British Thoracic Society

NICE National Institute for Health and Care Excellence

Healthcare Improvement Scotland | SIGN Makes sense of evidence

Draft for Consultation

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

Evidence Review for Bronchial Challenge Test with Mannitol

BTS/NICE/SIGN guideline <number>

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Draft for Consultation

Developed by NICE

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ISBN:

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1. Bronchial challenge testing with mannitol

1.1 Review question

In people under investigation for asthma, what is the diagnostic test accuracy and clinical and cost-effectiveness of bronchial challenge testing (indirect) with mannitol?

1.1.1 Introduction

Bronchial hyper-responsiveness (BHR) is a key characteristic of asthma, and measurement of this via bronchial challenge testing should be helpful in making the diagnosis. Bronchial challenge tests are most often performed using histamine or methacholine which both act directly on airway smooth muscle. Mannitol acts indirectly by causing the release of endogenous mediators which in turn stimulate airway smooth muscle, and it has been suggested that this is a better method of diagnostic testing for BHR since it is a closer mimic of the pathophysiological process of asthma. This review was therefore performed to explore the value of mannitol bronchial challenge as a test for asthma.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

No test-and-treat evidence was found so only the diagnostic accuracy evidence was reported.

Table 1: PICO characteristics of diagnostic accuracy review question

Population	Inclusion: • Adolescents/adults (≥12 years) with suspected asthma (presenting with respiratory symptoms). Stratified by smoking status: • Smokers • Non-smokers • Mixed populations Exclusion: • Children under 11 years as mannitol is not licenced in this population. • People on steroid medication (washout period minimum of 4 weeks for inclusion)
Target condition	Asthma
Index test	• Mannitol
Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • 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.
Statistical measures	• Sensitivity: thresholds: upper 90, lower 10 • Specificity: thresholds: 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 studies • 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

Two cross-sectional studies were included in the review; (Anderson, et al., 2009; Porpodis, et al., 2017) these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below in Table 3 and references in 1.3 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

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
Anderson 2009(Anderson, et al., 2009)	N=375 people with signs and symptoms suggestive of asthma without a firm diagnosis of asthma or non-asthma. Age, mean (SD): 24.3 (10.2) years. Range 6-50 years USA	Asthma	Mannitol test expressed as PD15 (dose of mannitol that caused a reduction in FEV_1 of 15% from baseline, or 10% fall between consecutive doses) Maximum cumulative dose: 635 mg	Diagnosis of asthma by a respiratory physician based on data from exercise challenge, examination, skin tests and FEV_1 reversibility	Prospective cross-sectional study ICS use: 4-week washout Smoking status: Smokers excluded
Porpodis 2017(Porpodis, et al., 2017)	N=88 people with asthma related symptoms in the past month visiting an asthma clinic for asthma diagnosis Age, mean (SD): 38.56 (16.73) years Greece	Asthma	Mannitol test expressed as PD15 (dose of mannitol that caused a reduction in FEV_1 of 15% from baseline, or 10% fall between consecutive doses) Maximum cumulative dose: 635 mg	Asthma diagnosis according to GINA guidelines: combination of at least a ≥12% (and ≥200 mL) increase in baseline FEV1 after albuterol, along with new symptoms of coughing, wheezing, or shortness of breath over the past month	Prospective cross-sectional study ICS use: Treatment naïve Smoking status: 15% current smokers

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% 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.

Table 3: Clinical evidence summary: bronchial challenge with mannitol vs clinician diagnosis of asthma in non-smoking adolescents/adults

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Mannitol (PD15 or 10% between consecutive doses) vs clinician diagnosis with exercise challenge, history, examination, skin test and bronchodilator reversibility data							
1 cross-sectional study	375	Serious[1]	Not serious	Not serious	Not serious	Sensitivity= 0.56 (0.49-0.62)	MODERATE
		Serious[1]	Not serious	Not serious	Serious[2]	Specificity= 0.75 (0.67-0.82)	LOW

1. *Downgraded by one increment due to concerns arising from the method of participant selection (method not reported)*
2. *Downgraded by one increment due to the 95%CI overlapping the threshold corresponding to 'high specificity' (80%)*

Table 4: Clinical evidence summary: bronchial challenge with mannitol vs clinician diagnosis of asthma in adolescents/adults with mixed smoking status

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Mannitol (PD15 or 10% between consecutive doses) vs clinician diagnosis with bronchodilator reversibility and symptom monitoring over one-month							
1 cross-sectional study	88	Very serious[1]	Not serious	Serious[2]	Not serious	Sensitivity= 0.64 (0.52-0.76)	VERY LOW
		Very serious[1]	Not serious	Serious[2]	Serious[3]	Specificity= 0.95 (0.76-1.00)	VERY LOW

1. *Downgraded by two increments due to concerns arising from the method of participant selection (method not reported) and the interpretation of the index test and reference standard (unclear if blinded)*
2. *Downgraded by one increment due to population (contains a mixture of smoking and non-smoking participants) indirectness*
3. *Downgraded by one increment due to the 95%CI overlapping the threshold corresponding to 'high specificity' (80%)*

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 4: Cost of a bronchial challenge test

Resource	Unit costs	Source
Bronchial challenge test with mannitol	£179.49	National Cost Collection 2021-22 – DZ36Z(NHS England, 2022)

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

Test and treat studies

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 the purpose 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 bronchial challenge testing with mannitol 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

Test and treat studies

No relevant clinical studies were identified comparing the clinical effectiveness of diagnosis of asthma based on bronchial challenge with mannitol.

