Key questions used to develop the guideline

This guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search.

Key question	*See guideline section*
DIAGNOSIS	
1. In children (under 5 and 5-12 years of age), what are the key symptoms or symptom combinations for the diagnosis of asthma? ▪ difficulty breathing ▪ wheeze ▪ chest tightness and/or pain ▪ cough ▪ breathlessness ▪ personal or family history of atopic illness ▪ night time respiratory symptoms.	3.1, Table 1
2. In children (under 5 and 5-12 years of age), what are the key signs for refuting a diagnosis of asthma? ▪ chest deformity ▪ use of accessory muscles ▪ finger clubbing ▪ pneumonia in first month of life ▪ persisting wet cough ▪ excessive vomiting ▪ severe upper respiratory tract infection ▪ birth or perinatal lung problem ▪ focal signs in chest ▪ abnormal cry ▪ dysphagia ▪ failure to thrive.	3.1.1, Tables 2 and 3
3. In children (under 5 and 5-12 years of age), what are the most effective objective tests for diagnosing reversible airway disease including airway disease that will respond to bronchodilators? ▪ peak expiratory flow variability (amplitude % mean) ▪ bronchodilator response (using PEF, FEV_1 and other lung function tests).	3.1.5-3.1.7, 3.2.1
4. In children (under 5 and 5-12 years of age), what are the most effective objective tests for diagnosing airway disease that will respond to inhaled corticosteroids? ▪ exhaled nitric oxide ▪ induced sputum eosinophil count ▪ airway responsiveness to methacholine, exercise, and indirect challenges such as mannitol and AMP ▪ lung function tests (PEF, FEV_1; home based, lab based).	3.1.5, 3.2.2
5. In children (under 5 and 5-12 years of age), what is the place of a trial of treatment with oral/inhaled/injectable/parenteral corticosteroids and what is the best marker (clinical, physiological or pathological) for assessing its efficacy?	3.1.3, 3.1.5
6. In children (under 5 and 5-12 years of age) with asthma, what is the best method for monitoring their asthma control? ▪ symptom scores ▪ lung function tests (eg spirometry, impulse oscillometry, airway	3.6.1, 3.6.3, Table 8

	resistance) ▪ bronchial reactivity/airway challenge (eg methacholine, histamine, adenosine, cold air, etc) ▪ exhaled nitric oxide ▪ sputum eosinophilia ▪ endobronchial biopsy ▪ exhaled breath condensate ▪ urinary metabolites (LT4, ECP) ▪ combinations of the above.	
7.	In adults (>12 years), what are the most effective objective tests for diagnosing reversible airway disease including airway disease that will respond to bronchodilators? ▪ peak expiratory flow variability (amplitude % mean) ▪ bronchodilator response (using PEF, FEV_1 and other lung function tests).	3.4.1, 3.5
8.	In adults (>12 years), what are the most effective objective tests for diagnosing airway disease that will respond to inhaled corticosteroids? ▪ exhaled nitric oxide ▪ induced sputum eosinophil count ▪ airway responsiveness to methacholine, exercise, and indirect challenges such as mannitol and AMP ▪ lung function tests (PEF, FEV_1; home based, lab based).	3.5, 3.5.1-3.5.4
9.	In adults (>12 years) with asthma, what is the best method for monitoring their condition? ▪ symptom scores ▪ lung function tests ▪ exhaled nitric oxide ▪ sputum eosinophilia ▪ endobronchial biopsy	3.6.2, 3.6.4, Table 8

