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Direct and indirect costs of paediatric asthma in the UK: a cost analysis

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ABSTRACT

Objective To estimate the cost of paediatric asthma from a UK National Health Service (NHS) and societal perspective and explore determinants of these costs.

Design Cost analysis based on data from a large clinical trial between 2017 and 2019. Case report forms recorded healthcare resource use and productivity losses attributable to asthma over a 12-month period. These were combined with national unit cost data to generate estimates of health service and indirect costs.

Setting Asthma clinics in primary and secondary care in England and Scotland.

Main outcome measures Cost per asthma attack stratified by highest level of care received. Total annual health service and indirect costs. Modelled effect of sex, age, severity, number of attacks and adherence on total annual costs.

Results Of 506 children included in the analysis, 252 experienced at least one attack. The mean (SD) cost per attack was £297 (806) (median £46, IQR 40–138) and the mean total annual cost to the NHS was £1086 (2504) (median £462, IQR 296–731). On average, children missed 6 days of school and their carers missed 13 hours of paid work, contributing to a mean annual indirect cost of £412 (879) (median £30, IQR 0–477). Health service costs increased significantly with number of attacks and participant age (>11 years). Indirect costs increased with asthma severity and number of attacks but were found to be lower in older children.

Conclusions Paediatric asthma imparts a significant economic burden on the health service, families and society. Efforts to improve asthma control may generate significant cost savings.

Trial registration number ISRCTN 67875351.

INTRODUCTION

Asthma affects between 5% and 10% of children in the UK.^{1–3} Asthma attacks are common, can be life threatening and impose a considerable economic burden on the health service, families and society.^{4–7} It has been estimated that provision of care for all patients with asthma costs the National Health Service (NHS) £3.03 billion per year.⁶

The cost of asthma is known to be associated with severity and control; more severe and less controlled asthma is linked to the greatest healthcare resource use (HCRU).^{8–10} There is a lack of recently published studies that have quantified the economic burden that paediatric asthma imposes on the health system and society in the UK. This may limit the ability of planners and commissioners to accurately budget for the delivery of asthma services

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Direct and indirect costs of paediatric asthma in the UK have not been estimated for many years.
- ⇒ Older data indicate that costs to the health service are higher for those with more severe and uncontrolled asthma due to an increased requirement for hospital care.
- ⇒ The condition is associated with considerable indirect costs arising from days missed from school and carers having to take time off work to care for children.

WHAT THIS STUDY ADDS

- ⇒ This study provides detailed contemporary healthcare resource use and productivity loss estimates resulting from paediatric asthma over a 1-year period, and quantifies their relationship with patient and disease characteristics.
- ⇒ Annual costs to the health service are more than threefold higher for children who experience three to four attacks compared with those with no attacks.
- ⇒ Productivity losses are 1.7 times higher for families of participants with more severe (British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) step 4) versus less severe (BTS/SIGN step 2) disease, and 6.7 times higher for those who experience three to four attacks per year compared with no attacks.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ This study highlights the potential economic savings of improved asthma treatment to reduce the number of attacks.
- ⇒ The estimates of resource use and cost can serve as key inputs to service planning and future economic modelling studies of asthma interventions and initiatives.

or determine the potential value of initiatives to improve its control. To address this evidence gap, we use data collected from a randomised controlled trial (RCT) which recruited children with asthma between 2017 and 2019 to describe the direct and indirect costs of childhood asthma in the UK.

METHODS

Study design

The Reduced Asthma Attacks in Children using Exhaled Nitric Oxide (RAACENO) trial recruited



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509 children from centres across the UK between 2017 and 2019, the majority (97%) from secondary care. Participants were aged 6–15 years, diagnosed with asthma, treated with inhaled corticosteroids and had at least one asthma attack in the past year. The trial found no evidence for a difference in clinical outcomes or costs between the randomised treatment groups (FeNO plus symptom-guided treatment or symptom-guided treatment alone), justifying the pooling of data for this cost analysis. Full details of the trial results, objectives and design are available elsewhere.¹¹

Data collection

Data were collected retrospectively from parent-held diaries and case report forms (CRFs) completed during four clinic assessments at 3-month intervals throughout the follow-up period. The information relevant to this analysis included asthma medications, treatment adherence, number of asthma attacks and associated healthcare use, other asthma-related healthcare use and participant and carer time lost from usual activities.

Cost estimation methods

The analysis took a UK NHS perspective for HCRU and a societal perspective for time losses. All costs are expressed in 2019/2020 UK sterling using the NHS inflation indices where necessary.¹² The costs incurred during each quarterly time interval were summed at the individual level across all observations over the 1-year follow-up period.

Three categories of asthma-related HCRU were identified from the CRFs: (1) HCRU associated with attacks; (2) HCRU not associated with attacks; and (3) medication. Direct NHS costs under each category were calculated by multiplying the reported HCRU by nationally representative unit costs (online supplemental table 1).^{12–14} Staff time required for pharmacist and NHS 111 contacts were informed by external literature.^{15 16} The cost of medications was sourced from the British National Formulary (BNF) and combined with the prescribed dose (online supplemental table 2).¹⁷ An NHS confidential discount is available for omalizumab injections. For this analysis we used the list price.¹⁸

Indirect costs were measured using the human capital approach.¹⁹ Time displaced was categorised as: school, leisure, study and paid or unpaid work. Details of the unit costs applied to time losses are presented in online supplemental material 1.