Diagnostic accuracy

Two cross-sectional studies were included in this review. One study was conducted in non-smoking participants, with the other containing a mixture of smoking and non-smoking participants. Both studies used the same cut-off, with a reduction in FEV_1 of ≥15% from

baseline or ≥10% with consecutive doses using a provocative dose <635 mg being considered diagnostic of asthma.

Evidence ranged from moderate-very low-quality. All evidence was downgraded by at least one increment due to risk of bias arising from an unclear method of participant selection, with further downgrading due to an unclear blinding procedure in one of the studies. Additionally, the evidence in adolescents/adults with mixed smoking status' was downgraded due to indirectness. Finally, imprecision was seen across both specificity estimates due to the 95%CI overlapping the upper threshold for decision-making.

1.2.3 Benefits and harms

Moderate-low-quality evidence in non-smoking adolescents/adults reported a sensitivity of 0.56 and a specificity of 0.75, neither of which met the decision-making threshold. Very low-quality evidence in people with mixed smoking status reported a sensitivity of 0.64 and a specificity of 0.95, with the latter meeting the threshold for decision-making. Whilst interpreting the evidence, the committee acknowledged the limitations in the quality of evidence, and also noted the relatively small number of participants (n=88) contributing to study in which high specificity was found.

Although the evidence is limited the committee agreed that mannitol was of potential value in the diagnosis of asthma because it shows good specificity without losing too much sensitivity. However, it would need to be used in conjunction with other tests since it is not accurate enough on its own. The diagnostic accuracy of mannitol in combination with other diagnostic tests was investigated in a separate review (1.11) in this guideline.

1.2.4 Cost effectiveness and resource use

No relevant published health economic analyses were identified for this review question. The cost of a bronchial challenge test was presented to aid committee consideration of cost effectiveness. The cost was estimated to reach £179.49 as the test is provided only in secondary care.

The committee considered bronchial challenge test with mannitol alongside or in combination with a variety of tests for asthma within a diagnostic algorithm in adults and children (see evidence review 1.11. Although potentially accurate, the committee agreed that the evidence was lacking and therefore recommended methacholine instead. This is also in line with current practice where methacholine is generally preferred.

1.2.5 Other factors the committee took into account

One factor that was considered when discussing the evidence was the risk of adverse side effects occurring during bronchial challenge testing with mannitol. This was initially raised as a point of concern by the lay members of the committee due to theoretical danger of deliberately restricting the airways. However, this concern was alleviated by the clinicians on the committee. It was explained that bronchial challenge tests only aim to achieve a reduction in FEV_1 of 15%, which in most individuals is not an uncomfortable level of bronchoconstriction. In very few cases a greater fall in FEV_1 of up to 40% may occur, but bronchial challenge tests are always followed by a rapid-acting bronchodilator to restore the functionality of the airway, thus limiting any discomfort experienced. Furthermore, bronchial challenge tests are conducted in secondary care where specialist input and facilities are available should any severe adverse events occur. Given the low likelihood of adverse events, combined with the safe testing environment, the committee agreed that the benefits of bronchial challenge testing with mannitol strongly outweighed the risks.

A second factor that was considered was the relatively easy access to and use of mannitol as a provocative agent. Unlike methacholine, mannitol requires no preparation and can be stored for longer, which was considered to be significant advantages.

1.2.5 Recommendations supported by this evidence review

No recommendations were made from this evidence review.

1.3 References

Anderson SD, Charlton B, Weiler JM, et al. (2009) Comparison of mannitol and methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma *Respiratory Research* 10: 4.

National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. . London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

NHS England. 2021/22 National Cost Collection data. 2022. Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/ Last accessed: 26/02/2024.

Porpodis K, Domvri K, Kontakiotis T, et al. (2017) Comparison of diagnostic validity of mannitol and methacholine challenges and relationship to clinical status and airway inflammation in steroid-naive asthmatic patients *The Journal of asthma : official journal of the Association for the Care of Asthma* 54 (5): 520-529.

Appendices

Appendix A – Review protocols

Review protocol for bronchial challenge testing with mannitol for the diagnosis of asthma

Field	Content
PROSPERO registration number	CRD42023438827
Review title	Accuracy and clinical and cost-effectiveness of bronchial challenge testing with mannitol for diagnosis of asthma
Review question	In people under investigation for asthma, what is the diagnostic test accuracy and clinical and cost-effectiveness of bronchial challenge testing (indirect) with mannitol?
Objective	To evaluate the diagnostic test value of mannitol 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: • 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: Adolescents/Adults (≥12 years old) with suspected asthma (presenting with respiratory symptoms). Exclusion:

	• Children under 5 years old • Children aged 5-11 years as mannitol is not licenced in this population. • People on steroid medication (washout period minimum of 4 weeks for inclusion) • Stratification: smokers vs non-smokers vs mixed population
Test	• Mannitol
Reference standard	Effectiveness (test-and-treat) • Compare to each other Diagnostic accuracy Reference standard: Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • 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.
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 occupational asthma /allergens • Not looking at validation studies, or studies comparing different methods of measuring the same test • Not looking at factors which influence measurements • Studies in which >10% of people are on inhaled and/or systemic corticosteroid treatment • Cross-sectional studies only included if they report sensitivity/specificity or the sensitivity and specificity can be calculated.
Context	Primary, secondary and community 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)

