > 16 ppb. At a cut off level of 16 ppb , the specificity for diagnosis of asthma of 90% and a positive predictive value of > 90%
General Comments	

33

NO. 6

Bibliographic Citation	Malmberg LP, Pelkonen AS, Haahtela T, Turpeinen M. Exhaled nitric oxide rather than lung function distinguishes preschool children with probable asthma. *Thorax .* 2003; 58: 494-499
Study Type / Methodology	Cross sectional study
LE	1b
Number of patients and patient characteristics	96 preschool children (age 3.8 – 7.5 years) with asthmatic symptoms or history. The 96 children were divided into 3 groups: First group – children with previously diagnosed asthma on regular medication, treated asthma n=25. Second group – children with persistent or recurrent respiratory symptoms associated with recent (within the previous 3 months) wheezing relieved by β_2 agonist n = 21 Third group – children with chronic (persistent or recurrent) cough only without wheezing episode n = 46. Controls: 62 age matched (4.0 – 7.0 years) healthy non-atopic children attending kindergardens who had satisfactory FE_{NO} and impulse oscillometry (IOS) measurements.
Intervention	Exhaled nitric oxide was measured using chemiluminescence analyzer (CLD 77 AM, Eco Physics, Duenten Switzerland) connected to a computerized system (Exhaled Breath Analyzer, Aerocrine AB) and calibrated with a certified NO calibration gas mixture.
Comparison	Conventional diagnostic tools The lung function was measured by impulse oscillometry (IOS; Jaeger, Wurburg, Germany). Bronchodilator response after salbutamol in a dose of 0.3 mg administered via a Baby haler.
Length of follow up (if applicable)	
Outcome measures/ Effect size	Children with probable asthma (n = 21), had a significantly higher mean (SE) concentration of FE_{NO} than controls (22.1 (3.4) ppb versus 5.3 (0.4) ppb; mean difference 16.8 ppb, 95% CI 12.0 to 21.5) and also higher baseline respiratory resistance, lower reactance, and larger bronchodilator responses expressed as change of resistance after inhalation of salbutamol. Children with chronic cough n=46, also had significantly raised mean FE_{NO} (9.2 (1.5) ppb; mean difference 3.9 ppb, 95% CI 0.8 to 7.0) but their lung function was significantly reduced. Children with inhaled steroids due to previously diagnosed asthma (n = 29) differed from controls only in their baseline lung function. The analysis of receiver operating characteristics (ROC) showed that FE_{NO} provided the best power for discriminating between children with probable asthma and healthy controls (AUC = 0.91, 95% CI 0.64-0.96). The optimal cut off level for FE_{NO} was 1.5 SD, corresponding approximately to a value of 9.7 ppb giving a sensitivity of 86% and specificity of 92%. In comparison, AUC for lung function was 0.77 and AUC for bronchodilator responsiveness measured using impulse oscillometry (IOS) was 0.76.
General Comments	

NO. 7

Bibliographic Citation	Zietkowski .Z, Bodzenta. A, Tomasiak. MM, Skiepko.R, Szmitkowski. M. Comparison of exhaled nitric oxide measurement with conventional tests in steroid-naïve asthma patients. *J Investig Allergol Clin Immunol.* 2006; *16(4):239-46*
Study Type / Methodology	Cross sectional study
LE	1b
Number of patients and patient characteristics	101 steroid-naïve mild to moderate asthmatic patients (56 allergic and 45 non allergic) 39 healthy volunteers as control Allergic asthma n=56; 25 Male: 31 Female Age 32 ± 12 Non allergic asthma n=45; 17 Male: 28 Female Age 40 ± 12 Healthy volunteer n=39 Age 33.5 ± 15.2 Exclusion: Patients who presented that could alter FE_{NO} such as smoking and nitrate rich diet, but not asthma, features of atopy or allergic rhinitis were excluded from the study. Asthmatic patients who had been treated with inhaled steroids in the past were excluded. Patients were allowed to take short and long acting β-agonists
Intervention	FE_{NO} measurement using chemiluminescence technique with a Sievers 280i NO Analyser (Boulder, Colorado, USA) at expiratory flow of 50 mL/s
Comparison	Conventional tests: ○ FEV_1 ○ PC20 histamine FEV_1 ○ Reversibility of airway obstruction ○ Serum ECP and Blood eosinophils ○ Serum IgE Test used for common in routine diagnosis of asthma (baseline lung function, reversibility of airway obstruction bronchial hyperreactivity and other laboratory tests commonly associated with asthma such serum concentration of Ig E, eosinophil cationic protein (ECP) , and peripheral blood eosinophilia
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	Significant positive correlation between FE_{NO} level and serum ECP r=0.57 ,p= 0.005 (allergic asthma) & r=0.47 p=.001(non allergic asthma) and Significant positive correlation FE_{NO} levels and blood eosinophil count in allergic asthma r=0.69,p=.0002 & r= 0.64,p=0.0001 in non allergic asthma FE_{NO} did not correlate with baseline FEV_1 in either allergic asthma (r= 0.02, p=0.87) or non allergic asthma (r= -0.22, p=0.13) Both groups of asthma, FE_{NO} level displayed significant negative correlation with the PC_{20} FEV_1 for histamine (allergic asthma, r=-0.62, p=0.00002; non allergic, r= -0.41, p=0.01) FE_{NO} level correlate significantly with the reversibility of airway obstruction after β_2-agonist inhalation in both groups (allergic, r=0.51, p=0.02; non allergic, r=0.47, p=0.03) Authors' conclusion – High F especially with allergic asthma. FE_{NO} correlates with the results of other tests used in the diagnosis of asthma. FE_{NO} level not correlated with baseline FEV_1 –important in patients with mild asthma since spirometric indices are not very useful in some patients.
General Comments	

NO. 8

Bibliographic Citation	Berry M.A.. Shaw D.E,. Green R.H, Brithtling C.E , Wardlaw A.J. and Pavord I.D. The Use of exhaled nitric oxide concentration to identify eosinophilic airway inflammation : an observational study in adults with asthma. *Clin exp allergy*. 2005;35: 1175-1179
Study Type / Methodology	Cross sectional study Exhaled NO was measured using chemiluminescence analyser (LR2000 Logan Research, Rochester, UK) at an exhalation of 250 mL/s; the mean three recordings of the plateau phase of NO was taken as the expired NO concentration. Sixty randomly selected patients had exhaled NO concentration measured on two chemiluminescence analysers, LR2000 (Logan- Sinclair, Rochester, UK) and NIOX (Aerocrine , Stockholm, Sweden), in random order at exhalation flow of 250mL/s and 10,30,50,100 and 200 mL/s respectively
LE	1b
Number of patients and patient characteristics	566 consecutive patients seen at Glenfield hospital outpatients with stable asthma. All subjects had symptoms of asthma and objective evidence of airway hyper –responsiveness and or/ airflow variability Subjects were classified as smokers (current smokers), ex-smokers (current non-smokers with >5 pack year smoking history) or non smokers (never smokers or ex-smokers with <5 pack year history).+
Intervention	Exhaled NO
Comparison	Measurement airway responsiveness , administration of Salbutamol and sputum collection Measurements- Spirometry using Vitalograph, Morning and evening peak flow was measured using Mini-Wright peak flow meters and skin test was performed using standard techniques. Induced sputum Eosinophil count was expressed as a percentage of non squamus cells based on 400 inflammatory cells.
Length of follow up (if applicable)	
Outcome measures/ Effect size	Outcome – Aim of study was to investigate the relationship between exhaled NO concentration and induced sputum eosinophil count in a large heterogeneous population of adult subjects with asthma and to identify important factors influences this relationship. There was significant association between exhaled NO and sputum eosinophil count in the group as a whole (R^2 0.26,P<0.001) The area under the curves for smokers (AUC= 0.63%,95% CI,048,.0. 78; p=0.10) Ex-smokers AUC= 0.62%,95% CI 0.47,0.77,p=0.09)- not significant different from 0.5 for identifying a sputum eosinophil count > 3% . Non-smoking group the area under the curve for identifying a sputum eosinophil count >3% was 0.77 (95%, CI 0.73,0.82, p<0.001) An exhaled NO concentration of 8.3% p.p.b identified a sputum eosinophils count 3% with 71% sensitivity and 72% specificity. With the exception of 10 mL/s exhalation flow, it did not greatly alter the ability of exhaled NO concentrations to identify the presence of a sputum eosinophilia. The correlation coefficients for the relationship between exhaled NO and sputum, eosinophil counts were broadly similar at all flows.
General Comments	

