British Thoracic Society

NICE National Institute for Health and Care Excellence

Healthcare Improvement Scotland | SIGN

Final

Asthma: diagnosis, monitoring and chronic asthma management (update)

[C] Evidence reviews for diagnostic test accuracy of peak expiratory flow variability for the diagnosis of asthma

BTS/NICE/SIGN collaborative guideline NG245

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Final

Developed by BTS, NICE and SIGN

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1. Peak expiratory flow (PEF) variability

1.1 Review question

In people under investigation for asthma, what is the diagnostic test accuracy and clinical and cost-effectiveness of peak expiratory flow (PEF) variability?

1.1.1 Introduction

Asthma can be a difficult condition to diagnose, and it is not clear which tests are most useful in supporting a diagnosis. Peak expiratory flow (PEF) is a single measurement of lung function assessed, as for spirometry, under maximal expiratory effort. It is largely determined by the calibre of the large airways. It does not require complex equipment and can be done in the home without direct medical supervision, providing adequate instruction has been given. Typically, patients are asked to record their PEF in the morning and evening every day for at least two weeks, so that the variability in PEF, as a surrogate for large airway calibre variability, can be calculated. Excessive variability in airway calibre is a key feature of asthma and PEF variability is therefore potentially useful in establishing a diagnosis. This evidence review was carried out to determine its clinical and cost-effectiveness as a diagnostic test.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

No test-and-treat evidence was included so only the diagnostic accuracy evidence was reported. See the excluded studies list in Appendix H.

Table 1: PICO characteristics of diagnostic accuracy review question

Population	Inclusion: People with suspected asthma (presenting with respiratory symptoms). Ages, stratified into the following 2 different groups: • Children and young people (5-16 years old) • Adults (≥17 years) Stratified based on smoking status: • Smoking • Non-smoking • Mixed populations Exclusion: • Children under 5 years old • People on steroid inhalers (washout period minimum of 4 weeks for inclusion)
Target condition	Asthma
Index test	PEF variability (diurnal variability usually expressed as amplitude (highest – lowest reading) as a percentage of the mean or the highest reading). PEFv values should be recorded as the mean over a period of at least 3 days)

Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) • FeNo
Statistical measures	• Sensitivity (Threshold: upper 90%, lower 10%) • Specificity (Threshold: upper 80%, lower 50%) • Raw data to calculate 2x2 tables to calculate sensitivity and specificity • Negative predictive value (NPV), Positive predictive value (PPV)
Study design	Cross sectional and cohort studies

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Diagnostic evidence

1.1.4.1 Included studies

No intervention studies were identified. A search was conducted for prospective and retrospective cross-sectional and cohort studies assessing the diagnostic test accuracy of peak expiratory flow variability to identify whether the condition is present (as indicated by the reference standard) in people under investigation for condition asthma.

Four prospective diagnostic cross-sectional study studies were included in the review;(Brouwer, et al., 2010, den Otter, et al., 1997, Smith, et al., 2004, Thiadens, et al., 1998). A variety of index tests and thresholds were used, which are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below in Table 4 and references in 1.4 References . The assessment of the evidence quality was conducted with emphasis on test sensitivity and specificity as this was identified by the committee as the primary measure in guiding decision-making. The committee set clinical decision thresholds as sensitivity: upper= 90% and lower= 10%, specificity: upper= 80% and lower= 50%. Values above the upper threshold indicated a test would be recommended and values below the lower threshold indicated a test is of no clinical use. See also the study selection flow chart in Appendix C, sensitivity and specificity forest plots in Appendix E, and study evidence tables in Appendix D.

1.1.4.2 Excluded studies

One study was excluded from the previous NICE guidance on this topic. This study was excluded due to containing a population that was not relevant to the present review protocol because it was made up of people from a general population, not those presenting with respiratory symptoms.

See the excluded studies list in Appendix H.

1.1.5 Summary of studies included in the diagnostic evidence

Table 2: Summary of studies included in the evidence review

Study	Population	Target condition	Index test	Reference standard	Comments
Brouwer 2010 (Brouwer et al., 2010)	Children (6-16 years, mean 10.4) with nonspecific respiratory symptoms such as cough and breathlessness in whom GP uncertain of diagnosis N= 61; mean age (SD): 10.4 (2.6) years The Netherlands	Asthma	PEF variation FEV_1 variability Cut-offs: >95th centile for healthy children i.e. ≥12.3% for PEF and ≥11.8% for FEV_1	Asthma diagnosed by paediatric pulmonologist including history. physical examination and lung function tests including methacholine challenge	Cross-sectional observational study Strata: Children/young people ICS use: Users within 4 weeks were excluded Smoking status: Mixed
den Otter 1997 (den Otter et al., 1997)	Adults with signs or symptoms indicating asthma (persistent or recurrent respiratory symptoms or signs of reversible bronchial obstruction) N= 323; mean age (range): 43 (25-70) years The Netherlands	Asthma	PEF variability = (PEFhighest – PEFlowest)/ PEFmean x 100% = amplitude % mean (average over period) Cut-offs: >5%, >10% and >15%	physician diagnosis plus BHR, defined as a PC20 histamine of ≤8 mg/ml	Cross-sectional observational study Strata: Adults ICS use: Not reported Smoking status; mixed Indirectness: Downgraded by one increment due to population (ICS use not reported) indirectness
Smith 2004 (Smith et al., 2004)	Consecutive patients aged 8–75 years referred by their family practitioner for asthma diagnosis. N= 47; mean age (range): 35.3 (9-72) years	Asthma	Peak flow variation over a 7-day period (amplitude percent mean) Cut-off: >20%	Relevant symptom history (present in all patients), using American Thoracic Society criteria, and a positive test for BHR and/or a positive	Prospective cross-sectional study Strata: Adults ICS use: 4-week washout Smoking status: Mixed

Study	Population	Target condition	Index test	Reference standard	Comments
	New Zealand			response to hypertonic saline. Cut-off Provocative dose of hypertonic saline resulting in a 15% fall in FEV_1 of less than 20 ml and increase in FEV_1 of ≥12% after receiving albuterol	Indirectness: Downgraded by one increment due to population (mixed children and adolescents/young people) indirectness
Thiadens 1998 (Thiadens et al., 1998)	Adults who consulted their GP with coughing that had lasted for at least 2 weeks N= 170; mean age (range): 44 (18-75) years The Netherlands	Asthma	PEF variability (DPV) = (PEFhighest – PEFlowest)/ PEFhighest x 100% = amplitude % highest (a) MDPV = mean over 2-week period (b) DPV more than threshold on 4 days or more (c) DPV more than threshold on 3 days or more Cut-offs: (a) MDPV > 10% and MDPV >15% (b) DPV >15% on 4 days or more (c) DPV >20% on 3 days or more	Previous period of respiratory symptoms for >3weeks in the last year, accompanied by a provocative dose causing a 20% fall in FEV1 (PD20) ≤15.6 µmol methacholine and/or reversibility ≥9% of predicted	Cross-sectional observational study Strata: Adults ICS use: Not reported Smoking status: Mixed Indirectness: Downgraded one increment due to population (ICS use not reported) indirectness

See Appendix D for full evidence tables

1.1.6 Summary of the diagnostic evidence

The assessment of the evidence quality was conducted with emphasis on test sensitivity and specificity as this was identified by the committee as the primary measure in guiding decision-making. The committee set clinical decision thresholds as sensitivity: upper= 90%, lower= 10% and specificity: upper= 80%, lower= 50%. Above the upper threshold indicated a test would be recommended and below the lower threshold indicated a test is of no clinical use.

Table 3: Clinical evidence summary: diagnostic test accuracy for peak expiratory flow variability for diagnosis of asthma in children and young people

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Mean peak flow variability ≥12.3% over 14 days vs clinical diagnosis with methacholine challenge (smoking status: 27% with a parent smoker, 1 smoking patient; atopy: 59% sensitive to aero and/or food allergens)							
1 prospective cross-sectional study	61	Not serious	Not serious	Not serious	Not serious	Sensitivity= 0.50 (0.27-0.73)	HIGH
		Not serious	Not serious	Not serious	Serious[1]	Specificity= 0.72 (0.55-0.85)	MODERATE
Mean FEV_1 variability ≥11.8% over 14 days vs clinical diagnosis with methacholine challenge (smoking status: 27% with a parent smoker, 1 smoking patient; atopy: 59% sensitive to aero and/or food allergens)							
1 prospective cross-sectional study	61	Not serious	Not serious	Not serious	Not serious	Sensitivity= 0.45 (0.23-0.68)	HIGH
		Not serious	Not serious	Not serious	Serious[1]	Specificity= 0.92 (0.79-0.98)	MODERATE

1. *Downgraded by one increment due to 95% CI overlapping the threshold corresponding to 'high specificity' (90%)*

Table 4: Clinical evidence summary: diagnostic test accuracy for peak expiratory flow variability for diagnosis of asthma in adults

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Mean peak expiratory flow variability ≥15% over 21 days vs clinical diagnosis with histamine challenge (smoking status: 39.9% ex-smokers; 60% never-smokers)							
1 prospective cross-sectional study	318	Serious[1]	Not serious	Serious[2]	Not serious	Sensitivity= 0.05 (0.02-0.10)	LOW
		Serious[1]	Not serious	Serious[2]	Not serious	Specificity= 0.98 (0.95-0.99)	LOW
Mean peak expiratory flow variability ≥10% over 21 days vs clinical diagnosis with histamine challenge (smoking status: 39.9% ex-smokers; 60% never-smokers)							
1 prospective cross-	318	Serious[1]	Not serious	Serious[2]	Serious[3]	Sensitivity= 0.14 (0.08-0.21)	VERY LOW
		Serious[1]	Not serious	Serious[2]	Not serious	Specificity= 0.96 (0.92-0.98)	LOW