	○ Acute symptoms (any symptom e.g. flushing, coughing, may be referred to as tolerability/acceptability – time frame immediately post test (10 mins) • Inflammatory markers; exhaled nitric oxide (continuous outcome at ≥8 weeks) Diagnostic accuracy outcomes: Asthma diagnosis • Sensitivity thresholds: upper 90, lower 10 • Specificity thresholds: 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) • 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. <u>Diagnostic accuracy:</u> 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	<u>Stratification (unconditional splitting)</u> • Different test thresholds • Different reference standards	
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) Qudsia Malik (Senior systematic reviewer) 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 (Technical Analyst)
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	N/A	
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	N/A	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	N/A	
Details of final publication	N/A	

1

1 Health economic review protocol

2 Table 5: 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

B.1 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 6: 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.	Bronchial Provocation Tests/
25.	(bronchial constrict* or bronchoconstrict* or broncho constrict* or bronchoprovocation or broncho provocation).ti,ab,kf.
26.	((bronchial or airway*) adj3 (provocat* or provok* or challeng* or test* or respons* or breath*)).ti,ab,kf.
27.	((challeng* or provocat* or inhalation or inhaling) adj2 test*).ti,ab,kf.
28.	BCT.ti,ab,kf.
29.	Bronchial Hyperreactivity/
30.	((bronchial or bronchus or airway) adj2 (hyperresponsiv* or hyperreactiv* or hyper-responsiv* or hyper-reactiv*)).ti,ab,kf.
31.	or/24-30
32.	exp Histamine/
33.	Methacholine Chloride/
34.	(histamin* or methacholine*).ti,ab,kf.
35.	provocholine*.ti,ab,kf.
36.	(HCT or MCT).ti,ab,kf.
37.	or/32-36
38.	exp Mannitol/
39.	mannit*.ti,ab,kf.
40.	or/38-39
41.	exp exercise tests/
42.	(exercise adj3 (provocat* or provok* or challeng* or test* or induced or inducing or brochosospasm* or stress or tolerance* or tolerating)).ti,ab,kf.
43.	((treadmill* or step* or bike* or bicycl* or cycl* or walk*) adj2 (test* or exert*)).ti,ab,kf.
44.	ergomet*.ti,ab,kf.
45.	or/41-44
46.	31 or 37 or 40 or 45

47.	23 and 46
48.	exp "sensitivity and specificity"/
49.	(sensitivity or specificity).ti,ab.
50.	((pre test or pretest or post test) adj probability).ti,ab.
51.	(predictive value* or PPV or NPV).ti,ab.
52.	likelihood ratio*.ti,ab.
53.	likelihood function/
54.	((area under adj4 curve) or AUC).ti,ab.
55.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
56.	gold standard.ab.
57.	exp Diagnostic errors/
58.	(false positiv* or false negativ*).ti,ab.
59.	Diagnosis, Differential/
60.	(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.
61.	or/48-60
62.	Epidemiologic studies/
63.	Observational study/
64.	exp Cohort studies/
65.	(cohort adj (study or studies or analys* or data)).ti,ab.
66.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
67.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
68.	Controlled Before-After Studies/
69.	Historically Controlled Study/
70.	Interrupted Time Series Analysis/
71.	(before adj2 after adj2 (study or studies or data)).ti,ab.
72.	exp case control study/
73.	case control*.ti,ab.
74.	Cross-sectional studies/
75.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
76.	or/62-75
77.	randomized controlled trial.pt.
78.	controlled clinical trial.pt.
79.	randomi#ed.ab.
80.	placebo.ab.
81.	randomly.ab.
82.	clinical trials as topic.sh.
83.	trial.ti.
84.	or/77-83
85.	Meta-Analysis/
86.	Meta-Analysis as Topic/
87.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.

88.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
89.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
90.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
91.	(search* adj4 literature).ab.
92.	(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.
93.	cochrane.jw.
94.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
95.	or/85-94
96.	47 and (61 or 76 or 84 or 95)

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.	Inhalation Test/
24.	(bronchial constrict* or bronchoconstrict* or broncho constrict* or bronchoprovocation or broncho provocation).ti,ab,kf.
25.	((bronchial or airway*) adj3 (provocat* or provok* or challeng* or test* or respons* or breath*)).ti,ab,kf.
26.	((challeng* or provocat* or inhalation or inhaling) adj2 test*).ti,ab,kf.
27.	BCT.ti,ab,kf.
28.	Bronchus hyperreactivity/

