NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Health Technology Evaluation

Review decision

Review of DG12: Measuring fractional exhaled nitric oxide concentration in asthma: NIOX MINO, NIOX VERO and NObreath

This guidance was issued in April 2014.

The review date for this guidance is April 2017. The review of this guidance was delayed until after the publication of the NICE guideline on asthma: diagnosis, monitoring and chronic asthma management.

NICE proposes an update of published guidance if the evidence base or clinical environment has changed to an extent that is likely to have a material effect on the recommendations in the existing guidance. Other factors such as the introduction of new technologies relevant to the guidance topic, or newer versions of technologies included in the guidance, will be considered relevant in the review process, but will not in individual cases always be sufficient cause to update existing guidance.

1. Decision

Transfer the guidance to the 'static guidance list'.

Recommendation 1.1 will be replaced with a statement that says: FeNO is recommended by NICE to help diagnose asthma; for further details please see NICE's guideline on asthma: diagnosis, monitoring and chronic asthma management (NG80).

The evidence gathered in this report will be passed to the Centre for Guidelines surveillance team and be considered during routine surveillance of NICE's guideline on asthma: diagnosis, monitoring and chronic asthma management.

At the Guidance Executive meeting of 5 March 2019 it was agreed that no consultation on the decision was required.

A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper.

2. Rationale

Since publication of DG12, NICE has published the Asthma: diagnosis, monitoring and chronic asthma management guideline (NG80; 2017).

Currently DG12 and NICE's guideline on asthma both recommend FeNO to help diagnose asthma in adults and children. New evidence identified in the review of DG12 supports this recommendation. Therefore recommendation 1.1 in the diagnostics guidance will be replaced with a statement to say that FeNO is recommended by NICE to help diagnose asthma and a link to NICE's guideline on asthma. This will avoid duplication between NICE outputs.

Currently in DG12, FeNO is also recommended as an option to support asthma management in people who are symptomatic despite using inhaled corticosteroids. NICE's guideline however, recommends that FeNO is not routinely used to monitor asthma control, but that FeNO can be considered an option to support asthma management in people who are symptomatic despite using inhaled corticosteroids (that is, it links to DG12). New evidence identified in the review of DG12 supports the current NICE recommendations. Therefore recommendation 1.2 in the diagnostics guidance will remain and the guidance will be placed on the static list.

3. Implications for other guidance producing programmes

The evidence gathered in this report will be passed to the Centre for Guidelines surveillance team and be considered during routine surveillance of NICE's guideline on asthma: diagnosis, monitoring and chronic asthma management.

The adoption team developed an adoption resource to support adoption of the diagnostic tests recommended in NICE's guideline on asthma: diagnosis, monitoring and chronic asthma management (NG80). The adoption team will review and update this as required based on the new information reported in section 6.1 of this review proposal.

4. Original objective of guidance

To assess the clinical and cost effectiveness of NIOX MINO, NIOX VERO and NObreath for measuring fractional exhaled nitric oxide concentration in asthma.

5. Current guidance

Adoption recommendations

1.1 Fractional exhaled nitric oxide (FeNO) testing is recommended as an option to help diagnose asthma in adults and children:

- who, after initial clinical examination, are considered to have an intermediate probability of having asthma (as defined in the British guideline on the management of asthma 2012) and

- when FeNO testing is intended to be done in combination with other diagnostic options according to the British guideline on the management of asthma (2012).

  Further investigation is recommended for people whose FeNO test result is negative because a negative result does not exclude asthma.

1.2 FeNO measurement is recommended as an option to support asthma management (in conjunction with the British guideline on the management of asthma 2012) in people who are symptomatic despite using inhaled corticosteroids.

Research recommendations

7.1 The Committee discussed the potential for future research. The Committee accepted that there is a need to further establish the accuracy of current practice in diagnosing asthma and the incremental accuracy associated with the addition of FeNO testing.

7.2 The Committee also considered the role of FeNO measurement in asthma management. It accepted that currently available evidence on the use of FeNO measurement in asthma management is unclear on whether benefits of treatment are maintained long-term. The Committee concluded that long-term studies following patients for several years could address this gap.

