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 risk stratified care for people with asthma

BTS/NICE/SIGN collaborative guideline <number>

Evidence reviews underpinning recommendation 1.15.1 in the BTS/NICE/SIGN guideline

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Draft for Consultation

Developed by NICE

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Contents

1 Risk stratified care for people with asthma

1.1 Review question

What is the clinical and cost-effectiveness of risk stratification in delivering asthma care in adults, children and young people?

1.1.1 Introduction

The rationale behind stratifying people with asthma by their level of risk of acute attacks is that this may help tailor the treatment, follow-up, and investigations they are offered. There are several known and unknown risk factors for asthma attacks. The evidence behind using these at population-level to identify individuals most at risk is important to consider as it has implications for people with asthma, healthcare services, and commissioners.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	People with a diagnosis of asthma. All ages, stratified into the following 2 different groups: • Infants <5 years, children and young people (5-16 years old) • Adults (17 years old and above)
Intervention	Asthma care of varying intensities stratified by risk of poor outcomes (any used by the studies) Examples could include variation of intensity of care which may or may not include difference in frequency of respiratory consultant reviews, differing frequency of medication reviews, frequency of medication pick up rate.
Comparisons	Risk stratified asthma care vs usual care
Outcomes	Critical outcomes: • Mortality (dichotomous outcome at ≥6 months; time-to-event) • Quality of life (QOL; validated scale, including asthma specific questionnaires AQLQ; health-related) (continuous outcome at ≥3 months) • Asthma control (assessed by validated questionnaire: ACQ, ACT, St George's respiratory; continuous outcome at ≥3 months) • Severe asthma exacerbations (event-rate and dichotomous) usually defined by the requirement of a course of oral steroids • Moderate asthma exacerbations (event rate and dichotomous)- as defined by the study • Steroid use • Unscheduled healthcare utilisation (hospital admissions, emergency room/A&E attendance and out of hours doctor/clinic visit; dichotomous outcome at ≥6 months)
Study design	• RCTs

- Systematic reviews of RCTs
- Prospective/retrospective longitudinal cohort studies
- Before and after 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 Effectiveness evidence

1.1.4.1 Included studies

Five studies (6 papers) were included in this review (Bender, et al., 2020, Charrois, et al., 2004, Charrois, et al., 2006, Kattan, et al., 2006, Noble, et al., 2006, Smith, et al., 2012). Two studies were in adults and one study was in children and young people, while two further studies were in a mixed population of children, young people and adults.

There were three RCTs, one cluster-RCT and one retrospective before-and-after study included in the review.

1.1.4.2 Excluded studies

See Appendix J

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

Study	Intervention	Population	Outcomes	Comments
Bender 2020(Bender et al., 2020)	2 digital communication technology tool (DCT) intervention groups: 1) Text/phone 2) Email Communications explained that the patient was being contacted as a result of their request for beta$_2$-agonist (BA) medication refill and asked this question: "Other than when you're getting ready to exercise, during the past 4 weeks have you used your quick reliever inhaler 2 or more times a week?" (from the Asthma control test). If the patient answered "No," they were thanked, the encounter closed	Adults ≥18 years with a diagnosis of intermittent or persistent asthma, with no history of COPD. N=1933 Mean age (SD): 48.8 (16.2) years 58.% never smokers; 32.1% former smokers; 8.7% current smokers Mean (SD) ICS dispensed during the 12 months prior date of first beta$_2$-agonist overuse: 5.9 (6.2)	Asthma exacerbations (oral/injectable corticosteroid bursts) Steroid use (short-acting corticosteroid inhalers dispensed during follow-up). Unscheduled healthcare utilisation (asthma-related after-hours/urgent care visits, emergency visits and hospitalisations).	Strata: Adults Breathwell study: RCT where asthma nurses screen patients for poor symptom control when beta$_2$-agonist refill requests came within 60 days of previous fill or in the absence of a controller medication fill within 4 months. Study included people meeting beta$_2$-agonist overfill criteria who were

Study	Intervention	Population	Outcomes	Comments
	and a notation added to their electronic health record. If they answered "Yes," a request for patient contact was forwarded to the asthma care management (ACM) group through the EHR. Key information automatically drawn from the EHR chart regarding exacerbations and previous ACM contacts was provided to the ACM. The ACM then contacted the patient for a shared decision-making discussion about possible increasing symptoms, therapy adjustment, or a clinic appointment. In the case where the patient did not respond, the encounter was either closed or forwarded to the ACM based on asthma events in the prior year relative to the BA request date. Usual care: includes a group of ACMs nurses who contact patients requesting a refill of their asthma reliever, usually a beta2-agonist (BA) if: (1) the request occurs more frequently than every 60 days; or (2) the patient attempts to fill a BA without filling an asthma controller medication (typically an ICS) in the last 4 months. Following the standard clinical protocol, the ACM reviews the patient's EHR to determine if further outreach is needed.	USA	At minimum 6 months	randomised in 1/3 interventions. The program was delivered utilising information from the (Kaiser Permanente Colorado) EHR (electronic health record) database. Results reported for the combined DCT interventions as one group vs usual care
Charrois 2006; Charrois 2004 (study design and methods) (Charrois et al., 2004, Charrois et al., 2006)	Community-management intervention (including pharmacists, respiratory therapist and family physicians) involving: Patient education, assessment and optimisation of drug therapy and respiratory therapist and physician	High-risk asthma patients 17-54 years (defined as having an ER visit or hospitalisation in the previous year, or using >2 canisters of short-acting beta-agonist in the previous 6 months), identified	Asthma control (ACQ) Asthma exacerbations (course of oral steroids) Steroid use (inhaled steroid use)	Strata: Adults Better Respiratory Education and Asthma Treatment in Hinton and Edson (BREATH) study.

Study	Intervention	Population	Outcomes	Comments
	referral as needed (if therapy adjustments are suggested as determined by the drug therapy assessment); physician referral form faxed to family physician to identify patients as high risk and list recommendations to the physician regarding current asthma therapy, the education being provided to the patient and the patient's written action plan Usual care: written asthma information (asthma education booklet: 'Take a holiday from your asthma symptoms' by Astra Zeneca), referral to respiratory therapist within 1 week of randomisation for measurement of FEV1 and usual pharmacy and physician care. Follow-up telephone call by pharmacist (at 2 weeks, 1, 2, 4 and 6 months for intervention, 2 and 6 months for usual care) for educational reinforcement, assessments and reassessment of written action plan in conjunction with respiratory therapist for the intervention group/ assessment of outcomes and minimal education, addressing concerns about usual care provision for the usual care group.	through community pharmacies. N=70 Mean age (SD): 37.2 (10.5) Canada	Unscheduled healthcare utilisation (ED visits or hospital admission) At 6 months	RCT For dichotomous outcomes, OR available from multivariable analysis was extracted as scores were adjusted for any baseline outcome levels.
Kattan 2006(Kattan et al., 2006)	Physician feedback group: every 2 months each child's caretaker underwent a computer assisted telephone interview (CATI) to determine asthma symptoms, use of controller and reliver medications and health service use. Information from the CATI call was used to generate a	Children aged 5-11 years with moderate to severe asthma receiving healthcare in hospital and community-based clinics and private practices. N=937 Mean age: 7.7 years	Unscheduled healthcare utilisation (hospitalisations, emergency-department visits) unscheduled clinic visits) At 1 year (during which time the	Strata: children and young people RCT Inner-City Asthma Study (ICAS) feedback intervention RCT.

Study	Intervention	Population	Outcomes	Comments
	feedback letter (1-sentence recommendation for treatment) emailed to the child's primary care provider. Possible recommendation actions were based on the NAEPP guidelines: to step-up, step-down or make no changes in medications. Control group: Letters were not sent to the providers of children in the control group; the information from the CATI calls was used to determine what recommendation would have been generated had the child been in the intervention group.	USA	intervention was being delivered)	
Noble 2006(Noble et al., 2006)	At-risk asthma register: patients identified as being at risk of adverse asthma events were given an electronic tag on the health practice computer system stating 'high risk asthma patient, prioritise appointment'. This computer prompt appeared whenever patients' electronic records were called-up, and needed actively clearing from the screen. A similar 'asthma alert' marker was also placed in these patients' written records. All practice staff were given training on the relevance of the alert tags and action to be taken when an at-risk patient contacted the surgery about their asthma or potentially related problems Reception and dispensary staff were instructed to give patients the choice of either speaking to the doctor or practice respiratory nurse on the telephone immediately, or of booking an appointment the same	At-risk asthma patients; defined as severe asthma (BTS step 4 or 5 treatment and/or a history of hospital admissions for asthma) and documented evidence of poor asthma control on the basis of reports of either symptoms, peak flow records, high use of reliever medication and/or frequent exacerbations. They also had one or more of the following: poor adherence, psychiatric problems, other psychosocial difficulties such as unemployment. N=26 Median age (range): 36 (5-61) UK	Severe asthma exacerbations (courses of oral steroids prescribed) Unscheduled healthcare utilisation (hospital admissions, A&E attendances, and contacts with the out-of-hours service Extracted using written and electronic patient records from the 12-month period prior and 12 months after the introduction of the register.	Strata: Adults (n=6 (23% less than 18 years in each group) Retrospective before and after study comparing patients added to the register to a matched control group. In addition to the patients added to the at risk register, an age, sex and BTS treatment step matched control group (N=26) of asthma patients who did not meet criteria for inclusion on the at-risk register was included. For the purpose of the present review, only before-and-after data for the intervention group have been used.

Study	Intervention	Population	Outcomes	Comments
	day. Where appropriate, patients would be asked to come directly to the surgery or offered a home visit. Doctors and nurses were advised on the importance of engaging with this group of patients to form a strong therapeutic alliance. The need to address psychosocial and other factors that were adversely affecting their asthma management was stressed. Comparison: 12 months before the register vs 12 months after.			
Smith 2012(Smith et al., 2012)	Risk stratified care (457 participants, 14 practices). Addition of electronic alerts visible to all staff to the computerised records of identified at-risk patients to flag their at-risk status at each contact. A one-hour practice-based staff training session to support effective use of the alerts, which advised staff on how to engage with, and improve the routine and emergency management of at-risk asthma patients using case examples to highlight potential actions for receptionists, clinicians and dispensary teams. Standard care (454 participants; 15 practices). Control practices continued usual care, comprising at least annual practice-based asthma reviews in nurse-led clinics, plus follow-up in secondary care outpatient clinics and emergency primary and secondary care for	At-risk asthma patients aged 5+ years. At-risk defined as severe asthma and psychological problems. Severe asthma indicated by: in the last 2 years medications approximating to BTS/SIGN Step 4-5 treatment; or asthma admission in the last 5 years or A&E visit in last year or Brittle asthma N=911 Mean age (SD): 45.5 (21.9) years UK	Severe asthma exacerbations (oral prednisolone course for asthma exacerbation) Unscheduled healthcare utilisation (hospitalisation, A&E attendance, out of hours contact) At 1 year	Strata: Adults (11.8% were aged <16 years) Cluster-RCT. Survey sent to GP practices. Clinicians at practices identified at-risk patients. Dichotomous & adjusted OR results available (extracted both but using adjusted OR for present analysis) All participants were ‘at-risk’. Actions following alerts to risk status of patients not specified; simply that training was provided for staff on how to respond to alerts, that is ‘case examples used to highlight potential actions for receptionists, clinicians and

Study	Intervention	Population	Outcomes	Comments
	some patients ‘as required’.			dispensary teams.’

1 See appendix D for full evidence tables

1.1.6 Summary of the effectiveness evidence

Table 3: Clinical evidence summary for digital communication technology tool (text/phone/email) versus usual care in adults

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with usual care	Risk difference with Digital communication technology tool (text/phone/email)	Comments
Severe asthma exacerbations (no. of oral/injectable corticosteroid bursts per patient, rate adjusted per person year, lower is better, 6 months)	1933 (1 RCT)	⊕⊕◯◯ Low[a,b]	-	The mean no. of oral/injectable corticosteroid bursts per patient (at 6 months) was **0.23**	MD **0.01 higher** (0.05 lower to 0.07 higher) **No clinically important difference**	MID=0.39 (calculated as baseline SD of control group/2)
Steroid use (short-acting corticosteroid inhalers dispensed, rate adjusted per person year, 6 months)	1933 (1 RCT)	⊕⊕◯◯ Low[a,c]	-	The mean short-acting corticosteroid inhalers dispensed was **6.43**	MD **0.27 higher** (0.37 lower to 0.91 higher) **No clinically important difference**	MID=3.45 (calculated as baseline SD of control group/2)
Unscheduled healthcare utilisation (patients with any asthma related after-hour visits/ED visits and/or hospitalisations, events, at 6 months)	1933 (1 RCT)	⊕◯◯◯ Very low[a,d]	**RR 0.82** (0.58 to 1.15)	75 per 1,000	**13 fewer per 1,000** (31 fewer to 11 more) **No clinically important difference**	MID (clinical importance) = 30 per 1000 (imprecision)= 0.8-1.25

a. Downgraded by 2 increments because the evidence was at high risk of bias (lack of blinding; handling of missing data in analysis unclear)
b. MID calculated using baseline SD of intervention and control groups/2= 0.37
c. MID calculated using baseline SD of intervention and control groups/2= 3.15
d. Downgraded for imprecision by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Standard MIDs for dichotomous outcomes were 0.8 & 1.25; for continuous outcomes: baseline intervention and control group SD/2 where available or SD/2 of the control group at the time-point reported if baseline scores are not available.

Table 4: Clinical evidence summary for community management intervention versus usual care in adults

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with usual care	Risk difference with Community management	Comments
Asthma control (ACQ, range 0-6, change score, lower is better, 6 months)	70 (1 RCT)	⊕◯◯◯ Very low[a,b]	-	The mean ACQ (at 6 months) was **0.33**	MD **0.1 higher** (0.34 lower to 0.54 higher) **No clinically important difference**	MID=0.5 (established MID)
Severe, asthma exacerbation (no. of courses of oral steroids, lower is better, 6 months)	70 (1 RCT)	⊕◯◯◯ Very low[a,b]	**RR 0.42** (0.14 to 1.24)	265 per 1,000	**154 fewer per 1,000** (228 fewer to 64 more) **Clinically important benefit favouring risk stratified care**	MID (clinical importance) = 30 per 1000 (imprecision)= 0.8-1.25
Steroid use (participants with inhaled steroid use, lower is better, 6 months)	70 (1 RCT)	⊕⊕⊕◯◯ Low[a]	**RR 1.01** (0.82 to 1.25)	824 per 1,000	**8 more per 1,000** (148 fewer to 206 more) **No clinically important difference**	MID (clinical importance) = 100 per 1000 (imprecision)= 0.8-1.25
Unscheduled healthcare utilisation (ED visits or hospital admissions, lower is better, 6 months)	70 (1 RCT)	⊕◯◯◯ Very low[a,b]	**RR 0.94** (0.34 to 2.65)	176 per 1,000	**11 fewer per 1,000** (116 fewer to 291 more) **No clinically important difference**	MID (clinical importance) = 30 per 1000 (imprecision)= 0.8-1.25

a. Downgraded by 2 increments because the evidence was at high risk of bias (baseline differences across arms; poor compliance to some aspects of intervention by pharmacists; differential rate of incomplete outcome data across groups; unclear analysis)b. Downgraded for imprecision by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Published MID for the ACQ=0.5; MIDs for dichotomous outcomes: 0.8& 1.25

Table 5: Clinical evidence summary for physician feedback intervention versus control in children and young people

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with control	Risk difference with Physician feedback	Comments
Unscheduled healthcare utilisation (number of hospitalisations, final values lower is better, 1 year)	929 (1 RCT)	⊕⊕⊕⊕ High[a]	-	The mean number of hospitalisations (at 1 year) was **0.24**	MD **0.02 lower** (0.1 lower to 0.06 higher) **No clinically important difference**	MID=0.33 (calculated as follow-up of control group/2)
Unscheduled healthcare utilisation (number of ED visits, final values, lower is better, 1 year)	929 (1 RCT)	⊕⊕⊕⊕ High[a]	-	The mean number of ED visits (at 1 year) was **1.14**	MD **0.27 lower** (0.48 lower to 0.06 lower) **No clinically important difference**	MID=0.86 (calculated as follow-up SD of control group/2)
Unscheduled healthcare utilisation (number of unscheduled clinic visits, final values, lower is better, 1 year)	929 (1 RCT)	⊕⊕⊕⊕ High[a]	-	The mean number of unscheduled clinic visits (at 1 year) was **1.31**	MD **0.17 lower** (0.39 lower to 0.05 higher) **No clinically important difference**	MID=0.86 (calculated as follow-up SD of control group/2)

a.Standard MIDs for continuous outcomes where baseline SDs are not given are follow-up SD of the control group /2; MIDs= 0.33 for number of hospitalisations, 0.86 for number of ED visits, for number of unscheduled clinic visits 0.86