PATIENT EDUCATION AND SELF MANAGEMENT

10.	In the elderly (eg over 70)/infants (eg under 5)/ethnic minorities/primary care patients with asthma, does self-management education compared to usual care/no self-management education reduce admissions/unscheduled appointments/A&E attendances/acute attacks, or improve asthma-related quality of life/asthma control/lung function (PF or FEV_1)/enablement/self-efficacy?	4.1-4.3
11.	In patients with asthma, does self-management education, compared to usual care/no self-management education, reduce admissions/unscheduled appointments/A&E attendances/acute attacks, or improve asthma-related quality of life/asthma control/lung function (PF or FEV_1)/enablement/self-efficacy?	4.1-4.3
12.	In any whole/unselected population with asthma, does self-management education delivered within normal clinical practice, compared to usual care with no self-management education, reduce admission /unscheduled appointments/A&E attendances/acute attacks, or improve asthma-related quality of life/asthma control/lung function (PF or FEV_1)/enablement/self-efficacy in the whole population or random sample of the population?	4.1-4.3

NON-PHARMACOLOGICAL MANAGEMENT

13.	Is there any evidence that for patients with asthma avoidance of contact with animals reduces disease severity? Include cats, dogs, horses, house dust mites, rodents.	5.2.1
14.	Is there any evidence that immunisation affects the prevalence of asthma? Include BCG, whooping cough, and measles vaccination.	5.1.11
15.	What evidence is there that complementary therapies can reduce asthma	5.2.11-5.2.19

	severity? Include acupuncture, homeopathy, hypnosis, herbal medicines, breathing control/physical therapies/hyperventilation, yoga, cognitive behavioural therapy.	
16.	What is the evidence that avoidance or reduction of exposure to environmental pollutants in the home/in the workplace/in the outdoor environment reduces asthma severity?	5.2.4
17.	Does change of environment affect the prevalence of asthma? Include changes in elevation; switch between rural and urban environments; and housing conditions – particularly ventilation and dampness, speleotherapy.	5.1.9, 5.1.10
18.	What evidence is there that maternal smoking has an effect on asthma in children?	5.1.10, 5.2.3
19.	What evidence is there that exposure of children to cigarette smoke affects their susceptibility to asthma?	5.1.10
20.	What evidence is there that smoking influences either the incidence or severity of asthma in children or adults?	5.1.10, 5.2.3
21.	What evidence is there that smoking cessation affects asthma severity?	5.2.3
22.	Does dietary modification affect the prevalence of asthma? Particularly antioxidants, selenium, and lipids.	5.1.7
23.	Does breast feeding affect the prevalence of asthma (both ante and post-natal)?	5.1.4
24.	In patients with asthma what is the evidence that weight management/ control of obesity can affect asthma severity?	5.2.8
PHARMACOLOGICAL MANAGEMENT		
25.	Are inhaled short acting ß2 agonists best given as required or on a regular basis in adults and in children above or below 5 years of age?	6.1
26.	In infants and young children are the following drugs of value as bronchodilators? ▪ inhaled short-acting ß2 agonists ▪ ipratropium bromide ▪ oral ß2 agonist tablets or syrup ▪ theophyllines. Having identified which work, which is the most effective?	6.1, 6.1.1
27.	Which of the following drugs prevent exercise-induced asthma in adults and in children above or below 5 years of age? ▪ inhaled steroids ▪ short-acting ß2 agonists ▪ long-acting ß2 agonists ▪ theophyllines ▪ oral ß2 agonists ▪ anticholinergics ▪ leukotriene receptor antagonists ▪ cromones. Having identified which work, which is the most effective?	6.7.2
28.	Which criteria should be used to indicate the need for the introduction of anti-inflammatory treatment in adults and in children above or below 5 years of age? ▪ relief inhaler needed more than once daily, once weekly, three times a week ▪ symptoms eg nocturnal asthma ▪ exacerbations.	6.2.2