7.3 The Committee also considered the role of FeNO in guiding inhaled corticosteroid dosing through stepping-up and stepping-down protocols. It accepted there is a need for more evidence on which protocols offer the safest and most optimal asthma management when used in UK clinical practice. Therefore, further studies are recommended, with consideration for the different protocols and cut-off points that may be necessary in different populations.

6. New evidence

The original DAR searches for DG12 were conducted in 2013. Searches for the NICE guideline on diagnosis and monitoring of asthma (NG80) were last run in March 2017. The search strategies and evidence selection criteria reported in NG80 were assessed for relevance to DG12. Therefore, the review approach was to screen the included and excluded studies from NG80 for relevant studies published since the date of the original DG12 searches (2013), plus to re-run the updated DG12 DAR searches to identify relevant published studies from March 2017 onwards.

The search strategy from the original diagnostics assessment report was re-run in September 2018. Additional searches of clinical trials registries were also carried out and relevant guidance from NICE and other professional bodies was reviewed to determine whether there have been any changes to the diagnostic and care pathways. Companies were asked to submit all new literature references relevant to their technology along with updated costs and details of any changes to the technology itself or the CE marked indication for use for their technology. Specialist committee members for this guidance topic were also consulted and asked to submit any information regarding changes to the technologies, the evidence base and clinical practice. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

6.1 Technologies

In June 2015, Circassia completed the acquisition of Aerocrine, the previous manufacturer of NIOX devices.

NIOX MINO

NIOX MINO was discontinued from sale on 31 December 2017. Existing NIOX MINO customers will be able to purchase consumables until 31 December 2020, when the last remaining installed NIOX MINO devices reach the end of their shelf life.

NIOX VERO

There have been no changes to the mechanism of action for the NIOX VERO or to the FeNO calculation algorithm. In terms of the NIOX VERO device specifications, there have been some changes to optimise the sensor functionality, the addition of the nasal nitric oxide (nNO) functionality and the device inventory shelf life has been extended in June 2018, but there has been no change to the in-use shelf life. The NIOX VERO EU Declaration of Conformity was updated on 31 August 2017 due to the additional nNO functionality. Nasal nitric oxide measurement is out of the scope for this guidance review.

NObreath

The manufacturer of NObreath did not provide any information relating to potential changes in the technology to NICE; therefore, the company's website was used as the main source of information. The company website suggests that a second generation NObreath FeNO monitor is available, with key differences between the first and second versions relating to the FeNO concentration range, power source, storage/transport temperature and operating humidity.

Alternative technologies

One alternative technology with a similar purpose to the NIOX VERO and NObreath was identified; the Bosch Healthcare Solutions Vivatmo pro is a new point of care FeNO device for professional use.

6.2 Clinical practice

In November 2017, NICE published Asthma: diagnosis, monitoring and chronic asthma management (NG80). In this clinical guideline, FeNO is recommended for use in the diagnosis of asthma in adults and for consideration in certain children over 5 years old, but is not recommend for routine monitoring of asthma. Further, cut-off thresholds for diagnosis are reported, measured in parts per billion (ppb), regardless of the device that is used.

On diagnosis of asthma, NG80 makes the following recommendations:

> 1.3.2. Offer a FeNO test to adults (aged 17 and over) if a diagnosis of asthma is being considered. Regard a FeNO level of 40 parts per billion (ppb) or more as a positive test.
>
> 1.3.3. Consider a FeNO test in children and young people (aged 5 to 16) if there is diagnostic uncertainty after initial assessment and they have either:
>
> - normal spirometry or
> - obstructive spirometry with a negative bronchodilator reversibility (BDR) test.
>
> Regard a FeNO level of 35 ppb or more as a positive test.
>
> 1.3.4. Be aware that a person's current smoking status can lower FeNO levels both acutely and cumulatively. However, a high level remains useful in supporting a diagnosis of asthma.

