

Measurement of exhaled nitric oxide concentration in asthma: a systematic review and economic evaluation of NIOX MINO, NIOX VERO and NObreath

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Scientific summary

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Background

Asthma is a chronic disorder of the airways, caused primarily by inflammatory processes and bronchoconstriction. Symptoms of asthma include recurrent episodes of wheezing, breathlessness, chest tightness and coughing. The diagnosis of asthma is a clinical one, based on symptoms and clinical respiratory measurements. However, there is no definitive, objective diagnostic test and as such there is significant over- and underdiagnosis.

In 2011, an estimated 5.4 million people in the UK were receiving treatment for asthma. Deaths from asthma are generally rare, with 1041 in England and Wales in 2011.

The management of asthma aims to control symptoms, prevent exacerbations and achieve the best lung function, with minimal side effects. For both children and adults, asthma is monitored and managed in primary care by routine clinical review on at least an annual basis. Patients are managed in a stepwise manner, with escalation of medication until control is reached.

High fractional exhaled nitric oxide (FeNO) levels in a patient with symptoms suggestive of asthma may suggest that the patient has eosinophilic asthma that could be treated with inhaled corticosteroids (ICSs). In individuals already diagnosed with asthma, FeNO levels may indicate how well they are responding to ICS-based medication, whether medication is being adhered to and whether medication dosage should be increased or decreased (step up/step down).

Objectives

To assess the clinical effectiveness and cost-effectiveness of FeNO measurement for the diagnosis and management of asthma in adults and children using the hand-held monitors NIOX MINO® (Aerocrine, Solna, Sweden), NIOX VERO® (Aerocrine) and NObreath® (Bedfont Scientific, Maidstone, UK).

Methods

This report consists of two main parts: (1) an assessment of the clinical effectiveness of FeNO in the diagnosis and management of asthma and (2) an assessment of the cost-effectiveness of FeNO compared with standard care in the diagnosis and management of asthma.

Clinical evidence review

The following systematic reviews were conducted:

- *Rapid review of the equivalence of FeNO devices.* Aimed at establishing whether studies that used other FeNO measurement devices could inform this appraisal.
- *Systematic review of the diagnostic accuracy of FeNO measurement for asthma.* All levels of evidence were considered but, because of a lack of higher levels of evidence, diagnostic cohort studies informed this assessment. When available, three pairs of sensitivity and specificity estimates were selected: (1) the highest sum of sensitivity and specificity; (2) the highest sensitivity for rule-in scenarios; and (3) the highest specificity for rule-out scenarios. In rule-in scenarios, patients testing positive are assumed to have asthma and those testing negative go on to have further tests for asthma. In rule-out scenarios, those who test negative are assumed not to have asthma and those who test positive go on to have further tests for asthma.

- *Systematic review of the efficacy of FeNO-guided management of asthma.* Randomised controlled trial (RCT) evidence was included and lower levels of evidence included when RCT evidence was not available for pre-defined subgroups.

Databases searched included MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, Science Citation Index Expanded and Conference Proceedings Citation Index – Science. Trial registers such as ClinicalTrials.gov and the *metaRegister* of Controlled Trials were also searched. Initial searches were undertaken between March 2013 and April 2013 and update searches for the diagnostic and management reviews were performed in September 2013. All reviews considered adults and children separately. Subgroups of interest included older adults, pregnant women and smokers. All three reviews were undertaken according to robust high-quality methodology.

Cost-effectiveness assessment

The cost-effectiveness assessment of FeNO included two components: a systematic review of existing economic analyses and the development of two *de novo* health economic models:

- *Systematic review and critical appraisal of existing economic evaluations.* This included published studies and evidence submitted by manufacturers.
- *Development of two de novo models.* Independent health economic models were developed to assess the incremental cost-effectiveness of FeNO compared with standard care in the diagnosis and management of asthma.

Results

Clinical effectiveness results

Rapid review of FeNO device equivalence

In total, 27 studies were included. Although there was often good correlation between FeNO measurement devices, equivalence of readings could not necessarily be assumed in all situations. The 95% limits of agreement were sometimes very wide (around ± 10 parts per billion) and equivalence was generally poorer between FeNO devices at higher FeNO levels. The direction of disagreement varied between studies and comparator devices.

Correlation between measurements across all devices was high. Consequently, sensitivities and specificities were assumed to be interchangeable, but it could not be assumed that the cut-off points used would be the same for each device; this is an important issue.

Test failure rates were generally low although there may be some problems with using the NIOX MINO device in younger children, with failure rates ranging from 5.5% to 27%.

