NICE National Institute for Health and Care Excellence

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

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	External Assessment Group's response
Consultee 1: Aerocrine Ltd (Manufacturer)	1.	53	3.6.3.1	In the time since the initial notification the number of NIOX MINO users in the UK has increased and is now; 18 x units in Primary Care settings (GP's and nurse outreach projects) 197 x units in 127 acute hospitals	No response required
	2.	154	5.2.3.1	New data to consider: Honkoop et al, "A cluster randomized trial comparing strict, partial, and FeNO-guided asthma control strategies in primary care" (conference abstract ERS 2013, manuscript under production, see separate literature list. Links to study protocol provided). A full manuscript can be submitted as AIC within a few weeks.	We have conducted an update search and have updated the review and meta analysis with this new data. This is described in an addendum to the report.
	3.	154	5.2.3.1	It seems as only preliminary data related to the re-analysis of the Petsky meta-analysis has been included in the DAR (reference nr 178 & 28). The final publication related to adult studies is now available, please consider for inclusion. In this, the primary outcome is exacerbations rates (mean per patient per year), which is the recommended outcome for exacerbations (see NHLBI report in JACI + ATS/ERS recommendations). Reference: Donohue and Jain, "Exhaled nitric oxide to predict corticosteroid responsiveness and reduce asthma exacerbation rates". See literature list for abstract.	The reference will be included in the HTA monograph version of the report.
	4.	154	5.2.3.1	Reference nr 109 is resubmitted again, the final manuscript is now in press in JACI In Practice (Syk et al).	No response required
	5.	189	5.2.3.2	New data to consider: Peirsman et al, "Exhaled Nitric Oxide in Childhood Allergic Asthma Management: A Randomised Controlled Trial" (published online as "early view", see separate	We have conducted an update search and have updated the review with this new data. This is described in an addendum to

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				literature list)  Academic in confidenceSyk et al J/	the report and will be included in the report itself.
	6.	154	5.2.3.1	New data to consider: Wan et al "Asthma diagnosis and severity monitoring in primary schoolchildren: Essential role of sequential testing of exhaled nitric oxide" (in press, available online)	This study does not meet our inclusion criteria and will not be considered in the review.
	7.	189	5.2.3.2	It seems as only a conference abstract related to the re-analysis of the paediatric studies in the Petsky meta-analysis has been included in the DAR (reference nr 28). The final publication is now available, please consider for inclusion. In this, the primary outcome is exacerbations rates (mean per patient per year), which is the recommended outcome for exacerbations (see NHLBI report in JACI + ATS/ERS recommendations). Reference: Mahr et al, "Inflammometry in pediatric asthma: A review of fractional exhaled nitric oxide in clinical practice"	The reference will be included in the HTA monograph version of the report.
	8.	251	6.3	Data to consider for the cost-effectiveness assessment in diagnosis and management: Dorinsky et al, "Cost savings using fractional exhaled nitric oxide (FeNO) testing in asthma management by specialists" (Conference abstract and poster from ERS 2013 included, see literature list)  2013-09-19_ERS201 3_Dorinsky-LaForce_I	As this is only a US conference abstract which does not provide sufficient detail for critical appraisal we do not consider this to be of direct relevance to the assessment.
	9.	303	6.4.5 Table 67	The pricing in the table for the NIOX MINO is current UK list price. The current average selling price for the NIOX MINO device in 2013 based on offers and special deals is approximately £1,000.	This information should have been made available to the EAG during the course of the assessment. We believe that this is a