Table 6: Clinical evidence summary for at-risk register (12 months before vs 12 months after) in mixed population of adults, children and young people (5-61 years)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with no at-risk register (before)	Risk difference with At-risk register (after)	Comments
Severe asthma exacerbations (courses of oral steroids) (dichotomous baseline vs 12 months)	26 (1 before and after study)	⊕◯◯◯ Very low[a,b]	**RR 0.50** (0.24 to 1.03)	538 per 1,000	**269 fewer per 1,000** (409 fewer to 16 more) **Clinically important benefit favouring risk stratified care**	MID (clinical importance) = 30 per 1000 (imprecision)= 0.8-1.25
Unscheduled healthcare utilisation (hospital admissions) (dichotomous baseline vs 12 months)	26 (1 before and after study)	⊕◯◯◯ Very low[a,b]	**Peto OR 0.12** (0.01 to 1.26)	115 per 1,000	**120 fewer per 1,000** (250 fewer to 20 more)[c] **Clinically important benefit favouring risk stratified care**	MID (clinical importance) = 30 per 1000 (imprecision)= 0.8-1.25

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with no at-risk register (before)	Risk difference with At-risk register (after)	Comments
Unscheduled healthcare utilisation (A&E attendance) (dichotomous baseline vs 12 months)	26 (1 before and after study)	⊕◯◯◯ Very low[a,b]	**Peto OR 0.14** (0.00 to 6.82)	38 per 1,000	**40 fewer per 1,000** (140 fewer to 60 more)[d] **Clinically important benefit favouring risk stratified care**	MID (clinical importance) = 30 per 1000 (imprecision)= 0.8-1.25
Unscheduled healthcare utilisation (out-of-hours contacts) (dichotomous baseline vs 12 months)	26 (1 before and after study)	⊕◯◯◯ Very low[a,b]	**RR 0.33** (0.07 to 1.50)	231 per 1,000	**155 fewer per 1,000** (215 fewer to 115 more) **Clinically important benefit favouring risk stratified care**	MID (clinical importance) = 100 per 1000 (imprecision)= 0.8-1.25

a. Downgraded by 2 increments because the evidence was at serious risk of bias (possible confounding, lack of details in the analysis and unclear how missing data handled)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs; for dichotomous outcomes MIDs= 0.8&1.25

c. Calculated based on the Risk Difference: -0.12 (-0.02, 0,25) due to zero events in one arm

d. Calculated based on the Risk Difference: -0.04 (-0.14, 0.06) due to zero events in one arm

Table 7: Clinical evidence summary for risk stratification vs standard care in mixed population of adults, children and young people (only 11.8% under 16 years)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
				Risk with standard care	Risk difference with Risk stratified care	Comments
Severe asthma exacerbation (oral prednisolone course for asthma exacerbation, lower is better, 1 year)	911 (1 RCT)	⊕⊕⊕◯ Moderate[a]	**RR 1.15** (1.01 to 1.31)	469 per 1,000	**70 more per 1,000** (5 more to 145 more) **Clinically important benefit favouring standard care**	MID (clinical importance) = 30 per 1000 (imprecision)= 0.8-1.25
Unscheduled healthcare utilisation (hospitalisation for asthma exacerbation, lower is better, 1 year)	911 (1 RCT)	⊕⊕⊕◯ Moderate[a]	**RR 0.51** (0.28 to 0.95)	64 per 1,000	**31 fewer per 1,000** (46 fewer to 3 fewer) **Clinically important benefit for risk stratified care**	MID (clinical importance) = 30 per 1000 (imprecision)= 0.8-1.25
Unscheduled healthcare utilisation (A&E attendance for asthma exacerbation, lower is better, 1 year)	911 (1 RCT)	⊕⊕⊕◯ Moderate[a]	**RR 0.78** (0.49 to 1.24)	81 per 1,000	**18 fewer per 1,000** (42 fewer to 20 more) **No clinical difference**	MID (clinical importance) = 30 per 1000 (imprecision)= 0.8-1.25
Unscheduled healthcare utilisation (out-of-hours contact for asthma exacerbation, lower is better, 1 year)	911 (1 RCT)	⊕⊕◯◯ Low[a]	**RR 0.81** (0.49 to 1.33)	70 per 1,000	**13 fewer per 1,000** (36 fewer to 23 more) **No clinical difference**	MID (clinical importance) = 100 per 1000 (imprecision)= 0.8-1.25

a. Downgraded for imprecision by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs; for dichotomous outcomes MIDs= 0.8&1.25

See appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

One health economic study with the relevant comparison was included in this review.(Smith et al., 2012) This is summarised in the health economic evidence profile below **Table 1** and the health economic evidence table in 96Appendix H.

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 G

1.1.8 Summary of included economic evidence

Table 1: Health economic evidence profile: Standard care versus electronic alerts and staff training to identify and effectively treat high risk asthma patients.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental outcomes	Uncertainty
Smith 2012 (Smith et al., 2012) (United Kingdom)	Partially applicable [a]	Potentially serious limitations [b]	• Cost consequence analysis (outcomes – asthma exacerbations) • Population: At risk asthma patients – identified using British asthma guideline criteria • Comparators: 1. Standard care 2. Electronic alerts and staff training to identify and effectively treat high risk asthma patients versus • Time horizon:1 year	2-1 (unadjusted)[c]: saves £89 2-1 (adjusted): saves £138 (95% CI: -£1,248 to £911)	Moderate-severe asthma exacerbations 2−1: 34 fewer (7.1% fewer) Hospitalisations for asthma exacerbation: 2−1: 14 fewer (3.1% fewer)	To take account of clustering, a two-stage bootstrap procedure was used to estimate the adjusted incremental cost between groups. Incremental cost: Saves £177.81 (95% CI: -£1,606 to £1,171)

Abbreviations: CI= Confidence interval; GP= General practitioner

(a) QALYs not reported.

(b) Unit costs in the study are presented in 2008 prices and therefore even after they have been adjusted for inflation, these costs may not be reflective of current healthcare costs. Methodology of how costs were calculated is only provided intervention and primary care costs. Primary care costs were estimated from a sub-sample of the population with no rationale given.

(c) 2008 UK pounds. Cost components incorporated: Intervention costs, Set-up costs, Training costs, Follow-up costs, Primary care costs, Secondary care costs, Out of hours costs, Medication costs.

1.1.11 Evidence statements

Economic evidence

- One cost-consequence analysis found that electronic alerts and staff training was more effective (fewer moderate to severe exacerbations and hospitalisations for exacerbations) and less costly (saved £138 per person) to identify and effectively treat high risk asthma patients. This analysis was assessed as partially applicable with potentially serious limitations.

1.2 The committee's discussion and interpretation of the evidence

1.2.1. The outcomes that matter most

The committee considered the outcomes of mortality, quality of life, asthma control, severe asthma exacerbations (usually defined by the requirement of a course of oral steroids), moderate asthma exacerbations (as defined by the study), steroid use and unscheduled healthcare utilisation (hospital admissions/emergency attendance/out of hours clinic/doctor attendance). For the purposes of decision making, all outcomes were considered equally important and were rated as critical.

In the evidence identified, asthma exacerbations were defined slightly differently between studies; definitions included oral/injectable corticosteroid use, courses of oral steroids and oral prednisolone course for asthma exacerbation. These were all considered severe asthma exacerbations, rather than moderate asthma exacerbations.

No evidence was identified for mortality and quality of life.

1.2.2 The quality of the evidence

There were five RCTs included in the clinical evidence. The quality of the evidence varied across comparisons ranging from very low to high for different outcomes. There was great variability in the risk stratification interventions used in the studies and thus evidence was not pooled and outcomes for each study were analysed and presented individually.

Evidence from two RCTs was available for adults. The quality of the evidence for all outcomes was very low or low. There were concerns over risk of bias in the studies (due to lack of blinding, baseline differences across arms, poor compliance to interventions, missing data and unclear analyses). The quality of the evidence was further downgraded to very low quality for outcomes of asthma control (ACQ), severe asthma exacerbations and unscheduled healthcare utilisation due to imprecision in the effect estimates with confidence intervals being wide and crossing agreed MIDs.

Evidence for children and young people was available from one RCT. The quality of the evidence was high across outcomes.

Evidence from two studies was available for a mixed population of adults, children and young people, although the majority were adults. The quality of the evidence for the outcomes of one study was very low largely due to its observational design (before and after study) Quality was additionally downgraded for risk of bias (possible confounding, unclear analysis and unclear how missing data handled) and imprecision related to the width of the confidence intervals around the effect estimates. Evidence relevant to a mixed age population from a second study was of moderate quality for the majority of outcomes including severe asthma exacerbations and unscheduled healthcare utilisation (hospitalisation and A&E attendance); it was downgraded once for imprecision due to the confidence interval crossing one agreed MID threshold. Evidence for the outcome of unscheduled healthcare utilisation (out-of-hours contacts for asthma) was downgraded twice

for very serious imprecision with the confidence interval being wider and crossing two MIDs, resulting in a low-quality rating.

1.2.3 Benefits and harms

When assessing the clinically significant impact of the evidence included, the GC agreed an approach for use of MIDs. For continuous outcomes, published MIDs were applied for asthma control (ACQ). In the absence of published MIDs, default calculations for MID were applied based on baseline SD (where available) for the rest of the continuous outcomes. For dichotomous outcomes a threshold of 100/1000 people for changes in absolute effects was applied when assessing the following outcomes: unscheduled healthcare utilisation (unscheduled/out of hours visits to doctors), and participants with inhaled steroid use. A threshold of 30/1000 people for changes in absolute effects was applied when assessing the following outcomes: severe asthma exacerbations; emergency department visits; and hospital admissions. This is because the committee considered small differences between the intervention and comparison groups likely to be important.

The wide variation in the nature of the risk stratification interventions across the included studies meant that the studies were not pooled and, instead, reported separately.

Evidence from one RCT showed there was no clinically important benefit of stratified care delivered via a digital communication technology tool compared to usual care in adults in terms of: severe asthma exacerbations, steroid use or unscheduled healthcare utilisation.

Evidence from one RCT showed a clinically important benefit of stratified care delivered via a community management intervention compared to usual care in adults in terms of severe asthma exacerbations (the number of courses of oral steroids received/dispensed) during a 6-month follow-up. No clinical difference was noted in terms of asthma control, steroid use and unscheduled healthcare utilisation (ED visits or hospital admissions).

Evidence from one RCT in children and young people showed there was no clinically important benefit of stratified care through a physician feedback intervention compared to the control intervention in terms of unscheduled healthcare utilisation (number of hospitalisations, number of ED visits and number of unscheduled clinic visits) during a one-year follow-up. However, the committee noted that the number of ED visits in the control group was very low (1.14), and the reduction achieved by the intervention (mean difference 0.27 lower) could indicate a clinical benefit despite not technically meeting the MID threshold. It was also noted that the quality of the evidence was high with no concerns lowering confidence in the results and that it came from a RCT with a large number of participants (N=929).

Evidence from one observational before-and-after study in a mixed population primarily of adults but including some children and young people, showed there was a clinical benefit of establishing an at-risk asthma register to deliver care for asthma in terms of severe asthma exacerbations (courses of oral steroids) and unscheduled healthcare utilisation (hospital admissions, A&E attendance and out-of-hours contacts) during a 12-month follow-up. The committee noted that this evidence came from a small sample (N=26) and the quality of the evidence was very low due to the observational study design and imprecision based on the confidence interval around the effect estimate. However, they noted that the effect sizes were very large, with the register resulting in 269 fewer people experiencing a severe asthma exacerbation (defined as the need for a course of oral steroids) per 1,000 treated, 120 fewer hospital admissions and 155 fewer people needing an out-of-hours contact. This indicated absolute effects that were well above the threshold set for clinical importance increasing the committee's confidence in the potential benefit of risk stratified care.

Evidence from one cluster-RCT taking place at different practices, in a mixed population of adults, children and young people (11.8% of total population was under 16 years), showed a clinically important benefit favouring standard care for severe asthma exacerbations (defined as oral prednisolone course). However, the committee noted there were also fewer people needing unscheduled healthcare utilisation (hospitalisation for asthma exacerbations, A&E attendance and out-of-hours contacts for asthma exacerbations) in the risk stratified care group compared to standard care. The absolute effect reached the MID for hospitalisation for asthma exacerbations, favouring risk-stratified care. The Committee reasoned that was likely to be the result of more people being given an oral prednisolone course for their asthma exacerbation, rather than a true harm of the intervention and overall considered there to be a benefit of risk stratified care. This was a reasonably large study (n=911) and performed in the UK. The committee agreed that this RCT better matched the review protocol in terms of the intervention and comparison examined compared to other included studies and considered it to be the key study for decision making. It was however noted that following the risk stratification of patients, the actions taken by the health-care professionals were not specified but it appeared risk stratified care had the potential to enable health professionals to better identify those who need a course of steroids which in turn can successfully decrease the number of hospitalisations and need for health-care utilisation.

1.2.4 Cost effectiveness and resource use

There was one health economic study included in the literature review. This was a within trial cost-consequence analysis based on an UK study included in the clinical review. The trial compared electronic alerts visible to NHS staff and flagging at-risk patients to standard care. The analysis was partially applicable, as it did not measure quality adjusted life years as an outcome, however it was based on a UK trial and took an NHS perspective. It was assessed as having potentially serious limitations due to the costs being outdated and its unclear methodology. The study found that the intervention was cheaper than current practice due to fewer people being hospitalised for asthma exacerbations though the results were not statistically significant.

The committee discussed the clinical and economic evidence on risk stratification. The clinical review highlighted benefits with the intervention particularly for moderate-to-severe exacerbations and hospital admissions although there was heterogeneity across the trials. Although the economic study showed that the intervention could be cost-saving, there was some uncertainty, which the committee agree could be solved only when the full cost-utility based on the large-trial ARRISSA-UK (ISRCTN95472706) is published.

Given the strength of the available evidence, the committee made a consider recommendation to stratify people based on their risk of poor outcomes. Some practices do not currently have an alert system in place, so the recommendation may change practice and require additional resources to set up the alert system and train staff. However, this is expected to provide healthcare professionals with more information regarding patients at risk of exacerbations. This, in turn, will facilitate tailored care and allow treatment adjustments, escalation or switch for people inadequately controlled under their existing treatment. As the economic evidence suggested, NHS savings and improve patients' outcomes could be expected.

1.2.5 Recommendations supported by this evidence review

This evidence review supports recommendation 1.15.1.

1.3 References

Bender BG, Wagner NM, Shoup JA, et al. (2020) Adults With Asthma Experience No Increase in Asthma-related Exacerbations When Digital Communication Technology Tools Are Employed to Offset Provider Workload: a Pragmatic Randomized Trial *Medical Care* 58 (4): 352-359.

Charrois T, Newman S, Sin D, et al. (2004) Improving asthma symptom control in rural communities: the design of the Better Respiratory Education and Asthma Treatment in Hinton and Edson study *Controlled Clinical Trials* 25 (5): 502-514.

Charrois TL, Newman SC, Senthilselvan A, et al. (2006) Improving Asthma Control in the Rural Setting: The BREATHE (Better Respiratory Education and Asthma Treatment in Hinton and Edson) Study *Canadian Pharmacists Journal / Revue des Pharmaciens du Canada* 139 (4): 44-50.

Kattan M, Crain EF, Steinbach S, et al. (2006) A randomized clinical trial of clinician feedback to improve quality of care for inner-city children with asthma *Pediatrics* 117 (6): e1095-e1103.

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

Noble MJ, Smith JR, Windley J (2006) A controlled retrospective pilot study of an 'at-risk asthma register' in primary care *Primary Care Respiratory Journal* 15 (2): 116-124.

Smith JR, Noble MJ, Musgrave S, et al. (2012) The at-risk registers in severe asthma (ARRISA) study: a cluster-randomised controlled trial examining effectiveness and costs in primary care *Thorax* 67 (12): 1052-1060.