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
sectional study							
Mean peak expiratory flow variability ≥5% over 21 days vs clinical diagnosis with histamine challenge (smoking status: 39.9% ex-smokers; 60% never-smokers)							
1 prospective cross-sectional study	318	Serious[1]	Not serious	Serious[2]	Not serious	Sensitivity= 0.56 (0.47-0.65)	LOW
		Serious[1]	Not serious	Serious[2]	Not serious	Specificity= 0.69 (0.62-0.76)	LOW
Mean peak expiratory flow variability >10% over 14 days vs clinical diagnosis with bronchial hyperresponsiveness and/or methacholine challenge (smoking status (mean pack years (SD)): 8.6 (11.8)							
1 prospective cross-sectional study	170	Very serious[4]	Not serious	Very serious[5]	Serious[3]	Sensitivity= 0.14 (0.07-0.25)	VERY LOW
		Very serious[4]	Not serious	Very serious[5]	Not serious	Specificity= 0.97 (0.92-0.99)	VERY LOW
Mean peak expiratory flow variability >15% over 14 days vs clinical diagnosis with bronchial hyperresponsiveness and/or methacholine challenge (smoking status (mean pack years (SD)): 8.6 (11.8)							
1 prospective cross-sectional study	170	Very serious[4]	Not serious	Very serious[5]	Not serious	Sensitivity= 0.03 (0.00-0.10)	VERY LOW
		Very serious[4]	Not serious	Very serious[5]	Not serious	Specificity= 0.99 (0.95-1.00)	VERY LOW
Diurnal peak flow variability >15% on ≥4 days vs clinical diagnosis with bronchial hyperresponsiveness and/or methacholine challenge (smoking status (mean pack years (SD)): 8.6 (11.8)							
1 prospective cross-sectional study	170	Very serious[4]	Not serious	Very serious[5]	Not serious	Sensitivity= 0.20 (0.12-0.32)	VERY LOW
		Very serious[4]	Not serious	Very serious[5]	Not serious	Specificity= 0.97 (0.92-0.99)	VERY LOW
Diurnal peak flow variability >20% on ≥3 days vs clinical diagnosis with bronchial hyperresponsiveness and/or methacholine challenge (smoking status (mean pack years (SD)): 8.6 (11.8)							
1 prospective cross-sectional study	170	Very serious[4]	Not serious	Very serious[5]	Serious[2]	Sensitivity= 0.12 (0.05-0.12)	VERY LOW
		Very serious[4]	Not serious	Very serious[5]	Not serious	Specificity= 0.99 (0.95-1.00)	VERY LOW
Amplitude percent mean >20% over 7 days vs clinical diagnosis with methacholine challenge or bronchodilator reversibility (smoking status: 42 non-smokers, 5 ex-smokers; atopy: not reported)							
1 prospective cross-sectional study	46	Serious[1]	Not serious	Serious[6]	Serious[2]	Sensitivity= 0.00 (0.00-0.20)	VERY LOW
		Serious[1]	Not serious	Serious[6]	Not serious	Specificity= 1.00 (0.88-1.00)	LOW

1. *Downgraded by one increment due to concerns arising from the interpretation of the index test and reference standard (unclear if blinded)*
2. *Downgraded by one increment due to population indirectness (ICS use not reported)*
3. *Downgraded by one increment due to 95%CI overlapping the threshold corresponding to 'low sensitivity' (10%)*
4. *Downgraded by two increments due to concerns arising from the interpretation of the index test and reference standard (unclear if blinded) and concerns arising from the flow and timing of the study (205 participants entered the study, data reported for 170)*
5. *Downgraded by two increments due to population (ICS use not reported) and reference standard (unclear if clinician diagnosis was involved) indirectness.*
6. *Downgraded by one increment due to population (included both children/young people and adults) indirectness.*

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

1.1.7.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix F.

1.1.8 Summary of included economic evidence

None.

1.1.9 Economic model

A health economic model was conducted focusing on sequences and combinations of diagnostic tests. This is reported in Evidence review 1.11.

1.1.10 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 5: PEF per-test cost

Resource	Quantity	Unit costs	Total cost	Source
Adult mini-wright peak flowmeter	1	£4.65 per flowmeter	£4.65	NHS Supply Chain Catalogue(NHS Supply Chain Catalogue., 2022)
Low range mini-wright paediatric	1	£4.75 per flowmeter	£4.75	NHS Supply Chain Catalogue(NHS Supply Chain Catalogue., 2022)
Time of practice nurse	10 – 20 minutes[(a)]	£63.38 per hour	£10.57 - £21.13	PSSRU 2022(Jones, et al.)
Total cost – adults	**£15.22 - £25.78**			
Total cost – children	**£15.32 - £25.88**			

Note: all prices are VAT exclusive

(a) 20 minutes assumed in the base case scenario of the health economic model conducted in Evidence Review 1.11

1.1.11 Evidence statements

Economic

- No relevant economic evaluations were identified.

1.2 The committee's discussion and interpretation of the evidence

1.2.1. The outcomes that matter most

The outcomes considered for this review were: severe asthma exacerbations, mortality, quality of life, asthma control, hospital admissions, reliever/rescue medication use, lung function (change in FEV1 or morning PEF – average over at least 7 days for morning PEF), adverse events (linear growth, pneumonia frequency, adrenal insufficiency, bone mineral density), inflammatory markers; exhaled nitric oxide (continuous outcome at ≥8 weeks). For purposed of decision making, all outcomes were considered equally important and were therefore rated as critical by the committee. No relevant evidence was identified for any of the outcomes.

Diagnostic accuracy

The committee considered the diagnostic measures of sensitivity and specificity of the index test for diagnosing asthma as well as the positive and negative predictive values where these were reported by the studies. Clinical decision thresholds were set by the committee as sensitivity/specificity 0.9 and 0.8 above which a test would be recommended and 0.1 and 0.5 below which a test is of no clinical use. The committee were interested in establishing whether there was an optimal cut-off value of PEF reversibility with sufficiently high sensitivity and specificity to be useful in making a diagnosis of asthma, but also in whether there are separate cut-off values which could usefully help either rule in or rule out an asthma diagnosis.

1.2.2 The quality of the evidence

Clinical and cost effectiveness

No relevant clinical studies were identified comparing the clinical effectiveness of peak expiratory flow variability expressed as the amplitude as percentage of the mean of the highest reading, recorded as the mean over a period of at least 3 days.

Diagnostic accuracy

Four prospective cross-sectional studies were included in this review. The studies examined a variety of thresholds for PEF recorded over a different number of days. There were three studies in the adult population and one study on children and young people.

One study examined the diagnostic accuracy of PEF variability at 3 thresholds (≥15%, ≥10% and ≥5%) over 21 days in adults. A second study conducted in adults examined PEF variability >10% and >15% over 14 days; diurnal PEF >15% on ≥4 days; and diurnal PEF >20% on ≥3 days. The final study defined PEF variability as amplitude percent mean >20% over a 7-day period. The quality of the evidence in adults ranged from very low to low, with the majority being of very low-quality. The most common reason for downgrading was risk of bias, with a lack of details over the method of participant recruitment and of blinding to the results of the index test and reference standard. Indirectness was also present in all evidence, most commonly due to not reporting the ICS use of participants, and less frequently due to a lack of clinician decision in the diagnosis of asthma or the inclusion of a mixture of children/young people and adults.

One study in children and young people looked at mean peak flow variability ≥12.3% or FEV_1 variability ≥11.8% over 14 days for detecting asthma. The quality of the evidence ranged from moderate to high. The specificity was downgraded due to imprecision as the 95%CI overlapped the higher threshold set for specificity.

1.2.3 Benefits and harms

Children and young people

Moderate-high quality evidence showed that a cut-off mean PEF ≥12.3% over 14 days produced a moderate sensitivity of 0.50 and a moderate specificity of 0.72. The same study reported FEV_1 variability over 14 days, showing a moderate sensitivity of 0.45 and a high specificity of 0.92. The committee noted that this evidence was limited by a small population size, reflected in imprecision around the specificity estimates. The committee noted that the cut-offs reported were calculated to determine the optimal combination of sensitivity and specificity, but in practice it would be more useful to obtain a cut-off point which is either highly sensitive or specific to rule in or rule out an asthma diagnosis with greater accuracy. Additionally, the committee noted that in clinical practice PEF variability is not widely used in children and young people due to the time-consuming nature of the test and the difficulty some may have accurately conducting the measurements.

Adults

Very low-low quality evidence for the diagnostic accuracy of PEF variability ≥15%, ≥10% and ≥5% over 21 days reported low-moderate sensitivities of 0.05, 0.14 and 0.56, respectively, with the former being below the threshold to indicate any clinical utility. High-moderate specificities of 0.98, 0.96 and 0.69 were seen at the same respective thresholds, with the ≥15% and ≥10% cut-offs exceeding the threshold to indicate a recommendation. This evidence was limited by serious risk of bias, arising from concerns surrounding the method of participant selection, and by indirectness due to the ICS status of the participants not being reported.

Very low quality evidence from a separate study reported PEF variability >10% and >15% over 14 days, showing very low sensitivities of 0.14 and 0.03 respectively and high specificities of 0.97 and 0.99. The same study reported diurnal PEF >15% on ≥4 days and >20% on ≥3 days, showing low sensitivities of 0.20 and 0.12, respectively and high specificities of 0.97 and 0.99. This evidence was limited by very serious risk of bias, arising due to a lack of clarity over blinding of the test results, and missing data for 35 participants who were not included in the analysis. Indirectness was also present due to ICS use not being reported, and a lack of clarity on whether a clinician decision was involved in the diagnosis of asthma.

Very low-low quality evidence from one study reported that amplitude percent mean, using a cut-off of >20% over a 7-day period, showed a low sensitivity of 0.00 and a high specificity of 1.00. This evidence was limited due to its small sample size, serious risk of bias due to a lack of clarity over blinding of test results, and indirectness due to including a mixed population of children/young people and adults.

The committee noted these are single use meters and in clinical practice the measurement and recording is done individually by patients at home. The committee agreed the data obtained using PEF variability are patient dependent and impacted significantly by the scrupulousness with which the data are collected.

Exposure to smoking in the current evidence was mixed across the study populations and it was not possible to draw conclusions about how this may have influenced the results.

These data in adults were in accordance with the clinical experience of the committee. PEF variability is a highly specific test providing the threshold for defining a positive result is not set too low.

1.2.4 Cost effectiveness and resource use

No relevant published health economic analyses were identified for this review question. The unit cost of PEF was presented to aid committee consideration of cost effectiveness. The unit cost of undertaking PEF for diagnostic purposes was £25.78 for adults and £25.88 for children. This included the health care professional time for instructing people on home testing and interpreting the result (£21.13) as well as the flowmeter (£4.65/£4.75 for adults/paediatrics respectively).