Regarding monitoring, NG80 makes the following recommendations, which refer to diagnostics guidance 12:

> 1.14.4. Do not routinely use FeNO to monitor asthma control.
>
> 1.14.5 Consider FeNO measurement as an option to support asthma management in people who are symptomatic despite using inhaled corticosteroids. (This recommendation is from NICE's diagnostics guidance on measuring fractional exhaled nitric oxide concentration in asthma).

The BTS/SIGN clinical guidelines on asthma, entitled British guideline on the management of asthma, were updated in 2016, superseding the 2012 hyperlinks in DG12 recommendations 1.1 and 1.2. The BTS/SIGN clinical guidelines make the following recommendation concerning diagnosis of asthma:

> Use measurement of FeNO (*if available*) to find evidence of eosinophilic inflammation. A positive test increases the probability of asthma but a negative test does not exclude asthma (GRADE D).

No explicit recommendations were made by the BTS/SIGN for the use of FeNO in asthma monitoring.

6.3 New studies

Diagnosis of asthma

No new primary studies of FeNO were identified that were within scope, that is studies reporting: prospectively on the use of FeNO as a diagnostic test for asthma (with or without other diagnostic test types); diagnostic outcomes that could be used to inform the economic model; in an appropriate setting; on a population relevant to the DG12 decision problem. However, 2 systematic review and meta-analyses were identified (one with *2* publications). The review by Wang et al. (2018) was broad in scope, and it would be difficult to generalise the results to UK NHS practice. The studies by Karrasch et al. (2017) and Schneider et al. (2017) identified 26 studies they considered fitted their inclusion criteria; with most of these studies having been included in the assessment report for DG12. The most important conclusion derived from these studies was that the diagnostic accuracy of FeNO is highly dependent on the characteristics of the population it is being used in, in particular the underlying prevalence of asthma.

Monitoring of asthma

Five randomised controlled trials (RCTs) were identified that considered the use of FeNO in the management of asthma (monitoring and subsequent drug regimen choice and titration). Three of these studies were identified in the assessment report for DG12 but only as unpublished data or abstracts. The full papers have now been published and it was found that Petsky et al. (2015) used a static FeNO device rather than a point of care device, and so is out of scope for DG12. This was the only study in the DG12 assessment to report significant decreases in the number of children having asthma exacerbations in the FeNO arm. The findings in Sky et al. 2013 did not differ materially from the findings of the unpublished data. Honkoop et al. 2014 found no significant difference in mean QALYs gained between strategies including FeNO and strategies without FeNO.

Two new RCTs on monitoring were identified which were published subsequent to DG12. The Garg et al. (2018) study included adults and adolescents, but was of borderline relevance due to its setting in a tertiary care Indian hospital. It reported no significant difference between FeNO and therapy guided by the Global Initiative for Asthma (GINA) guidelines for a range of outcomes. The study by Voorend van Bergen et al. (2015) compared FeNO monitoring with standard care and a web-based monitoring system in children. Results suggested that FeNO monitoring did not improve outcomes compared with alternative interventions, with no significant differences reported for most outcomes.

In addition to the RCTs, a systematic review and meta-analysis was identified. Petsky et al. (2018) included 16 studies and found that FeNO may reduce acute exacerbations of asthma in both children and adults. This result should be considered with caution considering the heterogeneity of the included studies.

6.4 Changes in cost

Device costs

The costs of NIOX MINO are not considered because this device has effectively been superseded by the NIOX VERO. The costs associated with NIOX VERO were provided to NICE by the manufacturer (Circassia) and the cost associated with NObreath were identified from the distributor website (Intermedical (UK) Limited). Costs and the percentage change between the current cost and the cost used in the DG12 assessment are presented in table 1. The cost of the NIOX VERO instrument has risen marginally above inflation, whereas the increase in costs of the consumables is below inflation. The costs of the NObreath monitor and consumables have fallen in real terms; however the requirement and costs for device sensor replacement are unknown.