NO. 9

Bibliographic Citation	Payne DNR, Adcock IA, Wilson NM, Oates T, Scallan M, Bush A. Relationship between exhale nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma, after treatment with oral predinisolone. *American Journal of Respiratory and Critical Care Medicine.* 2001; 163:1376-1381
Study Type / Methodology	Cross sectional study Patients underwent a full conventional assessment. If symptom persisted, they received a corticosteroid trial, followed by bronchoscopy and endobronchial biopsy, to examine the airway pathology and guide individual management. Corticosteroid trial Patients recorded symptoms and bronchodilator use in a diary for 2 weeks, followed by spirometry and measurement of FE_{NO}. Prednisolone, 40 mg/d, was given for 2 week, and the diary was continued. Spirometry and FEno, was repeated, serum prednisolone and cortisol levels were measured and broncoscopy was performed the next day.
LE	1b
Number of patients and patient characteristics	31 children with difficult asthma which was diagnosed according American Thoracic Society (ATS) criteria. Difficult asthma was defined as symptoms requiring bronchodilator $\geq$ 3 d/wk, despite $\geq$ 1600 ug/d of inhaled budesonide (or equivalent) , and regular long-acting β_2 agonist (or a previous unsuccessful trial of long-acting β_2 agonist), and/or regular prednisolone. Controls subject without asthma: 7 children without asthma undergoing bronchoscopy for other clinical indications
Intervention	FE_{NO} measured according to ERS guidelines
Comparison	Spirometry was performed using a portable spirometer according to ATS guidelines. Serum prednisolone and cortisol level using high performance liquid chromatography. Clinical response to prednisolone were examined for the last 7day of corticosteroid trial. Feberoptic bronchoscopy. Bronchoscopy with endobronchial biopsy was performed under general anesthesia using 4.9-mm bronchoscope (Olympus) Processing of biopsies and detection of eosinophils using a mouse monoclonal antihuman major basic protein. Coded section was counted blind by a single observer.
Length of follow up (if applicable)	
Outcome measures/ Effect size	FE_{NO} readings and suitable biopsies for analysis were both obtained in 21 of 31 children with asthma. Adherence to prednisolone was demonstrated in 17 of these 21.Within this group, there was a correlation between FE_{NO} and eosinophil score (r = 0.54, p = 0.03). The relationship was strongest in patients with persistent symptoms after prednisolone, in whom the FE_{NO} > 7ppb was associated with a raised eosinophil score.. For all patients, FE_{NO} < 7 ppb was associated with an eosinophil score within the non asthmatic range, regardless of symptoms.
General Comments	

NO. 10

Bibliographic Citation	Fortuna AM, Feixas T, Gonzalez M, Casan P.. Diagnostic utility of inflammatory biomarkers in asthma: exhaled nitric oxide and induced sputum eosinphil count. *Respir Med.*2007; 101(11):2416-2421
Study Type / Methodology	Cross sectional study 50 patients with asthma symptoms. Patients undergo spirometry, methacholine challenge test, FE_{NO} measurement and assessment of Eos% in induced sputum. The standard diagnosis of asthma followed the guidelines of Global Initiative for Asthma.
LE	
Number of patients and patient characteristics	50 patients with asthma symptoms.
Intervention	FE_{NO}
Comparison	Spirometry , methacholine challenge test and assessment of Eos% in induced sputum
Length of follow up (if applicable)	
Outcome measures/ Effect size	Twenty-two of the 50 patients presenting with asthma symptoms were diagnosed as asthma. The sensitivity and diagnostic accuracy were higher higher for FE_{NO} measurement (77%; AUC, 0.8) than for spirometry (22%; AUC, 0.63). The sensitivity, specificity and AUC for induced sputum eosinophil count were 40%, 82% and 0.58 respectively. When FE_{NO} and sputum eosinophil count were used together specificity increased to 76%.
General Comments	Abstract

Evidence Table : **Effectiveness of FENO measurement using chemiluminescence NO analyzer such as NIOX**

Question : **Is it effective in monitoring asthma?**

No.1

Bibliographic Citation	Kharitonov SA, Gonio F, Kelly C, Meah S, Barnes PJ. Reproducibility of exhaled nitric oxide measurements in healthy and asthmatic adults and children. *Eur Respir J.* 2003.; 21: 433-438
Study Type / Methodology	Cross-sectional study Fractional Exhaled NO (FE_{NO}) measured using ATS recommendations using NIOX system. Any exhalation which did not meet the ATS requirements, was not accepted by the NIOX system and the subjects were asked to perform a new exhalation manoeuvre. At each session three correctly executed exhalations were recorded. Adults had their FE_{NO} measured on five consecutive days. Once between 09:00 -10:00 h during visits 1,2,3 and 4, and during the last visit (5th day) FE_{NO} was measured four times. Children underwent two measurements on the 5th day, the first between 09:00 -10:00 h and the second between 14:00 -15:00 h. Reproducibility of FE_{NO} measurements was assessed in three different ways: 1) Bland and Altman analysis, 2) intraclass correlation coefficient (ICC), 3) by pooled SD. The authors decided to choose an ICC value of > 0.75 to represent a clinically useful method.
LE	1b
Number of patients and patient characteristics	60 patients • 40 children aged 7-13 yrs. Mean age – 10.7 ±1.79 years. • 20 adults aged 18-60yrs. Mean age 35.6 ± 9.39 years.26 males and 34 females Gp 1 (n=30) 10 adults and 20 children. Non-smoking • Healthy – no history of asthma or other diseases • Normal lung function Gp 2 = (n=30) 10 adults and 20 children • Atopic mild steroid-naïve asthma • No history of asthma exacerbation or URTI in the preceeding 4 weeks • Normal lung function • No change of asthma medication during study
Intervention	Fractional Exhaled NO (FE_{NO}) measured using ATS recommendations using NIOX system.
Comparison	Nil
Length of follow up (if applicable)	Nil
Outcome measures/ Effect size	**Reproducibility, repeatability and safety of FE_{NO} measurement.** FE_{NO} values of one of the adult asthmatic patients were not included in the final analysis because the levels were above 2SD (110-160 ppb) of the studied population. • The mean pooled SD of all measurements was 2.1±1.25 parts per billion (ppb) • All intraclass correlation coefficient (ICC) found were above the chosen accepted limit of 0.75. All ICC values were ≥ 0.90. • The repeatability of the FE_{NO} measurements as measured by the Bland-Altman limits of agreement was ±2.92 ppb. FE_{NO} is significantly higher in asthma subjects (for both adults and children) (32.3 ±25.9 ppb) than healthy subjects (16.3±8.4ppb ;p<0.005) Healthy adults females had significantly lower FE_{NO} levels (14.85±3.34 ppb) than healthy males(24.6±8.59 ppb; p<0.03) No correlations were found between FENO and duration of asthma, season, food intake, body weight or height. There was no significant difference in FENO between the subjects who consumed water before the measurement and subjects who did not consume water. Highly reproducible, no significant diurnal variation for adults or children No 'learning effect' – no sig. difference between beginning and end of study No significant difference between 2 and 3 readings (shorten time needed) Patients perception of FENO measurement using NIOX: • Safe, no adverse incidents during study • Easy to perform, simple, acceptable for routine use in clinics **Conclusion:** Exhaled NO measurements may provide a useful clinical tool to monitor airway inflammation in patients with asthma, and acceptable by both healthy and asthmatic adults and children as part of their routine visit to a physician.
General Comments	