Statistical analysis

Data were summarised using the mean, SD, median and IQR for continuous variables, and numbers and percentages for categorical variables. While healthcare cost data are often right skewed, whereby a minority of high-resource patients lift the mean above the median, the analysis and interpretation focuses on the mean as the most relevant measure of budgetary impact.²⁰ All analyses were conducted using STATA V.15.²¹

Missing data were minimised by asking about patient-reported resource use and time losses at each attended clinical assessment visit, covering the time elapsed since the last attended visit. If patients failed to attend their final follow-up assessment, they were followed by phone to collect data on all attacks and associated resource use. We assessed the sensitivity of results to missing data using multiple imputation with chained equations.²²

Generalised linear models (GLM) were used to explore the effect on total cost of several covariates: age, sex, asthma severity, number of attacks and treatment adherence. Age was categorised as per the minimisation criteria used in the RAACENO

trial (<11 years; ≥11 years). Asthma severity was categorised by level of asthma medication using the British Thoracic Society (BTS) / Scottish Intercollegiate Guidelines Network (SIGN) step system.²³ Adherence was measured on a scale between 0 and 1 (online supplemental material 2 and online supplemental table 3), with a value of ≥70% defined as adherent. The number of attacks was categorised as 0, 1–2, 3–4 or ≥5, to allow for non-linearity in the relationship between number of attacks and cost. The cost of study assessment visits was excluded from the GLM analysis of direct health service costs, as these were potentially protocol driven and invariable between patients. GLM results are expressed in terms of the average effect of each variable on the model's predicted cost. Given the skewed nature of the data, gamma family and log link functions were specified based on findings of modified Park and Box-Cox tests of functional form.^{24 25} A high proportion of zero values were observed for indirect costs, which creates challenges for statistical modelling. A two-part model was specified with a probit model first used to predict the probability of reporting time losses combined with a GLM model to predict costs among those with time losses.²⁶ These models are combined to estimate the effects of covariates on total indirect costs. Both models used robust SEs clustered by centre number. The trial was registered with the ISRCTN registry (ISRCTN 67875351).

RESULTS

Baseline characteristics

There were 509 participants recruited of whom 506 were included in the analysis. We have previously shown that the RAACENO participants were comparable to children attending secondary care asthma clinics in the UK.¹¹ Most patients (85%) were on step 3 or step 4 BTS/SIGN treatment levels and 56% had an inpatient admission for asthma in the year preceding recruitment (table 1).

Direct cost to the health service

Attacks

There were 509 attacks observed in 252 participants during follow-up. Associated HCRU data were available for 244 participants (497 attacks), with 49 (61 attacks) requiring inpatient hospital admission. The mean cost per attack was £297 (SD: 806) and the median was £46 (IQR: 40, 138). Table 2 presents the cost per attack overall and by the highest level of care received. The average number of healthcare contacts is provided in online supplemental table 4. Most attacks (n=291) were treated in primary care, predominantly by a general practitioner. Where secondary care was required, participants were typically treated in the emergency department, followed by hospital inpatient admissions. No healthcare contact was made for 46 attacks (29 participants) which were treated with a course of oral steroids available at home. Results by treatment group are provided in online supplemental table 5.

Total HCRU

Besides attack-related HCRU and study follow-up assessments, a large proportion of participants (n=225/443) did not report any additional HCRU. Table 3 reports the mean total cost of asthma-related HCRU over the trial follow-up period. The mean cost of asthma is driven by participants who had multiple attacks, required inpatient hospitalisation and were prescribed high-cost omalizumab (n=13/432). All participants used a preventer (inhaled corticosteroid±long-acting beta agonist) and reliever inhaler. Other medication use included leukotriene receptor

Table 1 Baseline characteristics

	N	n/Mean	%/SD	Median	IQR
Sex, male (n, %)	506	306	60.5		
Age, years (mean, SD)	506	10.1	2.6	10	(8, 12)
<11 (n, %)	506	285	56.3		
≥11 (n, %)	506	221	43.7		
Age at diagnosis, years (mean, SD)	503	3.8	2.6	3	(2, 5)
Weight, kg (mean, SD)	502	39.9	16.4	36.7	(27.6, 48.6)
Centre, secondary (n, %)	506	490	96.8		
Treatment level* (n, %)					
BTS/SIGN step 2	506	76	15.0		
BTS/SIGN step 3	506	217	42.9		
BTS/SIGN step 4	506	213	42.0		
Controlled† (n, %)	506	256	50.6		
Hospital admissions in the last year (n, %)					
None	506	221	43.7		
1–2	506	201	39.7		
3–4	506	55	10.9		
≥5	506	29	5.7		
Days absent from school in the last year (mean, SD)	504	15.0	14.4	10	(4.8, 20.0)
Oral steroid courses in the last year, count (mean, SD)	506	3.6	3.0	3	(1, 5)
Prescription details					
LTRA (n, %)	506	303	59.9		
Reliever inhaler (n, %)	506	506	100		

*Treatment levels based on the British Guideline on the Management of Asthma.²³
†Asthma Control Test score ≥20.
BTS, British Thoracic Society; LTRA, leukotriene receptor antagonist; SIGN, Scottish Intercollegiate Guidelines Network.

antagonist (n=287/432), theophylline (n=50/432) and ciclosporin (n=6/432). A detailed breakdown of cost by treatment group and corresponding HCRU is found in online supplemental tables 6 and 7.

Table 2 Healthcare cost associated with each attack stratified by highest level of care received

	All		Primary		Secondary		At home*	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Number of participants (N=244/252)†	244		171		115		29	
Number of attacks (N=497/509)‡	497		291		160		46	
Total cost per attack	£297	806	£57	52	£819	1271	£1.41	2.63
Primary care	£42	51	£55	52	£30	47		
GP	£31	33	£42	27	£21	39		
Nurse	£2.03	8.19	£2.09	8.42	£2.52	8.87		
NHS 24/111	£1.07	4.92	£1.07	5.97	£1.38	4.01		
Out-of-hours GP service	£5.66	37	£7.63	47	£3.70	18		
Walk-in centre	£1.75	9.69	£2.36	11	£1.14	7.16		
Pharmacist	£0.03	0.43	£0.02	0.40	£0.04	0.54		
Secondary care	£253	812			£787	1277		
Emergency department	£23	54			£71	74		
Hospital outpatient	£4.21	26			£13	45		
Hospital inpatient	£220	814			£684	1323		
Day case	£1.58	25			£4.92	44		
Ambulance	£4.56	37			£14	64		
Medication	£1.65	1.95	£1.66	1.81	£1.71	1.99	£1.41	2.63

*One-week course of 5 mg prednisolone per day.
†N=patients with attacks with complete resource use data/observed number of patients with attacks.
‡N=attacks with complete resource use data/observed attacks.
GP, general practitioner; NHS, National Health Service.