With regards to staff time, the committee agreed that it would usually be a general practice nurse (band 5) who would instruct the person on home testing and then interpret the result. The committee agreed that 10 minutes were required to instruct the person on how to use the flowmeter and record results in a diary. A subsequent appointment is need for interpretation of the diary/results; this also required 10 minutes. Some committee members noted that different interpretation approaches may influence the duration of this second appointment and therefore impact on the cost. A lower limit of 10 minutes is presented to account for this uncertainty.

In terms of equipment, a flowmeter is required. For diagnostic purposes these are single use and so the full cost of the flowmeter is included.

The committee considered PEF alongside or in combination with a variety of other tests for asthma within a diagnostic algorithm for both adults and children (see evidence review 1.11). A diagnostic algorithm including PEF as the initial test was found to be the third most cost-effective strategy in adults. Although the committee were concerned that poor patient compliance, particularly over a long period, could make this test less reliable than others, they acknowledged that they are widely available across the country. Hence, they decided to make a recommendation to use PEF if spirometry is not locally available.

1.2.5 Other factors the committee took into account

The committee noted the intrinsic advantage of measuring PEF variability in that it is not made at a single point in time but relies on measurements made over a period of days or weeks. This is important because asthma is by definition a disease in which airflow obstruction varies significantly over time. In addition, it is easier in practice to start measuring PEF straight after a primary care consultation than to obtain some of the other diagnostic tests for asthma such as spirometry with bronchodilator reversibility. This is important as it may capture data while the person is still symptomatic and therefore more likely to give helpful information.

There are also secondary advantages to a period of PEF monitoring such as its potential to help identify triggers of the person's asthma attacks.

The committee discussed that the PEF calculations can be complicated and there could be staff time saved if a calculator were imbedded into GP software or on a patient group website. It was noted however that asking patients to record results on an app could be difficult for some individuals.

Although not specifically looked at in this review, Smart Peak Flow was mentioned as another way of saving on staff time as this records results electronically. The unit cost of this technology is £9.87 per device (excluding VAT). The optional Bluetooth adapter costs £6 (excluding VAT) and the Smart Asthma app is free. The Smart Peak Flow device has a 2-year life expectancy. Cross reference NICE MIB282 (The technology | Smart Peak Flow for monitoring asthma | Advice | NICE).

1.2.6 Recommendations supported by this evidence review

Recommendations1.2.3 and 1.2.7

1.3 References

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Appendices

Appendix A – Review protocols

Diagnostic test accuracy and clinical and cost-effectiveness of peak expiratory flow (PEF) variability

Review protocol for diagnostic test accuracy and clinical and cost-effectiveness of peak expiratory flow variability for the diagnosis of asthma

Field	Content
PROSPERO registration number	CRD42023437226
Review title	Accuracy and clinical and cost-effectiveness of peak expiratory flow in the diagnosis of asthma
Review question	In people under investigation for asthma, what is the diagnostic test accuracy and clinical and cost-effectiveness of peak expiratory flow (PEF) variability?
Objective	To evaluate the diagnostic test value of PEF variability in diagnosing asthma. This evidence review will have two stages: (1) Identify the clinical and cost effectiveness of diagnosis with the test (test plus treatment) (2) If evidence on clinical effectiveness is limited, the diagnostic accuracy will instead be determined
Searches	.

	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • Diagnostic test accuracy from 2014 onwards • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
Condition or domain being studied	Asthma

Population	Inclusion: People with suspected asthma (presenting with respiratory symptoms). Ages, stratified into the following 2 different groups: • Children and young people (5-16 years old) Adults (≥17 years) Exclusion: Children under 5 years old People on steroid inhalers (washout period minimum of 4 weeks for inclusion) Not looking at occupational asthma /allergens Stratification Smokers' vs non-smokers vs mixed populations
Test	PEF variability (diurnal variability usually expressed as amplitude (highest – lowest reading) as a percentage of the mean or the highest reading). PEFv values should be recorded as the mean over a period of at least 3 days)
Reference standard	Effectiveness (test-and-treat) • Compared to each other Diagnostic accuracy • Reference standard defined as:

	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) • FeNo Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold. Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis. Maximum interval between initial diagnosis and confirmation of 'asthma' diagnosis: 12 months
Types of study to be included	Clinical effectiveness (test and treat): • Systematic reviews of RCTs • Parallel RCTs Published NMAs and IPDs will be considered for inclusion. Diagnostic test accuracy: • Cross sectional studies • Cohort studies will be included.

Other exclusion criteria	Non-English language studies. Non comparative cohort studies Before and after studies Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available. Not looking at validation studies, or studies comparing different PEF measures Not looking at factors which influence measurements
Context	Primary and secondary care settings
Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making a therefore have all been rated as critical: Clinical effectiveness (test and treat) outcomes: • Severe asthma exacerbations (defined as asthma exacerbations requiring oral corticosteroid use (dichotomous outcome at ≥6 months) • Mortality (dichotomous outcome at ≥6 months) • Quality of life (QOL; validated scale, including asthma specific questionnaires AQLQ; health-related) (continuous outcome at ≥3 months) • Asthma control assessed by a validated questionnaire (ACQ, ACT, St George's respiratory) (continuous outcome at ≥3 months) • Hospital admissions (dichotomous outcome at ≥6 months) • Reliever/rescue medication use (continuous outcome at ≥3 months) • Lung function (change in FEV1 or morning PEF – average over at least 7 days for morning PEF) (continuous outcome at ≥3 months). *Note: Extract FEV1 %pred*

	over litres if both are reported. If only litres is reported, extract and analyse separately (do not extract both). For children, only use FEV1 %pred.
	• Adverse events
	  ○ Linear growth (continuous outcome at ≥1 year),
	  ○ Pneumonia frequency (dichotomous outcome at ≥3 months)
	  ○ Adrenal insufficiency as defined by study, including short synacthen test and morning cortisol (dichotomous outcome at ≥3 months)
	  ○ Bone mineral density (continuous outcome at ≥6 months)
	Inflammatory markers; exhaled nitric oxide (continuous outcome at ≥8 weeks)
	
	Diagnostic accuracy outcomes: Asthma diagnosis
	Sensitivity (Threshold: upper 90%, lower 10%)
	Specificity (Threshold: upper 80%, lower 50%)
	• Raw data to calculate 2x2 tables to calculate sensitivity and specificity
	• Negative predictive value (NPV), Positive predictive value (PPV)

Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).

	10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: papers were included /excluded appropriately a sample of the data extractions correct methods are used to synthesise data a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0) Diagnostic studies: QUADAS-2 checklist
Strategy for data synthesis	Diagnostic intervention (test and treat): Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on

	pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. WinBUGS will be used for network meta-analysis, if possible given the data identified. Diagnostic accuracy: Where possible data will be meta-analysed where appropriate (if at least 3 studies reporting data at the same diagnostic threshold) in WinBUGS. Summary diagnostic outcomes will be reported from the meta-analyses with their 95% confidence intervals in adapted GRADE tables. Heterogeneity will be assessed by visual inspection of the sensitivity and specificity plots and summary area under the curve (AUC) plots. Particular attention will be placed on specificity determined by the committee to be the primary outcome for decision making. If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software.
Analysis of sub-groups	

Type and method of review	☒	Intervention
	☒	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)
Language	English	
Country	England	
Anticipated or actual start date		
Anticipated completion date	31 July 2024	

Stage of review at time of this submission	Review stage	Started	Completed
	Preliminary searches	☑	☑
	Piloting of the study selection process	☐	☐
	Formal screening of search results against eligibility criteria	☐	☐
	Data extraction	☐	☐
	Risk of bias (quality) assessment	☐	☐
	Data analysis	☐	☐

Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail asthmachronicmanagement@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre
Review team members	From the National Guideline Centre: Bernard Higgins (Guideline lead) Sharon Swain (Guideline lead) Toby Sands (Systematic reviewer) Alfredo Mariani (Senior health economist) Lina Gulhane (Head of information specialists) Stephen Deed (Information specialist) Amy Crisp (Senior project manager) Melina Vasileiou (Senior systematic reviewer)
Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a

	senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10186	
Other registration details	N/A	
Reference/URL for published protocol		
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords	N/A	
Details of existing review of same topic by same authors	N/A	
Current review status	☒	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued

Additional information	
Details of final publication	www.nice.org.uk

Health economic review protocol

Table 6: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2006, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).(National Institute for Health and Care Excellence) **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:*

	• UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2006 or later but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as 'Not applicable'. • Studies published before 2006 be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B Literature search strategies

In people under investigation for asthma, what is the diagnostic test accuracy and clinical and cost-effectiveness of peak expiratory flow (PEF) variability?

Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 7: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 20 Dec 2023	Randomised controlled trials Systematic review studies Observational studies Diagnostic tests studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 20 Dec 2023	Randomised controlled trials Systematic review studies Observational studies Diagnostic tests studies Exclusions (conference abstracts, animal studies, letters, comments, editorials, case studies/reports) English language
The Cochrane Library (Wiley)	Cochrane Reviews to 2023 Issue 12 of 12 CENTRAL to 2023 Issue 12 of 12	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	Inception to 20 Dec 2023	Exclusions (Cochrane reviews) English language

Medline (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter/
5.	editorial/
6.	news/

7.	exp historical article/
8.	Anecdotes as Topic/
9.	comment/
10.	case reports/
11.	(letter or comment*).ti.
12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/
19.	exp Rodentia/
20.	(rat or rats or mouse or mice or rodent*).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language
24.	exp *Spirometry/
25.	(spiromet* or spirograph* or spriogram* or pneumotachograph* or bronchospiromet* or microspiromet* or bronchospirograph*).ti,ab,kf.
26.	(volume* adj2 (time or curve*)).ti,ab,kf.
27.	(flow* adj2 (volume* or loop*)).ti,ab,kf.
28.	or/24-27
29.	*Vital Capacity/
30.	(forced adj2 (vital or capacity)).ti,ab,kf.
31.	FVC.ti,ab,kf.
32.	or/29-31
33.	*Forced Expiratory Volume/
34.	(forced adj2 (expiratory or expiration or exhal* or volume*)).ti,ab,kf.
35.	(FEV or FEV1*).ti,ab,kf.
36.	or/33-35
37.	*Peak Expiratory Flow Rate/
38.	(peak adj2 flow*).ti,ab,kf.
39.	(PEF or PEFR* or PFR* or PEFV).ti,ab,kf.
40.	or/37-39
41.	*Respiratory Function Tests/
42.	((pulmonary function or respiratory function) adj2 (test* or measure*)).ti,ab,kf.
43.	or/41-42
44.	(bronchoreversibility or broncho reversibility).ti,ab,kf.
45.	(reversibility adj2 (test* or respons* or respond*)).ti,ab,kf.
46.	((bronchodilator* or broncho dilator* or bronchial or broncholytic*) adj3 (test* or revers* or respons* or respond*)).ti,ab,kf.
47.	(BDR or BDT).ti,ab,kf.
48.	or/44-47
49.	28 or 32 or 36 or 40 or 43 or 48