NO. 2

Bibliographic Citation	Smith AD, Cowan J O, Brassett K P, Filsell S, McLachlan C, Monti- Sheehan G, Herbison P, Taylor D R .Exhaled Nitric oxide . A predictor of steroid response. *Am J Repir Crit Care Med.* 2005 ; 172:453-459
Study Type / Methodology	Single blind, fixed –sequence, placebo-controlled study. Subjects attended the research clinic on five separate occasions. Short acting β-agonists taken "as required" were the only inhaled medication permitted until the study were completed, but were withheld for a minimum 6 hours before each visit. After completing a questionnaire, subjects underwent a fixed sequence of diagnostic tests FE_{NO} measurement, Spirometry, Bronchodilator reversibility, Methacholine challenge, Adenosine monophosphate challenge, symptom diary and peak flow measurement, inhaled matching placebo and inhaled fluticasone). Between visits 3 and 4, subjects received single blind treatment with placebo (1 puff twice daily via metered dose inhaler and spacer for 4 weeks, followed by inhaled fluticasone (250 µg/ puff , l puff twice daily via matching inhaler) for 4 weeks between visits 4 and 5. At the final visit, asthma was diagnosed on the basis of relevant symptom history using American Thoracic Society criteria plus one or more of the following: 1. A positive response to bronchodilator, defined as an increase in FEV_1 of 12% or greater from baseline 15 minutes after inhaled albuterol. 2. A positive response to ICSs (fluticasone, 500 µg/day for 4 weeks), defined as increase in FEV_1 of 12% or greater or an increase in mean morning peak flow of 15% or greater. 3. A positive test for airway hyper-responsiveness, defined as a provocative dose of methacoline, resulting in a 20% reduction in FEV_1 (PD_{20}) of < 8 µmol. Respiratory symptoms, bronchodilator use, and peak flows were recorded twice daily in a diary during the run-in and each treatment period. Diurnal peak flow variation was calculated as amplitude % mean over 7 days: a 20% or greater was considered clinically significant , a composite symptom score (0-10) was calculated for each day using the diary data. FE_{NO} was measured using a chemiluminescence analyzer (NiOX). All readings were recorded by two staff members who were blinded to the patients identity and treatment period.
LE	1b
Number of patients and patient characteristics	60 consecutive patients referred by family practitioner to the Dunedin Hospital pulmonary function laboratory for investigation of persistent undiagnosed respiratory symptoms. Patients were 12 to 75 years and had respiratory symptoms for a minimum of 6 weeks. Exclusion criteria: Use of ICSs or oral corticosteroid s in the previous 4 weeks, respiratory tract infection in the previous 6 weeks, other established respiratory diagnosis, or significant comorbidity
Intervention	FE_{NO} measurements inhaled fluticasone 250 ug/puff, 1 puff twice daily x 4 weeks.
Comparison	Inhaled placebo. FEV1 % predicted FEV1 bronchodilator response PD_{20} methacholine Diurnal peak flow variation

Length of follow up (if applicable)	12 weeks
Outcome measures/ Effect size	The accuracy of baseline FE_{NO} measurements to predict a positive response to treatment with inhaled fluticasone. To evaluate the predictive accuracy of FE_{NO} measurements , comparisons were made against a range of other predictors (FEV_1 % predicted, FEV_1 bronchodilator response, PD_{20} methacholine, diurnal peak flow variation) Response to inhaled fluticasone was assessed using a number of outcome measures (Improvement in FEV_1 cut point of sig. response >12%, improvement in mean morning peak flow (over 7 d)-cut point of sig. response > 15% , reduction in composite symptom score-cut point of sig. response> 1%, and improvement in PC_{20} Adenosine Monophosphate-cut point of sig. response > 2 doubling dose shift. Steroid response was calculated as change with inhaled fluticasone minus change with inhaled placebo. From 60 patients , 52 patients completed the study. (6 patients failed to complete the placebo treatment period and two patients withdrew during the fluticasone treatment period. 17 patients had $FE_{NO} < 15$ ppb (lowest tertile), 18 patients had FE_{No} between 15-47 ppb (middle tertile) and 17 patients had $FE_{NO} > 47$ ppb (highest tertile) Diagnosis of asthma was made in 27 of the 52 patients. The proportion of patients with asthma was greatest in the highest FE_{NO} tertile (88%), compared with the middle (39%) and lowest tertile (29%) $P < 0.001$. Subjects with baseline FE_{NO} levels in the highest tertile (> 47 ppb) had significantly lower FEV_1 % predicted and FEV_1 /FVC ratio and significantly greater improvement in FEV_1 with bronchodilator compared to the other two tertiles. They also had a significantly greater response to inhaled fluticasone for all four categories of "Steroid response" (increase in FEV_1, increase in mean morning peak flows, improved respiratory symptoms, and reduction in air-way hyper-responsiveness to AMP. AUCs for predictors of steroid response (FE_{NO}) compared to other predictors are as follows: i. For Improvement in FEV_1 cut point of sig. response >12%, 0.76 significantly higher than FEV 1% predicted. ii. For Improvement in mean morning peak flow (over 7 d)-cut point of sig. response > 15% , 0.81 which is significantly higher than FEV_1 bronchodilator response, PD_{20} methacholine and peak flow variation. iii. For reduction in composite symptom score-cut point of sig. response> 1%, 0.64 significantly higher than FEV_1% predicted, FEV_1 bronchodilator response, and PD_{20} methacholine. iv. Improvement in PC_{20} Adenosine Monophosphate-cut point of sig. response > 2 doubling dose shift, 0.91 significantly higher than FEV_1% predicted, FEV_1 bronchodilator response and peak flow variation.
General Comments	

NO. 3

Bibliographic Citation	Petsky HL, Cates CJ, Li AM, Turner C, Chang AB. Tailored Interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults (Review). *The Cochrane Collaboration*. 2008; Issue 2: 1-21
Study Type / Methodology	Systematic review Search strategy. Cochrane Airways Group Specialised Register of Trials, the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and reference list of articles. Search completed in December 2006. Selection criteria All randomised controlled comparisons of adjustment of asthma therapy based on exhaled nitric oxide compared to traditional methods (primarily clinical symptoms and spirometry/peak flow) 4 studies were included Fritsch 2006, Pijnenburg 2005, Shaw 2007, Smith 2005.
LE	1a
Number of patients and patient characteristics	356 randomised participants with 324 completed the trials.
Intervention	Corticosteroid dose adjusted based on FE_{NO} measurements
Comparison	Corticosteroid dose adjusted based on clinical symptoms and spirometry/ peak flow
Length of follow up (if applicable)	
Outcome measures/ Effect size	Primary outcome : a) number of participants who had asthma exacerbations during follow up Secondary outcome: a)Mean difference in asthma related outcome measures b)Number of participants experiencing adverse effects of the interventions c)Number of participants experiencing complications e.g. requirement for medication change Dose of inhaled corticosteroid used was also described as a post-hoc analysis Adults (Shaw et. Al. 2007), Smith et al. 2005 combining adults and children). Combined data from the two studies showed that the number of participants experiencing any exacerbations was not significantly different (p=0.55) between the FE_{NO} group and CS group. Pooled OR estimate effect was 0.85 (95% CI 0.30 to 2.43). I^2 63.9%. Exacerbation rates. There was also no significant difference between the groups for the outcome of occurrence of any exacerbation, MD (fixed) = -0.14 (95% CI -0.41 to 0.12). Children (Fritsch 2006; Pijnenburg 2005) Number of subjects who had one or more exacerbations over the study period. Both studies described that there was no difference between the groups and the data could not be combined. In post-hoc analysis, a significant reduction in mean final daily dose inhaled corticosteroid (ICS) per adult was found where treatment was based on FE_{NO} in comparisons to clinical symptoms; WMD -282.42 (95% CI -42.81 to -143.03). There was no difference in ICS dose between the groups in the overall daily dose in the adult studies or in the paediatric studies.
General Comments	Heterogeneity between studies

NO. 4

Bibliographic Citation	Jones SL, Kittelson J, Cowan JO et al. The Predictive Value of Exhaled Nitric Oxide Measurements in Assessing Changes in Asthma Control. *Am J Respir Crit care Med.* 2001;164:738-743
Study Type / Methodology	Cross sectional study ICS treatment was stopped following a 2-4 wk run-in which maintenance dose unchanged. Pat. Then reviewed weekly until loss of control (LOC) occurred or after 6 wk. Pat. was seen within 24 hr of LOC. Visit 1=visit when ICS was stopped Visit F = final visit Visit P =prior to final visit. LOC criteria: 1) Fall in mean PEFR >10% from baseline or fall in morning or evening PEFR to 80% of baseline or less, on 2 consecutive days. 2) mean daily bronchodilator use >3 puffs (more during run-in) or 3) Nocturnal wakening with asthma sx, on 3 nights or more /wk (greater than during the run-in) or 4) Asthma sx (disagreeable or distressing
LE	1b
Number of patients and patient characteristics	78 pt. mild/moderate asthma Male: female=30:48 Age(yr) :42.9 Inclusion criteria: a) Mild-moderate asthma (ATS criteria) b) on ICS therapy at least 6 month (dose unchanged at least 6 wk.) Exclusion criteria: a) history of acute asthma requiring hospital admission b) asthma characterized by sudden attacks c)usage of O. Prednisolone in the previous 3 months
Intervention	eNO
Comparison	Sputum eosinophils and Airway hyper-responsiveness (AHR) to hypertonic saline (4.5%)
Length of follow up (if applicable)	6 week
Outcome measures/ Effect size	Coefficients of variation for eNO i) within-pt within sitting:4.1% ii) within pt between-sitting :10.5% LOC 60 (77.9%) developed LOC Significant difference between LOC and no LOC group were reported: i) increased in eNO (2.16-fold versus 1.44 fold) between visit 1 & F (p=0.004) ii) fall in mean morning PEFR(13% versus 1%) p<0.0001 iii) decrease in FEV_1 (mean fall 11.9% predicted versus 2.6% predicted) p=0.001 iv) increased in sputum eosinophils (4.73 fold versus 2.05 fold) p=0.044 v) decreased in saline PD_{15} (0.8 doubling doses versus 0.03 doubling doses) p=0.001 High correlations between changes in eNO between visit 1 & F with : i) symptoms (p<0.0001) ii) FEV1 (p<0.002) iii) sputum eosinophils (p<0.0002) vi) saline PD_{15} (p<0.0002) Single measurement and changes of eNO (10ppb,15ppb or increase of >60% over baseline) had positive predictive values ranged 80-90% for predicting & diagnosing LOC.(Similar values in sputum eosinophils & saline PD_{15} measurements) Performance of eNO was comparable to sputum eosinophils counts & saline PD_{15} measurement in diagnosing LOC.
General Comments	