Table 1: Comparative costs associated with NIOX VERO and NObreath (VAT not included)

Item	Cost in DG12	Current cost	Difference (% change)
Costs associated with NIOX VERO			
NIOX VERO Instrument [a]	£2,100.00	£2,640.00	£540 (+26%)
Test kit [b] (1000 tests)	£4,200.00 (£4.20 per test)	£4,580.00 (£4.58 per test)	£380 (+9%)
Test kit [b] (500 tests)	£2,200.00 (£4.40 per test)	£2,290.00 (£4.58 per test)	£90 (+4%)
Test kit [b] (300 tests)	£1,500.00 (£5 per test)	£1,510.00 (£5.03 per test)	£10 (<1%)

Item	Cost in DG12	Current cost	Difference (% change)
Costs associated with NObreath			
NObreath FeNO nitric oxide monitor [c]	£1,995.00	£1,795.00	-£200 (-10%)
NObreath mouthpieces [d] (box of 50)	£195.00 (£3.90 per mouthpiece)	£150.00 (£3 per mouthpiece)	-£45 (-23%)
[a] The instrument is also available in various combination with the test kit consumables [b] Contains a sensor for the required number of tests and 1 consumable filter for each test [c] Package comes complete with Bedfont NObreath FeNO Monitor, NObreathFLO mouthpiece attachment, an interpretation chart and 3 x AA batteries. [d] Mouthpieces are required to be purchased separately. The only pack size available on the Intermedical website is 50.			

Healthcare resource use

The models for DG12 included costs associated with healthcare resource, which were taken from standard reference sources. A comparison of the values used in DG12 with current costs is reported in table 2, which show that costs have decreased since the publication of DG12.

Table 2 Healthcare resource use costs

Resource cost parameter	Sources	Cost in DG12	Current cost
Primary care GP visit	PSSRU (2012 and 2017)	£43.00	£37.00
Primary care practice nurse visit	PSSRU (2012)	£13.69	Unknown
Secondary care respiratory medicine outpatient visit	NHS reference cost (2011-2012 and 2015-2016)	£204.29	£154.77
Secondary care laboratory visit	NHS reference cost (2011-2012 and 2015-2016)	£203.29	£133.56

Asthma drug management costs in the economic model for DG12 were derived from two published HTA studies (Main et al. 2008 and Shepherd et al. 2008). Guidelines on the treatment of asthma have changed since the publication of DG12, for example NICE's guideline on Asthma: diagnosis, monitoring and chronic asthma management (NG80) does not feature a stepwise approach to management and recommends a self-management programme in suitable patients. Therefore, there is considerable uncertainty regarding the costs of medical management in an "average" patient. Deterministic sensitivity analysis in the economic model for DG12 indicated that the model was not sensitive to changes in asthma treatment costs.

6.5 NICE's research commissioning activities

Diagnostics guidance 12 emphasised the need for further studies in order to confirm the effectiveness of FeNO in a UK context. Newcastle and York external assessment centre produced a report which assessed the current gaps in the evidence base on using FeNO levels to guide levels of therapy in people with asthma, and the feasibility of future studies in addressing these gaps.

The external assessment centre noted that in order to further inform the present evidence base, a prospective RCT set in primary care in the UK would be required. It noted further that the anticipated effect of FeNO monitoring on the primary outcome, reduction of exacerbations, is likely to be relatively small, therefore a large sample size would be required, and that this would make it an expensive trial to implement.

7. Summary of new evidence and implications for review

When the assessment for DG12 was done, current practice in the NHS for the diagnosis and treatment of asthma was based on the British guideline on the management of asthma (2012) from the British Thoracic Society and Scottish Intercollegiate Guidelines Network. This guideline was the comparator in the DG12 assessment, against which the FeNO devices were compared. Since publication of DG12, NICE has published the Asthma: diagnosis, monitoring and chronic asthma management guideline (NG80; 2017). The NICE guideline on asthma should now be the standard of care in the NHS, and any future assessment of FeNO should compare the devices with current practice based on the NICE guideline on asthma.

Currently in DG12, FeNO is recommended as an option to help diagnose asthma in adults and children who are considered to have an intermediate probability of having asthma and when testing is done in combination with other diagnostic options. NICE's guideline on asthma also recommends that FeNO should be offered to adults and considered in children to help diagnose asthma. New evidence identified in the review of DG12 supports the current NICE recommendations.