Appendices

Appendix A – Review protocol

Review protocol for risk stratified care

ID	Field	Content
0.	PROSPERO registration number	CRD42023442404
1.	Review title	Risk stratified care for people with asthma.
2.	Review question	What is the clinical and cost-effectiveness of risk stratification in delivering asthma care in adults, children and young people?
3.	Objective	To address whether targeting care stratified by risk of future asthma attacks is a cost-effective approach to organising care.
4.	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 Key papers: Derivation of a prototype asthma attack risk scale centred on blood eosinophils and exhaled nitric oxide - PubMed (nih.gov) (look for papers not focussed on severe asthma) 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).
5.	Condition or domain being studied	Asthma
6.	Population	Inclusion: People with a diagnosis of asthma ages: • Infants <5 years old, children and young people 5-16 years • Adults ≥17 years old Stratification:

		People with asthma ages: • Adults vs children and young people Exclusion: none applicable
7.	Interventions	Asthma care of varying intensities stratified by risk of poor outcomes (any used by the studies)
8.	Comparator	Risk stratified asthma care vs usual care
9.	Types of study to be included	RCT/Systematic review of RCTs Prospective longitudinal cohort studies Retrospective longitudinal cohort studies will also be considered if available. Before and after studies
10.	Other exclusion criteria	Non-English language studies. Conference abstracts
11.	Context	Primary, secondary and community care settings
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: Mortality (dichotomous outcome at ≥6 months; time-to-event) Quality of life (QOL; validated scale, including asthma specific questionnaires AQLQ; health-related) (continuous outcome at ≥3 months) Asthma control (assessed by validated questionnaire: ACQ, ACT, St George's respiratory; continuous outcome at ≥3 months) Severe asthma exacerbations (event-rate and dichotomous) usually defined by the requirement of a course of steroids Moderate asthma exacerbations (event rate and dichotomous)- as defined by the study Steroid use

		Unscheduled healthcare utilisation (hospital admissions, emergency room/A&E attendance and out of hours doctor/clinic visit; dichotomous outcome at ≥6 months)
13.	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.
14.	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) • Non-randomised study, including cohort studies: Cochrane ROBINS-I
15.	Strategy for data synthesis	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.	
16.	Analysis of sub-groups	Subgroups to be investigated if heterogeneity is present • Type of risk stratification • Type of intervention • Primary vs secondary care	
17.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic prediction
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery

		☐	Risk prediction	
18.	Language	English		
19.	Country	England		
20.	Anticipated or actual start date			
21.	Anticipated completion date	31 July 2024		
22.	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	☐	☐
23.	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
24.	Review team members	From the National Guideline Centre: Bernard Higgins Sharon Swain Melina Vasileiou Toby Sands Alfredo Mariani Lisa Miles Lina Gulhane Stephen Deed Amy Crisp
25.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
26.	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.
27.	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
28.	Other registration details	N/A

29.	Reference/URL for published protocol		
30.	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.	
31.	Keywords	Asthma	
32.	Details of existing review of same topic by same authors	N/A	
33.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information	N/A	
35.	Details of final publication	www.nice.org.uk	

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Table 2: 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.

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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 3: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 29 Dec 2023	Risk Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 29 Dec 2023	Risk 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 29 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.	delivery of health care/
25.	*patient care/
26.	(deliver* adj3 (care or caring or heathcare or service* or opportunistic or treatment or intervention* or therap*)).ti,ab.
27.	((frequen* or regular* or irregular* or urgent or emergenc* or routine or reduc* or increas* or schedule* or unschedule*) adj3 (review* or consult* or refer* or hospital* or appointment* or visit* or intervention*)).ti,ab.
28.	or/24-27
29.	((frequen* or sever* or risk* or control* or uncontrol* or reduc* or increas* or future or predict*) adj3 (attack* or exacerbat* or "flare up*" or "flaring up")).ti,ab.
30.	((reliever or rescue or emergenc* or increas*) adj3 (medicine* or medication* or prescription* or drug* or dose* or dosage or dosing)).ti,ab.
31.	(("lung function" or "peak flow") adj3 (test* or exam* or assess* or review* or score* or scoring* or screen*)).ti,ab.
32.	*registries/
33.	risk assessment/
34.	*severity of illness index/
35.	or/29-34
36.	28 and 35
37.	(risk* adj3 (register* or registr* or stratif* or assess* or model* or algorithm* or score* or scoring* or screen* or strateg* or index* or indice* or scale*)).ti,ab.
38.	(stratif* adj3 (organis* or manag* or care or caring or healthcare or treatment* or approach*)).ti,ab.
39.	or/36-38
40.	23 and 39

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.	*health care delivery/
24.	*patient care/
25.	(deliver* adj3 (care or caring or heathcare or service* or opportunistic or treatment or intervention* or therap*)).ti,ab.
26.	((frequen* or regular* or irregular* or urgent or emergenc* or routine or reduc* or increas* or schedule* or unschedule*) adj3 (review* or consult* or refer* or hospital* or appointment* or visit* or intervention*)).ti,ab.
27.	or/23-26
28.	((frequen* or sever* or risk* or control* or uncontrol* or reduc* or increas* or future or predict*) adj3 (attack* or exacerbat* or "flare up*" or "flaring up")).ti,ab.
29.	((reliever or rescue or emergenc* or increas*) adj3 (medicine* or medication* or prescription* or drug* or dose* or dosage or dosing)).ti,ab.
30.	(("lung function" or "peak flow") adj3 (test* or exam* or assess* or review* or score* or scoring* or screen*)).ti,ab.
31.	*register/
32.	*risk assessment/
33.	*severity of illness index/
34.	or/28-33
35.	27 and 34
36.	(risk* adj3 (register* or registr* or stratif* or assess* or model* or algorithm* or score* or scoring* or screen* or strateg* or index* or indice* or scale*)).ti,ab.
37.	(stratif* adj3 (organis* or manag* or care or caring or healthcare or treatment* or approach*)).ti,ab.
38.	or/35-37
39.	22 and 38

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.	((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or Anzctr or ICTRP or ISRCTN* or IRCT* or eudract* or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trial-com or current-controlled-trial or UMIN* or NTR* or ReBec* or ChiCTR* or CRiS or CTRI* or RPCEC* or EU-CTR* or EUCTR* or DRKS* or LBCTR* or TCTR* or SLCTR or JAPIC* or JRCT or JMCTR* or CTIS):so or (ctgov or ictrp)):an
#7.	#5 not #6
#8.	("Trial registry record" or conference):pt
#9.	#7 not #8
#10.	MeSH descriptor: [Delivery of Health Care] explode all trees
#11.	MeSH descriptor: [Patient Care] this term only
#12.	(deliver* near/3 (care or caring or heathcare or service* or opportunistic or treatment or intervention* or therap*)):ti,ab
#13.	((frequen* or regular* or irregular* or urgent or emergenc* or routine or reduc* or increas* or schedule* or unschedule*) near/3 (review* or consult* or refer* or hospital* or appointment* or visit* or intervention*)):ti,ab
#14.	(or #10-#13)
#15.	(frequen* or sever* or risk* or control* or uncontrol* or reduc* or increas* or future or predict*) near/3 (attack* or exacerbat* or flare next up* or "flaring up"):ti,ab
#16.	((reliever or rescue or emergenc* or increas*) near/3 (medicine* or medication* or prescription* or drug* or dose* or dosage or dosing)):ti,ab
#17.	(("lung function" or "peak flow") near/3 (test* or exam* or assess* or review* or score* or scoring* or screen*)):ti,ab
#18.	MeSH descriptor: [Registries] this term only
#19.	MeSH descriptor: [Risk Assessment] explode all trees
#20.	MeSH descriptor: [Severity of Illness Index] explode all trees
#21.	(or #15-#20)
#22.	#14 and #21
#23.	(risk* near/3 (register* or registr* or stratif* or assess* or model* or algorithm* or score* or scoring* or screen* or strateg* or index* or indice* or scale*)):ti,ab
#24.	(stratif* near/3 (organis* or manag* or care or caring or healthcare or treatment* or approach*)):ti,ab
#25.	#22 or #23 or #24
#26.	#9 and #25

Epistemonikos search terms

1.	(title:(deliver* AND (care OR caring OR heathcare OR service* OR opportunistic OR treatment OR intervention* OR therap*)) OR abstract:(deliver* AND (care OR caring OR heathcare OR service* OR opportunistic OR treatment OR intervention* OR therap*))) OR (title:((frequen* OR regular* OR irregular* OR urgent OR emergenc* OR routine OR reduc* OR increas* OR schedule* OR unschedule*) AND (review* OR consult* OR refer* OR hospital* OR appointment* OR visit* OR intervention*)) OR abstract:((frequen* OR regular* OR irregular* OR urgent OR emergenc* OR routine OR reduc* OR increas* OR schedule* OR unschedule*) AND (review* OR consult* OR refer* OR hospital* OR appointment* OR visit* OR intervention*))) AND (title:((frequen* OR regular* OR irregular* OR urgent OR emergenc* OR routine OR reduc* OR increas* OR schedule* OR unschedule*) AND (review* OR consult* OR refer* OR hospital* OR appointment* OR visit* OR intervention*)) OR abstract:((frequen* OR regular* OR irregular* OR urgent OR emergenc* OR routine OR reduc* OR increas* OR schedule* OR unschedule*) AND (review* OR consult* OR refer* OR hospital* OR appointment* OR visit* OR intervention*))) OR (title:((reliever OR rescue OR emergenc* OR increas*) AND (medicine* OR medication* OR prescription* OR drug* OR dose* OR dosage OR dosing)) OR abstract:((reliever OR rescue OR emergenc* OR increas*) AND (medicine* OR medication* OR prescription* OR drug* OR dose*

	OR dosage OR dosing))) OR (title:(("lung function" OR "peak flow") AND (test* OR exam* OR assess* OR review* OR score* OR scoring* OR screen*)) OR abstract:(("lung function" OR "peak flow") AND (test* OR exam* OR assess* OR review* OR score* OR scoring* OR screen*))) 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 4: 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)	Inception – 31st March 2018	

Database	Dates searched	Search filters and limits applied
(Centre for Research and Dissemination – CRD)		
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

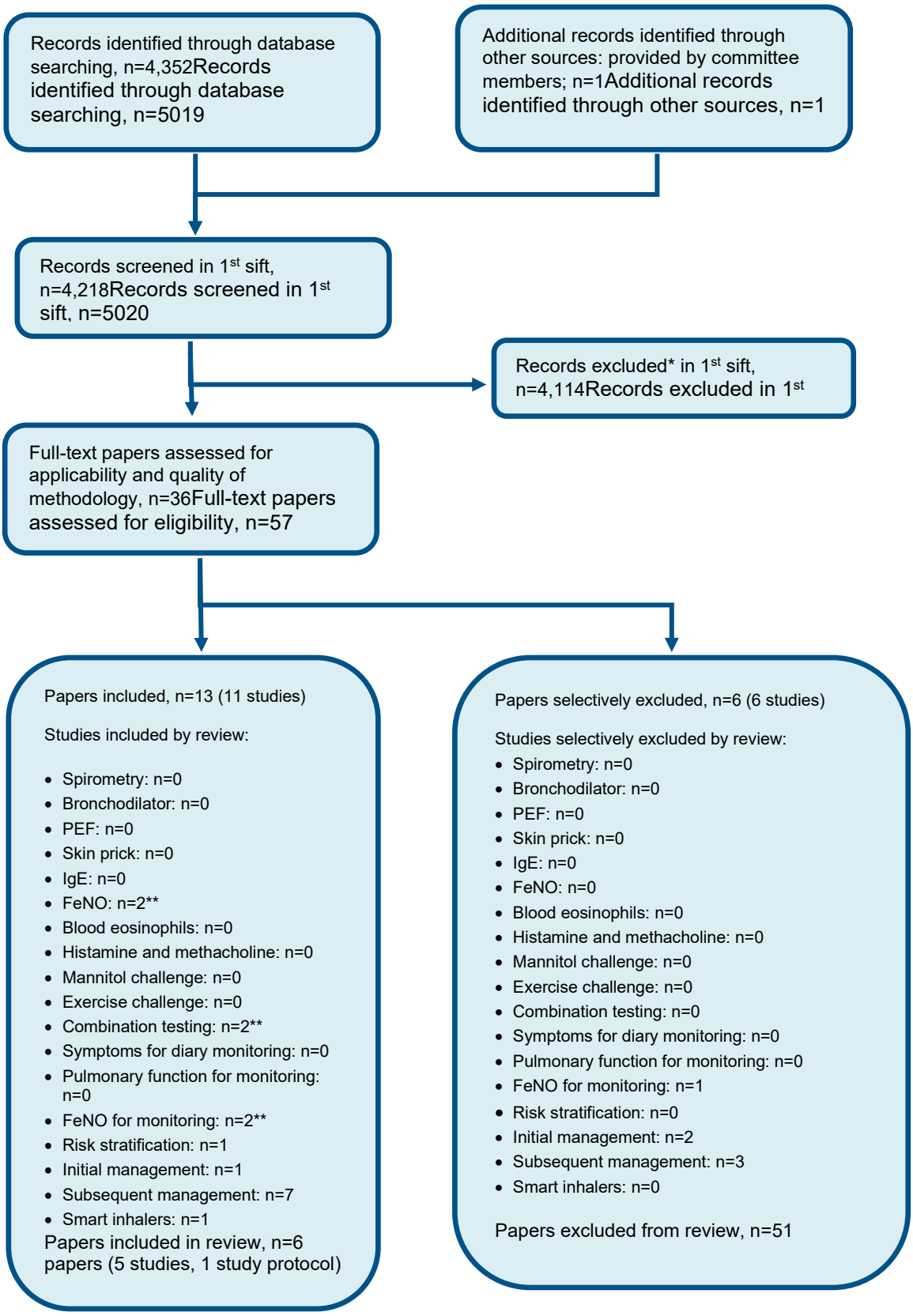
NHS EED and HTA (CRD) search terms

#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 – Effectiveness evidence study selection



Appendix D – Effectiveness evidence

Bender, 2020

Bibliographic Reference	Bender, BG; Wagner, NM; Shoup, JA; Goodrich, GK; Shetterly, SM; Cvietusa, PJ; Anderson, CB; Xu, S; Ritzwoller, DP; Tacinas, C; et, al.; Adults With Asthma Experience No Increase in Asthma-related Exacerbations When Digital Communication Technology Tools Are Employed to Offset Provider Workload: a Pragmatic Randomized Trial; Medical care; 2020; vol. 58 (no. 4); 352-359

Study details

Trial name / registration number	Breathwell study
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	This study was conducted within (Kaiser Permanente Colorado), an integrated health care organization serving ~600,000 members in the (Denver, Colorado Metropolitan Area) area. The intervention was delivered through a program utilizing information from the (Kaiser Permanente Colorado) EHR (electronic health record) database.
Study dates	Study enrolment began in February 2017 and continued for 12 months; study follow-up continued for a minimum of 6 months (for those who first met study enrolment criteria in February 2018) and up to 18 months (for those who met study criteria in February 2017)
Sources of funding	National Institute of Health, National Heart, Lung, and Blood Institute (grant number: R01HL084067-05)
Inclusion criteria	Adults 18 years and older who were current members of (Kaiser Permanente Colorado) and had a diagnosis of intermittent or persistent asthma at the time of randomization. Individuals whose most recent diagnosis was intermittent asthma had a further requirement that they had a diagnosis of persistent asthma at some point in the past year.
Exclusion criteria	Patients were excluded only if they had a diagnosis of chronic obstructive pulmonary disease or had previously documented that they did not want to be involved in research studies.

Recruitment / selection of participants	Current members of (Kaiser Permanente Colorado) and had a diagnosis of intermittent or persistent asthma at the time of randomization. All qualifying (Kaiser Permanente Colorado) adults with asthma who had not previously opted out of research were randomized to 1 of 3 groups: Text/Phone call intervention, Email intervention, or Usual Care (Fig. 1). Those who subsequently met beta2-agonist overfill (BAO) criteria received Text/Phone call intervention, Email intervention, or Usual Care consistent with their baseline randomization. Patients who did not have a BAO received no further study communication and were not included in the data analyses.
Intervention(s)	1) Text/phone call: participants were contacted by text if their phone was text-enabled. Where phones were not text-enabled, patients were contacted instead by an interactive voice response (IVR) phone call. The IVR system used speech recognition software able to conduct a simulated human conversation related to a patient's recent symptoms. The program utilized information in the EHR such as the name of the patient and the medication to tailor the conversation, asks questions, and gather responses. It distinguished cellular phones from landlines to determine whether the phone was text-enabled, thus allowing the system to determine when to send a text versus a phone call.1 2) Email: Patients in the Email group received an email. The Text, Phone call, and Email scripts contained similar content (see below) and were programmed for automated delivery. The Text/Phone call and Email communications explained that the patient was being contacted as a result of their request for BA medication refill and asked this question: "Other than when you're getting ready to exercise, during the past 4 weeks have you used your quick reliever inhaler 2 or more times a week?" (question from the Asthma control test). If the patient answered "No," they were thanked, the encounter closed and a notation added to the EHR. If they answered "Yes," a request for patient contact was forwarded to the asthma care management (ACM) group through the EHR. Key information automatically drawn from the EHR chart regarding exacerbations and previous ACM contacts was provided to the ACM. The ACM then contacted the patient for a shared decision-making discussion about possible increasing symptoms, therapy adjustment, or a clinic appointment. In the case where the patient did not respond, the encounter was either closed or forwarded to the ACM based on asthma events in the prior year relative to the BA request date. For example, if the patient had been contacted by an ACM within the previous 90 days, the event was closed regardless of asthma symptoms. If patients with a clinical diagnosis of persistent asthma had not received an ACM call within the

	previous 90 days but had evidence of a clinical asthma exacerbation in the past year, defined as an emergency room, urgent care visit, hospitalization stay, or oral corticosteroid bursts with an asthma diagnosis, and had not filled their ICS within the last 4 months, they were forwarded to the ACMs for review. If during the study interval a patient met BAO criteria more than once, they again receive the intervention. All standard clinical services, including telephone nursing and pharmacy consultation, clinic appointments, and access to educational information, were available to patients in both the intervention and Usual Care groups.
Population subgroups	not applicable
Comparator	Usual care: includes a group of ACMs nurses who contact patients requesting a refill of their asthma reliever, usually a beta2-agonist (BA) if: (1) the request occurs more frequently than every 60 days; or (2) the patient attempts to fill a BA without filling an asthma controller medication [typically an inhaled corticosteroid (ICS)] in the last 4 months. Following the standard clinical protocol, the ACM reviews the patient's EHR to determine if further outreach is needed.
Number of participants	1933
Duration of follow-up	Patients were followed from the time of the initial BAO refill (the 1 year intervention period was February 2017 to February 2018) until the end of the study (August 2018), disenrollment, or death. All patients had at least 6 months follow-up, whereas the maximum follow-up period was 18 months.
Additional comments	Poisson regression models were used to analyze count data (number of BAO refills, reliever canisters, controller canisters, and corticosteroid bursts with an asthma diagnosis) using the Poisson distribution and the log link function.18 In the Poisson regression models, log person years was included as an offset and overdispersion was accounted for due to the heavy right-tailed distributions of the count variables. Since the Asthma Medication Ratio (AMR; the ratio of asthma controller medication canisters to the total of asthma controller canisters plus asthma reliever medication canisters filled) was a fraction (counts in both the numerator and denominator) ranging from 0 to 1 inclusive, AMR was analysed using the fractional logit model with the logit link function. Logistic regression was used for the composite health care utilization outcome of any asthma-related urgent care visit, emergency visit, or hospitalization since this was a dichotomous variable. We did not account for multiple hypothesis testing in all analyses.