Table 3 Total healthcare resource use costs observed during trial follow-up

Category (patients contributing data (N))	Patients reporting any resource use (n (%))	Costs (£)			
		Mean*	SD	Median*	IQR
Total including clinical study visits (N=430)†	430 (100)	£1846	2514	£1230	(1055, 1518)
Total excluding clinical study visits (N=430)	430 (100)	£1086	2504	£462	(296, 731)
Attack related (N=498)	244 (49.0)	£604	1284	£140	(57, 393)
Primary care	206 (41.4)	£101	99	£79	(40, 119)
Secondary care	115 (23.1)	£1095	1698	266	(133, 1906)
Oral steroid	244 (49.0)	£3.36	4.45	£2.11	(0.36, 4.78)
Not associated with attacks (N=443)	218 (49.2)	£295	650	£133	(40, 250)
Primary care	178 (40.2)	£90	90	£50	(40, 114)
Secondary care	102 (23.0)	£476	888	£204	(133, 408)
Medication‡	4 (0.9)	£1.75	0.00	£1.75	(1.75, 1.75)
Medication for asthma management (N=432)	432 (100)	£647	2092	£345	(234, 433)
Immunoglobulin injections (omalizumab)	13 (3.0)	£10 824	5592	£11 150	(4520, 14 736)
Clinical study visits (N=506)†	481 (95.0)	£721	167	£816	(612, 816)

*Cost for those incurring any resource use (excluding those with zero cost).
†Quarterly clinical study visits were excluded from the regression analysis of cost determinants.
‡In addition to medication prescribed at regular monitoring visits for the participant's asthma.

Indirect cost

Table 4 summarises participant-reported time losses from productive activities and corresponding indirect costs for those reporting time losses. Most participants reported missing days of school due to asthma. Approximately half (52%) of adult family and carers reported time losses, mostly from paid employment.

Table 4 Indirect costs of asthma captured over the trial follow-up

Category (patients contributing (N))	Patients reporting any time losses (n (%))	Mean*	SD	Median*	IQR
Days displaced (child) (N=443)	333 (75.2)	8.2	9.2	5	(2, 11)
School	332 (74.9)	7.9	9.0	5	(2, 11)
Paid employment	45 (10.2)	2.6	2.3	2	(1, 3)
Hours displaced (adults†) (N=443)	225 (50.8)	56	85	26	(12, 60)
Paid employment	161 (36.3)	36	42	20	(8, 44)
Unpaid work	103 (23.3)	45	71	18	(7, 56)
Leisure	58 (13.1)	29	51	8	(4, 25)
Study	24 (5.4)	21	29	8.5	(4, 23)
Indirect costs (child)‡ (N=443)	45 (10.2)	£90	80	£70	(35, 104)
Indirect costs (adults†) (N=443)	219 (49.4)	£816	1096	£470	(159, 936)
Paid employment	161 (36.3)	£709	837	£397	(159, 874)
Unpaid work	103 (23.3)	£543	854	£216	(84, 673)
Leisure	58 (13.1)	£148	257	£40	(20, 126)
Total cost (N=443)	229 (51.7)	£798	1090	£451	(159, 914)

*Cost reported for those incurring any resource use (excluding those with zero cost).
†Any adult relative or carer of the participant.
‡Does not include indirect costs associated with time losses from education.

The mean indirect cost in the population, inclusive of those reporting zero time losses, was £412 (SD: 879). The median was £30 (IQR: 0, 477). On average, participants reported missing 5.9 (SD: 8.5) days of school. Results by treatment allocation group are provided in online supplemental table 8.

Table 5 Results of the GLM model of direct health service costs and the two-part model of indirect costs presented in terms of predictive margins and average marginal effects

Covariates	Direct cost (N=430)					Indirect cost (N=443)				
	Predictive margins	SE	Marginal effect	SE	P value*	Predictive margins	SE	Marginal effect	SE	P value*
Predicted cost	£1104	250				£415	45			
Sex										
Male	£1208	340				£405	60			
Female	£961	146	−£247	235	0.20	£431	53	£26	73	0.86
Age (years)										
<11	£885	162				£509	64			
≥11	£1423	425	£538	303	<0.01	£293	50	−£217	74	<0.01
Treatment level†										
BTS/SIGN step 2	£974	236				£275	52			
BTS/SIGN step 3	£1122	431	£148	426	0.72	£393	51	£118	66	0.06
BTS/SIGN step 4	£1113	153	£139	272	0.62	£465	80	£191	87	<0.01
Number of attacks										
0	£736	259				£144	28			
1–2	£1138	262	£402	122	<0.05	£504	60	£361	64	<0.01
3–4	£2302	588	£1565	562	<0.01	£985	185	£841	185	<0.01
≥5	£2188	434	£1452	417	<0.01	£1114	289	£970	281	<0.01
Adherence										
Not adherent (<70%)	£807	86				£317	60			
Adherent (≥70%)	£1271	354	£464	297	<0.05	£464	54	£146	70	0.11

*P value from generalised linear model (GLM) regression.

†Treatment levels based on the British Guideline on the Management of Asthma.²³

BTS, British Thoracic Society; SIGN, Scottish Intercollegiate Guidelines Network.

Determinants of total direct and indirect costs

The results from GLMs of direct and indirect costs are presented in table 5, in terms of the effect of each explanatory variable on modelled cost. The direct cost model predicts costs of £2841 (SE: 658) for patients ≥11 years old with more severe asthma (BTS step 4) who experience ≥5 attacks in the year. Patients <11 years old, with less severe asthma (BTS step 2), who experience no attacks, are predicted to cost the NHS £521 (SE: 137). A similar pattern was observed for indirect cost, but with a negative association for age. The probability of reporting no time losses was 0.65 (SE: 0.04, p<0.01) if the participant experienced no attacks.