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				Installation, education & training are included in the cost of the NIOX MINO.	matter for the committee to discuss and therefore we elect to wait until they agree acceptable pricing assumptions before undertaking any further analysis.
	10.	-	-	In addition to the use of FeNO for diagnosis and treatment adjustments, we would also like to highlight its use in assessment of adherence/compliance to corticosteroid treatment. For that purpose the following references has been added to the literature list: McNicholl et al "The Utility of Fractional Exhaled Nitric Oxide Suppression in the Identification of Nonadherence in Difficult Asthma" and Nolte et al "Dose-dependent anti-inflammatory effect of inhaled mometasone furoate/formoterol in subjects with asthma."  Reference list for NICE Sept 2013.docx	McNicholl did not satisfy our inclusion criteria by study design (it is a cohort study). Nolte was published after our search was conducted. Nolte et al also did not satisfy our inclusion criteria as it does not assess nonadherence. It has been assumed in the course of this assessment that adherence and compliance are or would be part of a management strategy, and therefore the addition of either study would not affect the cost-effectiveness evidence base.
	11.	-	-	Furthermore, we would like to emphasize the use of FeNO in assessing response to anti-inflammatory treatment. It is a biomarker not only for identifying response to corticosteroids but also to other anti-inflammatory treatments such as omalizumab (anti-IgE) and anti-IL-13. High FeNO levels have been able to identify patients subgroups that would benefit the most from these treatments (see Hanania and Corren in the literature list). Also, effects of treatment reducing exposure to allergens can be assessed by measuring FeNO (Boyle et al).	The scope and protocol did not include these uses of FeNO and as such these studies have not been included.
Consultee 2: Bedfont Scientific	1.	54	3.6.4	Whilst NObreath consumables (mouthpieces) are indeed lower cost already, this cost is reduced even further bearing in mind that Bedfont sell mouthpieces and not 'tests' as sold by Aerocrine for	The model assumes no test failures or repeat testing as observed rates were generally very low in all cohorts except for

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<tr><td>(Manufacturer)</td><td></td><td></td><td></td><td>their devices. These mouthpieces can be used up to 5 times each in the event that a patient does not carry the test out correctly, the health professional would like a comparative test or simply to comply with the ERS/ATS Guidance, which state "it may be better to achieve three reproducible FENO values", see page 917 of attached guidelines below:
ATS-ERS Guidelines 2005.pdf
This illustrates compliance with the test. Therefore the most expensive a NObreath patient would incur is £3.90 for the mouthpiece (pack of 50 NObreath mouthpieces is £195.00). However the NIOX products are sold with 'test kits' this means for every test performed a test is recorded and taken off the kit purchased. The most expensive per test for NIOX MINO being £4.50 and for NIOX VERO £5.00. Therefore if a patient were to provide 3 FENO values for the aforementioned reasons it would incur a per patient cost on NIOX MINO of £13.50 and on NIOX VERO £15.00.</td><td>very young children. We believe that the inclusion of this factor would not materially influence the marginal per test cost of the devices or the conclusions of the economic analysis.</td></tr>
<tr><td></td><td>2.</td><td>310</td><td>6.4.6 - Alternative assumptions concerning NObreath device lifetime</td><td>I believe the calculations here are not correct:
<table>
<tr><th>Device Lifetime</th><th>3 Years</th><th>5 Years</th><th>20 Years</th></tr>
<tr><td>Equipment</td><td>£1995.00</td><td>£1995.00</td><td>£1995.00</td></tr>
<tr><td>Test Kits</td><td>£2985.00 (900 Mouthpieces)</td><td>£4,975.00 (1,500 mouthpieces)</td><td>£19,900.00 (6,000 mouthpieces)</td></tr>
</table></td><td>We believe that there is an error in the marginal per-test costs presented in the sensitivity analysis, however it is not the one suggested by the manufacturer. It should be noted that in order to take account of when costs are incurred, we annuatised costs according to device lifetime and throughput/year. We also assumed the cheapest combination of test kits. The manufacturer's table does not</td></tr>
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<table>
<tr><td>Sensor Replacements</td><td>£295.00 (1 replacement)</td><td>£590.00 (2 replacements)</td><td>£2,950.00 (10 replacements)</td></tr>
<tr><td>Total for lifetime</td><td>£5,275.00</td><td>£7,560.00</td><td>£24,845.00</td></tr>
<tr><td>Annuatised marginal per-test cost</td><td>£5.86</td><td>£5.04</td><td>£4.14</td></tr>
</table>
Formulae:

Unit cost + mouthpieces cost + sensor replacement cost / number of patients
</td><td>fully account for either of these factors.