29.	In adults and in children above or below 5 years of age taking inhaled short-acting ß2 agonists alone and not adequately controlled are the following interventions of value in terms of: a. improving pulmonary function b. decreasing symptoms c. decreasing exacerbations ▪ inhaled steroids ▪ long-acting ß2 agonists ▪ theophyllines ▪ leukotriene receptor antagonists ▪ cromones. Having identified which work, which is the most effective?	6.2.5
30.	In adults and in children above or below 5 years of age taking inhaled steroids and not adequately controlled are the following interventions of value in terms of: a. improving pulmonary function b. decreasing symptoms c. decreasing exacerbations ▪ increasing the dose of inhaled steroids ▪ long-acting ß2 agonists ▪ short-acting ß2 agonists ▪ theophyllines ▪ oral ß2 agonists ▪ short-acting anticholinergics ▪ leukotriene receptor antagonists ▪ cromones ▪ long-acting anticholinergics (tiotropium). Having identified which work, which is the most effective?	6.3.2
31.	Having examined above at what dose of inhaled steroid should alternative strategies be considered?	6.3.2
32.	Which treatments can reduce the dose of oral steroids in adults and in children above or below 5 years of age? ▪ inhaled steroids ▪ long-acting ß2 agonists ▪ short-acting ß2 agonists ▪ theophyllines ▪ oral ß2 agonists ▪ anticholinergics ▪ leukotriene receptor antagonists ▪ cromones ▪ immunosuppressive agents.	6.5.4
33.	In patients on oral steroids which drugs/intervention are needed/effective in preventing or treating the following? ▪ osteoporosis ▪ growth in children ▪ hypertension.	6.5.1
34.	Are inhaled steroids best given once daily, twice weekly, four times daily in adults and in children above or below 5 years of age?	6.2.2
35.	Is there any evidence that high dose step down is more effective than step up in adults and in children above or below 5 years of age?	6.2.2
36.	Are there differences between inhaled steroid preparations in their ability to control asthma in adults and in children above or below 5 years of age?	6.2.1
37.	Is there any evidence that the combination of inhaled steroids and a long-acting ß2 agonist is best given as a combination inhaler (Seretide or	6.3.4

	Symbicort) or as separate inhalers?	
38.	At the onset of an exacerbation is there any value in increasing (doubling or more) the dose of inhaled steroids?	6.7.1
39.	Does treatment of rhinitis with intranasal steroids improve asthma control?	6.7.3
40.	Does treatment of allergic bronchopulmonary aspergillosis improve asthma control?	6.7.4
41.	Is there any evidence that treatment of aspirin intolerant asthma is different?	6.7.5
42.	How should treatment be stepped down?	6.6
43.	Does doubling or more the dose of both inhaled corticosteroids and long-acting ß2 agonists simultaneously improve lung function symptoms and/or reduce exacerbations with an acceptable safety profile?	6.3.4
44.	In patients on reducing doses of oral steroids or on high dose inhaled steroids: a. What clinical eg growth, bruising or biochemical test should be used to assess adrenocortical function? b. In what circumstances should these tests be performed?	6.2.3, 6.5.1
45.	Is there any difference in response to treatment in people with asthma who smoke?	6.2.4
46.	Is there any evidence for differences in the treatment of pre-menstrual asthma?	
47.	Is there any evidence that treatment of asthma should be different in the elderly?	
48.	Is there any benefit from using a combination inhaler of inhaled steroid and long acting ß2 agonist instead of a rescue short acting ß2 agonist in patients at either step 2 or step 3 of the asthma guidelines?	6.3.4
49.	Is there evidence for a beneficial effect of anti IgE monoclonal antibody Omalizumab in patients on high dose inhaled steroids and long acting ß2 agonists who are not controlled or in patients on oral corticosteroids?	6.5.4
50.	Is there evidence that any medication can be used to prevent asthma developing or becoming established in childhood in the first place (primary prevention)?	
51.	Is there any evidence that inhaled steroids, cromones, or anti-histamines are beneficial in treating episodic viral induced wheezing in childhood (exclude bronchiolitis)?	
52.	Is there any evidence for benefit or harm from using steroid alert cards (not limited to asthma)?	6.2.3
53.	What evidence is there that the treatment of gastro-oesophageal reflux disease affects the onset of/severity of asthma?	6.7.6
54.	What evidence is there that allergen immunotherapy is effective in reducing the severity of asthma?	6.5.5
55.	Is bronchial thermoplasty an effective treatment for asthma?	6.5.6