Study arms

Usual care (N = 655)

Combined text/phone/email (N = 1278)

Characteristics

Arm-level characteristics

Characteristic	Text/phone (N = 657)	Email (N = 621)	Usual care (N = 655)	Combined text/phone/email (N = 1278)
% Female Sample size	n = 389 ; % = 59.2	n = 378 ; % = 60.9	n = 400 ; % = 61.1	*empty data*
Mean age (SD) Mean (SD)	48.5 (15.9)	49.7 (16.2)	48.2 (16.6)	*empty data*
White Sample size	% = 64.8	% = 66.8	% = 68.7	*empty data*
Hispanic Sample size	% = 17.8	% = 15.6	% = 17	*empty data*
African-American Sample size	% = 5.9	% = 7.4	% = 4.9	*empty data*
Asthma diagnosis: Persistent only At date of randomisation Sample size	% = 86.9	% = 86.6	% = 87.9	*empty data*

Characteristic	Text/phone (N = 657)	Email (N = 621)	Usual care (N = 655)	Combined text/phone/email (N = 1278)
Current smoker Sample size	% = 9	% = 8.5	% = 8.6	*empty data*
Former smoker Sample size	% = 31.2	% = 32.8	% = 31.3	*empty data*
Never smoker Sample size	% = 59.1	% = 56.8	% = 59.4	*empty data*
Uknown Sample size	% = 0.8	% = 0.8	% = 0.8	*empty data*
Total number of ambulatory visits per patient Mean (SD)	5.3 (5.9)	5.6 (7.8)	5 (5.8)	*empty data*
Patients with any asthma exacerbation After-hour visits, emergency department visits, and/or hospitalizations. Sample size	n = 50 ; % = 7.6	n = 36 ; % = 5.8	n = 41 ; % = 6.3	*empty data*
Number of oral/injectable corticosteroid bursts per patient Mean (SD)	0.3 (1)	0.3 (0.7)	0.3 (0.8)	*empty data*
Beta2-agonist canisters dispensed Mean (SD)	5.3 (4.7)	4.8 (3.9)	5 (5.4)	*empty data*

Characteristic	Text/phone (N = 657)	Email (N = 621)	Usual care (N = 655)	Combined text/phone/email (N = 1278)
Inhaled corticosteroid dispensed Mean (SD)	5.7 (5.5)	6.1 (6)	6 (6.8)	*empty data*

Outcomes

Study timepoints

- Baseline
- 6 month (All patients had at least 6 months of follow-up. The maximum follow-up was 18 months. Follow-up time was defined as time from first beta2-agonist overuse to study end date or censoring (eg, disenrollment from health plan).)

Asthma exacerbations

Outcome	Usual care, Baseline, N = 655	Usual care, 6 month, N = 655	Combined text/phone/email, Baseline, N = 1278	Combined text/phone/email, 6 month, N = 1278
Asthma exacerbations (no. oral/injectable corticosteroid bursts per patient during follow-up) Rates adjusted for person years Mean (SD)	0.28 (0.77)	0.23 (0.51)	0.31 (0.71)	0.24 (0.71)
Unscheduled healthcare utilisation (patients with any asthma-related after-hour visits, emergency department visits, and/or hospitalizations) (% (SD)) Logistic regression used to evaluate ≥1 events versus 0 events	6.3(0.26)	7.5(0.26)	6.7(0.36)	6.1(0.36)

Outcome	Usual care, Baseline, N = 655	Usual care, 6 month, N = 655	Combined text/phone/email, Baseline, N = 1278	Combined text/phone/email, 6 month, N = 1278
Custom value				

Asthma exacerbations (no. oral/injectable corticosteroid bursts per patient during follow-up) - Polarity - Lower values are better
Unscheduled healthcare utilisation (patients with any asthma-related after-hour visits, emergency department visits, and/or hospitalizations) - Polarity - Lower values are better

Asthma medication use

Outcome	Usual care, Baseline, N = 655	Usual care, 6 month, N = 655	Combined text/phone/email, Baseline, N = 1278	Combined text/phone/email, 6 month, N = 1278
Steroid use (short-acting corticosteroid inhalers dispensed during follow-up) Mean (SD)	6.04 (6.9)	6.43 (6.7)	5.94 (5.7)	6.7 (7.1)

Steroid use (short-acting corticosteroid inhalers dispensed during follow-up) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT Asthmaexacerbations-No.oral/injectablecorticosteroidburstsperpatientduringfollow-up-MeanSD- -Usual care-Combined text/phone/email-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(lack of blinding; number with missing data and how that was dealt in the analysis is unclear)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Unscheduled healthcare utilisation-Patientswithanyasthma-relatedafter-hourvisits,emergencydepartmentvisits,and/orhospitalizations-CustomValue0- -Usual care-Combined text/phone/email-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(lack of blinding; number with missing data and how that was dealt in the analysis is unclear)*
Overall bias and Directness	Overall Directness	Directly applicable

Steroid use-Short-actingcorticosteroidinhalersdispensedduringfollow-up-MeanSD- -Usual care-Combined text/phone/email-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(lack of blinding; number with missing data and how that was dealt in the analysis is unclear)*
Overall bias and Directness	Overall Directness	Indirectly applicable

Charrois, 2006

Bibliographic Reference	Charrois, Theresa L.; Newman, Stephen C.; Senthilselvan, Ambikaipakan; Tsuyuki, Ross T.; Improving Asthma Control in the Rural Setting: The BREATHE (Better Respiratory Education and Asthma Treatment in Hinton and Edson) Study; Canadian Pharmacists Journal / Revue des Pharmaciens du Canada; 2006; vol. 139 (no. 4); 44-50

Study details

Other publications associated with this study included in review	Charrois 2004 (study design and methods)
Trial name / registration number	Better Respiratory Education and Asthma Treatment in Hinton and Edson (BREATH) study
Study type	Randomised controlled trial (RCT)
Study location	Canada
Study setting	Two rural communities in Alberta, Canada (Edson and Hinton). The communities both have populations of less than 10,000 and are over 200 km away from any tertiary care centres
Sources of funding	Institute of Health Economics, University of Alberta Hospital Foundation, Canadian Institutes of Health Research, A.S.T.H.M.A. (Alberta Strategy to Help Manage Asthma) Study
Inclusion criteria	High-risk asthma patients 17-54 years. High risk defined as having an ER visit or hospitalization in the previous year, or using >2 canisters of short-acting beta-agonist in the previous 6 months; identified through community pharmacies.
Exclusion criteria	Patients are excluded if they are not responsible for administering their own asthma medications, unable to understand English, are unavailable for 6-month follow-up, or do not provide written informed consent.
Recruitment / selection of participants	The community pharmacists are responsible for recruiting their patients that fit the inclusion criteria. They screen patients by their pharmacy refill records to identify over-users of beta-2 agonists. The hospital pharmacist identifies the patients who have been hospitalized or seen in the emergency room for asthma. With the patient's verbal consent, the hospital pharmacist then forwards this information to that patient's local community pharmacy for follow-up and potential recruitment

	into the study. The community pharmacist investigators are responsible for obtaining written consent prior to randomizing the patient to treatment groups.
Intervention(s)	Subjects assigned to the intervention group receive education on asthma, assessment and optimization of drug therapy, respiratory therapist referral and physician referral as needed. The education component includes medication teaching on all asthma medications, inhaler technique assessment/education, provision of written asthma education materials and development of a written action plan. The written action plan is based on the Canadian guidelines and has been developed and approved by the local pharmacists, physicians and respiratory therapist at the first investigators' meeting. The educational component is initiated by the pharmacists and reinforced by the respiratory therapist. Optimization of drug therapy includes an assessment of medications by the study pharmacist in concordance with the Canadian asthma guidelines, in particular, ensuring all patients are prescribed an inhaled corticosteroid. An assessment of adherence to current drug therapy helps determine if the patient is not taking their current therapy optimally. Patients are referred to their physician if therapy adjustments are suggested, as determined by the drug therapy assessment. A physician referral form is faxed to the patient's family physician identifying patients as high-risk and includes any recommendations to the physician regarding current asthma therapy (based on the Canadian guidelines for the treatment of asthma) and the education being provided to the patient, including a copy of the patient's written action plan. Furthermore, patients are referred to a respiratory therapist within 1 week of randomization for measurement of FEV1 and reinforcement of education. Follow-up by pharmacist: Follow-up for the intervention group includes a follow-up telephone call at 2 weeks by the pharmacist to determine if patients in the intervention group have made an appointment to see their family physician (if required) and to reinforce education. As well, they ensure that the patient has seen the respiratory therapist. The intervention group patients have follow-up, by the pharmacist, at 1, 2, 4 and 6 months for educational reinforcement, medication assessment, assessment of outcome events and reassessment of written action plan. Follow-up by respiratory therapist: The respiratory therapist administers the Asthma Control Questionnaire at 2 and 6 months. There are 2- and 6-month follow-up appointments with the respiratory therapist for educational reinforcement, measurement of pulmonary function, and reassessment of the written action plan in conjunction with the pharmacist.

Population subgroups	Not applicable
Comparator	Usual care: written asthma information, referral to a respiratory therapist and usual pharmacy and physician care. The usual care group is provided with an asthma education booklet only and general advice as needed. The asthma education booklet entitled 'Take a holiday from your asthma symptoms' (Astra Zeneca) was reviewed by asthma educators to ensure up-to-date, accurate information was included. Patients are referred to a respiratory therapist within 1 week of randomization for measurement of FEV1. Follow-up by pharmacist. The usual care group have follow-up with the pharmacist at 2 and 6 months. Follow-up includes assessment of any outcome events and minimal education (inhaler technique assessment). To address any concerns about provision of usual care, the patients in the usual care group are offered the intervention after the 6 months of study. Follow-up by respiratory therapist. Administration of the Asthma Control Questionnaire by the respiratory therapist occurs at 2 and 6 months. All patients have FEV1 measured initially and at 2 and 6 months. The patients in the usual care group are offered the intervention after the 6 months of study.
Number of participants	71
Duration of follow-up	6 months
Additional comments	Multivariate analysis with different variables being controlled for different outcomes: Age, gender, site for ACQ scores; inhaler technique, ICS use at baseline for Inhaled steroid use; previous use of oral steroids for course of oral steroids; previous ED visit or hospital admissions for ED visits and hospital admissions.

Study arms

Community management (N = 37)

Usual care (N = 34)

Characteristics

Arm-level characteristics

Characteristic	Community management (N = 37)	Usual care (N = 34)
% Female Sample size	n = 19 ; % = 52.8	n = 18 ; % = 52.9
Mean age (SD) Mean (SD)	35.7 (10.2)	38.7 (10.7)
Current smoker Sample size	n = 11 ; % = 30.6	n = 10 ; % = 29.4
Inhaled corticosteroid prescribed Sample size	n = 25 ; % = 69.4	n = 26 ; % = 76.5
Short course of oral steroid prescribed in the previous 6 months Sample size	n = 12 ; % = 33.3	n = 11 ; % = 32.4
Unscheduled physician visits in the previous 6 months Sample size	n = 10 ; % = 27.8	n = 18 ; % = 52.9
Hospital admissions for asthma in the previous 6 months	n = 6 ; % = 16.7	n = 9 ; % = 26.5

Characteristic	Community management (N = 37)	Usual care (N = 34)
Sample size		
Baseline ACQ Asthma control questionnaire Mean (SD)	1.45 (1.14)	1.91 (1.05)

Outcomes

Study timepoints

- 6 month

Asthma control

Outcome	Community management, 6 month, N = 36	Usual care, 6 month, N = 34
Asthma control (ACQ) range 0-7, change score Mean (SD)	0.43 (0.9)	0.33 (0.99)

Asthma control (ACQ) - Polarity - Lower values are better

Health service use

Outcome	Community management vs Usual care, 6 month, N2 = 34, N1 = 36
Steroid use (participants with inhaled steroid use) Scores adjusted for inhaler technique and ICS use at baseline; event rate was 83% vs 82% Odds ratio/95% CI	0.68 (0.22 to 2.06)

Outcome	Community management vs Usual care, 6 month, N2 = 34, N1 = 36
Severe asthma exacerbations (number of courses of oral steroids) Adjusted for previous courses of oral steroids; dichotomous: 11.1% vs 26.5% Odds ratio/95% CI	0.28 (0.07 to 1.12)
Unscheduled healthcare utilisation (ED visits or hospital admissions) Adjusted for previous ED visits/hospital admissions; 6 in each group Odds ratio/95% CI	1.08 (0.27 to 3.24)

Steroid use (participants with inhaled steroid use) - Polarity - Lower values are better
Severe asthma exacerbations (number of courses of oral steroids) - Polarity - Lower values are better
Unscheduled healthcare utilisation (ED visits or hospital admissions) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT Healthserviceuse-Inhaledsteroiduse-OddsRatioNineFivePercentCI-Community management-Usual care-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(baseline difference in e.g. unscheduled physician visits in the previous 6 months and previous pulmonary function tests, not adjusted for across outcomes; poor compliance to some aspects of intervention by pharmacists e.g. only 3/4 received written action plan; differential rate of incomplete outcome data across groups and unclear for which outcomes and how it was dealt with; lack of details over the analysis)*
Overall bias and Directness	Overall Directness	Directly applicable

Asthmacontrol-ACQ-MeanSD-Community management-Usual care-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(baseline difference in e.g. unscheduled physician visits in the previous 6 months and previous pulmonary function tests, not adjusted for across outcomes; poor compliance to some aspects of intervention by pharmacists e.g. only 3/4 received written action plan; differential rate of incomplete outcome data across groups and unclear for which outcomes and how it was dealt with; lack of details over the analysis)*
Overall bias and Directness	Overall Directness	Directly applicable

Healthserviceuse-Numberofcoursesoforalsteroids-OddsRatioNineFivePercentCI-Community management-Usual care-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(baseline difference in e.g. unscheduled physician visits in the previous 6 months and previous pulmonary function tests, not adjusted for across outcomes; poor compliance to some aspects of intervention by pharmacists e.g. only 3/4 received written action plan; differential rate of incomplete outcome data across groups and unclear for which outcomes and how it was dealt with; lack of details over the analysis)*
Overall bias and Directness	Overall Directness	Directly applicable

Healthserviceuse-EDvisitrsorhospitaladmissions-OddsRatioNineFivePercentCI-Community management-Usual care-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(baseline difference in e.g. unscheduled physician visits in the previous 6 months and previous pulmonary function tests, not adjusted for across outcomes; poor compliance to some aspects of intervention by pharmacists e.g. only 3/4 received written action plan; differential rate of incomplete outcome data across groups and unclear for which outcomes and how it was dealt with; lack of details over the analysis)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Kattan, 2006

Bibliographic Reference	Kattan, M.; Crain, E.F.; Steinbach, S.; Visness, C.M.; Walter, M.; Stout, J.W.; Evans III, R.; Smartt, E.; Gruchalla, R.S.; Morgan, W.J.; O'Connor, G.T.; Mitchell, H.E.; A randomized clinical trial of clinician feedback to improve quality of care for inner-city children with asthma; Pediatrics; 2006; vol. 117 (no. 6); e1095-e1103

Study details

Trial name / registration number	**Inner-City Asthma Study (ICAS) feedback intervention**
Study type	Randomised controlled trial (RCT)
Study location	Participants were recruited from centers in Boston, Massachusetts; Bronx, New York; Chicago, Illinois; Dallas, Texas; New York, New York; Seattle/Tacoma, Washington; and Tucson, Arizona
Study setting	Participants were identified for recruitment from inpatient units of hospitals, EDs, and community paediatrics clinics.
Study dates	The intervention took place between October 1998 and August 2000.
Sources of funding	Dr Steinbach has received lecture fees from GlaxoSmithKline and consulting fees from Aventis; Dr Gruchalla is a member of the GlaxoSmithKline Allergy Fellowship Grant review committee; Dr Morgan has received consulting fees from Genentech; and Dr O'Connor is GlaxoSmithKline-Data Safety and Monitoring Board chair and Astellas Pharma-Data Safety and Monitoring Board chair.
Inclusion criteria	Children 5-11 years with moderate to severe asthma. Eligibility was limited to residents of census tracts in which 20% of households had incomes below the federal poverty level except in Seattle, where participants could be enrolled if they met Medicaid eligibility. Other inclusion criteria included a history of 1 hospitalization or 2 unscheduled visits for asthma in the previous 6 months and a positive allergy skin test to 1 of 11 indoor allergens.
Exclusion criteria	Children were excluded if they made 2 visits to an asthma specialist or asthma clinic in the previous 6 months or if they had any other serious chronic illness.
Intervention(s)	Every 2 months for 1 year from the date of enrolment, each child's caretaker underwent a standardized computer-assisted telephone interview (CATI) to determine the child's asthma symptoms and use of controller and reliever medications in the past 2 weeks, and health service use (scheduled visits, ED visits, and hospitalizations) over the previous 2-month interval.