The corrected annuatised marginal per-test costs for NObreath over lifetimes of 3, 5 and 20 years should be £6.06, £5.21and £5.19 (see Table at end of document for corrected calculations). The consequence is that, ceteris paribus, NObreath would dominate the other FeNO devices in all costing scenarios for management and diagnosis settings.</td></tr>
<tr><td>Consultee 3: Royal College of Pathologists</td><td>1.</td><td>General</td><td></td><td>I'd tend to go along with the general view from the document that there appears to be a paucity of evidence in support of FeNO testing in diagnosis or management of asthma from the literature and that further research is needed.</td><td>No response required</td></tr>
<tr><td></td><td>2</td><td></td><td></td><td>In terms of the economic modelling, there doesn't appear to be any reference to additional costs that may be incurred in interfacing any of the meters to allow results to be directly recorded in electronic patient records, if this is possible with any of the instruments under study. Also, training costs seem to be touched upon, but a more thorough evaluation of this may be needed to get a more accurate idea of true costs of establishing the test.</td><td>We did not include these costs in the economic analysis. We would agree that training costs should be considered but did not have any evidence to suggest a meaningful estimate of what these might be, or whether they would be substantially different to training in the use of other devices used in the diagnosis of asthma. In principle they should also be covered under the reference costs used to populate the cost parameters. It is unlikely however to have a material impact upon the marginal per-test cost or the conclusions.</td></tr>
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Consultee 4: Stakeholder	1.	Throughout		Overall comment. This is an excellent, thorough and balanced piece of work. There is absence of evidence of clinical utility rather than evidence of absence.	No response required
	2.	116 and throughout		Following on from the point above, the report identifies that FENO cut off values for stepping up and down have not been identified and suggests that trials evaluate different approaches. I fully support this statement – if NICE were to approve this device how would clinicians interpret the results? I am pleased to see that one of the key messages to arise from this work – until we understand what is a significant change in FENO we cannot interpret the results.	No response required
	3	26		Apparently wide difference in £/QALY for adults (£2,100) compared to children (£45,200) for the NOBreath studies is unexpected given that there are generally many more similarities than differences between asthma adults and children. The difference may reflect the challenge/different methods in measuring QALY between adults and children. Given that NICE have historically considered approving interventions costing <£30,000/QALY, it would be wrong to approve FENO for management in adult and not children based on this evidence (especially when not confirmed in other studies)	No response required. This is a matter for the committee to deliberate on.
Consultee 5: Royal College of Nursing	1.	-	-	This is to inform you that there are no comments to submit on behalf of the Royal College of Nursing to inform on the Diagnostic Assessment report for the above technology. Thank you for the opportunity to participate.	No response required
Consultee 6: **Stakeholder**	1.	-	-	Well-structured report, providing summary of the evidence (or lack of) to facilitate discussion on 9th October. FYI – recent publications on issue - The value of FeNO measurement in childhood asthma:	No response required

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				uncertainties and perspectives. Multidisciplinary Respiratory Medicine 2013, 8:50 http://www.mrmjournal.com/content/8/1/50 Inflammometry in pediatric asthma: a review of fractional exhaled nitric oxide in clinical practice. http://www.ncbi.nlm.nih.gov/pubmed/23462278	
	2.	-	-	I was interested to see how other countries had assessed these devices. Seem conclusions not dissimilar. Germany http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=22008102247#.Ujid_cZ5Z8E USA http://www.healthplanofnevada.com/documents/provider%20files/PUL006_Nitric%20Oxide%20Breath%20Test%20Exhaled%20Breath%20Condensate%20Ph%20for%20Asthma_5-13.pdf USA recommendations http://www.thoracic.org/statements/resources/allergy-asthma/feno-document.pdf	No response required.

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Table A1: Corrected cost estimates for NObreath lifetime sensitivity analysis

Component / lifetime	3	5	10	20
Equipment	£1,995.00	£1,995.00	£1,995.00	£1,995.00
No mouthpieces	900	1500	3000	6000
Mouthpieces	£2,985.00	£4,720.00	£8,985.00	£17,970.00
Sensors	1	2	5	10
Sensor cost	£295.00	£590.00	£1,475.00	£2,950.00
Total cost	£5,275.00	£7,305.00	£12,455.00	£22,915.00
Annuatisation factor	2.90	4.67	8.61	14.71
Non-annuatised cost	£5.86	£4.87	£4.15	£3.82
Annuatised cost	£6.06	£5.21	£4.82	£5.19