29.	((bronchial or bronchus or airway) adj2 (hyperresponsiv* or hyperreactiv* or hyper-responsiv* or hyper-reactiv*)).ti,ab,kf.
30.	or/23-29
31.	exp Histamine/
32.	Methacholine Chloride/
33.	(histamin* or methacholine*).ti,ab,kf.
34.	provocholine*.ti,ab,kf.
35.	(HCT or MCT).ti,ab,kf.
36.	or/31-35
37.	exp Mannitol/
38.	mannit*.ti,ab,kf.
39.	or/37-38
40.	exp Exercise test/
41.	(exercise adj3 (provocat* or provok* or challeng* or test* or induced or inducing or brochosospasm* or stress or tolerance* or tolerating)).ti,ab,kf.
42.	((treadmill* or step* or bike* or bicycl* or cycl* or walk*) adj2 (test* or exert*)).ti,ab,kf.
43.	ergomet*.ti,ab,kf.
44.	or/40-43
45.	30 or 36 or 39 or 44
46.	22 and 45
47.	exp "sensitivity and specificity"/
48.	(sensitivity or specificity).ti,ab.
49.	((pre test or pretest or post test) adj probability).ti,ab.
50.	(predictive value* or PPV or NPV).ti,ab.
51.	likelihood ratio*.ti,ab.
52.	((area under adj4 curve) or AUC).ti,ab.
53.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
54.	diagnostic accuracy/
55.	diagnostic test accuracy study/
56.	gold standard.ab.
57.	exp diagnostic error/
58.	(false positiv* or false negativ*).ti,ab.
59.	differential diagnosis/
60.	(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.
61.	or/47-60
62.	Clinical study/
63.	Observational study/
64.	Family study/
65.	Longitudinal study/
66.	Retrospective study/
67.	Prospective study/
68.	Cohort analysis/
69.	Follow-up/

70.	cohort*.ti,ab.
71.	69 and 70
72.	(cohort adj (study or studies or analys* or data)).ti,ab.
73.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
74.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
75.	(before adj2 after adj2 (study or studies or data)).ti,ab.
76.	exp case control study/
77.	case control*.ti,ab.
78.	cross-sectional study/
79.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
80.	or/62-68,71-79
81.	random*.ti,ab.
82.	factorial*.ti,ab.
83.	(crossover* or cross over*).ti,ab.
84.	((doubl* or singl*) adj blind*).ti,ab.
85.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
86.	crossover procedure/
87.	single blind procedure/
88.	randomized controlled trial/
89.	double blind procedure/
90.	or/81-89
91.	Systematic Review/
92.	Meta-Analysis/
93.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
94.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
95.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
96.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
97.	(search* adj4 literature).ab.
98.	(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.
99.	cochrane.jw.
100.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
101.	or/91-100
102.	46 and (61 or 80 or 90 or 101)

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: [Bronchial Provocation Tests] this term only
#7.	(bronchial constrict* or bronchoconstrict* or "broncho constrict*" or bronchoprovocat* or "broncho provocat*"):ti,ab
#8.	((bronchial or airway*) near/3 (provocat* or provok* or challeng* or test* or respons* or breath*)):ti,ab
#9.	((challeng* or provocat* or inhalation or inhaling) near/2 test*):ti,ab
#10.	BCT:ti,ab
#11.	MeSH descriptor: [Bronchial Hyperreactivity] this term only
#12.	((bronchial or bronchus or airway) near/2 (hyperresponsiv* or hyperreactiv* or "hyper responsiv*" or "hyper reactiv*")):ti,ab
#13.	(or #6-#12)
#14.	MeSH descriptor: [Histamine] explode all trees
#15.	MeSH descriptor: [Methacholine Chloride] explode all trees
#16.	(histamin* or methacholine*):ti,ab
#17.	provocholine*:ti,ab
#18.	(HCT or MCT):ti,ab
#19.	(or #14-#18)
#20.	MeSH descriptor: [Mannitol] explode all trees
#21.	mannit*:ti,ab
#22.	(or #20-#21)
#23.	MeSH descriptor: [Exercise Test] explode all trees
#24.	(exercise near/3 (provocat* or provok* or challeng* or test* or induced or inducing or brochosospasm* or stress or tolerance* or tolerating)):ti,ab
#25.	((treadmill* or step* or bike* or bicycl* or cycl* or walk*) near/2 (test* or exert*)):ti,ab
#26.	ergomet*:ti,ab
#27.	(or #23-#26)
#28.	#13 or #19 or #22 or #27
#29.	#5 and #28

Epistemonikos search terms

1.	(title:((bronchial constrict* OR bronchoconstrict* OR "broncho constrict*" OR bronchoprovocat* OR "broncho provocat*")) OR abstract:((bronchial constrict* OR bronchoconstrict* OR "broncho constrict*" OR bronchoprovocat* OR "broncho provocat*"))) OR (title:((bronchial OR airway*) AND (provocat* OR provok* OR challeng* OR test* OR respons* OR breath*)) OR abstract:((bronchial OR airway*) AND (provocat* OR provok* OR challeng* OR test* OR respons* OR breath*))) OR (title:((challeng* OR provocat* OR inhalation OR inhaling) AND test*) OR abstract:((challeng* OR provocat* OR inhalation OR inhaling) AND test*)) OR (title:(bronchial OR bronchus OR airway) AND (hyperresponsiv* OR hyperreactiv* OR hyper-responsiv* OR hyper-reactiv*) OR abstract:(bronchial OR bronchus OR airway) AND (hyperresponsiv* OR hyperreactiv* OR hyper-responsiv* OR hyper-reactiv*)) OR (title:((histamin* OR methacholine*)) OR abstract:((histamin* OR methacholine*))) OR (title:(provocholine*) OR abstract:(provocholine*)) OR (title:(mannit*) OR abstract:(mannit*)) OR (title:(exercise AND (provocat* OR provok* OR challeng* OR test* OR induced OR inducing OR brochosospasm* OR stress OR tolerance* OR tolerating)) OR abstract:(exercise AND (provocat* OR provok* OR challeng* OR test* OR induced OR inducing OR brochosospasm* OR stress OR tolerance* OR tolerating))) OR (title:((treadmill* OR step* OR bike* OR bicycl* OR cycl* OR walk*) AND (test* OR exert*)) OR abstract:((treadmill* OR step* OR bike* OR bicycl* OR cycl*