NO. 5

Bibliographic Citation	Prieto L, Bruno L, Gutierrez V et al .Airway Responsiveness to Adenosine 5'-Monophosphate and Exhaled Nitric Oxide Measurements: Predictive Value as Markers for Reducing the Dose of Inhaled Corticosteroids in asthmatic subjects. *CHEST*.2003;124:1325-1333
Study Type / Methodology	Cross sectional study : Single-blind Inclusion criteria: a) Age:18-60 yr old b) History of asthma c) Treated with ICS at least 6 mo d) Stable asthma with ICS treatment at medium to high doses e) had asthma sx $\leq$2/week at 3mo before study f) did not wake at night due to asthma g) No change in ICS dose last 6 mo h) FEV_1 at baseline >80% of predicted. Exclusion criteria: current smokers, pregnant, have seasonal symptoms & skin sensitization to pollen allergens, patients with renal,hepatic or CVD. Diagnosis of asthma: a) presence of symptoms (wheeze,breathlessness or cough) plus b) methacholine airway hyper-responsiveness with provocative concentration of AMP causing 20% fall in FEV_1(PC20) of <8mg/mL if FEV_1/FVC was <70% or c) improvement of FEV_1 from predicted of $\geq$15% after 200 µg of inhaled albuterol if FEV_1/FVC was <70% . At 2 wk (baseline): patients received same doses of ICS. Pat. recorded : - PEF measured (morning & evening) - asthma sx (day & night) - use of rescue albuterol, at 12 wk : Pat. received half dose of ICS. Pat. recorded: - PEF (twice daily) - asthma Sx - use of rescue albuterol Measurement of eNO, spirometry, and AMP challenge. done at : - end of run-in period, - after 2wk, - 8 wk and - 12 wk: Study was suspended if exacerbation occurred or at 14 week.
LE	1b
Number of patients and patient characteristics	47 patients (selected), 37 patients analyzed. Age (yr) : 32.2 (28.7-35.6) M:F : 11:26 Duration of asthma, yr : 16.8 (13.9-19.7) Duration of ICS use, (month) : 27.7 (19.0-36.5) ICS dose, µg/d : 619 (510-728) FEV_1 (% predicted) : 96.8(92.2-101.3) FEV_1/FVC (%) : 81.3(78.9-83.6)
Intervention	Exhale Nitric Oxide, AMP
Comparison	Nil
Length of follow up (if applicable)	14 weeks
Outcome measures/ Effect size	**Kaplan-Meier survival curve**-baseline determination of AMP responsiveness and eNO levels at a cut-off point of 15ppb and 20 ppb. Having bronchoconstriction in response to AMP and increased eNO levels (cut-off points, 15ppb or 20 ppb) –significant predictor for failure in ICS reduction. At cut-off point 15ppb : OR:8.17 (95%CI:1.60-41.64) At cut-off point 20 ppb : OR:5.25(95%CI:1.11-24.91) Having bronchoconstriction in response to AMP or increased eNO levels alone was not a predictor. **Correlations:** Changes in PC_{20} values with -changes in daytime symptoms scores, (r=0.41,p=0.02) -amount of albuterol use (r=0.43, p=0.009) No significant correlation with eNO levels, nighttime symptom scores or pulmonary function.
General Comments	

NO. 6

Bibliographic Citation	Zacharasiewicz A, Wilson N, Lex C, Erin EM, Li AM, Hansel T, Khan M, Bush A. Clinical use of non invasive measurements of airway inflammation in steroid reduction in children. *Am J Respir Crit Care Med*. 2005; 171: 1077-1082
Study Type / Methodology	Cross sectional study Forty children with stable asthma eligible for inhaled steroid reduction were reviewed every 8 weeks, and their inhaled steroid dose halved if clinically indicated. eNO, sputum induction combined with bronchial hyperactivity testing, and exhaled breath condensate collection were performed at each visit to predict success or failure of reduction of inhaled steroids.
LE	1b
Number of patients and patient characteristics	40 children aged 6-17 with asthma, diagnosed by a paediatric respiratory system physician and stable for at least 2 months (bronchodilator use < 3 times/week in past 2 months) on a constant ICS dose were recruited from paediatric outpatient clinic.
Intervention	Treatment decisions were made based on clinical assessment and spirometry eNO level measured using a chemoluminescence analyzer (NIOX; Aerocrine, Stockholm, Sweden) according to published European Respiratory Society/ American Thoracic Society guidelines.
Comparison	
Length of follow up (if applicable)	
Outcome measures/ Effect size	Thirty of 40 (75%) children tolerated at least one dose reduction, 12 of 40 (38%) children experienced loss of asthma control. Treatment reduction was successful in all children who had no eosinophils in induced sputum before the attempted reduction. Using multiple logistic reduction, increased eNo (odds ratio, 6.3; confidence interval, 3.75 -10.58) and percentage of sputum eosinophils (odds ratio, 1.38; confidence interval, 1.06-1.81) were significant predictors of failed reduction.
General Comments	

NO. 7

Bibliographic Citation	Leuppi JD, Salome CM, Jenkins RJ, Anderson SD, Xuan W, Marks GB, Koskela H, Brannan JD, Freed R, Anderson M, Chan H, Woolcock AJ. Predictive markers of asthma exacerbation during stepwise dose reduction of inhaled corticosteroids. *Am J Respir Crit Care Med.* 2001; 163: 406-412
Study Type / Methodology	Cross sectional study Involving 2 study periods; A 4 wk run in phase (baseline) and a dose-reuction phase, in which the subjects current ICS dose was halved every 8 week. After a run in period of 4 wk, in which disease stability was monitored by peak flow and symptom diary cards, the current ICS dose was halved every eight weeks. The ICS treatment was stopped after a dose of 200 µg of budesonide or beclomethasone, or 125 µg of fluticasone was achieved after successive reductions in steroid dose. The subjects visited the laboratory at monthly intervals, and a BPT with mannitol was performed, eNO and spirometry were measured, and sputum was collected. Throughout the study subjects were asked to record their asthma symptoms, β agonist use, and peak expiratory flow (PEF), twice daily in a diary before inhaling their asthma medication. The physician responsible for steroid reduction and identifying asthma exacerbation was blinded to the result of mannitol challenge test and sputum test results.
LE	1b
Number of patients and patient characteristics	Fifty subjects with asthma using ICS to control their asthma who had a past history of wheezing and chest tightness and who had asthma previously diagnosed by a physician. Age 43.7(range 18-69), 22 males Asthma severity was graded on the basis of lung function. 41 atopic. Eight subjects were long term using β- agonist and all used short acting β- agonist when needed. All subjects were clinically stable. In the 4 week before the study, subjects had asthma symptoms no more than twice a week, did not wake up at night because of asthma, and had no respiratory tract infection. Had no changes in their dose of ICS in the last 4 wk and no major changes in dose (> 1000 µg daily0 in the last 3 months. Exclusion-current smoker and use of oral steroids within the previous 6 months.
Intervention	Airway hyper-responsiveness (AHR) to a bronchial provocation test (BPT) with histamine was measured at baseline. AHR to BPT with mannitol, spirometry, exhaled nitric oxide (eNO), and, in 31 subjects, sputum inflammatory cells were measured at baseline and at monthly intervals.
Comparison	
Length of follow up (if applicable)	
Outcome measures/ Effect size	39 subjects suffered an asthma exacerbation. 7 subjects were successfully weaned off ICS. Using the Kaplan Meier survival analysis, the significant predictors of a failure of ICS reduction were being hyper-responsiveness to both histamine and mannitol at baseline (p=0.039), and being hyper-responsive to mannitol during the dose –reduction phase of the study (p=0.02). Subjects older than 40 yr of age tend to be at a greater risk of ICS reduction failure (p=0.059) Response to mannitol and percentage sputum eosinophils were significantly greater before failed inhaled corticosteroids (ICS) reduction than before the last successful ICS reduction, whereas there were no significant difference in symptoms, spirometry, or eNO.
General Comments	