	These interviews were conducted by a centralized service for all of the study sites, and the interviewers were blinded to study group assignment. For children in the intervention group, information from each CATI call was used to generate a feedback letter that was mailed directly to the child's PCP. Although study staff and participants were aware of group assignments, they were not aware of the content of the letter. The computer-generated letter, designed with input from provider focus groups, was a single page that displayed a color photograph of the child, identifying information, and a current telephone number. A summary box detailed the child's symptoms and use of controller and quick-relief medications over the previous 2 weeks and the number of ED visits and hospitalizations over the previous 2 months, as reported by the caretaker. Based on reported symptoms, health care use and medication use, a computer algorithm developed from the severity classification of the National Asthma Education and Prevention Program (NAEPP) guidelines generated a 1-sentence recommendation for treating the child. The possible recommended actions based on the NAEPP guidelines were to step up, step down, or to make no changes in medications. To facilitate prescribing, each letter was accompanied by a single-page enclosure summarizing the NAEPP asthma severity classification and therapy guidelines on one side and recommended medication doses on the other. A study investigator met with the PCP of the child in the intervention group before any letters were mailed to explain the nature of the intervention, review a sample of the bimonthly letter, and provide a copy of the NAEPP guidelines. For a few providers, the study information was given over the telephone and the printed educational information mailed. A letter about the study and educational materials were mailed to any PCP that could not be contacted.
Comparator	Letters were not sent to the providers of children in the control group. For this group, the information from the CATI calls was used to determine what recommendation would have been generated had the child been in the intervention group.
Number of participants	937
Duration of follow-up	1-year (intervention duration with outcome being recorded during that year)
Indirectness	none
Additional comments	The intention-to-treat analysis on symptom outcomes used a mixed linear model, adjusting for site, baseline morbidity, and repeated observations per participant. Use of health care services was calculated over the entire intervention year and analysed using analysis of covariance. Because the intervention did not start until after the first 2 months of morbidity data were available for the generation of the first letter, the 1-year outcome was based on calls 2 to 7 (months 4 –14). Baseline morbidity was calculated as the average of the baseline visit and the first call. The intention-to-treat analysis included all of

	the randomly assigned study participants. For subsequent analyses, those children in the control group whose PCP also cared for intervention children were considered to be “contaminated” and were removed

Study arms

Physician feedback group (N = 471)

Control group (N = 466)

Characteristics

Arm-level characteristics

Characteristic	Physician feedback group (N = 471)	Control group (N = 466)
% Female Custom value	39.5	37.1
Mean age (SD) Mean (years) Custom value	7.7	7.6
Hispanic % Custom value	40.3	39.9
Black % Custom value	40.3	38.8
White Custom value	7.4	6.4

Characteristic	Physician feedback group (N = 471)	Control group (N = 466)
Asian % Custom value	1.1	1.3
Native-American Custom value	2.3	3.9
Mixed/other Custom value	8.5	9.7
Baseline symptoms: maximum symptom days per 2wk mean Custom value	6.1	5.9
Days limited in activities for more than half a day Custom value	2	2.1
School days missed Custom value	0.9	1.1
ED visits Annualised mean Custom value	3	3
Unscheduled clinic visits Annualised mean Custom value	5.6	5.5

Characteristic	Physician feedback group (N = 471)	Control group (N = 466)
Hospitalisations annualised mean Custom value	1.1	0.8
Type of letter sent/ that would have been sent based on reported symptoms from previous CATI call: Step-up (%) Custom value	58.7	61.5
Moderate symptoms (no change at this time) % Custom value	9.1	9.2
Well-controlled (no change at this time) % Custom value	6.5	5.2
Step-down Custom value	25.5	24
Not enough information to make a recommendation Custom value	0.2	0.1

Outcomes

Study timepoints

- 1 year

Health service use because of asthma

Outcome	Physician feedback group, 1 year, N = 466	Control group, 1 year, N = 463
Unscheduled healthcare utilisation (number of ED visits) Mean (SD)	0.87 (1.51)	1.14 (1.72)
Unscheduled healthcare utilisation (number of unscheduled clinic visits) Mean (SD)	1.14 (1.73)	1.31 (1.72)
Unscheduled healthcare utilisation (number of hospitalisations) Mean (SD)	0.22 (0.65)	0.24 (0.65)

Unscheduled healthcare utilisation (number of ED visits) - Polarity - Lower values are better
Unscheduled healthcare utilisation (number of unscheduled clinic visits) - Polarity - Lower values are better
Unscheduled healthcare utilisation (number of hospitalisations) - Polarity - Lower values are better
analysis of covariance, adjusting for site and baseline use, was used.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Healthserviceusebecauseofasthma-Numberofhospitalisations-MeanSD-Physician feedback group-Control group-t1

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Healthserviceusebecauseofasthma-NumberofEDvisits-MeanSD-Physician feedback group-Control group-t1

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Healthserviceusebecauseofasthma-Numberofunscheduledclinicvisits-MeanSD-Physician feedback group-Control group-t1

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Noble, 2006

Bibliographic Reference	Noble, M.J.; Smith, J.R.; Windley, J.; A controlled retrospective pilot study of an 'at-risk asthma register' in primary care; Primary Care Respiratory Journal; 2006; vol. 15 (no. 2); 116-124

Study details

Study type	Retrospective before and after study
Study location	Norfolk, United Kingdom
Study setting	Acle Medical Centre, a semi-rural practice in the Norfolk Broads.
Study dates	Registry established in January 2002. Data utilised from 12 months before 2002 and 12 months after.
Sources of funding	Not stated
Inclusion criteria	At-risk patients for inclusion on the register had severe asthma (BTS step 4 or 5 treatment and/or a history of hospital admissions for asthma) and documented evidence of poor asthma control on the basis of reports of either symptoms, peak flow records, high use of reliever medication and/or frequent exacerbations. They also had one or more of the following: 1) Poor adherence, recognised by: failure to attend scheduled appointments (two or more in the previous two years); failure to take inhaled corticosteroids; failure to monitor symptoms or peak flows as agreed; or by the patient previously self-discharging from hospital. 2) Psychiatric problems, recognised by a history of depression or prescription of anti-depressant or anti-psychotic medication. 3) Other psychosocial difficulties likely to be contributing to significant stress, such as unemployment or single parenthood. In addition to the patients added to the at risk register, a control group of asthma patients was identified who did not meet the criteria for inclusion on the at-risk register but who were matched according to age, sex and BTS treatment step.
Exclusion criteria	Not specified

Recruitment / selection of participants	Several patients with these characteristics were already known to clinical staff, but a search was made of computerised and written records to identify other patients who met the criteria.
Intervention(s)	In January 2002 patients identified as being at risk of adverse asthma events were given an electronic tag on the practice computer system stating 'high risk asthma patient, prioritise appointment'. This computer prompt appeared whenever patients' electronic records were called-up, and needed actively clearing from the screen. A similar 'asthma alert' marker was also placed in these patients' written records. The addition of these flags to the electronic and paper records comprised the 'at-risk register'. In addition to establishing the register, all practice staff were given training on the relevance of the alert tags and action to be taken when an at-risk patient contacted the surgery about their asthma or potentially related problems (e.g. chest infection). Reception and dispensary staff were instructed to give patients the choice of either speaking to the doctor or practice respiratory nurse on the telephone immediately, or of booking an appointment the same day. Where appropriate, patients would be asked to come directly to the surgery or offered a home visit. Doctors and nurses were advised on the importance of engaging with this group of patients to form a strong therapeutic alliance. The need to address psychosocial and other factors that were adversely affecting their asthma management was stressed. One of the practice GPs (MN), who also undertakes liaison psychiatry sessions in a clinic for patients with difficult asthma at the local acute hospital, facilitated the training
Comparator	Patients in the control group received standard care over the study period.
Number of participants	26 in each group
Duration of follow-up	12 months before and 12 months after the establishment of the register.
Indirectness	none
Additional comments	The numbers of patients in each group needing emergency treatments and making use of primary care services for their asthma at any point during each 12-month period were compared for the year before and year after the introduction of the register using Fisher's exact tests.

Study arms

At-risk register (N = 26)

Control group (N = 26)

Characteristics

Arm-level characteristics

Characteristic	At-risk register (N = 26)	Control group (N = 26)
% Female Sample size	n = 12 ; % = 46.2	n = 12 ; % = 46.2
Age Median (IQR)	36 (5 to 61)	36 (5 to 61)
Under the care of a hospital respiratory department Sample size	n = 4 ; % = 15.4	n = 0 ; % = 0

Outcomes

Study timepoints

- Baseline
- 12 month (Baseline and 12 months time points refer to the year before and the year after introduction of the at-risk asthma register)

Emergency treatments for Asthma- Dichotomous

Outcome	At-risk register, Baseline, N = 26	At-risk register, 12 month, N = 26	Control group, Baseline, N = 26	Control group, 12 month, N = 26
Unscheduled healthcare utilisation (hospital admission) number of patients No of events	n = 3 ; % = 11.54	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0
Unscheduled healthcare utilisation (A&E attandance) number of patients No of events	n = 1 ; % = 3.85	n = 0 ; % = 0	n = 0 ; % = 0	n = 0 ; % = 0
Unscheduled healthcare utilisation (Out of hours contact) number of patients No of events	n = 6 ; % = 23.08	n = 2 ; % = 7.69	n = 0 ; % = 0	n = 1 ; % = 3.85
Severe exacerbations (course of oral steroids prescribed) Number of patients No of events	n = 14 ; % = 53.85	n = 7 ; % = 26.92	n = 2 ; % = 7.69	n = 1 ; % = 3.85

Unscheduled healthcare utilisation (hospital admission) - Polarity - Lower values are better
Unscheduled healthcare utilisation (A&E attandance) - Polarity - Lower values are better
Unscheduled healthcare utilisation (Out of hours contact) - Polarity - Lower values are better
Severe exacerbations (course of oral steroids prescribed) - Polarity - Lower values are better
Note intervention group baseline V 12 months is only data used as it's a before and after study. Control group data not used.

Critical appraisal - ROBINS-I checklist
EmergencytreatmentsforAsthma-Dichotomous-Hospitaladmission-NoOfEvents-At-risk register-Control group-t12

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious *(proportionally to the sample sizes there is a difference in certain variables that could be confounding; lack of details over the analysis, any missing data and how it was dealt with)*
Overall bias	Directness	Directly applicable

EmergencytreatmentsforAsthma-Dichotomous-A&Eattandance-NoOfEvents-At-risk register-Control group-t12

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious *(proportionally to the sample sizes there is a difference in certain variables that could be confounding; lack of details over the analysis, any missing data and how it was dealt with)*
Overall bias	Directness	Directly applicable

EmergencytreatmentsforAsthma-Dichotomous-Outofhourscontact-NoOfEvents-At-risk register-Control group-t12

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious *(proportionally to the sample sizes there is a difference in certain variables that could be confounding; lack of details over the analysis, any missing data and how it was dealt with)*
Overall bias	Directness	Directly applicable

EmergencytreatmentsforAsthma-Dichotomous-Courseoforalsteroidsprescribed-NoOfEvents-At-risk register-Control group-t12

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious *(proportionally to the sample sizes there is a difference in certain variables that could be confounding; lack of details over the analysis, any missing data and how it was dealt with)*
Overall bias	Directness	Directly applicable

Smith, 2012

Bibliographic Reference	Smith, Jane Rebecca; Noble, Michael J; Musgrave, Stanley; Murdoch, Jamie; Price, Gill M; Barton, Garry R; Windley, Jennifer; Holland, Richard; Harrison, Brian Dw; Howe, Amanda; Price, David B; Harvey, Ian; Wilson, Andrew M; The at-risk registers in severe asthma (ARRISA) study: a cluster-randomised controlled trial examining effectiveness and costs in primary care.; Thorax; 2012; vol. 67 (no. 12); 1052-60

Study details

Trial name / registration number	ISRCTN trial register number 36918958
Study type	Cluster randomised controlled trial
Study location	UK
Study setting	Primary care practices in Norfolk, UK.
Study dates	Data collected spanned the period November 2006-May 2009
Sources of funding	Study funded by industry (Asthma UK)
Inclusion criteria	At-risk asthma patients aged 5+ years using British guideline criteria. Severe asthma indicated by: in the last 2 years medications approximating to BTS/SIGN Step 4-5 treatment; or asthma admission in the last 5 years or A&E visit in last year or Brittle asthma
Exclusion criteria	Not reported
Recruitment / selection of participants	Survey sent to GP practices. Clinicians at practices identified at-risk asthma patients aged 5+ years in two stages using British guideline criteria. A database manager then randomised practices using a computer-generated list of random permutations with a block size of two and stratified according to whether their Index of Multiple Deprivation score was above or below the Norfolk median. Practices in a block were randomised simultaneously to ensure allocation concealment.
Intervention(s)	Risk stratified care. Addition of electronic alerts visible to all staff to the computerised records of identified at-risk patients to flag their at-risk status at each contact. A one hour practice-based training session to support effective use of the alerts, which advised staff on how to engage with, and improve the routine and emergency management of at-risk asthma patients using case examples to highlight potential actions for receptionists, clinicians and dispensary teams. Alerts were activated once dissemination was complete. Duration 1 year.

Population subgroups	Not applicable
Comparator	Control practices continued usual care, comprising at least annual practice-based asthma reviews in nurse-led clinics, plus follow-up in secondary care outpatient clinics and emergency primary and secondary care for some patients as required. Duration: 1 year
Number of participants	911
Duration of follow-up	1 year
Additional comments	Mixed-effect models were used to adjust for clustering of outcomes within practices21 in producing effect sizes, 95% CIs and p values. Analyses were conducted with random effect for practice, adjusted for stratification (above/below-average Index of Multiple Deprivation) alone ('unadjusted') and additionally adjusted for baseline values of the outcome and other selected covariates ('adjusted'). Random-effects logistic models producing ORs were used for binary outcomes (n, %) since there was no difference in follow-up times between groups (p¼0.458; ManneWhitney test). ICCs were estimated in these models for the primary outcome and its components. Random-effects negative-binomial models, producing rate-ratios (RRs), taking into account each patient's observation time, were used for outcomes experienced by the majority of patients where ORs exaggerate effects. Results for these were described using median and IQR rates (counts per year), since they were generally heavily positively skewed with extra-Poisson variation. The main analyses were undertaken on an intention to-treat (ITT) basis including all at-risk patients identified pre-randomisation who were alive and registered with practices on the date alerts were activated at intervention practices. .