Systematic review of the diagnostic accuracy of FeNO measurement for asthma

In total, 27 studies were included in the review, 23 in adults (all ages) and four in children. Studies that were similar to one another in terms of the position of the patients in the UK diagnostic pathway [Scottish Intercollegiate Guidelines Network (SIGN) guidelines] and the reference standards used were grouped together. No meta-analysis was conducted in any group as the clinical heterogeneity between studies was very high.

Estimates of cut-off points, sensitivity and specificity were not consistent within groups and ranged widely when used as a rule-in test and a rule-out test and when considering the highest sum of sensitivity and specificity. The large variation in estimates within groups may obscure any true underlying differences in the accuracy of FeNO between groups and compared with different reference standards. The evidence is

especially difficult to interpret in the context of inserting FeNO into the UK diagnostic pathway. The nearest equivalent to a pathway was reported in two studies in which FeNO was interpreted in conjunction with results from another test, resulting in a change in both sensitivity and specificity, but it was not clear whether clinical effectiveness and cost-effectiveness would also change. Some limited observations were made: 100% specificity was achieved more often than 100% sensitivity and ranges of specificity were generally smaller. This may indicate that FeNO has the highest potential for consistency and accuracy as a rule-in test. It was also concluded that FeNO cut-off points should probably be lower in children than in adults.

No cohort studies were found that provided evidence relating to pregnancy, the elderly and smokers/children with environmental tobacco exposure. Consequently, lower levels of evidence were consulted.

- smokers: accuracy seemed similar but FeNO was generally lower in smokers and children exposed to tobacco smoke
- the elderly: FeNO is unlikely to be a useful test in the diagnosis of asthma in the elderly
- pregnant women: pregnancy did not alter FeNO levels in asthmatics or non-asthmatics and FeNO distinguished between asthmatic and non-asthmatic pregnant and healthy women.

Systematic review of the efficacy of FeNO-guided management of asthma

Five adult population studies were included. High levels of heterogeneity in multiple study characteristics and outcome definitions prevented the External Assessment Group (EAG) from drawing any firm conclusions with regard to which step-up/step-down protocol or cut-off points offered the best efficacy. All studies reported fewer exacerbations in the FeNO arm, mostly driven by mild and moderate exacerbations, which was statistically significant in only one study. The effects on ICS use were heterogeneous, although it was not possible to conclude if this was because of differences in study populations or differences in management protocols. Pooled analysis showed less ICS use in the intervention arm, but the difference was not statistically significant. Health-related quality of life (HRQoL) was infrequently reported; two studies both showed no effect on the global Asthma Quality of Life Questionnaire (AQLQ) score, but one found a statistically significant difference in the symptoms score.

No study exceeded 12 months' follow-up; it is unclear if any observed effects would be maintained over longer time periods.

Seven studies in children were included. The severity of the patients' symptoms varied between studies. All studies except one reported a decrease in exacerbations in the intervention arm, but only one reported a statistically significant reduction. The effects on ICS use were heterogeneous with two studies showing a statistically significant increase in ICS use, two showing a non-significant increase, one showing no difference, one being difficult to interpret and one further study not reporting this outcome. HRQoL was reported in only one study; insufficient details were reported to draw conclusions.

A RCT of asthma management using FeNO in pregnant asthmatics was included. Statistically significant differences in all exacerbations, OCS use and ICS use were reported, favouring the intervention.

Non-RCT evidence indicated that FeNO was unlikely to be useful in elderly asthmatics. In smokers, the four non-RCT studies identified suggested that FeNO levels were lower in adult asthmatic smokers than in adult asthmatic non-smokers and that FeNO can no longer detect asthma control in those smokers treated with ICSs. The use of repeated measures and within-patient change from baseline may be worth further investigation.

Cost-effectiveness results

There is very limited available evidence concerning the cost-effectiveness of FeNO for the diagnosis and/or management of asthma. The systematic review identified one published UK model of FeNO testing in the diagnostic setting and one published UK model of FeNO testing in the management setting. Both models

were published within the same paper. Aerocrine also submitted a model of FeNO testing for diagnosis and a model of FeNO testing for management; these models were similar to, but not the same as, the published UK models. The existing economic diagnostic models indicate that NIOX MINO is likely to be cost saving compared with other tests routinely used in the diagnosis of asthma, but may be more expensive than standard diagnostic tests when used in conjunction with other tests. Neither diagnostic model captures the health consequences associated with correct or incorrect diagnostic outcomes; hence, these models do not provide any information regarding the economic trade-off between additional health gains resulting from the more accurate diagnosis of asthma and health losses associated with displacing existing services. The existing management models indicate that NIOX MINO produces more health gains at a lower cost than guidelines alone. The EAG critique of these management models highlighted several problems including the use of short time horizons, the selective use of efficacy evidence from different sources, the assumptions about the equivalence between sputum count monitoring and FeNO and invalid assumptions about the health losses associated with exacerbations. No economic evidence was submitted by the manufacturers for either NIOX VERO or NObreath.