Currently in DG12, FeNO is recommended as an option to support asthma management (in conjunction with the British guideline on the management of asthma 2012) in people who are symptomatic despite using inhaled corticosteroids. NICE's guideline however, recommends that FeNO is not routinely used to monitor asthma control, but that FeNO can be considered an option to support asthma management in people who are symptomatic despite using inhaled corticosteroids (that is, it links to DG12). New evidence identified in the review of DG12 has shown that FeNO has only a small effect, or no effect, on clinical outcomes when compared with current practice or alternative strategies for monitoring asthma. This new evidence therefore supports the current NICE recommendations.

Given that the new evidence identified is unlikely to change the underlying recommendations, no update is proposed at this time. Further, because of the substantial overlap between DG12 and NG80, it would be sensible for future updates relating to FeNO to be done by the centre for guidelines in order to avoid duplication of effort and conflicting recommendations from NICE.

8. Implementation

NICE's guideline on Asthma: diagnosis, monitoring and chronic asthma management (NG80) includes a statement about putting the guideline into practice using a phased implementation approach. It notes that testing with spirometry and FeNO will take the NHS some time to implement, and it may involve establishing diagnostic hubs to make testing efficient and affordable. Further, centres will be able to draw on the positive experience of NICE's primary care pilot sites, which trialled the use of FeNO.

9. Equality issues

No potential equality issues were raised in the original guidance.

Paper sign off: Sarah Byron, Associate Director,

Contributors to this paper:

Technical Lead: Frances Nixon

Technical Adviser: Rebecca Albrow

Project Manager: Donna Barnes

Appendix 1 – Explanation of options

If the published diagnostics guidance needs updating NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
Standard update of the guidance	A standard update of the diagnostics guidance will be planned into NICE's work programme.	No
Accelerated update of the guidance	An accelerated update of the diagnostics guidance will be planned into NICE's work programme. Accelerated updates are only undertaken in circumstances where the new evidence is likely to result in minimal changes to the decision problem, and the subsequent assessment will require less time to complete than a standard update or assessment.	No
Update of the guidance within another piece of NICE guidance	The guidance is updated according to the processes and timetable of that programme.	No

If the published diagnostics guidance does not need updating NICE must select one of the options in the table below:

Options	Consequences	Selected – 'Yes/No'
Transfer the guidance to the 'static guidance list'	The guidance remains valid and is designated as static guidance. Literature searches are carried out every 5 years to check whether any of the diagnostics guidance on the static list should be flagged for review.	Yes
Produce a technical supplement	A technical supplement describing newer versions of the technologies is planned into NICE's work programme.	No
Defer the decision to review the guidance to	NICE will reconsider whether a review is necessary at the specified date.	No
Withdraw the guidance	The diagnostics guidance is no longer valid and is withdrawn.	No

Appendix 2 – Supporting information

Relevant Institute work

Published

Asthma: diagnosis, monitoring and chronic asthma management (2017) NICE guideline NG80

Asthma (2018) NICE quality standard 25

Mepolizumab for treating severe refractory eosinophilic asthma (2017) NICE technology appraisal guidance 431

Reslizumab for treating severe eosinophilic asthma (2017) NICE technology appraisal guidance 479

Omalizumab for treating severe persistent allergic asthma (2013) NICE technology appraisal guidance 278

Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over (2008) NICE technology appraisal guidance 138

Inhaled corticosteroids for the treatment of chronic asthma in children under the age of 12 years (2007) NICE technology appraisal guidance 131

In progress

Benralizumab for treating severe asthma. NICE technology appraisal guidance. Publication expected December 2018

Details of new technologies

Device (manufacturer)	**Details (phase of development, expected launch date,)**
Vitamo pro (Bosch Healthcare Solutions)	This device has been available since June 2017 from UK and Ireland distributor Healthcare 21