50.	23 and 49
51.	exp "sensitivity and specificity"/
52.	(sensitivity or specificity).ti,ab.
53.	((pre test or pretest or post test) adj probability).ti,ab.
54.	(predictive value* or PPV or NPV).ti,ab.
55.	likelihood ratio*.ti,ab.
56.	likelihood function/
57.	((area under adj4 curve) or AUC).ti,ab.
58.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
59.	gold standard.ab.
60.	exp Diagnostic errors/
61.	(false positiv* or false negativ*).ti,ab.
62.	Diagnosis, Differential/
63.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness or precision or validat* or validity or differential or error*)).ti,ab.
64.	or/51-63
65.	randomized controlled trial.pt.
66.	controlled clinical trial.pt.
67.	randomi#ed.ab.
68.	placebo.ab.
69.	randomly.ab.
70.	clinical trials as topic.sh.
71.	trial.ti.
72.	or/65-71
73.	Meta-Analysis/
74.	Meta-Analysis as Topic/
75.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
76.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
77.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
78.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
79.	(search* adj4 literature).ab.
80.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
81.	cochrane.jw.
82.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
83.	or/73-82
84.	Epidemiologic studies/
85.	Observational study/
86.	exp Cohort studies/
87.	(cohort adj (study or studies or analys* or data)).ti,ab.
88.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
89.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.

90.	Controlled Before-After Studies/
91.	Historically Controlled Study/
92.	Interrupted Time Series Analysis/
93.	(before adj2 after adj2 (study or studies or data)).ti,ab.
94.	exp case control study/
95.	case control*.ti,ab.
96.	Cross-sectional studies/
97.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
98.	or/84-97
99.	50 and (64 or 72 or 83 or 98)

Embase (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter.pt. or letter/
5.	note.pt.
6.	editorial.pt.
7.	case report/ or case study/
8.	(letter or comment*).ti.
9.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
10.	or/4-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice or rodent*).ti.
20.	or/12-19
21.	3 not 20
22.	limit 21 to English language
23.	*Spirometry/ or *Spirography/ or *Bronchospirography/ or *Pneumotachygraphy/
24.	(spiromet* or spirograph* or spriogram* or pneumotachograph* or bronchospiromet* or microspiromet* or bronchospirograph*).ti,ab,kf.
25.	(volume* adj2 (time or curve*)).ti,ab,kf.
26.	(flow* adj2 (volume* or loop*)).ti,ab,kf.
27.	or/23-26
28.	*Vital Capacity/
29.	(forced adj2 (vital or capacity)).ti,ab,kf.
30.	FVC.ti,ab,kf.
31.	or/28-30
32.	*Forced Expiratory Volume/

33.	(forced adj2 (expiratory or expiration or exhal* or volume*)).ti,ab,kf.
34.	(FEV or FEV1*).ti,ab,kf.
35.	or/32-34
36.	*Peak Expiratory Flow/
37.	(peak adj2 flow*).ti,ab,kf.
38.	(PEF or PEFR* or PFR* or PEFV).ti,ab,kf.
39.	or/36-38
40.	*Lung Function Test/
41.	((pulmonary function or respiratory function) adj2 (test* or measure*)).ti,ab,kf.
42.	or/40-41
43.	(bronchoreversibility or broncho reversibility).ti,ab,kf.
44.	(reversibility adj2 (test* or respons* or respond*)).ti,ab,kf.
45.	((bronchodilator* or broncho dilat* or bronchial or broncholytic*) adj3 (test* or revers* or respons* or respond*)).ti,ab,kf.
46.	(BDR or BDT).ti,ab,kf.
47.	or/43-46
48.	27 or 31 or 35 or 39 or 42 or 47
49.	22 and 48
50.	exp "sensitivity and specificity"/
51.	(sensitivity or specificity).ti,ab.
52.	((pre test or pretest or post test) adj probability).ti,ab.
53.	(predictive value* or PPV or NPV).ti,ab.
54.	likelihood ratio*.ti,ab.
55.	((area under adj4 curve) or AUC).ti,ab.
56.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
57.	diagnostic accuracy/
58.	diagnostic test accuracy study/
59.	gold standard.ab.
60.	exp diagnostic error/
61.	(false positiv* or false negativ*).ti,ab.
62.	differential diagnosis/
63.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness or precision or validat* or validity or differential or error*)).ti,ab.
64.	or/50-63
65.	random*.ti,ab.
66.	factorial*.ti,ab.
67.	(crossover* or cross over*).ti,ab.
68.	((doubl* or singl*) adj blind*).ti,ab.
69.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
70.	crossover procedure/
71.	single blind procedure/
72.	randomized controlled trial/
73.	double blind procedure/
74.	or/65-73
75.	Systematic Review/

76.	Meta-Analysis/
77.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
78.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
79.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
80.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
81.	(search* adj4 literature).ab.
82.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
83.	cochrane.jw.
84.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
85.	or/75-84
86.	Clinical study/
87.	Observational study/
88.	Family study/
89.	Longitudinal study/
90.	Retrospective study/
91.	Prospective study/
92.	Cohort analysis/
93.	Follow-up/
94.	cohort*.ti,ab.
95.	93 and 94
96.	(cohort adj (study or studies or analys* or data)).ti,ab.
97.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
98.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
99.	(before adj2 after adj2 (study or studies or data)).ti,ab.
100.	exp case control study/
101.	case control*.ti,ab.
102.	cross-sectional study/
103.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
104.	or/86-92,95-103
105.	49 and (64 or 74 or 85 or 104)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Asthma] explode all trees
#2.	asthma*:ti,ab
#3.	#1 or #2
#4.	conference:pt or (clinicaltrials or trialsearch):so
#5.	#3 not #4
#6.	MeSH descriptor: [Spirometry] explode all trees
#7.	(spiromet* or spirograph* or spriogram* or pneumotachograph* or bronchospiromet* or microspiromet* or bronchospirograph*):ti,ab,kw
#8.	(volume* near/2 (time or curve*)):ti,ab,kw

#9.	(flow* near/2 (volume* or loop*)):ti,ab,kw
#10.	(or #6-#9)
#11.	MeSH descriptor: [Vital Capacity] this term only
#12.	(forced near/2 (vital or capacity)):ti,ab,kw
#13.	FVC:ti,ab,kw
#14.	(or #11-#13)
#15.	MeSH descriptor: [Forced Expiratory Volume] this term only
#16.	(forced near/2 (expiratory or expiration or exhal* or volume*)):ti,ab,kw
#17.	(FEV or FEV1*):ti,ab,kw
#18.	(or #15-#17)
#19.	MeSH descriptor: [Peak Expiratory Flow Rate] this term only
#20.	(peak near/2 flow*):ti,ab,kw
#21.	(PEF or PEFR* or PFR* or PEFV):ti,ab,kw
#22.	(or #19-#21)
#23.	MeSH descriptor: [Respiratory Function Tests] this term only
#24.	((pulmonary function or respiratory function) near/2 (test* or measure*)):ti,ab,kw
#25.	(or #23-#24)
#26.	(bronchoreversibility or broncho reversibility):ti,ab,kw
#27.	(reversibility near/2 (test* or respons* or respond*)):ti,ab,kw
#28.	((bronchodilator* or broncho dilator* or bronchial or broncholytic*) near/3 (test* or revers* or respons* or respond*)):ti,ab,kw
#29.	(BDR or BDT):ti,ab,kw
#30.	(or #26-#29)
#31.	#10 or #14 or #18 or #22 or #25 or #30
#32.	#5 and #31

Epistemonikos search terms

1.	(advanced_title_en:((advanced_title_en:(asthma) OR advanced_abstract_en:(asthma))) OR advanced_abstract_en:((advanced_title_en:(asthma) OR advanced_abstract_en:(asthma)))) AND (advanced_title_en:(spiromet* OR spirograph* OR spriogram* OR pneumotachograph* OR bronchospiromet* OR microspiromet* OR bronchospirograph* OR "forced vital capacity" OR FVC OR "forced expiratory volume" OR FEV1 OR "peak expiratory flow" OR PEFR* OR PFR* OR PEFV OR bronchoreversibility OR "broncho reversibility" OR "reversibility test*" OR "bronchodilator* respons*" OR "broncho dilator* respons*" OR BDR OR "bronchodilator* test*" OR "broncho dilator* test*" OR BDT) OR advanced_abstract_en:(spiromet* OR spirograph* OR spriogram* OR pneumotachograph* OR bronchospiromet* OR microspiromet* OR bronchospirograph* OR "forced vital capacity" OR FVC OR "forced expiratory volume" OR FEV1 OR "peak expiratory flow" OR PEFR* OR PFR* OR PEFV OR bronchoreversibility OR "broncho reversibility" OR "reversibility test*" OR "bronchodilator* respons*" OR "broncho dilator* respons*" OR BDR OR "bronchodilator* test*" OR "broncho dilator* test*" OR BDT))

Health economic literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Asthma population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The

International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies and modelling.