Study arms

Risk stratified care (N = 457)

Standard care (N = 454)

Characteristics

Arm-level characteristics

Characteristic	Risk stratified care (N = 457)	Standard care (N = 454)
% Female Sample size	n = 287 ; % = 62.8	n = 271 ; % = 59.8
Mean age (SD) Mean (SD)	46.4 (22.1)	44.6 (21.7)
Aged <16 years Sample size	n = 51 ; % = 11.2	n = 56 ; % = 12.3
Median (IQR) severity score based on no. classes of asthma medications prescribed (0-9) Custom value	4 (2)	4 (2)
Charlson co-morbidity index score: 0 Sample size	n = 325 ; % = 71.1	n = 321 ; % = 70.7
score 1-2 Sample size	n = 105 ; % = 23	n = 98 ; % = 21.6
Score 3+ Sample size	n = 27 ; % = 5.9	n = 35 ; % = 7.7
Never smoked Sample size	n = 176 ; % = 38.5	n = 158 ; % = 34.8

Characteristic	Risk stratified care (N = 457)	Standard care (N = 454)
Non-smoker Sample size	n = 17 ; % = 3.7	n = 32 ; % = 7.1
Ex-smokers Sample size	n = 118 ; % = 25.8	n = 93 ; % = 20.5
Smoker Sample size	n = 95 ; % = 20.8	n = 100 ; % = 22
Moderate-severe exacerbation in past year Sample size	n = 293 ; % = 64.1	n = 266 ; % = 58.6
Hospitalisation for asthma Sample size	n = 28 ; % = 6.1	n = 32 ; % = 7.1
A&E attendance for asthma exacerbation Sample size	n = 50 ; % = 10.9	n = 49 ; % = 10.8
out-of hours contact for asthma exacerbation Sample size	n = 45 ; % = 9.9	n = 36 ; % = 7.9
oral prednisolone course for asthma exacerbation Sample size	n = 293 ; % = 64.1	n = 272 ; % = 59.9
b-agonist inhalers prescribed median IQR Custom value	7 (9)	8 (11)

Characteristic	Risk stratified care (N = 457)	Standard care (N = 454)
BDP-equivalent dose of inhaled corticosteroid prescribed (µg/day) Median (IQR) Custom value	723 (986)	657 (986)
long-acting b-agonist inhalers prescribed Median (IQR) Custom value	8 (7)	6 (9)
leukotreine receptor antagonists prescribed Sample size	n = 101 ; % = 22.1	n = 125 ; % = 27.5
Theophyllines prescribed Sample size	n = 27 ; % = 5.9	n = 42 ; % = 9.3

Outcomes

Study timepoints

- 1 year

Moderate-severe asthma exacerbation

Outcome	Risk stratified care, 1 year, N = 457	Standard care, 1 year, N = 454
Unscheduled healthcare utilisation (hospitalisation for asthma exacerbation) No of events	n = 15 ; % = 3.3	n = 29 ; % = 6.4

Outcome	Risk stratified care, 1 year, N = 457	Standard care, 1 year, N = 454
Unscheduled healthcare utilisation (A&E attandance for asthma exacerbation) No of events	n = 29 ; % = 6.4	n = 37 ; % = 8.2
Unscheduled healthcare utilisation (out-of-hours contact for asthma exacerbation) No of events	n = 26 ; % = 5.7	n = 32 ; % = 7.1
Severe asthma exacerbation (oral prednisolone course of asthma exacerbation) No of events	n = 247 ; % = 54.1	n = 213 ; % = 46.9

Moderate-severe asthma exacerbation - Polarity - Lower values are better
defined as those resulting in death (determined in a blinded review of records by two physicians), hospitalisation, accident and emergency (A&E) attendance, out-of-hours medical contact, or a course or boost in oral corticosteroids (prednisolone) for asthma

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Moderate-severeasthmaexacerbation-Moderate-severeasthmaexacerbation-NoOfEvents-Risk stratified care-Standard care-t1

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

-Moderate-severeasthmaexacerbation-Hospitalisationforasthmaexacerbation-NoOfEvents-Risk stratified care-Standard care-t1

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Moderate-severeasthmaexacerbation-A&Eattandanceforasthmaexacerbation-NoOfEvents-Risk stratified care-Standard care-t1

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Moderate-severeasthmaexacerbation-out-of-hourscontactforasthmaexacerbation-NoOfEvents-Risk stratified care-Standard care-t1

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Moderate-severeasthmaexacerbation-Oralprednisolonecourseofasthmaexacerbation-NoOfEvents-Risk stratified care-Standard care-t1

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Appendix E – Forest plots

E.1 Digital communication technology tool versus usual care

Figure 1: Severe asthma exacerbations (no. of oral/injectable corticosteroid bursts per patient, rate adjusted for person years, lower is better,6 months)

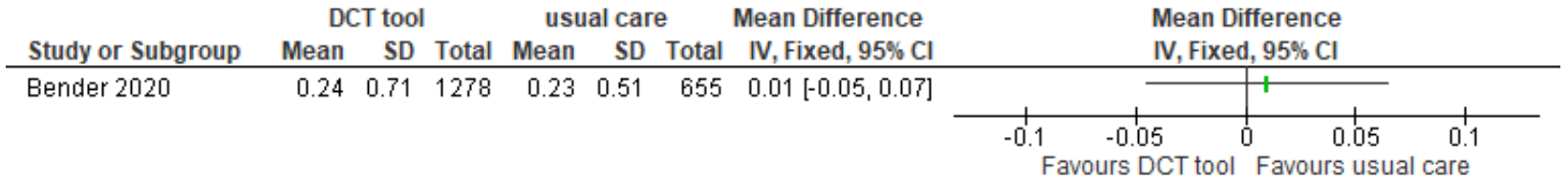


Figure 2: Steroid use (short-acting corticosteroid inhalers dispensed, rate adjusted for person years, lower is better, 6 months)

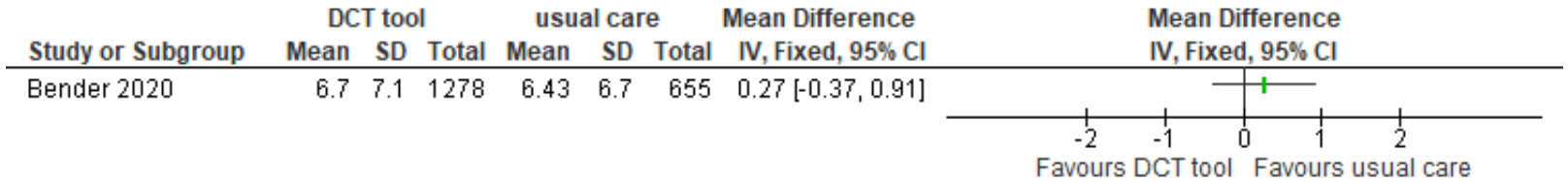
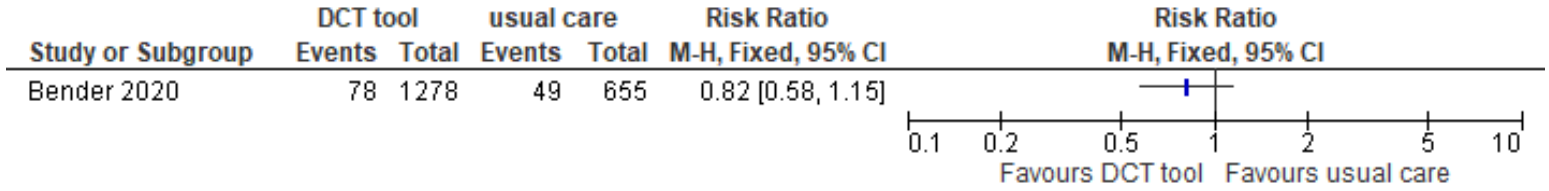


Figure 3: Unscheduled healthcare utilisation (patients with any asthma related after-hour visits/ED visits and/or hospitalisations, lower is better, events 6 months)



E.2 Community management versus usual care

Figure 4: Asthma control (ACQ, range 0-6, lower is better, at 6 months)

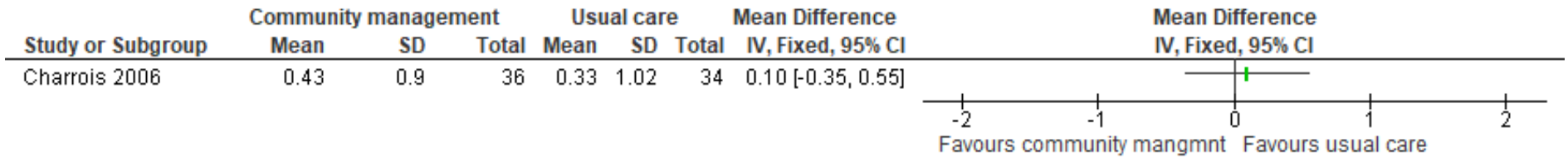


Figure 5: Severe asthma exacerbations (no. of courses of oral steroids, lower is better, at 6 months)

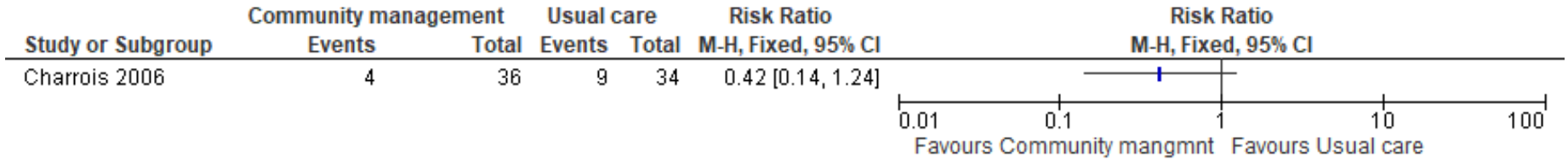


Figure 6: Steroid use (inhaled steroid use, lower is better, 6 months)

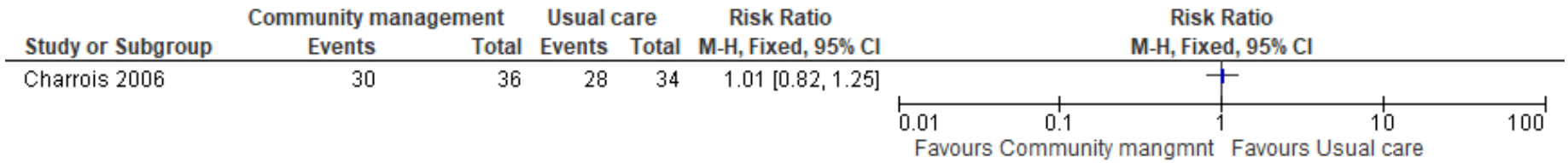
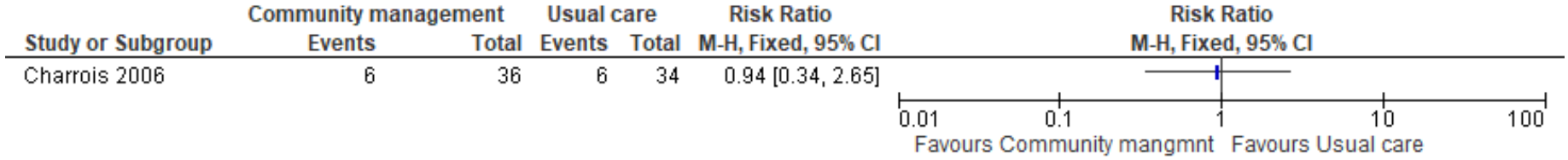


Figure 7: Unscheduled healthcare utilisation (ED visits and hospital admissions, lower is better, 6 months)



E.3 Physician feedback versus control

Figure 8: Unscheduled healthcare utilisation (number of hospitalisations, lower is better,1 year)

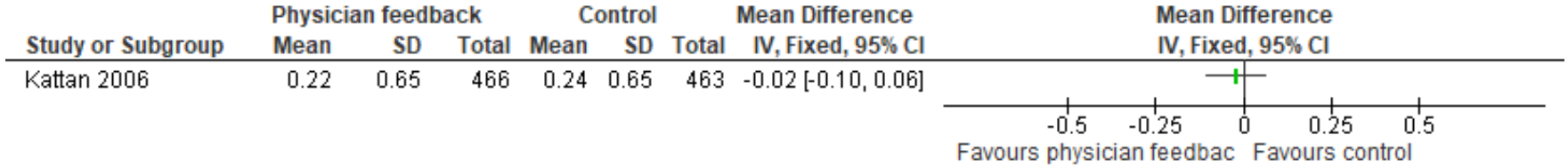


Figure 9: Unscheduled healthcare utilisation (number of ED visits, lower is better, 1 year)

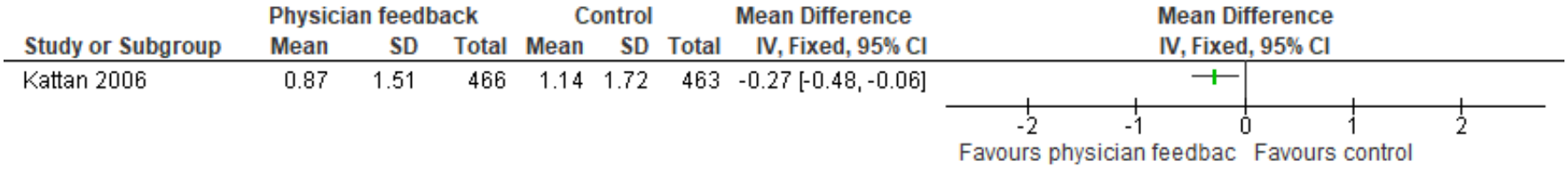
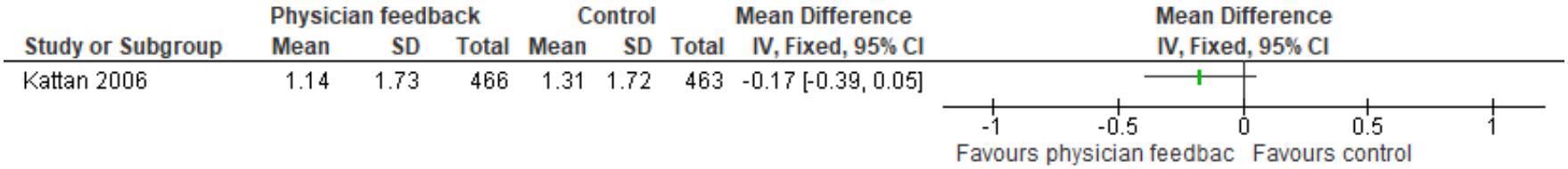


Figure 10: Unscheduled healthcare utilisation (number of unscheduled clinic visits, lower is better, 1 year)



E.4 At-risk asthma register (12 months after versus 12 months before)

Figure 11: Severe asthma exacerbations (courses of oral steroids prescribed, lower is better, dichotomous baseline vs 12 months)

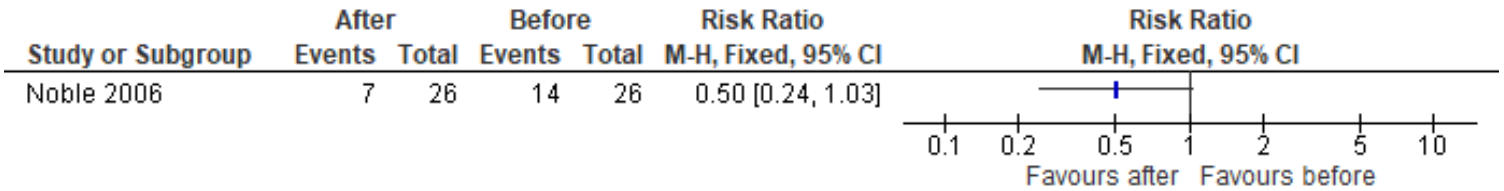


Figure 12: Unscheduled healthcare utilisation (hospital admissions, lower is better, dichotomous baseline vs 12 months)

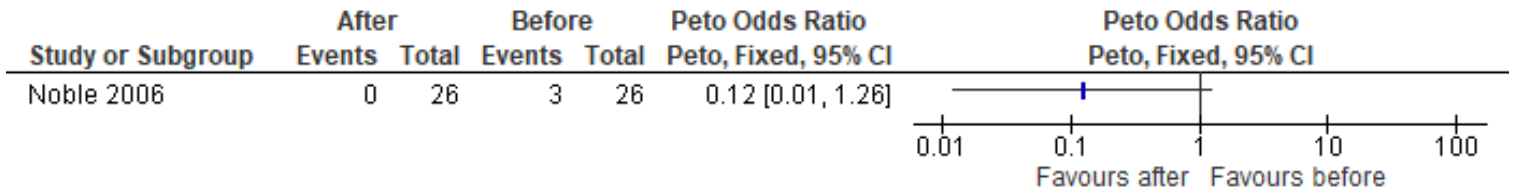
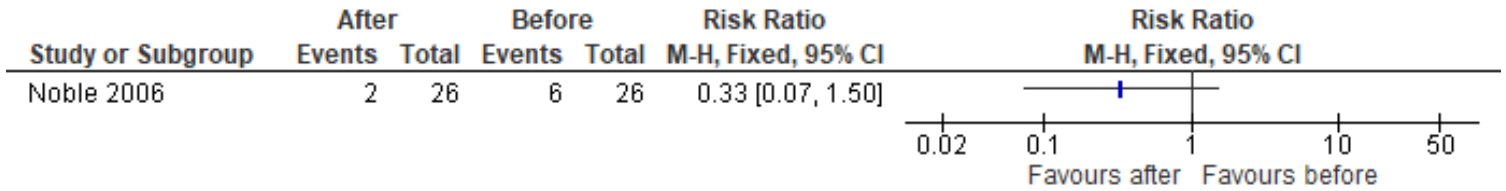


Figure 13: Unscheduled healthcare utilisation (A&E attendance, lower is better, dichotomous baseline vs 12 months)