NO. 8

Bibliographic Citation	Buchvald F, Hermansen Nielsen KG, Bisgaard H. Exhaled nitric oxide predicts exercise-induced bronchoconstriction in asthmatic school children. Chest. 2005; 128 (4): 1964-7
Study Type / Methodology	Cross sectional study 111 asthmatic children from 6 to 15 years old with mild-to-moderate asthma were recruited from outpatient paediatric clinic. The diagnosis was determined from well known symptom history compatible with asthma, response to inhaled β_2-agonists or corticosteroids, or previous significant decrease of lung function after standardized exercise testing. Asthma was stable and considered clinically well controlled in all patients. Treatment had remained unchanged within the last 4 weeks. Current smokers and children with an airway infection within the previous fortnight were excluded. Excecise challenge test performed according to American Thoracic Society (ATS) guidelines. Spirometry performed in accordance with ATS guidelines. FE_{NO} measurement.
LE	1b
Number of patients and patient characteristics	122 asthmatic children from 6 to 15 years old with mild-to-moderate asthma
Intervention	FE_{NO} measurements were performed before exercise testing in accordance with ATS and European Respiratory Society recommendations at an exhalation flow of 50 mL/s using Aerocrine NO system; chemiluminescence analyzer.
Comparison	Exercise challenge test
Length of follow up (if applicable)	
Outcome measures/ Effect size	All children were able to perform FE_{NO} measurement, but 11 children could not cooperate with the exercise test or lung function test. FE_{NO} was significantly higher in the children with EIB. Median FE_{NO} (95% CI) 19.5 (21-55) ppb compared to 10.2 (8-15) ppb. The cut off value of FE_{NO} with the highest accuracy for EIB was 21 ppb with the area under curve (AUC) of 0.77 (95% CI, 0.631 to 0.876) in children not currently receiving inhaled steroids. In the steroid treated children , the cut off value of FE_{NO} for prediction of significant EIB was 12 ppb (AUC) 0.744 (95% CI, 0.614 to 0.864). EIB can be excluded with the probability of 90% in asthmatic children with FE_{NO} levels < 20 ppb without current inhaled corticosteroid treatment, and < 12 ppb in children with current inhaled corticosteroid treatment. The authors concluded FE_{NO} measurement is a cost-saving procedure that can be used in paediatric asthma management as a rapid and feasible screening tool to assess the need for exercise testing in children with asthma.
General Comments	

NO. 9

Bibliographic Citation	Katsara M, Donnelly, Iqbal S et al. Relationship between exhaled nitric oxide levels and compliance with inhaled corticosteroids in asthmatic children. *Respiratory medicine.*2006;100:1512-1517
Study Type / Methodology	Cross sectional study at Sheffield Children's Hospital, UK.
LE	1b
Number of patients and patient characteristics	20 children Age : (7-14 years old) Patient on stable dose of ICS at least 3 months prior to study. Patient had experienced symptoms at least 3 times /week but had no exacerbation in the previous 6 wk. Using pressurized metered dose inhalers & holding chambers
Intervention	Pt. attended clinic on 4 occasions at 1-monthly interval. On each visit, measurements done: a) eNO measurements b) Lung function c) Clinical assessment
Comparison	
Length of follow up (if applicable)	
Outcome measures/ Effect size	From 20 children: 13 had evidence of personal atopy with raised IgE, positive skin prick tests, atopic dermatitis and/or hay fever. 4- had strong family history of atopy. 3-had no atopy. Correlation between eNO and compliance (doses and day). <u>Day compliance-number</u> of days the advised number of doses were taken. Dose compliance-number of doses taken as a proportion of the nominal prescribed doses Day compliance & eNO : r=-0.055, (P=0.67) Dose compliance & eNO : r=0.153, (P=0.24) Negative but non-significant. 7 subjects had satisfactory compliance (>60%,eNO <10) 3 subjects (eNO <10ppb) had poor compliance (2 had atopy) 9 subjects had persistent /intermittent high eNO 19subjects had eNO values>12ppb -15 a/w <50% day compliance -4 a/w >60% day compliance
General Comments	

Evidence Table : **Effectiveness of FE$_{NO}$ measurement using NIOX MINO**
Question : **Is it effective in asthma diagnosis?**
No.1

Bibliographic Citation	Alving K, Janson C, Nordvall L. Performance of a new hand held device for exhaled nitric oxide measurement in adults and children. *Respiratory Research.* 2006 ; 7 :67
Study Type / Methodology	Cross-Sectional Study Measurements were performed in randomized device order (at most 6 attempts per device). The mean of 3 measurement in each device, or the first approved measurement in NIOX MINO were used for agreement studies. Subjects also attempted one valid FE$_{NO}$ measurement (at most 3 attempts) in the hand- held device in a simulated home- use environment where each subject performed FE$_{NO}$ measurement without assistance of clinical personnel. For comparison between devices, intraclass correlation coefficients (ICC) were calculated and presented as reliability coefficients, and Bland-Altman plots were constructed. Repeatability was calculated from intrasubject SD.
LE	1b
Number of patients and patient characteristics	75 patients • 34 adults (38 ± 11 years) 6 males, 28 females • 41 children (12 ± 3 years), 30 males, 11 females • Age range: 6-60 years • 21 non atopic healthy controls and the rest were atopic patients with and without asthma • None of them had used any NO instruments over the preceding 6 months and thus were considered inexperienced with usage
Intervention	Use NIOX MINO (new hand held device with electrochemical sensor) to record exhaled NO
Comparison	NIOX (established stationary, chemiluminescence-based NO analyzer)
Length of follow up (if applicable)	NIL

Outcome measures/ Effect size	i) Success rate (calculated as the proportion of subjects succeeding in obtaining three valid FE$_{NO}$ measurements out of maximum six attempts in each device, or one successful measurement out of a maximum of three attempts using NIOX MINO in the simulated home use.
	
	    Four subjects out of 75 had FE$_{NO}$ measurements < 8 ppb and were excluded from the study.
	
	• In all subjects, there was no sig. difference in success rate between both devices (NIOX and NIOX MINO) 94% and 92% respectively, or between clinical setting and simulated home use of NIOX MINO (both 92%). Children were less successful than adults when attempting to use the NIOX MINO (84% versus 100%) p< 0.05.
	
	• The mean number of attempts needed required to obtain 3 approved measurements was significantly lower in the NIOX MINO (3.4 ±0.8) compared to the NIOX (3.8±1.0). p<0.05
	
	ii) **Agreement between devices.**
	
	• The subjects represented a FE$_{NO}$ range of 8-147 ppb. The Bland-Altman plot shows agreement between the NIOX and NIOX MINO when comparing the mean of three valid NO Measurements. The median of the intra-subject FE$_{NO}$ difference was -1.2. NIOX MINO gave FE$_{NO}$ readings that were generally slightly higher than the FE$_{NO}$ measurement s obtained using NIOX. The 95% limit of agreement were -9.8 and 8.0 ppb.
	
	• The same degree of agreement was obtained when comparing the mean of the three approved exhaled measurements in the NIOX and the first approved measurement in NIOX MINO. The median of the intra-subject FE$_{NO}$ difference was -2.0. The 95% limit of agreement were -13.2 and 1.2 ppb.
	
	iii) **Measurement repeatability**
	
	    Repeatability was similar in the NIOX and the NIOX NINO. The median repeatability for NIOX and NIOX NINO was 1.1 and 1.2 respectively.
	
	• **Adverse events reported – mental stress, mild throat dryness, uncomfortable inhalation**
	
	Conclusion:
	
	• NIOX MINO and NIOX are in clinically acceptable agreement.
	
	• NIOX MINO shows good repeatability and can be used successfully on adults and most children.
	
	This will enable the introduction of FE$_{NO}$ measurements in primary health care.