The mean adherence was 72.5% (SD: 20.0). Adherence was found to be predictive of direct cost (p=0.03); adherent patients were projected to cost £464 (SE: 298) more than non-adherent. Previous asthma studies^{27 28} defined 'adherent' as ≥80%. Under this definition, adherence was not found to be a predictor of direct cost (p=0.93). The estimates were robust to missing data assumptions, with similar results obtained using multiple imputation. In a further sensitivity analysis which removed participants who received omalizumab, the effects of age and adherence on direct costs were no longer significant, and the predicted annual direct costs were substantially lower (£728) (online supplemental table 9).

DISCUSSION

This study provides detailed estimates of the cost of paediatric asthma from both the NHS and societal perspective, for a population prone to attacks, followed up mainly in secondary care. The cost per attack to the health service (£297) was driven by hospital inpatient admissions, despite only 12% of attacks leading to admission. The mean cost to the health service was £1086 per participant over the 12-month follow-up period, inclusive

of £647 for medication, £296 of attack-related resource use and £145 for other resource use. Participants missed on average 5.9 (SD: 8.5) days of school and parents and carers missed 13.0 (SD: 30.6) hours of work in relation to the child's asthma. These findings highlight the often unrecognised costs of asthma to children and families.

The higher direct cost for older relative to younger children and the unexpected finding of higher cost for adherent compared with non-adherent children can be explained by omalizumab prescribing being clustered in more adherent children over the age of 11, at a cost of up to £18 078 per year based on the list price. Just 13 participants received this medication, 10 of whom were >11 years old and had adherence >70%. Adherence and age were no longer predictive of direct costs when these participants were removed from the analysis. The finding of lower indirect costs for older participants may be explained by families becoming more knowledgeable of the condition as children age, and therefore better able to manage it without taking time off work. We also know that severity and control improve as children age,^{29 30} so we may be observing a mediation between asthma severity and age.

A strength of this analysis is that it is based on data from a large multicentre RCT conducted in England and Scotland. A high degree of complete data was achieved, particularly in relation to attack-related resource use. The number of attacks, hospitalisations and school days missed were substantially higher in the year preceding randomisation. It is unclear if such improvement would be achieved outside the trial setting, meaning that 'real world' costs might be higher. Data may be subject to protocol biases as participants attended clinical assessments more regularly than in routine practice and may have had better control as a result. It would be of value to externally validate these findings using observational data. Nevertheless, our estimated cost per attack, and effects of covariates on direct and indirect costs, should be generalisable to the wider paediatric asthma population. A further weakness is that our study did not collect information regarding attack severity. There is scope to better understand the determinants of attack cost to the NHS given the high variability observed. There are also limitations of how adherence was measured and defined, with some discrepancies between different sources leading to uncertainty regarding its accuracy. Finally, our estimate of indirect costs is restricted to productivity losses arising from absenteeism. It does not capture presenteeism so may underestimate the full indirect costs of asthma.

There is a paucity of contemporary studies reporting on the cost of paediatric asthma in the UK.^{8 10} Kerkhof *et al* reported a mean annual HCRU cost of £861 (2015 prices) for patients with severe, uncontrolled eosinophilic asthma. Our estimate for secondary care managed paediatric asthma, inclusive of quarterly clinical assessment visits, is higher at £1846. This may be explained by differences between the study populations—only 2% of the population reported by Kerkhof *et al* were under 18 years of age—and more intensive routine monitoring within the RAACENO trial. Gokhale *et al*⁸ assessed the HCRU of 265 paediatric asthma patients aged 6–17 years in England who had severe refractory asthma. During a 1-year period, 42.6% of patients experienced at least one oral corticosteroids (OCS)-defined attack (excluding attacks treated at home), and 24.5% of attacks resulted in a hospital attendance. In RAACENO, we found that 48.6% (242/498) of participants experienced at least one attack requiring contact with primary or secondary care, with 35.5% of these resulting in secondary care contact.

Our results with respect to productivity losses are broadly consistent with those reported in the literature. Based on a review of published evidence, Nunes *et al* reported that a child experiencing an exacerbation can expect to miss 3–5 days of school, with parents missing a similar number of days of work.⁵ RAACENO participants experienced two attacks on average. Those who experienced at least one attack reported missing 9.4 (SD: 10.3) days of school and their carers reported missing 20.9 (SD: 39.2) hours of paid work.

The results of this study can support the planning of asthma services for similar populations. This is directly relevant to initiatives to improve asthma care and outcomes in the NHS such as phase 1 of the National Bundle of Care for Children and Young People with Asthma.³¹ It is estimated there are currently 1.1 million children receiving treatment for asthma in the UK.³² A recent UK-based cohort study of children with asthma in primary care suggests an annual attack rate of at least 0.18 per patient-year.³³ Assuming our cost per attack estimate is generalisable to attacks experienced by the wider paediatric asthma population, the expected annual cost of asthma attacks would be in the region of £59.2 million at the population level ($1.1M \times 0.18 \times \297). Acknowledging the caveats around generalisability of hospitalisation rates for attacks observed in the RAACENO study, this simple calculation illustrates how our results could be used to inform service planning and future modelling initiatives.

In conclusion, paediatric asthma imparts a significant economic burden on the health service, families and society. Our data provide a useful input to future studies that seek to model the broader costs and savings of efforts to improve paediatric asthma control and reduce attack frequency.