Table 8: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 29 Dec 2023	Health economics studies Quality of life studies Modelling Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
	Quality of Life 1946 – 29 Dec 2023	
	Modelling 1946 – 29 Dec 2023	
Embase (OVID)	Health Economics 1 January 2014 – 29 Dec 2023	Health economics studies Quality of life studies Modelling Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1974 – 29 Dec 2023	
	Modelling 1974 – 29 Dec 2023	
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 29 Dec 2023	English language

Medline (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter/

5.	editorial/
6.	news/
7.	exp historical article/
8.	Anecdotes as Topic/
9.	comment/
10.	case reports/
11.	(letter or comment*).ti.
12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/
19.	exp Rodentia/
20.	(rat or rats or mouse or mice or rodent*).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language
24.	quality-adjusted life years/
25.	sickness impact profile/
26.	(quality adj2 (wellbeing or well being)).ti,ab.
27.	sickness impact profile.ti,ab.
28.	disability adjusted life.ti,ab.
29.	(qal* or qtime* or qwb* or daly*).ti,ab.
30.	(euroqol* or eq5d* or eq 5*).ti,ab.
31.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
32.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
33.	(hui or hui1 or hui2 or hui3).ti,ab.
34.	(health* year* equivalent* or hye or hyes).ti,ab.
35.	discrete choice*.ti,ab.
36.	rosser.ti,ab.
37.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
38.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
39.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
40.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
41.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
42.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
43.	or/24-42
44.	exp models, economic/

45.	*Models, Theoretical/
46.	*Models, Organizational/
47.	markov chains/
48.	monte carlo method/
49.	exp Decision Theory/
50.	(markov* or monte carlo).ti,ab.
51.	econom* model*.ti,ab.
52.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
53.	or/44-52
54.	Economics/
55.	Value of life/
56.	exp "Costs and Cost Analysis"/
57.	exp Economics, Hospital/
58.	exp Economics, Medical/
59.	Economics, Nursing/
60.	Economics, Pharmaceutical/
61.	exp "Fees and Charges"/
62.	exp Budgets/
63.	budget*.ti,ab.
64.	cost*.ti.
65.	(economic* or pharmaco?economic*).ti.
66.	(price* or pricing*).ti,ab.
67.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
68.	(financ* or fee or fees).ti,ab.
69.	(value adj2 (money or monetary)).ti,ab.
70.	or/54-69
71.	23 and 43
72.	23 and 53
73.	23 and 70

Embase (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter.pt. or letter/
5.	note.pt.
6.	editorial.pt.
7.	case report/ or case study/
8.	(letter or comment*).ti.
9.	(conference abstract or conference paper).pt.

10.	or/4-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice or rodent*).ti.
20.	or/12-19
21.	3 not 20
22.	limit 21 to English language
23.	quality adjusted life year/
24.	"quality of life index"/
25.	short form 12/ or short form 20/ or short form 36/ or short form 8/
26.	sickness impact profile/
27.	(quality adj2 (wellbeing or well being)).ti,ab.
28.	sickness impact profile.ti,ab.
29.	disability adjusted life.ti,ab.
30.	(qal* or qtime* or qwb* or daly*).ti,ab.
31.	(euroqol* or eq5d* or eq 5*).ti,ab.
32.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
33.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
34.	(hui or hui1 or hui2 or hui3).ti,ab.
35.	(health* year* equivalent* or hye or hyes).ti,ab.
36.	discrete choice*.ti,ab.
37.	rosser.ti,ab.
38.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
39.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
40.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
41.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
42.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
43.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
44.	or/23-43
45.	statistical model/
46.	exp economic aspect/
47.	45 and 46
48.	*theoretical model/
49.	*nonbiological model/

50.	stochastic model/
51.	decision theory/
52.	decision tree/
53.	monte carlo method/
54.	(markov* or monte carlo).ti,ab.
55.	econom* model*.ti,ab.
56.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
57.	or/47-56
58.	health economics/
59.	exp economic evaluation/
60.	exp health care cost/
61.	exp fee/
62.	budget/
63.	funding/
64.	budget*.ti,ab.
65.	cost*.ti.
66.	(economic* or pharmaco?economic*).ti.
67.	(price* or pricing*).ti,ab.
68.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
69.	(financ* or fee or fees).ti,ab.
70.	(value adj2 (money or monetary)).ti,ab.
71.	or/58-70
72.	22 and 44
73.	22 and 57
74.	22 and 71

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Asthma EXPLODE ALL TREES
#2.	(asthma*)
#3.	#1 OR #2

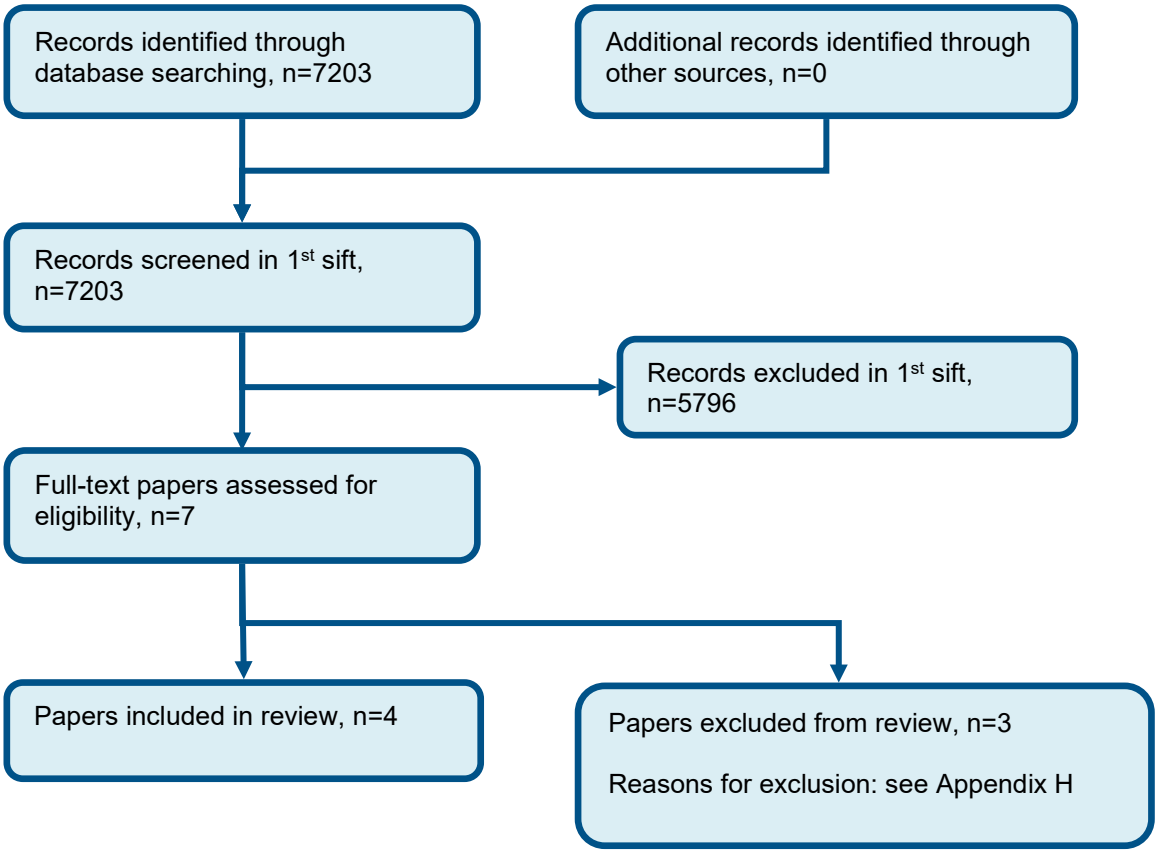
INAHTA search terms

1.	(Asthma)[mh] OR (asthma*)[Title] OR (asthma*)[abs]

Appendix C –Diagnostic evidence study selection

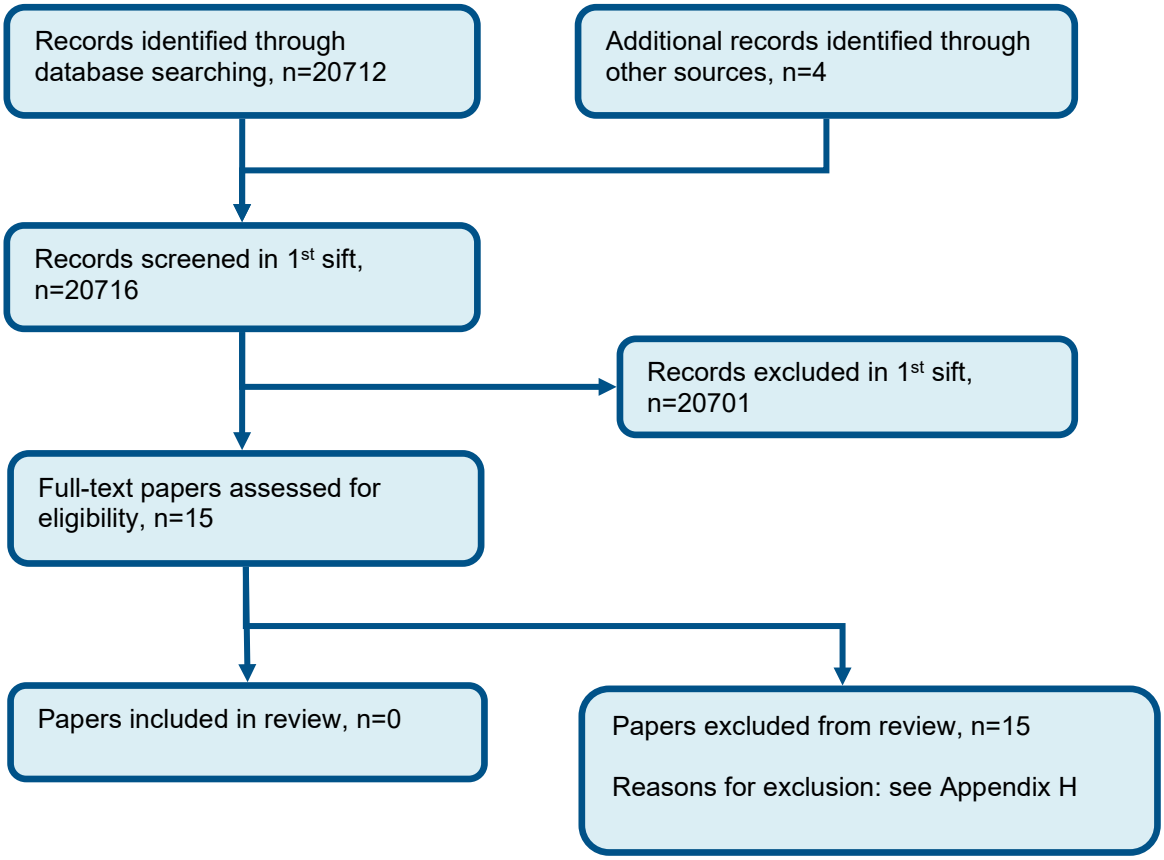
Diagnostic test accuracy of peak expiratory flow (PEF) variability