General Comments	

NO. 2

Bibliographic Citation	Menzies D, Nair A, and Lipworth BJ. Portable Exhaled Nitric Oxide Measurement* Comparison With the "Gold Standard" Technique. *CHEST*.2007;131:410-414
Study Type / Methodology	Cross sectional study
LE	1 b
Number of patients and patient characteristics	A total of 101 patients known to have persistent mild-to moderate asthma 64 of whom were receiving ICSs from clinical trials database and 50 healthy volunteers were invited to participate
Intervention	A portable nitric oxide analyzer (MINO; Aerocrine AB; Smidesva¨gen, Sweden) All participants underwent the measurement of FE_{NO} using the NIOX analyzer at a mouth flow rate of 50 mL/s and a Pressure of 10 cm H2O. Three technically adequate measurements were performed with a sustained plateau of at least 8 s, and the arithmetic mean derived was in line with the current European Respiratory Society/American Thoracic Society recommendations
Comparison	Larger laboratory-based analyzers (NIOX; Aerocrine AB).
Length of follow up (if applicable)	
Outcome measures/ Effect size	In both asthmatic patients and healthy volunteers, there was a good correlation between The measure-ments obtained using each device (r = 0.94 and 0.96, respectively). Altman-Bland Plots confirmed this agreement. Receiver operating characteristic curves discriminating asthmatic patients from healthy volunteers obtained using the NIOX and MINO showed a sensitivity of 83.2% and a specificity of 72% using cuto ff values of 13 and 12.5 parts per billion, respectively. FE_{NO} values obtained using a portable analyzer correlate well with those obtained using an established laboratory analyzer and can be used to discriminate asthmatic from no asthmatic patients. This may facilitate the measurement of asthmatic airway inflammation in primary care.
General Comments	

NO. 3

Bibliographic Citation	Hemmingsson T, Linnarsson D and Gambert R. Novel hand-held device for exhaled nitric oxide analysis in research and clinical applications. *Journal of Clinical Monitoring and Computing*. 2004;18:379-387
Study Type / Methodology	Cross sectional study
LE	1b
Number of patients and patient characteristics	19 healthy volunteers
Intervention	**Agreement study NIOX MINO** 19 healthy volunteers performed FE_{NO} measurements with one hand-held instrument and one NIOX instrument. At each occasion subjects performed the FE_{NO} procedure once with each of the instruments during a total of 251 sessions. **Precision study** Nine healthy subjects performed triplicate FE_{NO} measurements with both instrument types. Subjects came on three occasions on consecutive days. For the hand held instrument such triplicate tests were repeated with six different sensor units, in order to define performance variability.
Comparison	NIOX
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Agreement study** Data from NO- analyzer versus NIOX investigation showed the average disagreement of 0.5 ppb with the mean SD of 3.8 ppb. **Precision study** NIOX MINO- precision(average SD of 1.4 ppb) NIOX- precision (average SD of 1.1 ppb) Present test of NIOX MINO measurements regarding agreement, precision and linearity are comparable to currently accepted chemiluminescence, thus fulfilling requirements for intended clinical use.
General Comments	

NO. 4

Bibliographic Citation	Khallili B, Boggs PB, Bahna SL. Reliability of new hand-held device for the measurement of exhaled nitric oxide. *Allergy*. 2007;62(10):1171-1174
Study Type / Methodology	Cross sectional study
LE	
Number of patients and patient characteristics	110 patients 6-86 years, presenting to an allergy and asthma clinic
Intervention	Underwent FE_{NO} by NIOX MINO
Comparison	Underwent FE_{NO} evaluation by NIOX
Length of follow up (if applicable)	
Outcome measures/ Effect size	Intra-subject FE_{NO} levels obtained by each of the three NIOX MINOs revealed no significant difference between the measurements (p= 0.59). Very strong correlation between FE_{NO} measurements by NIOX and by NIOX MINO (r=0.98, P<0.001). The mean intra-subject FE_{NO} difference between the two devices was -0.5 ppb which was not statistically significant. FE_{NO} measurements by NIOX MINO showed strong correlation and high degree of agreement and reliable to be used in clinical practice.
General Comments	Abstract

NO. 5

Bibliographic Citation	Sovijarvi ARA, Jarvinen H, Simola J, Nikkinen P, Piirila PL. Accuracy and repeatability of a hand held nitric oxide analyzer in adults with respiratory symptoms. laboratory of nuclear medicine, Helsinki University Hospital Helsinki 00029 HUS, FINLAND.
Study Type / Methodology	Cross sectional study
LE	
Number of patients and patient characteristics	35 adult patients. Mean age (43,2y), with respiratory symptoms: 13 with diagnosed asthma and one with chronic bronchitis, 4 dyspnea symptoms, 7 with cough, 1 with increased sputum production, and 9 other respiratory symptoms.
Intervention	FE_{NO} measurement using NIOX MINO
Comparison	FE_{NO} measurement using NIOX
Length of follow up (if applicable)	
Outcome measures/ Effect size	FE_{NO} recorded (SD) with NIOX MINO was 43.2 ppb.(range – 8-228ppb) NIOX- 39.3ppb (41) Linear inter device correlation coefficient for FE_{NO}- 0.992(p<0.0001) The repeatability –(CoR) for NIOX MINO- 7.4% with mean (SD) difference between the first and second determination- 1.3ppb (3.5) NIOX MINO- repeatability was good Overestimation of FE_{NO} in NIOX MINO.
General Comments	Poster presentation

NO. 6

Bibliographic Citation	Torre O, Spencer A, Olivier D, Barnes PJ, Kharitonov SA. Feasibility and repeatability of fractional Exhaled Nitric Oxide (FE_{NO}) Measurements Using a hand Held NO Monitoring Device in Asthma in General practice. Proceedings of the American Thoracic Society, Volume 3, Abstract Issue, April 2006 page A484 (session Info: Poster Discussion Session, [B91] BIOMARKERS TO ASSESS AIRWAY INFLAMATION)
Study Type / Methodology	Cross sectional study
LE	
Number of patients and patient characteristics	82 patients with asthma 31 male-mean age 54.7y at five general practice surgeries
Intervention	All patients performed 2 valid measurements with new device. In 22 patients compared FE_{NO} measured with NIOX MINO and NIOX. Two repeated measurements were performed with the NIOX MINO and three with the NIOX; mean values of each device were used for inter-device comparisons.
Comparison	NIOX
Length of follow up (if applicable)	
Outcome measures/ Effect size	For patients in the community the success rate in the NIOX MINO was 85.9%; the mean difference between the first and the second determination was -1.1 ±6 ppb ;the repeatability coefficient (CoR) was 7.7%. The inter device (NIOX versus NIOX MINO) correlation coefficient was 0.99 (p<0.0001) Inter-device correlation coefficient was good but NIOX MINO slightly overestimated compared with NIOX New hand held seems useful for monitoring asthma in general practice.
General Comments	Abstract

NO. 7

Bibliographic Citation	Sardon Prado O, Aldasoro Ruiz A, Korta Murua J, et al. Agreement between two devices for measuring exhaled nitric oxide. An Pediatr (Barc). 2007 ;67 (6) : 572-577
Study Type / Methodology	Cross sectional study
LE	
Number of patients and patient characteristics	30 children, 14 (46.67%) boys and 16 (53.33%) girls.Mean age 11.3±3.09 years Asthma patients
Intervention	FE_{NO} was measured by single breath on- line method. Using NIOX MINO –a single measurement was made successfully in each children
Comparison	NIOX, In children, 3 consecutives measurements were obtained with NIOX, maximum 6 attempts.
Length of follow up (if applicable)	
Outcome measures/ Effect size	Correlation between (NIOX,Aerocrine,Sweeden) and NIOX-MINO,Aerocrine) The relationship between the means and the differences – MINO and NIOX were statistically significant (p<0.005) Cohen's Kappa – (0.78) Suggesting high degree of agreement between the results of the two devices. The two analyzers MINO and NIOX were not equivalent. NIOX MINO- seems valid and feasible in children older than 5 years.
General Comments	Abstract, Article in Spanish