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Contributors ST was the chief investigator of the RAACENO trial and contributed to the conception and design of the trial, conduct of the trial, recruitment and follow-up of participants, and the interpretation of results. SC was the trial manager and contributed to the design and conduct of the trial, the interpretation of results, and was responsible for the day-to-day management of the trial. GS was the senior health economist on the RAACENO trial and oversaw the health economic analysis and contributed to the interpretation of results. CK was responsible for the health economic analysis of the RAACENO trial and contributed to the interpretation of results. CK, GS, ST and SC contributed to the analysis plans for the cost analysis reported in this paper. CK conducted the data analysis and wrote the first draft of the manuscript. CK, GS, ST and SC revised it critically for important intellectual content and gave approval for final submission. GS is the guarantor for this research and publication.

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Supplemental material

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Supplemental material 1: Calculation of indirect costs and outcomes

A cost per hour was applied dependent upon the activity reported. The value of time forgone by carers from for paid employment was determined using a weighted average of the age distribution of the parents of primary school age children (1) against the gross average wage rates by age from the Annual Survey of Hours and Earnings (ASHE). (2) Time lost from unpaid work for carers was valued using the average cost per hour of housework, volunteering and informal care published by the Office for National Statistics (ONS). (3) The value of time lost from leisure activities was valued using the current value of non-working time published by the Department of Transport. (4) Time lost from paid employment for participants was estimated using an 8-hour workday multiplied by the national minimum wage. (5)

We did not apply a unit cost for time losses from education (i.e., study or school days), as there is no accepted monetary value. Therefore, we present educational losses in unvalued units of time.

Supplemental material 2: Calculation of adherence score

Asthma management medication (i.e., ICS inhalers) adherence was measured using a variety of factors during the trial. This was through smart inhaler devices, research nurse opinion and family reported adherence at quarterly trial follow up visits. All adherence outcomes were reported in the trial Case Report Forms (CRFs).

The smart inhaler records daily adherence as a percentage measure – where a score $\geq 70\%$ was defined as “adherent” in the trial. However, several issues were found with the smart inhaler measurement. (6) Firstly, it was not possible to capture the adherence data where follow-up visits were carried out over the phone. Secondly, missing data issues were also observed where the participant would forget the inhaler at their follow-up visit. Finally, the smart inhaler score was not always consistent with the other two measures of adherence: research nurse opinion and family reported adherence. The discordance between measures can be attributed to technical issues of the device in recording and uploading the data and user issues where participants had two smart inhalers or where the device was insufficiently charged for example.

Therefore, to calculate a score of adherence we constructed an algorithm which takes all three measures to alleviate issues where the smart inhaler under-estimated true adherence (Online supplementary material table 3). Using this measure, it is possible that where a participant scores 0% on the smart inhaler, they can still score 100% if the family and clinical team are of the opinion the participant used their inhaler “all of the time”.

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Supplemental tables

Supplemental table 1: Unit cost of health care contacts

Resource use	Type of contact	Unit cost	Source
Primary care			
GP	Visit to surgery	£39.65	PSSRU 2019 (£4.30 per minute of staff time at average consultation length of 9.22 minutes)(7,8)
	Phone	£23.22	PSSRU 2019 (£4.30 per minute of staff time at average phone consultation length of 5.4 minutes) (7,8)
Community asthma nurse	Visit to surgery	£28.00	PSSRU 2019 ⁶⁹ (£84 per hour of participant contact of band 6 GP nurse at average Nurse consultation visit length of 20minutes)(7)
	Home visit	£23.14	PSSRU 2010 (Inflated to 2019 prices)(9)
	Phone	£7.97	PSSRU 2019 (£84 per hour of participant contact of band 6 GP nurse at average nurse phone consultation length of 5.69 minutes) (7,8)
	NHS 24/111	£12.96	Pope, Turnbull et al. (2017). £12.26 inflated to 2019 prices using the PSSRU inflation indices.(7,10)
	Out of hours GP service	£74.02	Weighted average of T03A & T03NA (excluding emergency dental), NHS reference costs 2018/19.(11)
	Walk-in centre	£45.71	Weighted average of T04A & T04NA (excluding emergency dental), NHS reference costs 2018/19. (11)
	Pharmacist	£6.82	9.22 minutes of band 6 community-based scientific and professional staff. (7,10)
Secondary care			
Emergency department	Non-admitted	£133.00	VB09Z Emergency medicine, category 1 investigation with category 1-2 treatment (type 1 non-admitted) ⁷²
	Admitted	£264.00	Weighted average of VB06Z and VB04Z ⁷³ by severity of admission. (11)
Hospital Outpatient	Consultant visit	£204.00	CL WF01C, Non-admitted Face-to-Face attendance, Follow-up. Paediatric Respiratory Medicine. (11)
	Consultant phone	£105.00	CL WF01C, Non-admitted Non-Face-to-Face attendance, Follow-up. Paediatric Respiratory Medicine. (11)
	Nurse visit	£133.00	CHS NURS N08CF F2F, Child, Specialist Nursing, Asthma and Respiratory Nursing/Liaison, Child, Face to face. (11)

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	Nurse phone	£24.00	CHS NURS N08CF, Child. Specialist Nursing, Asthma and Respiratory Nursing/Liaison, Child, Non-face to face. (11)
	Day case	£394.00	DC, Weighted average of PD12 Paediatric Asthma or Wheezing. (11)
	Bronchoscopy	£952.00	DZ69B Diagnostic Bronchoscopy, 18 years and under, Combined day case/ordinary elective spell tariff. Admitted participant care & outpatient procedure prices 2018/19. Annex A.(12)
Hospital inpatient	Short stay (≤1 night)	£594.00	NES, Weighted average of PD12 Paediatric, Asthma or Wheezing. (11)
	Long stay	£1,913.00	NEL, Weighted average of PD12 Paediatric, Asthma or Wheezing. Inflated to 2019 prices. (7,11)
	Excess bed days	£575.00	NEL excess bed day, Weighted average of PD12 Paediatric, Asthma or Wheezing. Inflated to 2019 prices. (7,11)
Ambulance	See & treat	£209.00	AMB ASS01. (11)
	See & convey	£257.00	AMB ASS02. (11)
	Clinical psychologist	£54.00	1 hour of a clinical psychologist's time. Band 7 scientific and professional staff.(7)
	Physiotherapist	£57.00	1 hour of a specialist (respiratory problems) physiotherapist's time. Band 7 Hospital-based scientific and professional staff. (7)
	Speech and language therapist	£34.00	1 hour of a speech therapist's time. Band 5 scientific and professional staff. (7)