INHALER DEVICES

56.	Which inhaler device is the most effective for the delivery of ß2 agonists in children with asthma (under 5 and 5-12 yrs)? (Include only studies that compare device A versus device B in delivery of product C – not product A versus product B.) ▪ Consider cost effectiveness	7.2.2
57.	Which inhaler device is the most effective for the delivery of corticosteroids in children (< 5 and 5-12 yrs)? (Include only studies that compare device A versus device B in delivery of product C – not product A versus product B). ▪ Consider cost effectiveness	7.3

58.	How is inhaler technique best assessed? a. How frequently should this assessment be performed? b. How is inhaler technique best taught to optimise device effectiveness?	7.1
59.	What role does patient preference play in deciding which inhaler to prescribe? a. Does this improve compliance? b. Does this improve effectiveness of treatment?	7.4
60.	In adults (over 12 years), which inhaler devices are the most effective for the delivery of: ▪ ß2 agonists? ▪ corticosteroids? (Include only studies that compare device A versus device B in delivery of product C – not product A versus product B.)	7.2, 7.3
61.	Is the cleaning and reuse of placebo inhalers (used in teaching and assessing inhaler technique), compared with single-patient use placebo inhalers, associated with a significant risk of infection?	7.5
62.	Are there any case reports of cross-infection associated with reuse or sharing of an inhaler device (consider also COPD, other respiratory disease)?	7.5

MANAGEMENT OF ACUTE ASTHMA

a. in 'uncontrolled asthma', 'acute severe asthma', 'life threatening asthma' and 'near fatal asthma (NFA)', and
b. acute asthma exacerbations in pre-school children (infants 0-1 year, children 1-5 years); school children, adults:-

63.	What is the role of clinical signs (respiratory rate, heart rate, blood pressure, wheezing, silent chest, cyanosis) in severity assessment??	8.2.1, 8.2.3, 8.7.1, 8.10, Tables 12 and 14
64.	Is there any evidence that blood pressure and/or systolic paradox are of value in assessing severity?	8.2.3, Table 13
65.	What is the role of objective measurements (peak flow, FEV_1, oxygen saturation, arterial blood gases) in severity assessment?	8.2.3, 8.7.2-8.7.5, Table 13
66.	Is there any evidence that FEV_1 is better than PEF?	8.2.3, Table 13
67.	Which set of normal values should be used for PEF and FEV_1?	8.2.3
68.	Can acute deterioration be prevented by appropriate treatment 48 hours earlier or the use of 'At Risk' registers?	8.2.4
69.	In immediate treatment, what is the evidence for:- oxygen, steroids in children under 5 years of age (dose, inhaled, oral or IV), ß2 agonists – salbutamol, terbutaline, adrenaline (MDI + spacer, nebulised, intermittent or continuous, should nebuliser be driven by oxygen or air pre hospital and in hospital, intravenous, long-acting,) ipratropium, aminophylline, magnesium sulphate, heliox, leucotriene receptor antagonists?	8.3.1-8.3.7, 8.3.9, 8.8.1-8.8.6, 8.11.1-8.11.3
70.	In continuation treatment who needs IV fluid replacement? duration of nebulised therapy? duration of oral prednisolone? optimisation of inhaled drug delivery, dose and device?	8.3.10, 8.9
71.	Are antibiotics necessary?	8.3.8, 8.9.4
72.	Are further investigations, including CXR, differential wbc, potassium, ECG, necessary?	8.2.3, Table 13