	OR walk*) AND (test* OR exert*))) OR (title:(ergomet*) OR abstract:(ergomet*)) AND (title:(asthma*) OR abstract:(asthma*))

B.2 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 7: 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	

Database	Dates searched	Search filters and limits applied
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

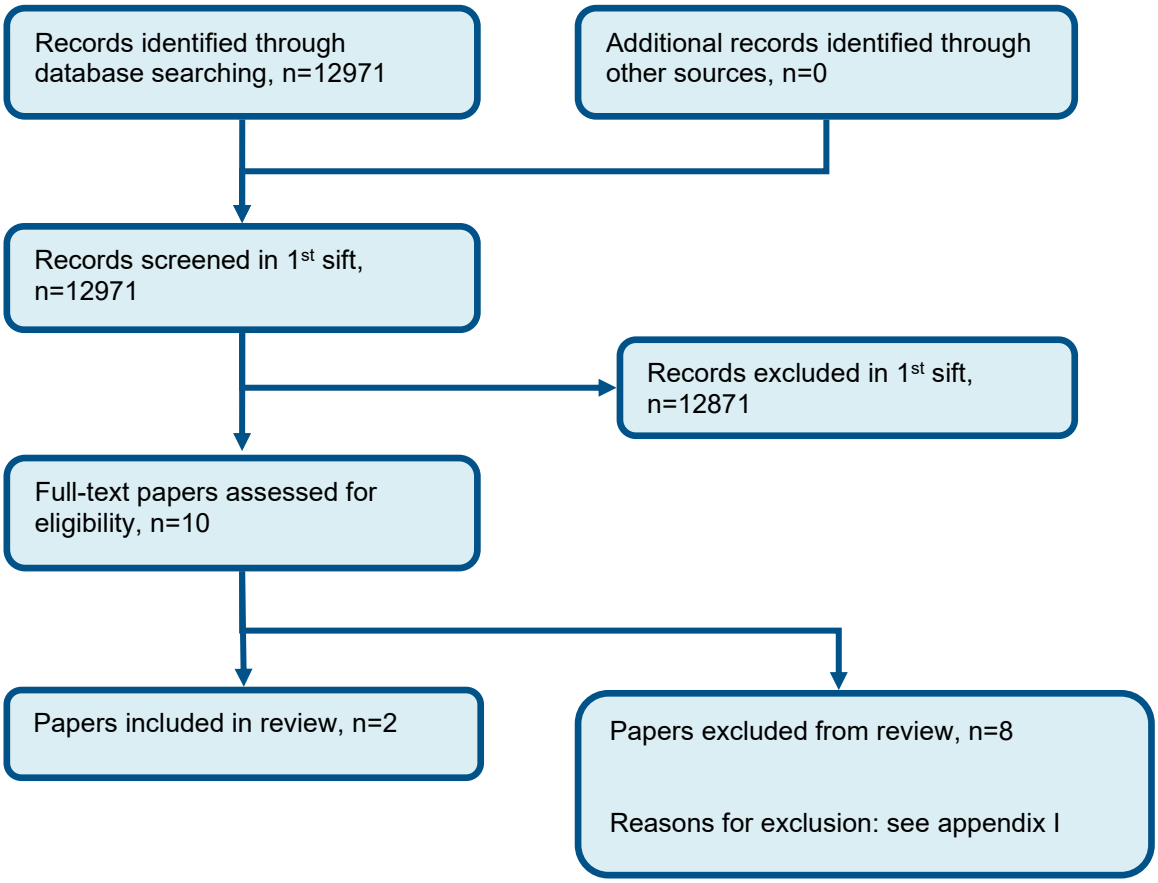
#1.	MeSH DESCRIPTOR Asthma EXPLODE ALL TREES
#2.	(asthma*)
#3.	#1 OR #2

INAHTA search terms

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

Appendix C –Diagnostic evidence study selection

Figure 1: Flow chart of clinical study selection for the review of diagnostic test accuracy of bronchial challenge test with mannitol



Appendix D –Diagnostic evidence

Reference	**Anderson 2009 (Anderson et al., 2009)**
Study type	Prospective cross-sectional study
Study methodology	Data source: People with signs and symptoms suggestive of asthma without a firm diagnosis of asthma or non-asthma Recruitment: Not reported
Number of patients	n = 375 per protocol (as reported, 391 in intention to treat population, those excluded from per protocol analysis were due to major protocol violations or not completing all challenge tests (exercise, methacholine, and mannitol))
Patient characteristics (per protocol)	Age, mean (SD): 24.3 (10.2) years. Range 6-50 years Gender (male to female ratio): 182:193 Ethnicity: 76.3% Caucasian, 8.3% Hispanic, 8.5% Black Setting: Secondary care (clinic) Country: USA Smoking status: Non-smokers ICS use: 4-week washout Inclusion criteria: Aged 6–50 years, BMI <35, Step 1 symptoms suggestive of asthma according to NAEPPII asthma severity grading (symptoms ≤ 2 times per week; asymptomatic between exacerbations; exacerbations of only a few hours to a few days; and night-time symptoms ≤ 2 times per month), with an FEV_1 ≥70% of predicted Exclusion criteria: Any known other pulmonary disease, smoked more than 1 cigarette per week within the past year or had a ≥10 pack year smoking history, respiratory tract infection within the previous 4 weeks, skin prick test positive to aeroallergens that were present in the environment during the time of enrolment and reported worsening of symptoms when exposed to these aeroallergens during the study, diagnosed at the Screening Visit as definitively having asthma (95 to 100% likelihood) or not having asthma (0 to < 5% likelihood), clinically significantly abnormal chest x-ray or ECG, failed to observe washout of medications that would interfere with BPT (including, but not limited to, no use of corticosteroids within 4 weeks of the Screening Visit).