NO. 8

Bibliographic Citation	McGill C, Malik G, Tuerner SW. Validation of a hand-held exhaled nitric oxide analyzer for use in children. Pediatr Pulmonol .2006 ; 41(11):1053-1057
Study Type / Methodology	Randomized cross over study Participants were recruited from children attending a respiratory clinic. Paired measurements of FE_{NO} were made during a single assessment lasting approximately 20 minutes. Children were randomized to use either the NIOX or NIOX MINO for the first set of six attempts The same NIOX and NIOX MINO were used throughout this study. Measurements were taken in accordance with 2005 ATS/ERS guidelines A mean FE_{NO} value obtained in 39 children with MINO and 44 with NIOX
LE	
Number of patients and patient characteristics	55 children 33 boys, 33 asthmatics- median age of 9
Intervention	Measurement of exhaled nitric oxide using NIOX MINO
Comparison	FE_{NO} measured in a single assessment using the NIOX.
Length of follow up (if applicable)	
Outcome measures/ Effect size	Intraclass correlation co-efficient for mean FE_{NO} values obtained from NOX and NIOX MINO was 0.986 (95% CI 0.972, 0.993). The mean FE_{NO} values (n=34) from NIOX were higher than NIOX MINO median difference 2.4 ppb, mean difference 3.9 ppb (limits of agreement -1.1, 8.9). The differences between analysers became greater at higher FE_{NO} values. The mean first acceptable FE_{NO} value using the NIOX MINO was 24 ppb and the mean of all FE_{NO} values using the MINO was 27 ppb (different not significant). Exhaled NO values were comparable between the two analysers although there was greater consistency at lower values.
General Comments	Abstract and poster presentation

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NO. 9

Bibliographic Citation	Hewitt RS, Modrich CM, Medlicott T, Cowan JO, Taylor DR. Supporting the diagnosis of non-specific respiratory symptoms in primary care: the role of exhaled nitric oxide measurement and spirometry. Primary Care Respiratory Journal. 2008; 17(2):97-103
Study Type / Methodology	Cross sectional study 14 general practitioners (GPs) in a large care practice (15,500 patients) in Dunedin, New Zealand were explained about the study. 55 patients aged 12-80, with a history of cough, wheeze or shortness of breath were invited by their GP to participate. Excluded if had received oral or inhaled corticosteroids within last six weeks, smokers and recent ex-smokers (< 6 months). FE_{NO} measurement and spirometry were performed. Using these results and with reference to an algorithm, the GP then made a provisional clinical diagnosis for each patient. GP then recorded a response to a series of questions and management was then instituted based on clinical judgement and the results of the FE_{NO} and spirometric tests as appropriate. Final clinical diagnosis made at 3 months.
LE	3b
Number of patients and patient characteristics	55 patients aged 12-80, with a history of cough, wheeze or shortness of breath.
Intervention	Measurement of exhaled nitric oxide using NIOX MINO or NIOX, and spirometry, algorithm
Comparison	
Length of follow up (if applicable)	3 months
Outcome measures/ Effect size	Of the 55 patients recruited, four were excluded because of retrospective correction of FE_{NO} results led to changes that affected the use of the diagnostic algorithm. Working diagnosis of atopic asthma was defined as variable respiratory symptoms either a FE_{NO} level of >35ppb and/or a positive response to a trial of corticosteroid, where such therapy was administered. The working diagnosis was changed at 3-month follow-up in 10 out of 51 cases (19.6%). In 48/51 (94%) of cases FE_{NO} was considered significant in formulating a diagnosis. Spirometry was deemed helpful in 27/51(54%). The authors concluded that FE_{NO} measurements improved diagnostic confidence when assessing non-specific respiratory symptoms
General Comments	

Evidence Table : **Effectiveness of FE$_{NO}$ measurement using NIOX MINO**
Question : **Is it effective in asthma monitoring?**
No.1

Bibliographic Citation	Bodini A, Peroni D, Loiacono A et al. Exhaled nitric oxide daily evaluation is effective in monitoring exposure to relevant allergens in asthmatic children. Chest. 2007; 132(5) : 1520-1525.
Study Type / Methodology	Cross sectional study
LE	
Number of patients and patient characteristics	22 children, allergic to mites
Intervention	Children allergic to mites underwent twice daily fractional exhaled nitric oxide therapy using a portable NIOX MINO and peak expiratory flow measurements taken before, during and after periods of natural exposure to mite allergens. The children were admitted to study if they had lived in a mite free environment for 3 months and were observed for 10 days. Then they were moved to site with natural mite exposure at sea level for 19 days. Finally relocated to mite free environment for 6 days for follow up measurements
Comparison	Compared NIOX MINO and peak expiratory flow measurement.
Length of follow up (if applicable)	
Outcome measures/ Effect size	Significant different noted between the mite- free baseline FE$_{NO}$ level (26.4 ppb), range 19.3 to 36.3ppb and FE$_{NO}$ levels measured during natural exposure (37.3 ppb; 27.3 to 51 ppb) and after natural exposure – (34.9 natural mite exposure, 25.2 to 48.2 ppb. 6 children reported asthma symptoms during mite exposure and an increased in FE$_{NO}$ in each case (p<0.031) PEF values showed no significant differences in all the environments. Possible role of frequent determinations of FE$_{NO}$ in order to promptly assess changes in level of airway inflammation in asthmatic children.
General Comments	Abstract

NO. 2

Bibliographic Citation	Vahlkvist S, Sinding M, Skamstrup K, Bisgaard H. Daily home measurement of exhaled nitric oxide in asthmatic children during natural birch pollen exposure. J Allergy Clin Immunol. 2006; 117(6): 1272-1276
Study Type / Methodology	Cross sectional study
LE	
Number of patients and patient characteristics	11 children with mild asthma and allergy to birch pollen.
Intervention	Performed daily measurements of FE$_{NO}$ for 6 weeks before and during the birch pollen season by using a hand held NIOX MINO. Additionally FE$_{NO}$ (NIOX) and spirometry were measured at the inclusion and completion visit in the clinic. Peak expiratory flow rate (PEFR) and symptoms were recorded daily
Comparison	Measurement by NIOX, and spirometry.
Length of follow up (if applicable)	
Outcome measures/ Effect size	Daily FE$_{NO}$ (NIOX MINO) increased significantly (p<.001) with increased pollen count. FE$_{NO}$ (NIOX MINO) and FE$_{NO}$(NIOX) exhibited a correlation coefficient of 0.98, but FE$_{NO}$ (NIOX MINO)- was significantly higher than FE$_{NO}$(NIOX) (p<0.01). PEFR and FEV1 remained unchanged. Few symptoms recorded. Useful for clinic and home use – hand held FE$_{NO}$ (NIOX MINO)
General Comments	Abstract

NO. 3

Bibliographic Citation	Pijnenburg MW, Floor SE, Hop WC, De Jongste JC. Daily ambulatory exhaled nitric oxide measurements in asthma. Pediatr Allergy Immunol. 2006; 17:189-193
Study Type / Methodology	Cross sectional study Patients measured FE_{NO} twice daily for 2 weeks at home using NIOX MINO. NIOX MINO is provided with smart card, which records all measurement results and time of measurements. Symptoms score recorded in electronic diary. Mixed Model ANOVA was used to compare morning and evening FE_{NO} values and to investigate the correlation between FE_{NO} and cumulative symptom scores. In these analyses FE_{NO} values were log transformed.
LE	3b
Number of patients and patient characteristics	21 asthmatics (11 males). Mean (range) age was 14.5 year (8.1-25.8), 18 of them atopic.
Intervention	Measurement of exhaled nitric oxide using NIOX MINO, symptoms score.
Comparison	
Length of follow up (if applicable)	2 weeks
Outcome measures/ Effect size	3 patients were non atopic and were excluded from further analysis. Measurements showed a success rate of 93%.The authors found significant diurnal variation in FE_{NO} with geometric mean morning levels 14% higher than evening levels (95% CI: 4%-25%; p=0.013). Individual subjects showed fluctuation of FE_{NO}. The mean intra subject coefficient of variation of FE_{NO} was 40% for morning and 36% for evening values. The difference in coefficient of variation for morning and evening values was not significant (p=0.35). FE_{NO} and cumulative symptom scores did not correlate. The authors concluded that home FE_{NO} measurements are feasible, and offer the possibility to assess airway inflammation on a daily basis.
General Comments	

Evidence Table : Effectiveness of FE$_{NO}$ measurement using chemiluminescence NO analyzer or NIOX MINO

Question No.1 : Is it effective in other respiratory diseases?