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Supplemental table 2: Unit cost of medication sourced from the British National Formulary for Children

Name	NHS indicative price	Pack size/ Doses	Description
Prednisolone	£31.24	28	Prednisolone 20mg tablets (A A H Pharmaceuticals Ltd)
Dexamethasone	£7.62	50	Dexamethasone 2mg tablets (A A H Pharmaceuticals Ltd)
Amoxicillin	£1.75	21	Amoxicillin 500mg capsules (A A H Pharmaceuticals Ltd)
Paracetamol (liquid)	£4.40	200	200ml Calpol Six Plus 250mg/5ml oral suspension sugar free (McNeil Products Ltd)
Paracetamol (tablet)	£1.19	16	Anadin Paracetamol 500mg tablets (Pfizer Consumer Healthcare Ltd)
Ibuprofen	£1.57	12	Nurofen 200mg tablets (Reckitt Benckiser Healthcare (UK) Ltd)
Omalizumab (75mg)	£128.07	1	Xolair 75mg/0.5ml solution for injection pre-filled syringes (Novartis Pharmaceuticals UK Ltd)
Omalizumab (150mg)	£256.15	1	Xolair 150mg/1ml solution for injection pre-filled syringes (Novartis Pharmaceuticals UK Ltd)
Theophylline	£2.96	56	Uniphyllin Continus 200mg tablets (Napp Pharmaceuticals Ltd)
Ciclosporin	£48.50	30	Capimune 100mg capsules (Mylan)
Preventer inhaler			
Beclomethasone	£3.70	200	Beclomethasone (Clenil) 50 mcg MDI/spacer
	£7.42	200	Beclomethasone (Clenil) 100 mcg MDI/spacer
	£16.17	200	Beclomethasone (Clenil) 200 mcg MDI/spacer
Budesonide	£14.25	200	Pulmicort 100 Turbohaler (AstraZeneca UK Ltd)
	£14.25	100	Pulmicort 200 Turbohaler (AstraZeneca UK Ltd)]
	£14.25	50	Pulmicort 400 Turbohaler (AstraZeneca UK Ltd)
Budesonide with formoterol	£28.00	120	Symbicort 100/6 Turbohaler (AstraZeneca UK Ltd)
	£28.00	120	Symbicort 200/6 Turbohaler (AstraZeneca UK Ltd)
	£28.00	60	Symbicort 400/12 Turbohaler (AstraZeneca UK Ltd)
Fluticasone	£4.00	60	Flixotide 50micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
	£8.00	60	Flixotide 100micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
	£6.53	120	Flixotide 50micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
	£21.26	120	Flixotide 125micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
Fluticasone with vilanterol	£22.00	30	Relvar Ellipta 92micrograms/dose / 22micrograms/dose dry powder inhaler (GlaxoSmithKline UK Ltd)

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	£29.50	30	Relvar Ellipta 184micrograms/dose / 22micrograms/dose dry powder inhaler (GlaxoSmithKline UK Ltd)
Fluticasone with formoterol	£14.40	120	Flutiform 50micrograms/dose / 5micrograms/dose inhaler (Napp Pharmaceuticals Ltd)
Fluticasone with salmeterol	£22.45	120	Aloflute 25micrograms/dose / 125micrograms/dose inhaler (Mylan)
	£17.46	60	Seretide 100 Accuhaler (GlaxoSmithKline UK Ltd)
	£33.95	60	Seretide 250 Accuhaler (GlaxoSmithKline UK Ltd)
	£32.74	60	Seretide 500 Accuhaler (GlaxoSmithKline UK Ltd)
	£17.46	120	Seretide 50 Evohaler (GlaxoSmithKline UK Ltd)
	£23.45	120	Seretide 125 Evohaler (GlaxoSmithKline UK Ltd)
	£29.32	120	Seretide 250 Evohaler (GlaxoSmithKline UK Ltd)
Ciclesonide	£38.62	120	Alvesco 160 inhaler (AstraZeneca UK Ltd)
Reliever inhaler			
Salbutamol	£1.50	200	Ventolin 100micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
	£3.60	60	Ventolin 200micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
	£3.31	200	Easyhaler Salbutamol sulfate 100micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
	£6.30	200	Salamol 100micrograms/dose Easi-Breathe inhaler (Teva UK Ltd)
	£3.60	60	Ventolin 200micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
Terbutaline sulfate	£8.30	120	Bricanyl 500micrograms/dose Turbohaler (AstraZeneca UK Ltd)
Ipratropium bromide	£4.14	20	Atrovent 250micrograms/1ml nebuliser liquid UDV's (Boehringer Ingelheim Ltd)
LABA inhaler			
Salmeterol	£29.26	120	Serevent 25micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
	£35.11	60	Serevent 50micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
LTRA			
Montelukast	£25.69	28	Singulair Paediatric 5mg chewable tablets (Merck Sharp & Dohme Ltd)
	£26.97	28	Singulair 10mg tablets (Merck Sharp & Dohme Ltd)

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Supplemental table 3: Decision rules for participant's adherence score

Clinical team opinion	Smart inhaler adherence score		
	<70%	>=70%	Not available
Adherent	<ul style="list-style-type: none"> - If family response is “all of the time”, assume 100% - If family response is “most of the time”, assume 75% 	<ul style="list-style-type: none"> - Use figure from smart inhaler 	<ul style="list-style-type: none"> - If family response is “all of the time”, assume 100% - If family response is “most of the time”, assume 75%
Not adherent	<ul style="list-style-type: none"> - Use figure from smart inhaler 	<ul style="list-style-type: none"> - If family response is “never”, assume 0% - If family response is “occasionally”, assume 25% - If family response is “about half of the time”, assume 50% 	<ul style="list-style-type: none"> - If family response is “never”, assume 0% - If family response is “occasionally”, assume 25% - If family response is “about half of the time”, assume 50%