Figure 1: Flow chart of clinical study selection for the review of diagnostic test accuracy of peak expiratory flow for the diagnosis of asthma



Clinical and cost effectiveness of peak expiratory flow (PEF) variability

Figure 2: Flow chart of clinical study selection for the review of clinical and cost effectiveness of peak expiratory flow variability for the diagnosis of asthma



Appendix D –Diagnostic evidence

Diagnostic test accuracy of peak expiratory flow (PEF) variability

Reference	**Brouwer 2010 (Brouwer et al., 2010)**
Study type	Diagnostic cross-sectional study
Study methodology	Data source: Paediatric asthma clinic Recruitment: Not reported
Number of patients	n = 61
Patient characteristics	Age, mean (range): 10.4 (6-16 years) Gender (male to female ratio): 27:34 Smoking status: 27% parent smokers, 1 smoking participant Atopy: 59% sensitive to aero and/or food allergens Ethnicity: Not reported Setting: Secondary care Country: the Netherlands Inclusion criteria: Children with non-specific respiratory symptoms such as cough and breathlessness in whom GP was uncertain of diagnosis, referred to hospital-based asthma clinic Exclusion criteria: Straightforward diagnosis of asthma based on classical respiratory symptoms, referred for poorly controlled asthma, receiving systemic corticosteroids or long-acting beta-2-agonists in the last month
Target condition(s)	Asthma

<table>
<tr><td>Reference</td><td colspan="5">Brouwer 2010 (Brouwer et al., 2010)</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5">Index test
During the 2-week study period between the two study visits, children measured PEF and FEV_1 twice daily on a home spirometer. These results were not revealed to the paediatric pulmonologist at any time during the study. Patients were instructed to perform three forced expiratory flow manoeuvres twice daily between 6 and 10 a.m. and between 6 and 10 p.m. throughout the whole study period of 2 weeks. The device automatically stored the highest of the three correctly performed PEFs on a microchip, along with the accompanying FEV_1. Patients were instructed to achieve PEF as rapidly as possible and to continue the forced expiratory manoeuvre for at least 2 seconds. An integrated quality check warned the user by an exclamation mark when a cough was detected, the blow was not long enough, or there was a slow start.

Cut-off: (pre-specified)
positive = >95th centile for healthy children i.e. ≥12.3% for PEF variability, ≥11.8% for FEV_1 variability

Reference standard
Clinical Diagnosis including objective test: Asthma diagnosed by paediatric pulmonologist including history, physical examination and lung function tests including methacholine challenge

Time between measurement of index test and reference standard: same time</td></tr>
<tr><td rowspan="4">2×2 table PEF variability ≥12.3%</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4">Prevalence= 33.8%</td></tr>
<tr><td>Index test +</td><td>10</td><td>11</td><td>21</td></tr>
<tr><td>Index test −</td><td>10</td><td>28</td><td>38</td></tr>
<tr><td>Total</td><td>20</td><td>39</td><td>59</td></tr>
<tr><td rowspan="4">2×2 table FEV_1 variability ≤11.8%</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4"></td></tr>
<tr><td>Index test +</td><td>9</td><td>3</td><td>12</td></tr>
<tr><td>Index test −</td><td>11</td><td>36</td><td>47</td></tr>
<tr><td>Total</td><td>20</td><td>39</td><td>59</td></tr>
<tr><td>Statistical measures</td><td colspan="5">Index text: PEF variability ≥12.3%
Sensitivity: 0.50 (95%CI 0.30-0.70)
Specificity: 0.72 (95%CI 0.56-0.84)
PPV: 48% (95%CI 28–68)
NPV: 74% (95%CI 58–85)

Index text: FEV_1 variability ≤11.8%
Sensitivity: 0.45 (95%CI 0.25-0.67)
Specificity: 0.92 (95%CI 0.80-0.97)
PPV: 75% (95%CI 47–91)</td></tr>
</table>

Reference	**Brouwer 2010 (Brouwer et al., 2010)**
	NPV: 77% (95%CI 63–86)
Source of funding	AstraZeneca NL
Limitations	Risk of bias: None Indirectness: None
Comments	2x2 data calculated from reported sensitivity and specificity (prevalence 33.8%)

Reference	**den Otter 1997 (den Otter et al., 1997)**
Study type	Diagnostic cross-sectional study
Study methodology	Data source: Subset of population screening with asthma symptoms Recruitment: Not reported
Number of patients	n = 323
Patient characteristics	Age, mean (SD): 43 (12) Gender (male to female ratio): 135:188 Smoking status: 39.9% current or ex-smokers Atopy: Not reported Ethnicity: Not reported Setting: General population Country: the Netherlands Inclusion criteria: Adults between 25-70 years with signs or symptoms indicating asthma (persistent or recurrent respiratory symptoms or signs of reversible bronchial obstruction) Exclusion criteria: None reported
Target condition(s)	Asthma

Reference	**den Otter 1997 (den Otter et al., 1997)**				
Index test(s) and reference standard	Index test All subjects eligible for study were visited and instructed at home by five trained investigators. After three weeks of measuring PEF twice a day, they were invited to a lung function laboratory. All patients were visited at home and trained in how to perform and to use a mini-Wright peak flow meter, and how to register PEF in a diary. They recorded their PEF for three weeks, twice a day at the same time in the morning and in the evening. For analysis, the highest value of three measurements was taken. The diurnal PEF index was calculated as:21 In order to test for learning effects, the mean morning PEF values on days 1–7 were first compared with the mean morning values on days 8–21. Since this showed no significant difference (P>0.2, paired t-test), measurements for the total period of 21 days were used for analysis. For analysis, the mean diurnal PEF index was calculated by taking the arithmetic mean of 21 daily PEF variabilities PEF variability = (PEFhighest – PEFlowest)/ PEFmean x 100% (mean over 21 days' readings) Cut-offs: (pre-specified) ≥5%, 10% or 15% Reference standard Clinical Diagnosis including objective test: symptoms plus bronchial hyperresponsiveness, defined as a PC20 histamine of ≤8 mg/ml or bronchodilator reversibility, defined as ≥9% bronchodilation after 800 mg salbutamol. Time between measurement of index test and reference standard: unclear				
2×2 table PEF variability ≥15%		Reference standard +	Reference standard −	Total	Prevalence= 40.8%
	Index test +	6	4	10	
	Index test −	124	184	308	
	Total	130	188	318	
PEF variability ≥10%		Reference standard +	Reference standard −	Total	
	Index test +	18	8	26	
	Index test −	112	180	292	
	Total	130	188	318	
PEF variability ≥5%		Reference standard +	Reference standard −	Total	
	Index test +	73	58	131	
	Index test −	57	130	187	
	Total	130	188	318	

Reference	den Otter 1997 (den Otter et al., 1997)
Statistical measures	Index text: PEF variability ≥15% Sensitivity: 0.05 (95%CI 0.02-0.10) Specificity: 0.98 (95%CI 0.95-0.99) PPV: 60% NPV: 60% Index text: PEF variability ≥10% Sensitivity: 0.14 (95%CI 0.08-0.21) Specificity: 0.96 (95%CI 0.92-0.98) PPV: 69% NPV: 62% Index text: PEF variability ≥5% Sensitivity: 0.56 (95%CI 0.47-0.65) Specificity: 0.69 (95%CI 0.62-0.76) PPV: 56% NPV: 66%
Source of funding	None reported
Limitations	Risk of bias: Serious due to concerns due to the interpretation of the index test and reference standard (unclear if blinded) Indirectness: Serious due to population indirectness (ICS use not reported)
Comments	Sensitivity and specificity calculated using 2x2 data reported

Reference	Smith 2004 (Smith et al.)
Study type	Prospective cross-sectional diagnostic accuracy study
Study methodology	Data source: 47 consecutive patients aged 8–75 years referred by their family practitioner to Dunedin Hospital Recruitment: Consecutive patients
Number of patients	n = 47
Patient characteristics	Age, mean (range): Diagnosed with asthma: 41.6 (9-72), without asthma: 31.8 (9-64) Gender (male to female ratio): 20: 27

<table>
<tr><td>Reference</td><td colspan="5">Smith 2004 (Smith et al.)</td></tr>
<tr><td></td><td colspan="5">Smoking status: 42 non-smokers, 5 ex-smokers

Atopy: Not reported

Ethnicity: Not reported

Setting: Primary care

Country: New Zealand

Inclusion criteria: people having respiratory symptoms in the preceding 4 weeks
Exclusion criteria: used oral or inhaled corticosteroid in the preceding 4 weeks or if they had a typical respiratory tract infection in the previous 6 weeks</td></tr>
<tr><td>Target condition(s)</td><td colspan="5">Asthma</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5"><u>Index test</u>
Twice daily peak flows were carried out for seven days

Cut-off: >20% (pre-specified)

<u>Reference standard</u>
Diagnosis of asthma was ascertained on the basis of the following: relevant symptom history (present in all patients), using American Thoracic Society criteria, and a positive test for BHR and/or a positive response to bronchodilator. These were defined as: provocative dose of hypertonic saline resulting in a 15% fall in FEV1(PD15) of less than 20 ml and an increase in FEV_1 of 12% or greater from baseline 15 minutes after inhaled albuterol, respectively

Time between measurement of index test and reference standard: 2-4 weeks</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4">Prevalence= 36.9%</td></tr>
<tr><td></td><td>Index test +</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td></td><td>Index test −</td><td>17</td><td>29</td><td>46</td></tr>
<tr><td></td><td>Total</td><td>17</td><td>29</td><td>46</td></tr>
<tr><td>Statistical measures</td><td colspan="5">Sensitivity: 0.00 (95%CI 0.00-0.20)
Specificity: 1.00 (95%CI 0.88-1.00)
PPV: 0%
NPV: 63%</td></tr>
</table>

Reference	**Smith 2004 (Smith et al.)**
Source of funding	Supported by the Otago Medical Research Foundation and the Otago Respiratory Research Trust. GlaxoSmithKline provided a personal educational grant to A.D.S. as GSK Research Fellow
Limitations	Risk of bias: Serious risk of bias due to lack of clarity in the interpretation of the index test and reference standard (unclear if blinded) Indirectness: Downgraded by one increment due to population (mixed children and adolescents/young people) indirectness
Comments	2x2 data reported in paper, sensitivity and specificity calculated by analyst