Bibliographic Citation	Fabbri LM, Romagnoli M, Corbetta L, Casoni G, Busljetic K, Turato G, Ligabue G, Ciaccia A, Saetta M and Papi A. Differences in airway Inflammation in patients with fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2003;167:418-423
Study Type / Methodology	Cross sectional study Each patient was characterised by medical history and physical examination. Each patient performed pulmonary function tests, including reversibility to inhaled bronchodilator and to corticosteroids; airway responsiveness to metacholine; tests for atopic status and exhaled NO; induced sputum; arterial blood gas; and white cell count. In addition 13 of 19 patients with a history of asthma and 15 of the 27 patients with history of COPD underwent bronchoscopy, bronchoalveolar lavage, and bronchial biopsy. A subgroup of 31 (10 asthma and 21 COPD) underwent HRCT of the chest for radiologic assessment of emphysema. ROC curve analysis was performed.
LE	1b
Number of patients and patient characteristics	46 consecutive patients 19 had history of asthma and 27 had history of COPD.
Intervention	Pulmonary function tests, including reversibility to inhaled bronchodilator and to corticosteroids; airway responsiveness to metacholine; tests for atopic status and exhaled NO; induced sputum; arterial blood gas; and white cell count, bronchoscopy, bronchoalveolar lavage, and bronchial biopsy, HRCT of the chest
Comparison	
Length of follow up (if applicable)	
Outcome measures/ Effect size	Subject with history of asthma had lower residual volume, higher diffusing capacity and oxygen tension in arterial blood, and increased response to inhaled albuterol and steroids. Patients with asthma had a lower HRCT scan emphysema score than did patients with COPD (0.6±0.3 versus 3.6±0.7; p=0.01). Patients with history of asthma had more eosinophils in peripheral blood, sputum, bronchoalveolar lavage fluid, and airway mucosa. Had higher level of exhaled NO (37.5 ± 9.2 ppb versus 11.1 ppb; p < 0.01). For sputum eosinophils the best cut off point was 4.6% (with a sensitivity of 0.96 and a specificity of 0.74), indicating that values higher than or equal to 4.6% predicted history of asthma, whereas values lower than 4.6% predicted a history of COPD. For exhaled nitric oxide, the best cut off point was 16 ppb, which had a sensitivity of 0.91 and a specificity of 0.77, values higher than 16 ppb predicted history of asthma, whereas values lower than 16 ppb predicted a history of COPD.
General Comments	

NO. 2

Bibliographic Citation	Liu J, Sandrini A, Thurston MC, Yates DH, Thomas PS. Nitric oxide and exhaled breath nitrate/nitrates in chronic obstructive pulmonary disease patients. Respiration. 2007;74:617-623
Study Type / Methodology	Cross sectional study Each patient was characterised by medical history and physical examination. Each patient performed pulmonary function tests, including reversibility to inhaled bronchodilator and to corticosteroids; airway responsiveness to metacholine; tests for atopic status and exhaled NO; induced sputum; arterial blood gas; and white cell count. In addition 13 of 19 patients with a history of asthma and 15 of the 27 patients with history of COPD underwent bronchoscopy, bronchoalveolar lavage, and bronchial biopsy. A subgroup of 31 (10 asthma and 21 COPD) underwent HRCT of the chest for radiologic assessment of emphysema. ROC curve analysis was performed.
LE	1b
Number of patients and patient characteristics	46 consecutive patients 19 had history of asthma and 27 had history of COPD.
Intervention	Pulmonary function tests, including reversibility to inhaled bronchodilator and to corticosteroids; airway responsiveness to metacholine; tests for atopic status and exhaled NO; induced sputum; arterial blood gas; and white cell count, bronchoscopy, bronchoalveolar lavage, and bronchial biopsy, HRCT of the chest
Comparison	
Length of follow up (if applicable)	
Outcome measures/ Effect size	Subject with history of asthma had lower residual volume, higher diffusing capacity and oxygen tension in arterial blood, and increased response to inhaled albuterol and steroids. Patients with asthma had a lower HRCT scan emphysema score than did patients with COPD (0.6±0.3 versus 3.6±0.7; p=0.01). Patients with history of asthma had more eosinophils in peripheral blood, sputum, bronchoalveolar lavage fluid, and airway mucosa. Had higher level of exhaled NO (37.5 ± 9.2 ppb versus 11.1 ppb; p < 0.01). For sputum eosinophils the best cut off point was 4.6% (with a sensitivity of 0.96 and a specificity of 0.74), indicating that values higher than or equal to 4.6% predicted history of asthma, whereas values lower than 4.6% predicted a history of COPD. For exhaled nitric oxide, the best cut off point was 16 ppb, which had a sensitivity of 0.91 and a specificity of 0.77, values higher than 16 ppb predicted history of asthma, whereas values lower than 16 ppb predicted a history of COPD.
General Comments	

NO. 3

Bibliographic Citation	Delen FM, Sieppel JM, Osborne ML, Law S, Thukkani N and Hoden WE. Increased exhaled nitric oxide in chronic bronchitis: comparison with asthma and COPD. CHEST. 2000;117:695-701
Study Type / Methodology	Cross sectional study Conducted cross sectional survey of exhaled NO in consecutive patients referred for routine pulmonary function testing to the Veterans Administration Medical Center in Portland. Administered a standardized demographic and pulmonary symptom questionnaire to each subject and measured exhaled carbon monoxide (CO) and exhaled NO concentrations. Each subject then performed spiromery before and after receiving an aerosolized bronchodilator.
LE	1b
Number of patients and patient characteristics	179 consecutive patients referred for routine pulmonary function testing. 2 control groups First consist of 18 patients defined within the cross-sectional study population and second control group consisted 20 subjects who were of similar age and sex to patient population recruited from staff and volunteer workers in the hospital.
Intervention	Questinnaire CO analysis Exhaled NO analysis Spirometry
Comparison	
Length of follow up (if applicable)	
Outcome measures/ Effect size	Current smoking status was associated with reduced levels of exhaled NO (smokers, 9.2 ± 0.9 parts per billion; never and ex-smokers, 14.3 ± 0.6 ppb; $p < 0.0001$). Current smokers (n = 57) were excluded from further analysis. Among non smokers the levels of exhaled NO were significantly higher in patients with chronic bronchitis (17 ± 1.1 ppb; $p = 0.035$) and asthma (16.4 ± 1.3 ppb; $p = 0.05$) but not in those with COPD (14.7 ± 1.0 ppb) when compared to either control group (patient control subjects, 11.1 ± 1.6 ppb; outside control subjects, 11.5 ± 1.5 ppb).
General Comments	

NO. 4

Bibliographic Citation	Tsang KW, Leung R, Chin-wan Fung P, Chan SL, Tipoe GL, Ooi GC and Lam WK. Exhaled and sputum nitric oxide in bronchiectasis. Correlation with clinical parameters. CHEST. 2002;121:88-94
Study Type / Methodology	Cross sectional study
LE	1b
Number of patients and patient characteristics	109 consecutive non-smoking patients with proven bronchiectsis who were not treated with inhaled steroid therapy and diagnosed by HRCT Control – 78 healthy non smoking subjects
Intervention	Questinnaire Exhaled NO measurement using chemiluminescence analyzer Lung spirometry Collection and microbial assessment of fresh sputum Measurement of total sputum NO contents
Comparison	
Length of follow up (if applicable)	
Outcome measures/ Effect size	There was no significant difference in exhaled nitric oxide between patients with bronchiectasis and control subjects (p = 0.11). Bronchiectasis patients with Pseudomonas aeruginosa infection had a significantly lower exhaled, but not sputum, NO levels than their counterparts and control subjects (p = 0.04 and p = 0.009, respectively). There was no significant difference between the exhaled No levels between control subjects and bronchiectasis patients without P aeruginosa infection (p = 0.96)
General Comments	

Cost effectiveness

Question   : Is FE$_{NO}$ measurement using NIOX MINO cost effective?

Bibliographic Citation	Berg J, Lindgren P. Economic evaluation of FE$_{NO}$ measurement in diagnosis and 1-year management of asthma in Germany. Respir Med. 2008; 102(2):219-31
Study Type / Methodology	
LE	
Number of patients and patient characteristics	
Intervention	Two decision trees were constructed to capture the different alternatives and consequences in asthma diagnosis and management, comparing FE$_{NO}$ measurement against standard diagnostics and treatment guidelines. A German payer perspective was chosen. Effectiveness was measured in quality-adjusted life-years.
Comparison	
Length of follow up (if applicable)	The impact of asthma management with FE$_{NO}$ measurement on resource use and health outcomes was evaluated over a 1-year timeframe
Outcome measures/ Effect size	Asthma diagnosis based on FE$_{NO}$ measurement results in a cost of 38 per patient compared with 326 for standard diagnostics. In mild to severe patients, asthma management with FE$_{NO}$ measurement instead of standard guidelines results in cost-savings of 30 per patient and year. In a more severe population, management with FE$_{NO}$ measurement would save costs of 160 per patient. Asthma diagnosis based on FE$_{NO}$ measurement alone (exemplified with NIOX MINO) costs 12 more per patient than standard diagnostic methods. Improved accuracy. The use of FE$_{NO}$ measurement in treatment decisions is less costly than asthma management based on standard guidelines and provides similar health benefits.
General Comments	Abstract

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