Supplemental table 4: Healthcare resource use contacts associated with each attack stratified by highest level of care received.¹

	All		Primary care		Secondary care	
Number of participants (N= 244/252)²	244		171		115	
Number of exacerbations (N=497/509)³	497		291		160	
	Mean	SD	Mean	SD	Mean	SD
Total contacts per attack	1.5	1.3	1.4	1.0	2.0	1.6
Primary care	1.1	1.2	1.4	1.0	0.9	1.5
GP	0.8	0.9	1.1	0.7	0.6	1.1
Nurse	0.1	0.5	0.1	0.4	0.2	0.6
NHS 24/111	0.1	0.4	0.1	0.4	0.1	0.3
Out of hours GP service	0.1	0.5	0.1	0.6	0.1	0.3
Walk-in centre	0.04	0.2	0.1	0.3	0.03	0.2
Pharmacist	0.0	0.06	0.0	0.06	0.01	0.1

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Secondary care	0.4	0.6			1.1	0.4
Emergency department	0.2	0.4			0.5	0.6
Hospital Outpatient	0.03	0.2			0.1	0.3
Hospital inpatient	0.1	0.4			0.4	0.5
Day case	0.0	0.06			0.01	0.1
Ambulance	0.02	0.2			0.1	0.3
Medication⁴	1.6	0.7	1.6	0.7	1.6	0.8

¹Excludes attacks managed without contacting health service. ²N= Patients with attacks with complete resource use data/Observed number of patients with attacks. ³N= Attacks with complete resource use data/Observed attacks. ⁴One-week course of 5mg prednisolone per day.

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Supplemental table 5: Healthcare resource use cost associated with each attack by treatment arm (N=497/509¹)

	Intervention (N=248/254)		Standard care (N=249/255)		Overall (N=497/509)	
Number of children with at least one attack (n, %)	123	48	129	51	252	50
Mean number of attacks per participant among those having at least one exacerbation (mean, SD)	2.1	1.4	2.0	1.3	2.0	1.4
Cost per exacerbation (mean, SD)	£302	920	£291	675	£297	806
Primary care	£45	63	£39	35	£42	51
GP	£33	35	£30	31	£31	33
Nurse	£2.14	8.87	£1.93	7.47	£2.03	8.19
NHS 24/111	£0.94	4.42	£1.20	5.39	£1.07	4.92
Out of hours GP service	£7.76	50	£3.57	17	£5.66	37
Walk-in centre	£1.11	8.15	£2.39	11	£1.75	9.69
Pharmacist	£0.06	0.61	£0.00	0.00	£0.03	0.43
Secondary care	£256	925	£251	682	£253	812
Emergency department	£19	47	£26	59	£23	54
Hospital Outpatient	£4.37	27	£4.04	26	£4.21	26
Hospital inpatient	£230	929	£211	684	£220	815
Day case	£1.59	25	£1.58	25	£1.58	25
Ambulance	£1.04	16	£8.06	49	£4.56	37
Medication	£1.53	1.93	£1.77	1.98	£1.65	1.95

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Supplemental table 6: Total healthcare resource use contacts observed during trial follow-up¹

	Proportion of patients reporting any resource use (n (%))	Mean contact per patient	SD	Median contact per patient	IQR
Healthcare contacts including follow-up visits (N=430)	430 (100)	6.7	4.5	5	[4, 8]
Healthcare contacts (N=430)	309 (71.9)	4.4	4.7	3	[2, 5]
Follow-up visits (N=506)	481 (95.1)	3.5	0.8	4	[3, 4]
Attack-related (N=498)	244 (49.0)	6.2	4.8	5	[3, 8]
Primary care	206 (41.4)	2.7	2.6	2	[1, 3]
GP	176 (35.3)	2.3	1.9	2	[1, 3]
Nurse	28 (5.6)	2.0	1.7	1	[1, 2]
NHS 24/111	31 (6.2)	1.3	1.0	1	[1, 1]
Out of hours GP service	25 (5.0)	1.5	1.8	1	[1, 1]
Walk-in centre	15 (3.0)	1.3	0.5	1	[1, 1]
Pharmacist	2 (0.4)	1.0	0.0	1	[1, 1]
Secondary care	115 (23.1)	1.5	1.0	1	[1, 2]
Emergency department	67 (13.5)	1.3	0.6	1	[1, 1]
Hospital Outpatient	16 (3.2)	1.0	0.0	1	[1, 1]
Hospital inpatient	49 (9.8)	1.3	0.8	1	[1, 1]
Day case	2 (0.4)	1.0	0.0	1	[1, 1]
Ambulance	7 (1.4)	1.3	0.50	1	[1, 2]

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Not associated with attacks (N=443)	218 (49.2)	3.0	3.8	2	[1, 3]
Primary care	178 (40.2)	2.6	3.0	2	[1, 3]
GP	142 (32.1)	2.2	2.1	1	[1, 3]
Nurse	43 (9.7)	2.0	3.4	1	[1, 2]
NHS 24/111	18 (4.0)	1.4	1.2	1	[1, 1]
Out of hours GP service	15 (3.4)	1.1	0.4	1	[1, 1]
Walk-in centre	12 (2.7)	1.3	0.5	1	[1, 1.5]
Pharmacist	2 (0.5)	1.0	0.0	1	[1, 1]
Secondary care	102 (23.0)	2.0	3.3	1	[1, 2]
Emergency department	31(7.0)	1.3	0.8	1	[1, 1]
Hospital Outpatient	64 (14.4)	1.6	1.2	1	[1, 2]
Hospital inpatient	8 (1.8)	1.0	0.0	1	[1, 1]
Day case	2 (0.5)	1.0	0.0	1	[1, 1]
Bronchoscopy	4 (0.9)	1.0	0.0	1	[1, 1]
Ambulance	5 (1.1)	1.0	0.0	1	[1, 1]
Other ²	4 (0.9)	11.0	11.5	8	[2, 20]
Medication³	4 (0.9)	1.0	0.0	1	[1, 1.]