Reference	**Thiadens 1998 (Thiadens et al., 1998)**
Study type	Diagnostic cross-sectional study
Study methodology	Data source: Community Recruitment: January 1994 – March 1995
Number of patients	n = 170
Patient characteristics	Age, mean (SD): 44 (16) years Gender (male to female ratio): 61:170 Smoking status (mean pack years (SD)): 8.6 (11.8) Atopy: Not reported Ethnicity: Not reported Setting: Primary care Country: the Netherlands Inclusion criteria: Adults (18-75 years) who consulted their GP with coughing that had lasted for at least 2 weeks Exclusion criteria: Already had a diagnosis of asthma or COPD, pregnant, or had a cardiovascular disease or concomitant pulmonary disease
Target condition(s)	Asthma

Reference	**Thiadens 1998 (Thiadens et al., 1998)**
Index test(s) and reference standard	Index test Patients measured and recorded their PEF with a MiniWright meter (Clement Clarke International, London, UK) first thing in the morning and before the evening meal for a period of 14 days (between the first and second visits). The highest of the three values of morning and evening measurements was used for analysis. The first day was excluded from analysis in order to reduce any learning effect. Only diaries with at least 6 days of measurements were analysed. PEF variability (DPV) = (PEFhighest – PEFlowest)/ PEFhighest x 100% = amplitude % highest (a) MDPV = mean over 2-week period (b) DPV more than threshold on 4 days or more (c) DPV more than threshold on 3 days or more Cut-offs: (pre-specified) (a) MDPV > 10% and MDPV >15% (b) DPV >15% on 4 days or more (c) DPV >20% on 3 days or more Reference standard Clinical Diagnosis including objective test: A patient was considered to have asthma if there had been a previous period of respiratory symptoms for >3 weeks in the last year, accompanied by a provocative dose causing a 20% fall in FEV1 (PD20) ≤15.6 µmol methacholine and/or bronchodilator reversibility ≥9% of predicted Bronchodilator reversibility Lung function was measured by a Microlab 3300 (Sensormedics, Rochester, UK) on all three occasions. Forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) were measured until three reproducible recordings (a difference of <5%) were obtained, with the highest values being used for analyses. Reference values were those from the European Respiratory Society. Reversibility was measured 15 min after inhalation of 400 µg salbutamol, administered through a spacer device (Volumatic; Glaxo, Zeist, The Netherlands). Reversibility was considered to be present if FEV1 improved by ≥9% of the predictive value. Methacholine challenge On the second visit a methacholine provocation test was carried out. Two-fold increments of methacholine chloride were administered from a starting dose of 0.06 µmol to a cumulative dose of 15.6 µmol. The challenge was discontinued if FEV1 fell by ≥20% from the post-saline value or when a cumulative dose of 15.6 µmol was reached. Time between measurement of index test and reference standard: same time

2×2 table Mean Diurnal Peak Flow

	Reference standard +	Reference standard −	Total	Prevalence= 40.5%
Index test +	10	3	13	
Index test −	59	98	157	

Reference	**Thiadens 1998 (Thiadens et al., 1998)**				
Variability >10%	Total	69	101	170	
2x2 table Mean Diurnal Peak Flow Variability >15%		Reference standard +	Reference standard −	Total	
	Index test +	2	1	3	
	Index test −	67	100	167	
	Total	69	101	170	
2x2 table Diurnal Peak Flow Variability >15% on ≥4 days		Reference standard +	Reference standard −	Total	
	Index test +	14	3	17	
	Index test −	55	98	153	
	Total	69	101	170	
2x2 table Diurnal Peak Flow Variability >20% on ≥3 days		Reference standard +	Reference standard −	Total	
	Index test +	8	1	9	
	Index test −	61	100	161	
	Total	69	101	170	
Statistical measures	<u>Index text: Mean Diurnal Peak Flow Variability >10%</u> Sensitivity: 0.14 (95%CI 0.07-0.25) Specificity: 0.97 (95%CI 0.92-0.99) PPV: 77% NPV: 62% <u>Index text: Mean Diurnal Peak Flow Variability >15%</u> Sensitivity: 0.03 (95%CI 0.00-0.10) Specificity: 0.99 (95%CI 0.95-1.00) PPV: 67% NPV: 60% <u>Index text: Diurnal Peak flow Variability >15% on ≥4 days</u> Sensitivity: 0.20 (95%CI 0.12-0.32) Specificity: 0.97 (95%CI 0.92-0.99) PPV: 82% NPV: 64%				

Reference	**Thiadens 1998 (Thiadens et al., 1998)**
	Index text: Diurnal Peak Flow Variability >20% on ≥3 days Sensitivity: 0.12 (95%CI 0.05-0.22) Specificity: 0.99 (95%CI 0.95-1.00) PPV: 89% NPV: 62%
Source of funding	GlaxoWellcome BV, Medical Division, NL
Limitations	Risk of bias: Very serious due to concerns arising from interpretation of the index test and reference standard (unclear if blinded) and concerns arising from the patient flow through the study (205 participants entered study, data reported for 170) Indirectness: Downgraded by one increment due to population (ICS use not reported) indirectness
Comments	Sensitivity and specificity calculated using 2x2 data reported

Clinical and cost effectiveness of peak expiratory flow (PEF) variability

No clinical evidence identified.

Appendix E – Forest plots

Diagnostic test accuracy of peak expiratory flow (PEF) variability

Children and young people

Figure 3: Mean peak flow variability ≥12.3% over 14 days vs clinical diagnosis with methacholine challenge

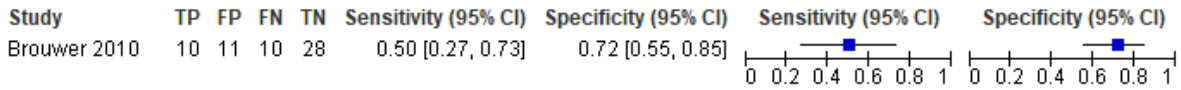


Figure 4: Mean FEV_1 variability ≥11.8% over 14 days vs clinical diagnosis with methacholine challenge

Adults with mixed smoking status

Figure 5: Mean peak expiratory flow variability ≥15% over 21 days vs clinical diagnosis with histamine challenge

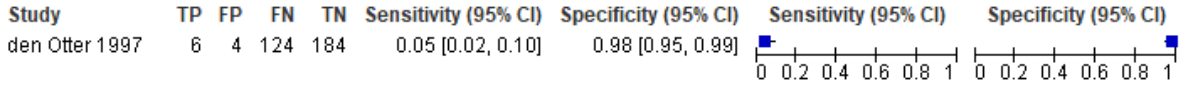


Figure 6: Mean peak expiratory flow variability ≥10% over 21 days vs clinical diagnosis with histamine challenge

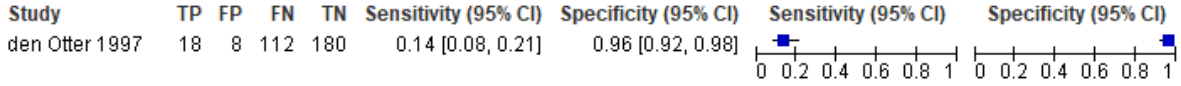


Figure 7: Mean peak expiratory flow variability ≥5% over 21 days vs clinical diagnosis with histamine challenge

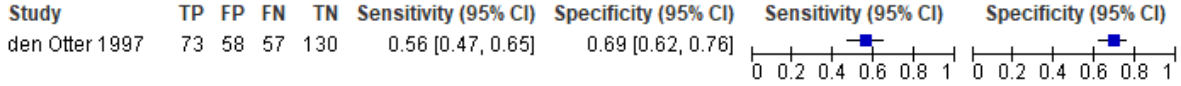


Figure 8: Mean peak expiratory flow variability >10% over 14 days vs clinical diagnosis with bronchial hyperresponsiveness and/or methacholine challenge

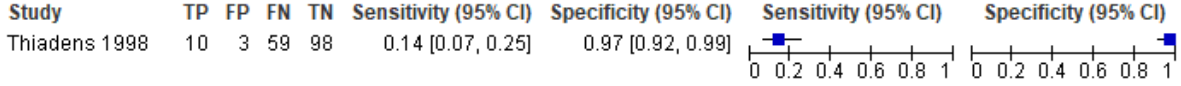


Figure 9: Mean peak expiratory flow variability >15% over 14 days vs clinical diagnosis with bronchial hyperresponsiveness and/or methacholine challenge

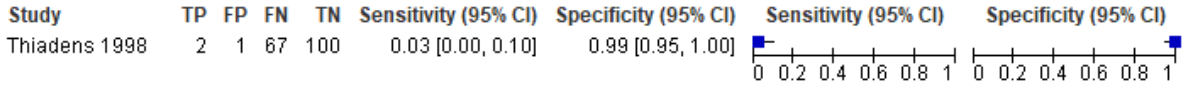


Figure 10: Diurnal peak flow variability >15% on ≥4 days vs clinical diagnosis with bronchial hyperresponsiveness and/or methacholine challenge

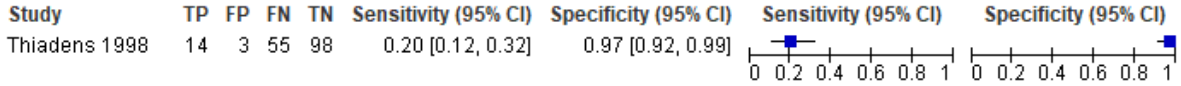


Figure 11: Diurnal Peak Flow Variability >20% on ≥3 days vs clinical diagnosis with bronchial hyperresponsiveness and/or methacholine challenge

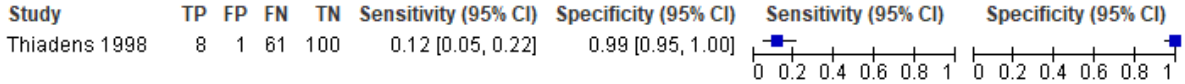
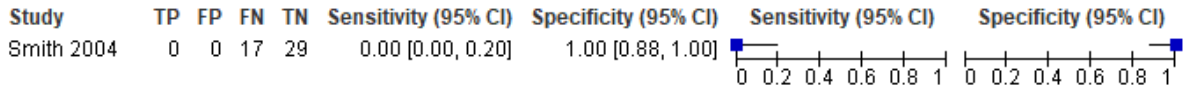