Figure 15: Unscheduled healthcare utilisation (out-of-hours contacts, lower is better, dichotomous baseline vs 12 months)



E.5 Risk stratified care versus standard care

Figure 16: Severe asthma exacerbations (oral prednisolone course for asthma exacerbation, lower is better, 1 year)

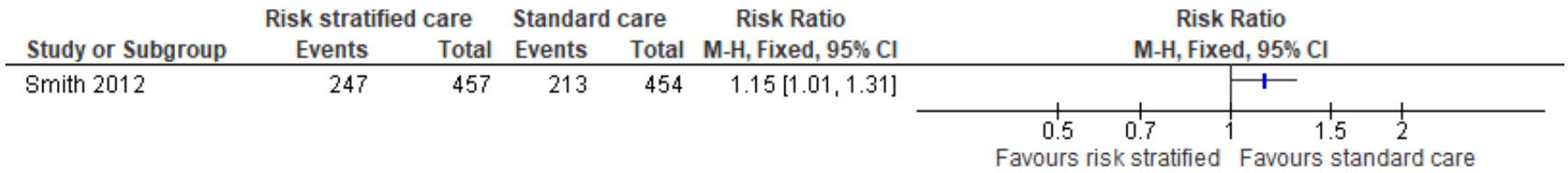


Figure 17: Unscheduled healthcare utilisation (hospitalisation for asthma exacerbation, lower is better, 1 year)

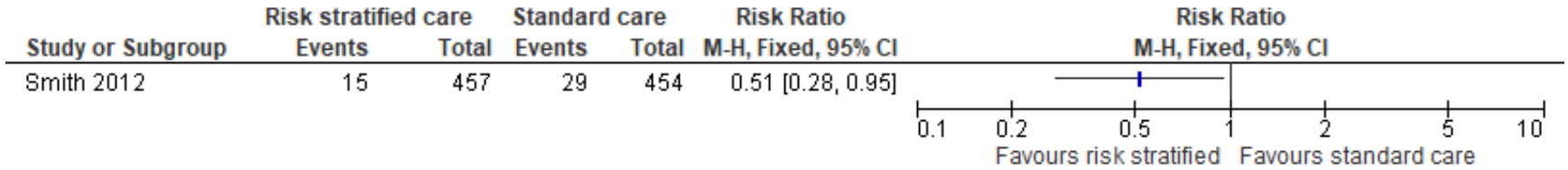


Figure 18: Unscheduled healthcare utilisation (A&E attendance for asthma exacerbation, lower is better, 1 year)

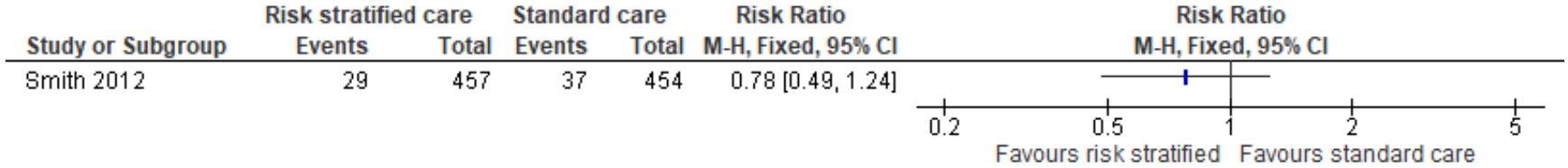
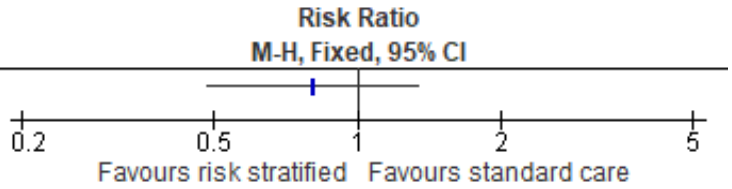


Figure 19: Unscheduled healthcare utilisation (out-of-hours contact for asthma exacerbation, lower is better, 1 year)

Study or Subgroup	Risk stratified care Events	Total	Standard care Events	Total	Risk Ratio M-H, Fixed, 95% CI
Smith 2012	26	457	32	454	0.81 [0.49, 1.33]



Appendix F – GRADE tables

Digital communication technology tools versus usual care in adults

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Digital communication technology tool (text/phone/email)	usual care	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations (no. of oral/injectable corticosteroid bursts per patient, rate adjusted per person year , lower is better, at 6 months)												
1	randomised trials	Very serious[a]	not serious	not serious	not serious[b]	none	1278	655	-	MD **0.01 higher** (0.05 lower to 0.07 higher)	⨁⨁◯◯ Low	CRITICAL
Steroid use (short-acting corticosteroid inhalers dispensed, rate adjusted per person year, lower is better, 6 months)												
1	randomised trials	Very serious[a]	not serious	not serious	not serious[d]	none	1278	655	-	MD **0.27 higher** (0.37 lower to 0.91 higher)	⨁⨁◯◯ Low	CRITICAL
Unscheduled healthcare utilisation (patients with any asthma related after-hour visits/ED visits and/or hospitalisations, lower is better, 6 months)												
1	randomised trials	Very serious[a]	not serious	not serious	serious[c]	none	78/1278 (6.1%)	49/655 (7.5%)	**RR 0.82** (0.58 to 1.15)	**13 fewer per 1,000** (from 31 fewer to 11 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 2 increments because the evidence was at high risk of bias (lack of blinding; handling of missing data in analysis unclear)
b. MID calculated using baseline SD of intervention and control groups/2= 0.37
c. MID calculated using baseline SD of intervention and control groups/2= 3.15
d. Downgraded for imprecision by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Standard MIDs for dichotomous outcomes were 0.8 & 1.25; for continuous outcomes: baseline intervention and control group SD/2 where available or SD/2 of the control group at the time-point reported if baseline scores are not available

Community management intervention versus usual care in adults

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Community management	usual care	Relative (95% CI)	Absolute (95% CI)		
Asthma control (ACQ, scale 0-6, lower is better, t 6-months)												
1	randomised trials	Very serious[a]	not serious	not serious	serious[b]	none	36	34	-	MD **0.1 higher** (0.34 lower to 0.54 higher)	⨁◯◯◯ Very low	CRITICAL
Severe asthma exacerbations (no. Of courses of oral steroids, lower is better, 6 months)												
1	randomised trials	Very serious[a]	not serious	not serious	serious[b]	none	4/36 (11.1%)	9/34 (26.5%)	**RR 0.42** (0.14 to 1.24)	**154 fewer per 1,000** (from 228 fewer to 64 more)	⨁◯◯◯ Very low	CRITICAL
Steroid use (inhaled steroid use, lower is better, 6 months)												
1	randomised trials	Very serious[a]	not serious	not serious	not serious	none	30/36 (83.3%)	28/34 (82.4%)	**RR 1.01** (0.82 to 1.25)	**8 more per 1,000** (from 148 fewer to 206 more)	⨁⨁◯◯ Low	CRITICAL
Unscheduled healthcare utilisation, (ED visits or hospital admissions, lower is better, 6 months)												
1	randomised trials	Very serious[a]	not serious	not serious	very serious[b]	none	6/36 (16.7%)	6/34 (17.6%)	**RR 0.94** (0.34 to 2.65)	**11 fewer per 1,000** (from 116 fewer to 291 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 2 increments because the evidence was at high risk of bias (baseline differences across arms; poor compliance to some aspects of intervention by pharmacists; differential rate of incomplete outcome data across groups; unclear analysis)

b. Downgraded for imprecision by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. Published MID for the ACQ=0.5; MIDs for dichotomous outcomes: 0.8& 1.25

Physician feedback versus usual care in children and young people

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physician feedback	control	Relative (95% CI)	Absolute (95% CI)		
Unscheduled healthcare utilisation (n**umber of hospitalisations, lower is better, 1 year)**												
1	randomised trials	not serious	not serious	not serious	not serious[a]	none	466	463	-	MD **0.02 lower** (0.1 lower to 0.06 higher)	⨁⨁⨁⨁ High	CRITICAL
Unscheduled healthcare utilisation (n**umber of ED visits, lower is better, 1 year)**												
1	randomised trials	not serious	not serious	not serious	not serious[a]	none	466	463	-	MD **0.27 lower** (0.48 lower to 0.06 lower)	⨁⨁⨁⨁ High	CRITICAL
Unscheduled healthcare utilisation (n**umber of unscheduled clinic visits, lower is better, 1 year)**												
1	randomised trials	not serious	not serious	not serious	not serious[a]	none	466	463	-	MD **0.17 lower** (0.39 lower to 0.05 higher)	⨁⨁⨁⨁ High	CRITICAL

a. MIDs for continuous outcomes where baseline SDs are not given are SD/2 of the control group; MIDs= 0.33 for number of hospitalisations, 0.86 for number of ED visits, for number of unscheduled clinic visits 0.86

At-risk register (12 months after versus 12 months before) in adults (including children and young people)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	At-risk register (after)	no at-risk register (before)	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations (**courses of oral steroids, lower is better, dichotomous baseline vs 12 months**)												
1	non-randomised studies	serious[a]	not serious	not serious	serious[b]	none	7/26 (26.9%)	14/26 (53.8%)	**RR 0.50** (0.24 to 1.03)	**269 fewer per 1,000** (from 409 fewer to 16 more)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	At-risk register (after)	no at-risk register (before)	Relative (95% CI)	Absolute (95% CI)		
Unscheduled healthcare utilisation (hospital admissions, lower is better, dichotomous baseline vs 12 months)												
1	Non-randomised trials	serious[a]	not serious	not serious	very serious[b]	none	3/26 (11.5%)	0/26 (0.0%)	**Peto OR 0.12** (0.01 to 1.26)	**120 fewer per 1,000** (from 250 fewer to 20 more)[c]	⨁◯◯◯ Very low	CRITICAL
Unscheduled healthcare utilisation (A&E attendance, lower is better, dichotomous baseline vs 12 months)												
1	Non-randomised trials	serious[a]	not serious	not serious	very serious[b]	none	0/26 (0.0%)	1/26 (3.8%)	**Peto OR 0.14** (0.00 to 6.82)	**40 fewer per 1,000** (from 140 fewer to 60 more)[d]	⨁◯◯◯ Very low	CRITICAL
Unscheduled healthcare utilisation (out-of-hours contacts, lower is better, dichotomous baseline vs 12 months)												
1	non-randomised studies	serious[a]	not serious	not serious	very serious[b]	none	2/26 (7.7%)	6/26 (23.1%)	**RR 0.33** (0.07 to 1.50)	**155 fewer per 1,000** (from 215 fewer to 115 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 1 increment if the evidence was at high risk of bias, and downgraded by 2 increments if the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs; for dichotomous outcomes MIDs= 0.8&1.25

c. Calculated based on the Risk difference: -0.12 (-0.02, 0,25) due to zero events in one arm

d. Calculated based on the Risk difference : -0.04 (-0.14, 0.06) due to zero events in one arm

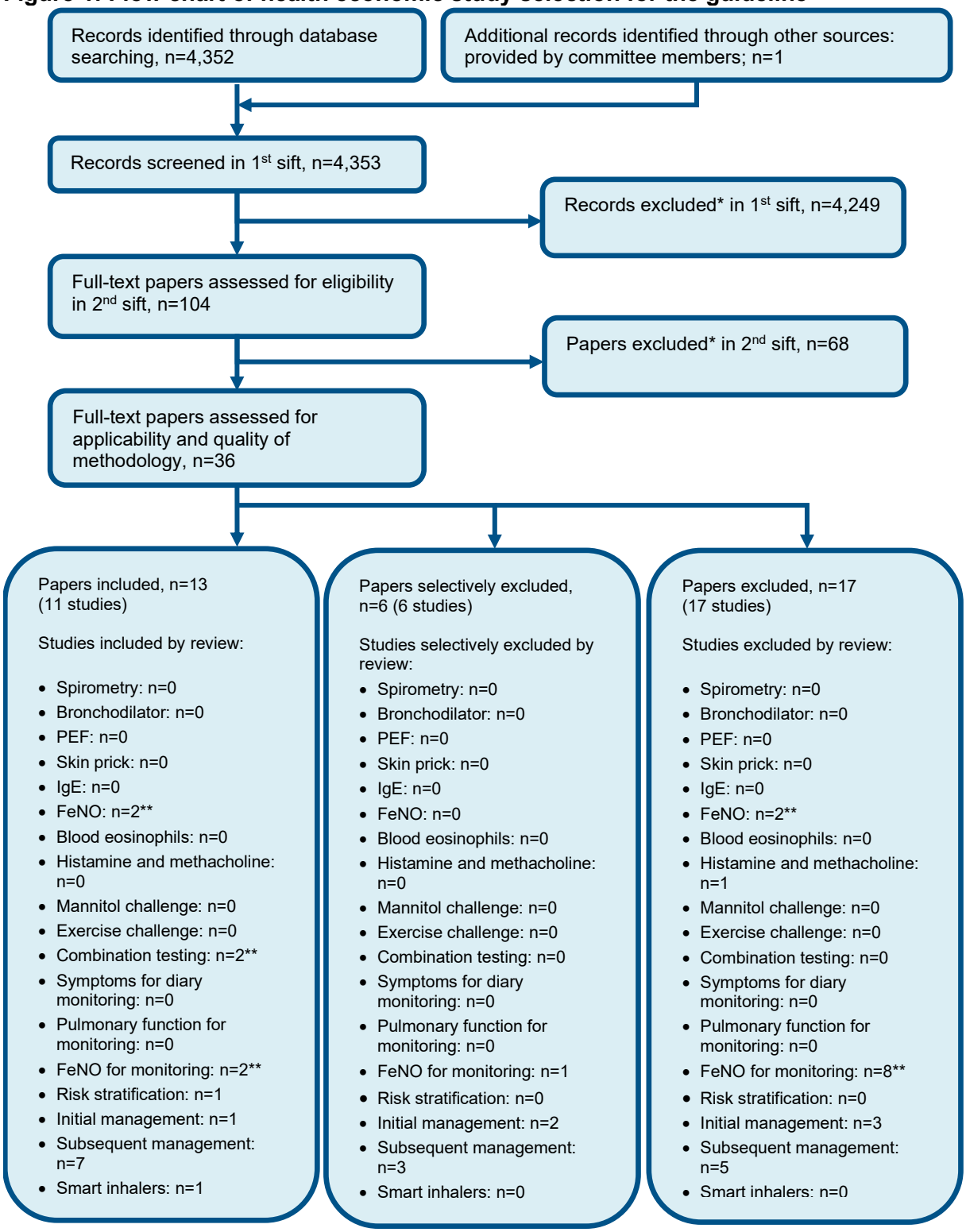
Risk stratification versus standard care in mixed population of adults, children and young people (only 11.8% under 16 years)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Risk stratified care	standard care	Relative (95% CI)	Absolute (95% CI)		
Severe asthma exacerbations (oral prednisolone course for asthma exacerbation, lower is better, 1 year)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	247/457 (54.0%)	213/454 (46.9%)	**RR 1.15** (1.01 to 1.31)	**70 more per 1,000** (from 5 more to 145 more)	⨁⨁⨁◯ Moderate	CRITICAL
Unscheduled healthcare utilisation (hospitalisation for asthma exacerbation, lower is better, 1 year)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	15/457 (3.3%)	29/454 (6.4%)	**RR 0.51** (0.28 to 0.95)	**31 fewer per 1,000** (from 46 fewer to 3 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Unscheduled healthcare utilisation (A&E attendance for asthma exacerbation, lower is better, at 1 year)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	29/457 (6.3%)	37/454 (8.1%)	**RR 0.78** (0.49 to 1.24)	**18 fewer per 1,000** (from 42 fewer to 20 more)	⨁⨁⨁◯ Moderate	CRITICAL
Unscheduled healthcare utilisation (out-of-hours contact for asthma exacerbation, lower is better, 1 year)												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	26/457 (5.7%)	32/454 (7.0%)	**RR 0.81** (0.49 to 1.33)	**13 fewer per 1,000** (from 36 fewer to 23 more)	⨁⨁◯◯ Low	CRITICAL

a. Downgraded for imprecision by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs; for dichotomous outcomes MIDs= 0.8&1.25

Appendix G – Economic evidence study selection

Figure 1: 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 H – Economic evidence tables

Study	Smith 2012(Smith et al., 2012)			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CCA (outcome = asthma exacerbations) **Study design:** Within trial analysis (same paper) **Approach to analysis:** Costs of the intervention and comparator were compared at baseline and 1 year follow-up to calculate the overall change in costs (from baseline to follow-up). The overall change in costs was used to calculate the total incremental costs. **Perspective:** UK NHS **Follow-up:** 1 year **Discounting:** Costs: NA; Outcomes: NA	**Population:** At risk asthma patients identified by clinicians using British asthma guideline criteria. **Patient characteristics:** N (int. 1/ int. 2): 454 / 457 Age: 45.5 Male: 38.7% **Intervention 1:** Usual care: practice-based asthma reviews in nurse-led clinics, plus follow-up in secondary care outpatient clinics and emergency primary and secondary care for some patients as required. **Intervention 2:** Addition of electronic alerts visible to all staff to identify at risk asthma patients. In addition to a one-hour practice-based training session on how to engage with, and improve the routine and emergency management of at-risk asthma patients.	**Change in total costs (mean per patient):** Intervention 1: £149 Intervention 2: £60 Incremental (2−1): saves £89 (95% CI: NR; p=NR) Adjusted for clustering: Incremental (2−1): saves £138 (95% CI: -£1,248 to £910) **Currency & cost year:** 2008 UK pounds **Cost components incorporated:** Intervention costs • Set-up costs • Training costs • Follow-up costs Primary care costs Secondary care costs Out of hours costs Medication costs	**Mean number of people (%) experiencing a moderate-severe asthma exacerbation:** Intervention 1: 245 (53.6%) Intervention 2: 211 (46.5%) Incremental (2−1): 34 fewer (7.1% fewer) (95% CI: NR; p=NR) **Mean number of people (%) hospitalised for asthma exacerbation:** Intervention 1: 15 (3.3%) Intervention 2: 29 (6.4%) Incremental (2−1): 14 fewer (3.1% fewer) (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** NA **Analysis of uncertainty:** To take account of clustering, a two-stage bootstrap procedure was used to estimate the adjusted incremental cost between groups. Incremental cost: saves £177.81 (95% CI -£1,606 to £1,171)

Data sources
Health outcomes: Within trial analysis of cluster randomised trial (same paper). Study conducted within the UK healthcare system with large patient numbers. **Quality-of-life weights:** NA **Cost sources:** PSSRU, NHS reference costs, BNF, Prescription cost analysis
Comments
Source of funding: Asthma UK. **Limitations:** QALYs not reported. Unit costs in the study are presented in 2008 prices and therefore even after they have been adjusted for inflation, these costs may not be reflective of current healthcare costs. Methodology of how costs were calculated is only provided for the intervention and primary care costs. Primary care costs were estimated from a sub-sample of the population with no rationale given. **Other:** NA
Overall applicability:[a] Partially applicable **Overall quality:**[b] Potentially serious limitations

Abbreviations: CCA= cost–consequences analysis; 95% CI= 95% confidence interval; ICER= incremental cost-effectiveness ratio; NR= not reported
(a) Directly applicable / Partially applicable / Not applicable
(b) Minor limitations / Potentially serious limitations / Very serious limitations Intervention number in order of least to most effective (in terms of QALYs)

Appendix I – Health economic model

This area was not prioritised for health economic modelling.