Registered and unpublished trials

Trial name and registration number	Details
A Pragmatic Trial of Corticosteroid Optimisation in Severe Asthma NCT02717689	A multicentre RCT designed to test the efficacy of FeNO monitoring in adults (n=300) with severe asthma. The study will compare "biomarker (composite biomarker strategy using FeNO, blood eosinophils and serum periostin) based adjustment of corticosteroid dose" with standard care (corticosteroid dose based on asthma symptom control and lung function). The trial has a follow up period of 1 year. The primary outcome is the proportion of patients with any reduction in corticosteroid dose. Secondary outcomes include rate of exacerbations and biomarker levels. Eleven UK centres are participating. The study was due to complete in June 2018.
The RACCENO trial (Reducing Asthma Attacks in Children using Exhaled Nitric Oxide as a biomarker to inform treatment strategy) ISRCTN67875351	A large multicentre RCT set across 21 centres in the UK. The aim of the study is to compare treatment guided by FeNO and symptoms with treatment guided by symptoms alone (standard care) in children with asthma who are at risk of an asthma attack. The target sample size is 502 children. Follow-up visits will be performed at 3, 6, 9 and 12 months. The primary outcome of the study is occurrence of an asthma attack requiring prescription of oral corticosteroids for 3 to 7 consecutive days. Secondary outcomes include lung function tests, asthma control, ICS dose and quality of life.

References

Wang Z, Pianosi PT, Keogh KA, Zaiem F, Alsawas M, Alahdab F, et al. The Diagnostic Accuracy of Fractional Exhaled Nitric Oxide Testing in Asthma: A Systematic Review and Meta-analyses. Mayo Clinic Proceedings. 2018 Feb;93(2):191-8.

Karrasch S, Linde K, Rucker G, Sommer H, Karsch-Volk M, Kleijnen J, et al. Accuracy of FENO for diagnosing asthma: a systematic review. Thorax. 2017 02;72(2):109-16.

Schneider A, Linde K, Reitsma JB, Steinhauser S, Rucker G. A novel statistical model for analyzing data of a systematic review generates optimal cutoff values for fractional exhaled nitric oxide for asthma diagnosis. Journal of Clinical Epidemiology. 2017 Dec;92:69-78.

Syk J, Malinovschi A, Johansson G, Unden A-L, Andreasson A, Lekander M, et al. Anti-inflammatory treatment of atopic asthma guided by exhaled nitric oxide: a

randomized, controlled trial. J Allergy Clin Immunol Pract. 2013 Nov-Dec;1(6):639-48.e1-8.

Honkoop PJ, Loijmans RJB, Termeer EH, Snoeck-Stroband JB, van den Hout WB, Bakker MJ, et al. Symptom- and fraction of exhaled nitric oxide-driven strategies for asthma control: A cluster-randomized trial in primary care. J Allergy Clin Immunol. 2015 Mar;135(3):682-8.e11.

Garg Y, Kakria N, Katoch CDS, Bhattacharyya D. Exhaled nitric oxide as a guiding tool for bronchial asthma: A randomised controlled trial. Medical Journal Armed Forces India. 2018.

Petsky HL, Li AM, Au CT, Kynaston JA, Turner C, Chang AB. Management based on exhaled nitric oxide levels adjusted for atopy reduces asthma exacerbations in children: A dual centre randomized controlled trial. Pediatric Pulmonology. 2015 Jun;50(6):535-43.

Voorend-van Bergen S, Vaessen-Verberne AA, Brackel HJ, Landstra AM, van den Berg NJ, Hop WC, et al. Monitoring strategies in children with asthma: a randomised controlled trial. Thorax. 2015 Jun;70(6):543-50.

Petsky HL, Cates CJ, Kew KM, Chang AB. Tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils): a systematic review and meta-analysis. Thorax. 2018 Jun 01;01:01.

Petsky HL, Li A, Chang AB. Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults. Cochrane Database of Systematic Reviews. 2017(8).

Main C, Shepherd J, Anderson R, Rogers G, Thompson-Coon J, Liu Z, et al. Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta2 agonists for the treatment of chronic asthma in children under the age of 12 years. Health Technol Assess. 2008 May;12(20):1-174, iii-iv.

Shepherd J, Rogers G, Anderson R, Main C, Thompson-Coon J, Hartwell D. Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta2 agonists for the treatment of chronic asthma in adults and children aged 12 years and over. 2008;12(19).