Reference	Anderson 2009 (Anderson et al., 2009)
Target condition(s)	Asthma
Index test(s) and reference standard	The study consisted of 5 visits to the clinic. On the Screening Visit the following were assessed: eligibility; demographic data; medical history; medications; spirometry with reversibility (following 360 mcg of albuterol); allergy skin test reactivity to common allergens (positive test taken as 3 mm wheal). The NIH NAEPPII questionnaire was answered and a score was assigned]. Based on this information, a respiratory physician assigned one of 6 diagnoses at this visit on the basis of the likelihood of asthma as follows: asthma is extremely likely or definite (95%–100% likelihood); asthma is very likely (72.5 to < 95%); asthma is probable (50 to < 72.5%); asthma is possible (27.5 to < 50%); asthma is unlikely but cannot be excluded (5 to 27.5%); and asthma is very unlikely (0--<5%). Those with 5-95% likelihood were included in the study. Visit 2 occurred 1–4 days after Visit 1 and within 2 hrs of the time of Screening. Adverse events, medications, and withholding times were reviewed, and spirometry measured to confirm values on the screening day. This was followed by a brief physical examination. Exercise was performed with vital signs being measured before and after exercise. At Visit 3, the procedures were the same as Visit 2 and occurred within 1–4 days. At Visit 4, adverse events and medications were reviewed, withholding times were checked, and spirometry was performed to confirm FEV_1 was within 15% of Visit 1. The challenge agent was either mannitol or methacholine, and the choice was randomly determined. The time of the test was documented for each challenge. Vital signs were measured in the sitting position before and after the challenge test. Cough and pulse oximetry were recorded during mannitol challenges. Full spirometry was measured before and at 15 minutes after completion of the mannitol challenge with FEV_1 only being performed after each dose. Visit 5 was a repeat of the procedures of Visit 4 with the reciprocal challenge being administered (either mannitol or methacholine. A respiratory physician then assigned one of the diagnoses of likelihood of asthma evaluated at the Screening Visit. The NAEPII asthma severity grading score was also re-evaluated at Visit 5 but not necessarily by the same physician. <u>Index test</u> The mannitol test was carried out as per the standard laboratory protocol for this challenge test using a commercially available mannitol test kit. FEV_1 was measured 60 seconds after each mannitol dose (0, 5, 10, 20, 40, 80, 160, 160, 160 mg). The subjects were asked to exhale completely before taking a controlled deep inspiration from the device and to hold their breath for 5 seconds then exhale through their mouth before removal of the nose clip. Sixty seconds after inhalation of the 0 mg capsule, FEV_1 was measured in duplicate. The highest of these values was taken as the baseline FEV_1 and was used to calculate the target FEV_1 value that indicated a 15% fall in response to the mannitol challenge. The procedure outlined above for the 0 mg capsule was repeated for each dose step until a 15% fall in FEV_1 was achieved (or a 10% fall between consecutive doses) or the cumulative dose of 635 mg had been administered. Cut-off: PD15 FEV_1 <635 mg or >10% between consecutive doses (pre-specified) <u>Reference standard</u>

Reference	**Anderson 2009 (Anderson et al., 2009)**				
	A respiratory physician was to make the Clinician diagnosis at the final visit (Visit 5) with access to the data on the exercise challenges, history, examination, skin tests, and FEV_1 reversibility but not the mannitol and methacholine challenge test results. Time between measurement of index test and reference standard: Unclear				
2×2 table		Reference standard +	Reference standard −	Total	Prevalence= 64%
	Index test +	134	34	168	
	Index test −	106	101	207	
	Total	240	135	375	
Statistical measures	Sensitivity: 0.56 (95%CI 0.49-0.62) Specificity: 0.75 (95%CI 0.67-0.82) PPV: 79% NPV: 48%				
Source of funding	Funded by Pharmaxis Ltd Who were involved in the design and statistical analysis of the study				
Limitations	Risk of bias: Downgraded by one increment due concerns arising from the method of participant recruitment (method not reported) Indirectness: None				
Comments	Sensitivity and specificity calculated from 2x2 data reported in paper				

Reference	**Porpodis 2017 (Porpodis et al., 2017)**
Study type	Prospective cross-sectional study
Study methodology	Data source: Conducted in the Outpatient Clinic for Asthma, Pulmonary Department, within the Aristotle University of Thessaloniki Recruitment: Subjects were recruited in the study when they visited the Asthma Clinic either for a formal examination of asthma diagnosis or after the referral of another specialist for work-up of respiratory symptoms
Number of patients	n = 88
Patient characteristics (per protocol)	Age, mean (SD): 38.56 (16.73) years Gender (male to female ratio): 41:47 Ethnicity: Not reported Setting: Secondary care