The EAG developed two de novo models. The first model assesses the cost-effectiveness of FeNO testing using NIOX MINO, NIOX VERO and NObreath in addition to, or in place of, existing tests compared with other diagnostic options commonly used in the diagnosis of asthma. The second model assesses the cost-effectiveness of NIOX MINO, NIOX VERO and NObreath plus guidelines compared with guidelines alone for the management of asthma.

The EAG diagnostic model suggests that, across the diagnostic options included in the economic analysis, the expected difference in quality-adjusted life-year (QALY) gains is likely to be very small. Airway hyper-responsiveness [assessed using the methacholine challenge test (MCT)] is expected to produce the greatest QALY gain. The incremental cost-effectiveness ratio (ICER) of airway hyper-responsiveness (MCT) compared with FeNO (NObreath) plus bronchodilator reversibility is expected to be £1.125M per QALY gained. All remaining options are expected to be ruled out because of dominance. The results of the analysis are sensitive to assumptions about the time required to resolve misdiagnoses, assumptions about health losses associated with false-negative diagnoses, the costs of asthma management and the use of 'rule-in' and 'rule-out' diagnostic decision rules.

The EAG management model was evaluated across two subgroups: (1) children and (2) adults. Studies from the clinical effectiveness review were selected for the model, based on similarity to UK practice and patient populations. Sensitivity analyses were conducted using alternative studies to test the stability of the results in other populations and against different comparators. Within both the child and adult subgroup analyses, FeNO testing is expected to produce a small incremental QALY gain compared with guidelines alone. In both subgroups, NIOX MINO and NIOX VERO are expected to be dominated as their marginal per-test cost is higher than that for NObreath. Within the child subgroup, the ICER of guidelines plus FeNO monitoring using NObreath compared with guidelines alone is expected to be approximately £45,200 per QALY gained. Within the adult subgroup, FeNO monitoring using NObreath compared with guidelines alone is expected to cost approximately £2100 per QALY gained. A similarly favourable result was produced within a further analysis based on a subgroup of women who are pregnant. Importantly, these positive results are not held when alternative trials are used to inform the analysis. The results in the child and adult subgroups are particularly sensitive to assumptions about changes in ICS use over time, the number of nurse visits for FeNO monitoring and the duration over which FeNO monitoring impacts on exacerbations and ICS use.

Conclusions

Implications for service provision

There is considerable uncertainty associated with all analyses within this assessment. This is largely because of the limitations of the evidence base.

Studies using the devices that are the focus of this review were not available for all analyses and, in the absence of an alternative, equivalence has been assumed but is not assured.

The clinical evidence relating to the use of FeNO for the diagnosis of asthma is highly heterogeneous and difficult to interpret in the context of the insertion of FeNO into a diagnostic pathway.

Evidence for management is also inconclusive although consistent with FeNO resulting in fewer exacerbations, with a small or zero reduction in ICS use in adults and a possible increase in ICS use in children or patients with more severe asthma. It is unclear which specific management protocol is likely to be most effective. There was no evidence relating to whether these effects would be maintained over a longer time period.

The health economic analysis indicates that FeNO could have value in both the diagnostic setting and the management setting. In particular, the diagnostic model indicates that FeNO plus bronchodilator reversibility dominates many other diagnostic tests and may render airway hyper-responsiveness cost-ineffective. In the management setting, FeNO-guided management has the potential to appear cost-effective although this is largely dependent on the expected duration over which it continues to impact on medication decisions. The conclusions drawn from both models require strong technical value judgements with respect to several aspects of the decision problem in which little or no empirical evidence exists.

Suggested research priorities

Several research priorities were identified. The two key priorities, of equal importance, were:

1. What is the clinical utility of FeNO used in sequence with current guidelines for the diagnosis of asthma and/or ICS responsiveness compared with current guidelines alone, when a reference standard of long-term follow-up of diagnoses is used? What is the optimal placement for FeNO testing within the diagnostic pathway?
2. What is the most effective step-up/step-down protocol for the management of asthma using FeNO? Is it safe to step down treatment on the basis of low FeNO alone (e.g. in the presence of symptoms)?

Study registration

This study is registered as PROSPERO CRD42013004149.

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