73.	Monitoring treatment. What is the evidence for the value of PEF, $Sa0_2$ FEV_1?	8.4, 8.11.4
74.	Deterioration in the home — action by patient including when to call for GP, when to self-admit?	8.2.1, 8.2.2
75.	How should acute asthma be managed in primary care? Consider: immediate action; subsequent management; criteria for admission; action by GP?	8.2.3-8.2.6, 8.8.2
76.	How should acute asthma be managed in ambulance? Consider: immediate action, subsequent management; action by paramedics?	8.8.2
77.	How should acute asthma be managed in A & E? Consider: immediate action; subsequent management; criteria for admission?	8.2.6
78.	How should acute asthma be managed when patients are admitted to hospital? Consider: immediate action; subsequent management?	8.3, 8.8, 8.9, 8.11
79.	What are the indications for intensive or high dependency care?	8.3.12
80.	What are the indications for IPPV?	8.3.13
81.	Is there any evidence relating to the use of NIPPV and severe asthma?	8.3.13
82.	What are the criteria for discharge from hospital, discharge procedures?	8.6.1, 8.9.5
83.	In follow up following recovery, what is the role of the asthma liaison nurse, role of home PEF charts, role of symptom diary?	8.6.3
84.	In near fatal Asthma (NFA) or Severe Life Threatening Asthma (SLTA), what is the role of follow-up management (consider 'At Risk' registers, lessons from asthma death studies)?	8.1, 8.6.3, 8.9.5,
85.	In acute asthma, what is the role of patient: education and interventions by asthma nurses and pharmacists; self management plans?	8.6.2
86.	In implementation and monitoring of the guideline, what is the evidence for efficacy and techniques of implementation, eg, asthma management proformas?	8.5

DIFFICULT ASTHMA

87.	What is the definition of difficult asthma in adults (>12 years) and children (≤12 years)?	9.1
88.	What is the prevalence of difficult asthma (using above definition)?	9.1
89.	Is there evidence that a particular assessment/management model (investigations, service delivery etc) is best in the evaluation of difficult asthma (specifically identifying severe refractory asthma)?	9.1
90.	Is there evidence that a particular assessment/management model delivers better outcomes in difficult asthma?	9.1
91.	Is there evidence for a role for psychosocial dysfunction in difficult asthma? Is there evidence that this can be treated with improved outcome?	9.2.2
92.	Is there evidence for a role for dysfunctional breathing/hyperventilation in difficult asthma? Is there evidence that this can be treated with improved outcome?	9.2.3
93.	Is there evidence for a role for poor adherence in difficult asthma? Is there evidence that poor adherence in difficult asthma can be treated?	9.2.1
94.	Is there evidence for a role for ongoing allergen exposure in difficult asthma? Is there evidence that this can be identified and managed with improved outcome?	9.2.4
95.	Is there evidence that non-invasive measurement of airways inflammation improve outcomes in difficult asthma (above definition)?	9.2.5

ASTHMA IN ADOLESCENTS

96.	In adolescents presenting with new symptoms suggestive of asthma, are there any symptoms that differ from children or adults with asthma that should be considered during diagnosis? What alternative diagnoses should be considered?	10.2, 10.3
97.	Are there any non-pharmacological therapies that are more or less effective in controlling asthma symptoms in adolescents compared to treatment of children and adults?	10.8
98.	Are there any pharmacological treatments that are more or less effective in controlling asthma symptoms in adolescents compared to treatment of children and adults?	10.9
99.	Are there any devices that are more (or less) appropriate for the treatment of asthma in adolescents?	10.10
100.	What is the best healthcare setting to encourage attendance amongst adolescents with asthma?	10.11.1, 10.11.2
101.	What is the best setting to deliver care to adolescents with asthma?	10.11.1, 10.11.2
102.	What is the best approach to facilitate transition to adult services?	10.11.3
103.	What is the most effective format for delivering patient education to adolescents with asthma?	10.12.1
104.	What is the most effective approach to promoting self-management in adolescents with asthma?	10.12.1
105.	What are the most effective ways for promoting concordance and compliance in adolescents with asthma?	10.12.2