<table>
<tr><td>Reference</td><td colspan="5">Porpodis 2017 (Porpodis et al., 2017)</td></tr>
<tr><td></td><td colspan="5">Country: Greece

Smoking status: Mixed (15% smokers)

ICS use: Treatment naïve

Inclusion criteria: Asthma related symptoms in the previous month but without previous diagnosis of asthma and without initiation of treatment

Exclusion criteria: Any other known cardiopulmonary or systematic disease</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>
The mannitol test was conducted using a standardized test kit that contained pre-filled mannitol capsules and a handheld powder device, where the patient inhaled escalating doses of powdered mannitol until either a drop of 15% of the FEV_1 baseline was achieved (PD15), or a more than 10% drop of FEV_1 between two consecutive measurements was observed. The maximum cumulative dose of mannitol was 635 mg.

Cut-off: PD15 FEV_1 <635 mg or >10% between consecutive doses (pre-specified)

<u>Reference standard</u>
According to GINA guidelines, the clinician diagnosis of asthma was established by the combination of at least a ≥12% (and at least 200 mL) increase in baseline FEV_1 after albuterol, along with new symptoms of coughing, wheezing, or shortness of breath over the past month, and no previous diagnosis of asthma

Time between measurement of index test and reference standard: Unclear</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= 76.1%</td></tr>
<tr><td></td><td>Index test +</td><td>43</td><td>1</td><td>44</td></tr>
<tr><td></td><td>Index test −</td><td>24</td><td>20</td><td>44</td></tr>
<tr><td></td><td>Total</td><td>67</td><td>21</td><td>88</td></tr>
<tr><td>Statistical measures</td><td colspan="5"><u>Index text</u>
Sensitivity: 0.64 (95%CI 0.52-0.76
Specificity: 0.95 (95%CI 0.76-1.00)
PPV: 98%
NPV: 45%</td></tr>
</table>

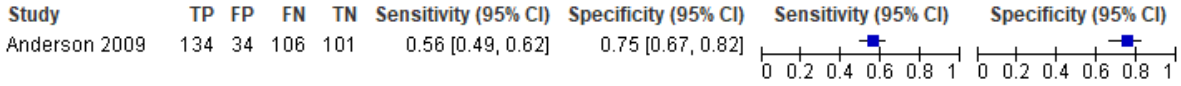
Reference	**Porpodis 2017 (Porpodis et al., 2017)**
Source of funding	None reported
Limitations	Risk of bias: Downgraded by two increments due to unclear method of patient selection (method not reported) and unclear interpretation of the index test and reference standard (unclear if clinician diagnosing asthma was blinded to mannitol challenge result) Indirectness: None
Comments	Sensitivity and specificity calculated from 2x2 data reported in paper

Appendix E – Forest plots

E.1 Coupled sensitivity and specificity forest plots

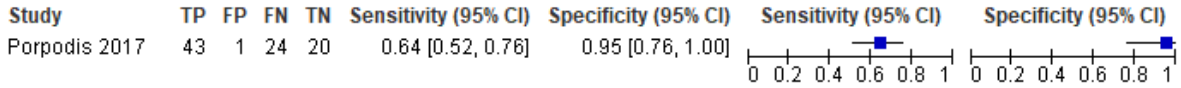
Non-smoking adolescents/adults

Figure 2: Mannitol (PD15 or 10% between consecutive doses) vs clinician diagnosis with exercise challenge, history, examination, skin test and bronchodilator reversibility data in non-smoking adolescents/adults