Appendix J – Excluded studies

Study	Exclusion reason
Abdelhamid, E; Awad, A; Gismallah, A (2008) Evaluation of a hospital pharmacy-based pharmaceutical care services for asthma patients. Pharmacy practice 6(1): 25-32	- Conference abstract
Adams, R. and Ruffin, R. (1996) Options in asthma management. Australian family physician 25(3): 309-315	- Full text paper not available
Afolabi, Titilola and Fairman, Kathleen A (2022) Association of Asthma Exacerbation Risk and Physician Time Expenditure With Provision of Asthma Action Plans and Education for Pediatric Patients. The journal of pediatric pharmacology and therapeutics : JPPT : the official journal of PPAG 27(3): 244-253	- Comparator in study does not match that specified in this review protocol *Study examining factors underlying provision of asthma action plans (AAPs); not comparing different types of care*
Anonymous. (2004) Peak expiratory flow rate does not predict asthma exacerbations. Journal of Family Practice 53(8): 608	- Not a peer-reviewed publication
Anonymous. (2012) A Primary Care Register for High-Risk Asthma Patients Prevents Hospitalizations. Journal of the National Medical Association 104(1112): 581	- Conference abstract
Armour, C., Bosnic-Anticevich, S., Brillant, M. et al. (2007) Pharmacy Asthma Care Program (PACP) improves outcomes for patients in the community. Thorax 62(6): 496-502	- Study does not contain an intervention relevant to this review protocol *Patients are not receiving care of different intensity based on any characteristic*
Avery, AJ, Rodgers, S, Cantrill, JA et al. (2009) Protocol for the PINCER trial: a cluster randomised trial comparing the effectiveness of a pharmacist-led IT-based intervention with simple feedback in reducing rates of clinically important errors in medicines management in general practices. Trials 10: 28	- study protocol *related to study not limited to people with asthma*
Baishnab, Elora and Karner, Charlotta (2012) Primary care based clinics for asthma. The Cochrane database of systematic reviews: cd003533	- Systematic review used as source of primary studies
Bartminski, Grzegorz; Crossley, Matthew; Turcanu, Victor (2015) Novel biomarkers for asthma stratification and personalized therapy.	- Review article but not a systematic review

Study	Exclusion reason
Expert review of molecular diagnostics 15(3): 415-30	
Bender, BG, Apter, A, Bogen, DK et al. (2010) Test of an interactive voice response intervention to improve adherence to controller medications in adults with asthma. Journal of the American Board of Family Medicine 23(2): 159-165	- Study does not contain an intervention relevant to this review protocol *No risk stratified care; comparison group unclear and time-point for outcome reporting does not meet protocol (only 10 weeks follow-up)*
Bengtson, Lindsay G S, Yu, Yanni, Wang, Weijia et al. (2017) Inhaled Corticosteroid-Containing Treatment Escalation and Outcomes for Patients with Asthma in a U.S. Health Care Organization. Journal of managed care & specialty pharmacy 23(11): 1149-1159	- Study does not contain an intervention relevant to this review protocol *Study compares outcomes in people who escalated their ICS regime vs people who did not have an escalation; difference in ICS intensity was not based on any defined characteristic increasing the risk of poor outcomes*
Bereznicki, B., Peterson, G., Jackson, S. et al. (2011) The sustainability of a community pharmacy intervention to improve the quality use of asthma medication. Journal of Clinical Pharmacy and Therapeutics 36(2): 144-151	- No relevant outcomes matching protocol
Bjerregaard, A, Laing, I A, Backer, V et al. (2017) High fractional exhaled nitric oxide and sputum eosinophils are associated with an increased risk of future virus-induced exacerbations: A prospective cohort study. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 47(8): 1007-1013	- Study does not contain an intervention relevant to this review protocol *Identifying predictors (characteristics) for future asthma exacerbations, no adjustment of care based on any characteristic*
Blakey, John D, Woolnough, Kerry, Fellows, Jodie et al. (2013) Assessing the risk of attack in the management of asthma: a review and proposal for revision of the current control-centred paradigm. Primary care respiratory journal : journal of the General Practice Airways Group 22(3): 344-52	- Review article but not a systematic review
Boer, Suzanne, Sont, Jacob K, Loijmans, Rik J B et al. (2019) Development and Validation of Personalized Prediction to Estimate Future Risk of Severe Exacerbations and Uncontrolled Asthma in Patients with Asthma, Using Clinical Parameters and Early Treatment Response. The journal of allergy and clinical immunology. In practice 7(1): 175-182e5	- Study does not contain an intervention relevant to this review protocol *identifies characteristics predictive of future risk but does not compare stratified care vs usual care*

Study	Exclusion reason
Burke, Hannah, Davis, Jenny, Evans, Sian et al. (2016) A multidisciplinary team case management approach reduces the burden of frequent asthma admissions. ERJ open research 2(3)	- Comparator in study does not match that specified in this review protocol *MDT care vs no MDT care not stratified according to any characteristic*
Couillard, Simon, Laugerud, Annette, Jabeen, Maisha et al. (2022) Derivation of a prototype asthma attack risk scale centred on blood eosinophils and exhaled nitric oxide. Thorax 77(2): 199-202	- Study does not contain an intervention relevant to this review protocol *Predictors of future asthma attacks; study not comparing risk stratified care with usual care*
Cowie, R.L., Revitt, S.G., Underwood, M.F. et al. (1997) The effect of a peak flow-based action plan in the prevention of exacerbations of asthma. Chest 112(6): 1534-1538	- Comparator in study does not match that specified in this review protocol *no intervention received. Does not meet protocol criteria of usual care*
Craig, Simon S, Dalziel, Stuart R, Powell, Colin Ve et al. (2020) Interventions for escalation of therapy for acute exacerbations of asthma in children: an overview of Cochrane Reviews. The Cochrane database of systematic reviews 8: cd012977	- Comparator in study does not match that specified in this review protocol *Review of Cochrane reviews whose comparison did not match review protocol: examining different pharmacological treatments as secondary treatments*
Cunningham, S, Logan, C, Lockerbie, L et al. (2008) Effect of an integrated care pathway on acute asthma/wheeze in children attending hospital: cluster randomized trial. Journal of pediatrics 152(3): 315-320	- No relevant outcomes matching protocol
Deschildre, A., Beghin, L., Salleron, J. et al. (2012) Home telemonitoring (forced expiratory volume in 1 s) in children with severe asthma does not reduce exacerbations. European Respiratory Journal 39(2): 290-296	- No relevant outcomes matching protocol *data given as median (range) not possible to meta-analyse; comparison does not entirely meet protocol*
Fielding, Shona, Pijnenburg, Marielle, de Jongste, Johan C et al. (2019) Change in FEV1 and Feno Measurements as Predictors of Future Asthma Outcomes in Children. Chest 155(2): 331-341	- Study does not contain an intervention relevant to this review protocol *meta-analysis of RCTs examining changes in spirometric measurements and FeNO and future asthma outcomes*
FitzGerald, J.M.; Boulet, L.-P.; Follows, R.M.A. (2005) The CONCEPT trial: A 1-year, multicenter, randomized, double-blind, double-dummy comparison of a stable dosing regimen of salmeterol/fluticasone propionate with an adjustable maintenance dosing regimen of	- Comparator in study does not match that specified in this review protocol *Incorrect comparison: study compares different pharmacological regimes*

Study	Exclusion reason
formoterol/ budesonide in adults with persistent asthma. Clinical Therapeutics 27(4): 393-406	
Forno, E., Fuhlbrigge, A., Soto-Quiros, M.E. et al. (2010) Risk factors and predictive clinical scores for asthma exacerbations in childhood. Chest 138(5): 1156-1165	- Comparator in study does not match that specified in this review protocol *identifies risk factors predictive of exacerbation but no interventions stratified accordingly*
Frey, U. (2007) Predicting asthma control and exacerbations: Chronic asthma as a complex dynamic model. Current Opinion in Allergy and Clinical Immunology 7(3): 223-230	- Review article but not a systematic review
Grana, J., Preston, S., McDermott, P.D. et al. (1997) The use of administrative data to risk-stratify asthmatic patients. American journal of medical quality : the official journal of the American College of Medical Quality 12(2): 113-119	- Study does not contain an intervention relevant to this review protocol *presentation and validation of model to identify those with asthma at higher risk of hospitalisation; but does not compare stratified care vs usual care*
Hanratty, Catherine E, Matthews, John G, Arron, Joseph R et al. (2018) A randomised pragmatic trial of corticosteroid optimization in severe asthma using a composite biomarker algorithm to adjust corticosteroid dose versus standard care: study protocol for a randomised trial. Trials 19(1): 5	- study protocol
Heaney, Liam G, Busby, John, Hanratty, Catherine E et al. (2021) Composite type-2 biomarker strategy versus a symptom-risk-based algorithm to adjust corticosteroid dose in patients with severe asthma: a multicentre, single-blind, parallel group, randomised controlled trial. The Lancet. Respiratory medicine 9(1): 57-68	- Study does not contain an intervention relevant to this review protocol
Holgate, Stephen T (2013) Stratified approaches to the treatment of asthma. British journal of clinical pharmacology 76(2): 277-91	- Review article but not a systematic review
Leone, F.T., Grana, J.R., Mcdermott, P. et al. (1999) Pharmaceutically-based severity stratification of an asthmatic population. Respiratory Medicine 93(11): 788-793	- Comparator in study does not match that specified in this review protocol *incorrect comparison: study uses model to stratify asthma patients to 5 different severity groups and reports outcomes for the different groups. Does not compare risk stratified care vs non-stratified/usual care*

Study	Exclusion reason
Li, D., German, D., Lulla, S. et al. (1995) Prospective study of hospitalization for asthma: A preliminary risk factor model. American Journal of Respiratory and Critical Care Medicine 151(3i): 647-655	- Comparator in study does not match that specified in this review protocol *examining factors associated with increased risk of hospitalisation; study does not compare stratified care vs usual care*
Luo, Gang, Stone, Bryan L, Sakaguchi, Farrant et al. (2015) Using Computational Approaches to Improve Risk-Stratified Patient Management: Rationale and Methods. JMIR research protocols 4(4): e128	- study protocol
Luo, Gang, Stone, Bryan L, Sheng, Xiaoming et al. (2021) Using Computational Methods to Improve Integrated Disease Management for Asthma and Chronic Obstructive Pulmonary Disease: Protocol for a Secondary Analysis. JMIR research protocols 10(5): e27065	- study protocol *protocol for unpublished study with no relevant comparison*
Marosi, A. and Stiesmeyer, J. (2001) Improving pediatric asthma patient outcomes by incorporation of effective interventions. Journal of Asthma 38(8): 681-690	- Comparator in study does not match that specified in this review protocol *no comparison group*
Mckeever, T., Mortimer, K., Duley, L. et al. (2017) Late Breaking Abstract-Can a self-management plan, which includes a four-fold increase in inhaled corticosteroid dose, reduce severe asthma exacerbations: a randomised, pragmatic trial. European Respiratory Journal 50(supplement61)	- Conference abstract
McKeever, Tricia, Mortimer, Kevin, Wilson, Andrew et al. (2018) Quadrupling Inhaled Glucocorticoid Dose to Abort Asthma Exacerbations. The New England journal of medicine 378(10): 902-910	- Comparator in study does not match that specified in this review protocol *incorrect comparison: study comparing a self-management plan with quadrupling ICS dose vs no increase in the ICS dose*
Navanandan, Nidhya, Hatoun, Jonathan, Celedon, Juan C et al. (2021) Predicting Severe Asthma Exacerbations in Children: Blueprint for Today and Tomorrow. The journal of allergy and clinical immunology. In practice 9(7): 2619-2626	- Review article but not a systematic review
Skeggs, Andrew, McKeever, Tricia, Duley, Lelia et al. (2016) FourFold Asthma Study (FAST): a study protocol for a randomised controlled trial evaluating the clinical cost-effectiveness of	- study protocol

Study	Exclusion reason
temporarily quadrupling the dose of inhaled steroid to prevent asthma exacerbations. Trials 17(1): 499	
Smith, J.R., Noble, M.J., Musgrave, S.D. et al. (2010) The at-risk registers in severe asthma (ARRISA) study: A cluster-randomised controlled trial in primary care. Thorax 65(suppl4): a62	- Not a peer-reviewed publication
Smith, J.R., Noble, M.J., Winder, R. et al. (2019) Initial process evaluation findings from the at-risk registers integrated into primary care to stop asthma crises in the UK (ARRISA-UK) trial: Practice characteristics, engagement and early experiences of the intervention. Thorax 74(supplement2): a184-a185	- Conference abstract
Smith, Jane R, Musgrave, Stanley, Payerne, Estelle et al. (2018) At-risk registers integrated into primary care to stop asthma crises in the UK (ARRISA-UK): study protocol for a pragmatic, cluster randomised trial with nested health economic and process evaluations. Trials 19(1): 466	- study protocol *results not yet published*
Turner, Steve (2016) Predicting and reducing risk of exacerbations in children with asthma in the primary care setting: current perspectives. Pragmatic and observational research 7: 33-39	- Systematic review used as source of primary studies
Yawn, BP, Wollan, PC, Rank, MA et al. (2018) Use of Asthma APGAR Tools in Primary Care Practices: a Cluster-Randomized Controlled Trial. Annals of family medicine 16(2): 100-110	- Comparator in study does not match that specified in this review protocol *not usual care*
Zhang, Yu, He, Jialing, Yuan, Yulai et al. (2019) Increased versus stable dose of inhaled corticosteroids for asthma exacerbations: A systematic review and meta-analysis. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 49(10): 1283-1290	- No relevant outcomes matching protocol *systematic review of studies using a comparison not matching protocol*
Zheng, X, Guan, W, Zheng, J et al. (2012) Smoking influences response to inhaled corticosteroids in patients with asthma: a meta-analysis. Current medical research and opinion 28(11): 1791-8	- Systematic review used as source of primary studies *review and meta-analysis of studies comparing the effectiveness of interventions for asthma in smokers vs non-smokers*

Study	Exclusion reason
Zuurhout, Miranda J L, Vijverberg, Susanne J H, Raaijmakers, Jan A M et al. (2013) Arg16 ADRB2 genotype increases the risk of asthma exacerbation in children with a reported use of long-acting beta2-agonists: results of the PACMAN cohort. Pharmacogenomics 14(16): 1965-71	- Study does not contain an intervention relevant to this review protocol *no risk stratified care vs usual care: case control study of children on ICS with or without LABA*

J.1 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.