ASTHMA IN PREGNANCY

106.	Does asthma behave differently in patients when pregnant?	11.1
107.	Is the management of asthma in pregnancy different from that of the routine management in non-pregnant individuals?	11.2
108.	Are the drugs used to treat asthma harmful to the mother or fetus? Should any of them be used with caution, not at all or used as normal? Consider: ▪ sodium cromoglicate/nedocromil ▪ leukotriene receptor antagonists ▪ β_2 agonists ▪ corticosteroids.	11.3
109.	Should asthma be monitored more carefully/differently in pregnancy when compared with other adult situations?	11.1
110.	What precautions/arrangements should be made before and during labour and delivery for women with asthma?	11.4
111.	In the patient with severe asthma which deteriorates in pregnancy what is the best way to manage and monitor the condition?	11.2
112.	Does asthma have any adverse consequences for the outcome of pregnancy?	11.1
113.	Are the drugs used to treat maternal asthma harmful to the infant during breastfeeding? Consider: ▪ sodium cromoglicate/nedocromil ▪ leukotriene receptor antagonists ▪ β_2 agonists ▪ corticosteroids.	11.5
114.	Is magnesium sulfate effective and safe in the treatment of acute asthma in pregnancy?	11.3

OCCUPATIONAL ASTHMA	
115. What is the evidence for obtaining objective confirmation of the diagnosis of occupational asthma? Consider sensitivity and specificity of diagnosis based on history alone or surveillance questionnaires alone versus objective information.	12.3
116. What is the evidence for relocation away from exposure? Consider prognosis away from exposure related to the period of symptomatic exposure.	12.4
117. What is the evidence for delayed assessment of long term disability following relocation away from exposure? Consider the time period of recovery after the causative agent has been removed.	12.4
118. Is there a relationship between the interval between the first work related symptom and removal from exposure to the offending agent and the ultimate prognosis?	12.4
119. What is the time course of recovery of FEV_1 symptoms and bronchial reactivity following cessation of exposure to the causative agent?	12.4
ORGANISATION AND DELIVERY OF CARE	
120. In patients with asthma does the introduction of care pathways in a) acute and b) community settings compared to usual care reduce admissions/ unscheduled care/A&E attendances/acute attacks, or improve asthma-related quality of life/asthma control/lung function (PF or FEV_1)?	13.1
121. In patients with asthma do clinician education interventions compared to usual care reduce admissions/unscheduled care/A&E attendances/acute attacks, or improve asthma-related quality of life/asthma control/lung function (PF or FEV_1)?.	13.2
122. In patients with asthma do a) primary care asthma clinics and b) secondary care specialist/'difficult' asthma clinics compared to usual care reduce admissions/unscheduled care/A&E attendances/acute attacks, or improve asthma-related quality of life/asthma control/lung function (PF or FEV_1)?	13.3.3, 13.3.3
123. In patients with asthma do telehealth interventions compared to usual care reduce admissions/unscheduled care/A&E attendances/acute attacks, or improve asthma-related quality of life/asthma control/lung function (PF or FEV_1)?	13.4
124. In children with asthma do school-based interventions compared to usual care reduce admissions/unscheduled care/A&E attendances/acute attacks, or improve asthma-related quality of life/asthma control/lung function (PF or FEV_1)?	13.5
125. In patients with asthma from ethnic minority groups do ethnicity/culture-based interventions compared to usual care reduce admissions/unscheduled care/A&E attendances/acute attacks, or improve asthma-related quality of life/asthma control/lung function (PF or FEV_1)?	13.6
126. In patients with asthma do lay-led interventions compared to usual care reduce admissions/unscheduled care/A&E attendances/acute attacks, or improve asthma-related quality of life/asthma control/lung function (PF or FEV_1)?	13.7
127. In patients with asthma do pharmacy/pharmacist interventions compared to usual care reduce admissions/unscheduled care/A&E attendances/acute attacks, or improve asthma-related quality of life/asthma control/lung function (PF or FEV_1)?	13.8