Figure 12: Amplitude percent mean >20% over 7 days vs clinical diagnosis with methacholine challenge or bronchodilator reversibility

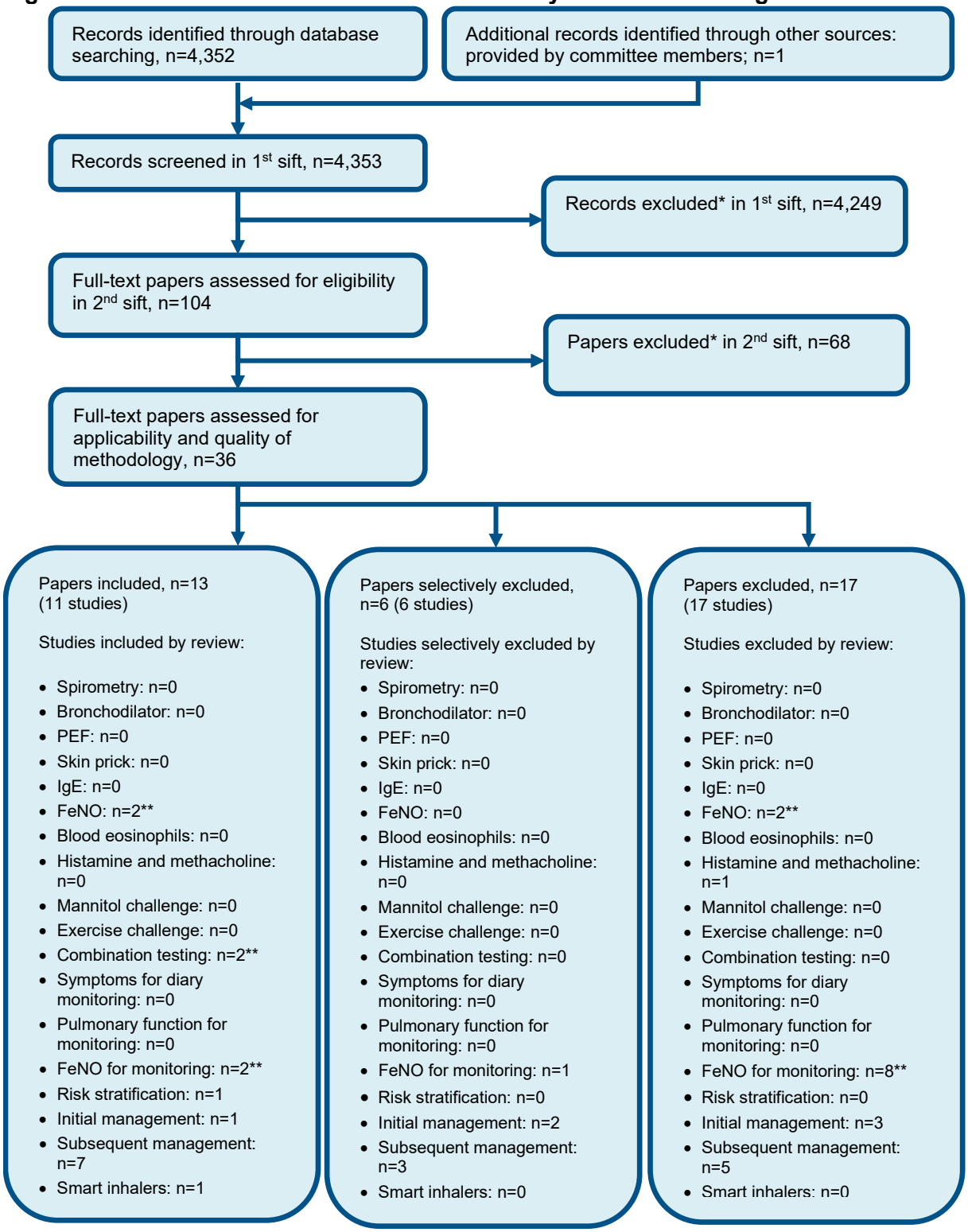


Clinical and cost effectiveness of peak expiratory flow (PEF) variability

No clinical evidence identified.

Appendix F – Economic evidence study selection

Figure 13: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language
** Includes studies that are in multiple reviews

Appendix G – Economic evidence tables

None.

Appendix H – Excluded studies

Clinical studies

Diagnostic test accuracy of peak expiratory flow (PEF) variability

Table 9: Studies excluded from the clinical review

Study	Code [Reason]
Csonka, Leon, Tikkakoski, Antti, Tikkakoski, Anna P et al. (2023) Relation of changes in PEF and FEV1 in exercise challenge in children. Clinical physiology and functional imaging	- Study design not relevant to this review protocol *Study aims to diagnose exercise induced bronchoconstriction with decreases in PEF compared to FEV1 - not a relevant index test vs reference standard*
Domingos Neto, J., Myung, E., Murta, G. et al. (2018) Asthma and occupation: Diagnosis using serial peak flow measurements. Revista Da Associacao Medica Brasileira 64(2): 95-99	- Review article but not a systematic review
Ulrik CS; Postma DS; Backer V (2005) Recognition of asthma in adolescents and young adults: which objective measure is best?. The Journal of asthma : official journal of the Association for the Care of Asthma 42(7): 549-554	- Population not relevant to this review protocol *Participants were from a random population sample - not people presenting with respiratory symptoms*

Clinical and cost effectiveness of peak expiratory flow (PEF) variability

Table 10: Studies excluded from the clinical review

Study	Code [Reason]
Anees, W. (2003) Use of pulmonary function tests in the diagnosis of occupational asthma. Annals of Allergy, Asthma, & Immunology 90(5suppl2): 47-51	- Review article but not a systematic review
Anees, W., Gannon, P. F., Huggins, V. et al. (2004) Effect of peak expiratory flow data quantity on diagnostic sensitivity and specificity in occupational asthma. European Respiratory Journal 23(5): 730-4	- Population not relevant to this review protocol *Participants already diagnosed with asthma*
Brouwer, A. F., Visser, C. A., Duiverman, E. J. et al. (2010) Is home spirometry useful in	- Study design not relevant to this review protocol

Study	Code [Reason]
diagnosing asthma in children with nonspecific respiratory symptoms?. Pediatric Pulmonology 45(4): 326-32	*Not a randomised trial*
Chiry, S., Cartier, A., Malo, J. L. et al. (2007) Comparison of peak expiratory flow variability between workers with work-exacerbated asthma and occupational asthma. Chest 132(2): 483-8	- Study design not relevant to this review protocol *Not a randomised trial*
Higgins, B. G., Britton, J. R., Chinn, S. et al. (1993) Factors affecting peak expiratory flow variability and bronchial reactivity in a random population sample. Thorax 48(9): 899-905	- Population not relevant to this review protocol *Random population sample - not people presenting with respiratory symptoms*
Jamison, J. P. and McKinley, R. K. (1993) Validity of peak expiratory flow rate variability for the diagnosis of asthma. Clinical Science 85(3): 367-71	- Population not relevant to this review protocol *Participants already diagnosed with asthma - not presenting with respiratory symptoms*
Kongerud, J.; Soyseth, V.; Burge, S. (1992) Serial measurements of peak expiratory flow and responsiveness to methacholine in the diagnosis of aluminium potroom asthma. Thorax 47(4): 292-7	- Study design not relevant to this review protocol *Not a randomised trial*
Leroyer, C., Perfetti, L., Trudeau, C. et al. (1998) Comparison of serial monitoring of peak expiratory flow and FEV1 in the diagnosis of occupational asthma. American Journal of Respiratory & Critical Care Medicine 158(3): 827-32	- Study aiming to diagnose a condition not relevant to this review protocol *Aiming to diagnose occupational asthma*
Park, D., Moore, V. C., Burge, C. B. et al. (2009) Serial PEF measurement is superior to cross-shift change in diagnosing occupational asthma. European Respiratory Journal 34(3): 574-8	- Study design not relevant to this review protocol *Not a randomised trial*
Perrin, B., Lagier, F., L'Archeveque, J. et al. (1992) Occupational asthma: validity of monitoring of peak expiratory flow rates and non-allergic bronchial responsiveness as compared to specific inhalation challenge. European Respiratory Journal 5(1): 40-8	- Study design not relevant to this review protocol *Not a randomised trial*
Siersted, H. C., Hansen, H. S., Hansen, N. C. et al. (1994) Evaluation of peak expiratory flow variability in an adolescent population sample. The Odense Schoolchild Study. American Journal of Respiratory & Critical Care Medicine 149(3pt1): 598-603	- Population not relevant to this review protocol *Random population sample - not people with respiratory symptoms*

Study	Code [Reason]
Thiadens, H. A., De Bock, G. H., Dekker, F. W. et al. (1998) Value of measuring diurnal peak flow variability in the recognition of asthma: a study in general practice. European Respiratory Journal 12(4): 842-7	- Study design not relevant to this review protocol *Not a randomised trial*
Turner, M. O., Taylor, D., Bennett, R. et al. (1998) A randomized trial comparing peak expiratory flow and symptom self-management plans for patients with asthma attending a primary care clinic. American Journal of Respiratory & Critical Care Medicine 157(2): 540-6	- Study does not contain an intervention relevant to this review protocol *FeNO used as the diagnostic tool, not PEF*
Ulrik, C. S.; Postma, D. S.; Backer, V. (2005) Recognition of asthma in adolescents and young adults: which objective measure is best?. Journal of Asthma 42(7): 549-54	- Study design not relevant to this review protocol *Not a randomised trial*
Zangrilli, J., McElhattan, J., O'Brien, Cd et al. (2009) Predose and Postdose Forced Expiratory Flow Between 25% and 75% (FEF25-75%) in Adolescents and Adults With Asthma Treated With Twice-Daily Budesonide/Formoterol Pressurized Metered-Dose Inhaler (BUD/FM pMDI) or BUD pMDI for 1 Year. Journal of allergy and clinical immunology 123(2suppl1): 79	- Population not relevant to this review protocol *Participants already diagnosed with asthma - not presenting with respiratory symptoms*

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2006 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

None.