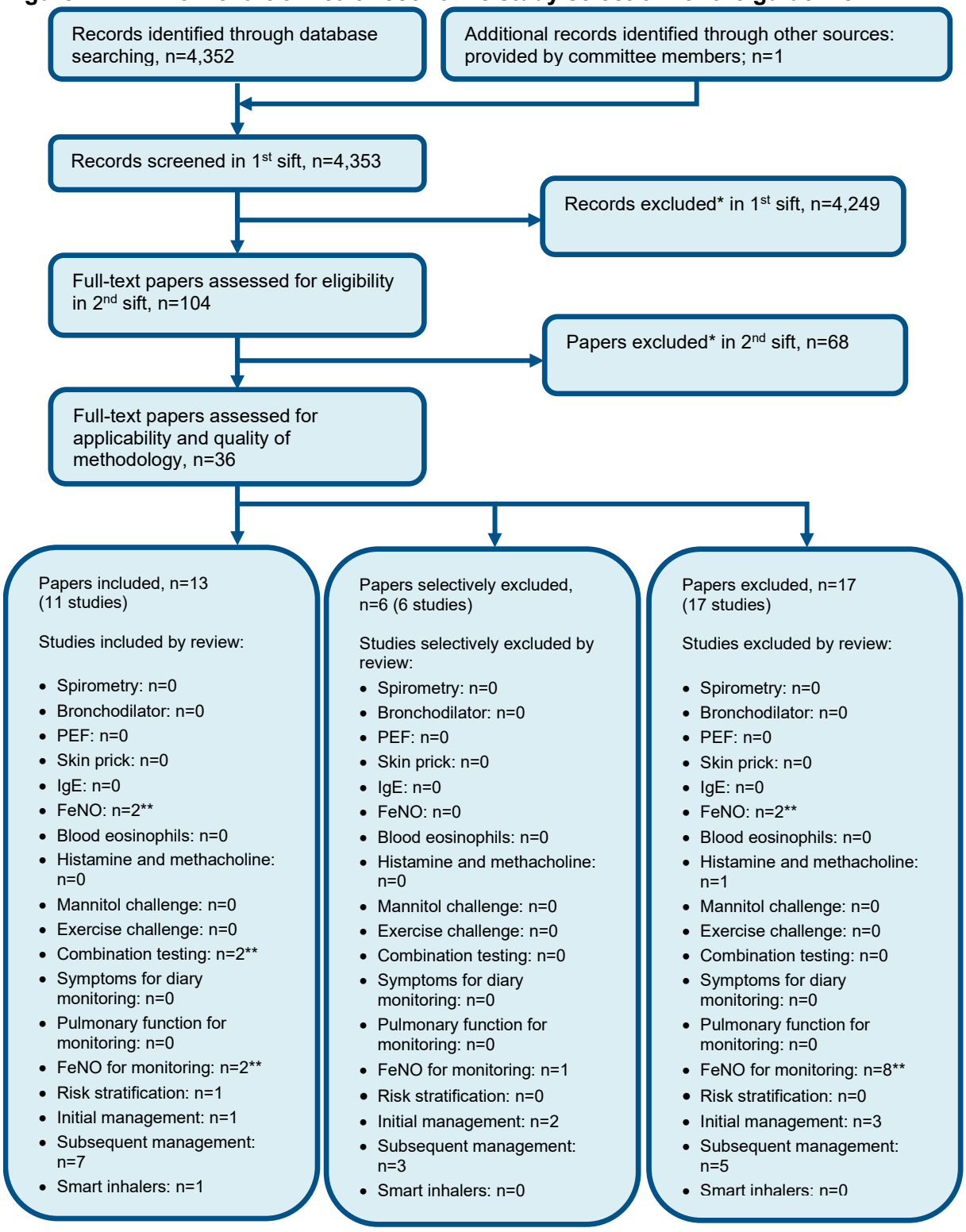
Adolescents/adults with mixed smoking status

Figure 3: Mannitol (PD15 or 10% between consecutive doses) vs clinician diagnosis with bronchodilator reversibility and symptom monitoring over one-month in adolescents/adults with mixed smoking status



Appendix F – Economic evidence study selection

Figure 4: 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

H.1 Clinical studies

Table 8: Studies excluded from the clinical review

Study	Code [Reason]
Backer, Vibeke; Sverrild, Asger; Porsbjerg, Celeste (2014) FENO and AHR mannitol in patients referred to an out-of-hospital asthma clinic: a real-life study. The Journal of asthma : official journal of the Association for the Care of Asthma 51(4): 411-6	- Reference standard not relevant to this review protocol *Reference standard was an objective test (FeNO) without clinician diagnosis*
Barben, Juerg, Kuehni, Claudia E, Strippoli, Marie-Pierre F et al. (2011) Mannitol dry powder challenge in comparison with exercise testing in children. Pediatric pulmonology 46(9): 842-8	- Population not relevant to this review protocol *>10% of population receiving ICS and no appropriate washout period included*
de Menezes, M.B., Ferraz, E., Brannan, J.D. et al. (2018) The efficacy and safety of mannitol challenge in a workplace setting for assessing asthma prevalence. Journal of Asthma 55(12): 1278-1285	- Study aiming to diagnose a condition other than asthma *Occupational asthma is outside scope of this guideline*
Georas, Steve, Ransom, Nicole, Hillman, Sara et al. (2019) The leaky lung test: a pilot study using inhaled mannitol to measure airway barrier function in asthma. The Journal of asthma : official journal of the Association for the Care of Asthma 56(12): 1257-1265	- Population not relevant to this review protocol *Study contains people already diagnosed with asthma*
Kernen, Philipp, Steveling-Klein, Esther H, Saccilotto, Ramon T et al. (2019) The sensitivity and specificity of the mannitol bronchial challenge test to identify asthma in different populations: a systematic review. Swiss medical weekly 149: w20100	- Systematic review used as source of primary studies
Knag Pedersen, Signe, Ustrup, Amalie S, Baarnes, Camilla B et al. (2020) Usefulness of mannitol challenge testing for diagnosing asthma in everyday clinical practice. The Journal of asthma : official journal of the Association for the Care of Asthma 57(6): 663-669	- Reference standard not relevant to this review protocol *Clinician diagnosis included bronchial challenge with mannitol*
Porsbjerg, C, Rasmussen, L, Thomsen, S F et al. (2007) Response to mannitol in	- Population not relevant to this review protocol

Study	Code [Reason]
asymptomatic subjects with airway hyper-responsiveness to methacholine. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 37(1): 22-8	*Study included participants not presenting with respiratory symptoms*
White, Elisha C, de Klerk, Nicholas, Hantos, Zoltan et al. (2017) Mannitol challenge testing for asthma in a community cohort of young adults. Respirology (Carlton, Vic.) 22(4): 678-683	- Population not relevant to this review protocol *Study included participants already diagnosed with asthma*

H.2 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.