¹Results exclude 5 trial follow-up visits in secondary care (including baseline). ²Physiotherapist/Speech and Language Therapist/Psychologist. ³In addition to medication for asthma management prescribed at regular trial follow-up visits.

*The direct and indirect cost of paediatric asthma in the UK: a cost analysis*Supplemental table 7: Total healthcare resource use cost observed during trial follow up by treatment arm¹ (N=443/506)

	Intervention (N=255)			Standard care (N=251)			Overall (N=506)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
Total	223	£1,138	2790	207	£1,030	2160	430	£1,086	2504
Attack-related	252	£297	1032	246	£295	854	498	£296	947
Primary care	252	£44	93	246	£39	66	498	£42	81
GP	252	£32	66	246	£30	55	498	£31	61
Nurse	252	£2.10	12	246	£1.96	8.09	498	£2.03	10
NHS 24/111	252	£0.93	5.09	246	£1.21	5.42	498	£1.07	5.25
Out of hours GP service	252	£7.64	51	246	£3.61	20	498	£5.65	39
Walk-in centre	252	£1.09	8.09	246	£2.42	13	498	£1.74	10.51
Pharmacist	252	£0.05	0.61	246	£0.00	0.00	498	£0.03	0.43
Secondary care	252	£252	1017	246	£254	855	498	£253	935
Emergency department	252	£19	56	246	£26	71	498	£23	64
Hospital Outpatient	252	£4.30	26	246	£4.09	26	498	£4.20	26
Hospital inpatient	252	£226	1012	246	£213	821	498	£220	922
Day case	252	£1.56	25	246	£1.60	25	498	£1.58	25
Ambulance	252	£1.02	16	246	£8.16	55	498	£4.55	40
Oral steroid	252	£1.51	3.79	246	£1.79	3.26	498	£1.65	3.54
Not associated with attacks	230	£116	247	213	£177	641	443	£145	479
Primary care	230	£34	69	213	£37	74	443	£35	72
GP	230	£25	58	213	£28	61	443	£26	59
Nurse	230	£4.40	24	213	£3.29	12	443	£3.87	19

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NHS 24/111	230	£0.34	2.07	213	£1.22	6.55	443	£0.76	4.79
Out of hours GP service	230	£2.90	16	213	£2.78	16	443	£2.84	16
Walk-in centre	230	£0.99	6.68	213	£2.15	12	443	£1.55	9.84
Pharmacist	230	£0.00	0.00	213	£0.06	0.66	443	£0.03	0.46
Secondary care	230	£82	224	213	£140	635	443	£110	470
Emergency department	230	£13	62	213	£12	42	443	£12	53.
Hospital Outpatient	230	£38	90	213	£43	160	443	£40	128
Hospital inpatient	230	£8.90	79	213	£72	582	443	£39	408
Day case	230	£3.42	37	213	£0.00	0.00	443	£1.78	26
Bronchoscopy	230	£8.28	89	213	£8.94	92	443	£8.60	90
Ambulance	230	£2.23	24	213	£3.62	30	443	£2.90	27
Other ²	230	£8.52	89	213	£0.54	7.81	443	£4.68	64
Medication³	230	£0.02	0.16	213	£0.02	0.17	443	£0.02	0.17
Medication for asthma management	225	£709	2364	207	£580	1753	432	£647	2092
Preventer inhaler (±LABA)	225	£290	131	207	£286	135	432	£288	133
Reliever inhaler ⁴	225	£4.15	3.98	207	£3.58	2.13	432	£3.88	3.23
Separate LABA inhaler	225	£0.31	4.68	207	£1.78	26	432	£1.02	18.
LTRA	225	£20	17	207	£20	17	432	£20	17
Theophylline	225	£4.32	131	207	£4.00	12	432	£4.17	12.
Cyclosporin	225	£4.53	39	207	£4.92	41	432	£4.72	40
Omalizumab injections	225	£386	2344	207	£260	1736	432	£326	2073

¹Results exclude 5 trial follow-up visits in secondary care (including baseline). ²Physiotherapist/Speech and Language Therapist/Psychologist. ³In addition to medication prescribed at regular monitoring visits for the participants asthma. ⁴Assumed all patients require 4 doses per week.

*The direct and indirect cost of paediatric asthma in the UK: a cost analysis***Supplemental table 8: Indirect cost of asthma captured over the trial follow-up by treatment arm (N=443/506)**

	Intervention (N=228/255)		Standard care (N=213/251)		Overall (N=443/506)	
	Mean	SD	Mean	SD	Mean	SD
Total	£427	974	£397	765	£412	879
Indirect costs (child)	£8.17	37	£10	37	£9.11	37
Indirect costs (adults¹)	£419	969	£387	753	£403	871
Paid employment	£266	639	£249	576	£258	609
Unpaid work	£136	569	£116	334	£126	470
Leisure	£17	102	£21	109	£19	105

¹Where adults describes parents, friends, and relatives of the participant

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Supplemental table 9: Results of the GLM model of direct health service costs including and excluding patients prescribed omalizumab (n=13) during trial follow-up

Covariates	Direct cost (N=430)					Direct cost (N=417)				
	Predictive margins	SE	Marginal effect	SE	p-value ¹	Predictive margins	SE	Marginal effect	SE	p-value ¹
Predicted cost	£1,104	250				£728	44			
Sex										
Male	£1,208	340				£696	57			
Female	£961	146	£-247	235	0.2	£774	52	£79.00	67	0.25
Age										
< 11 years old	£885	162				£701	47			
≥ 11 years old	£1,423	425	£538	303	<0.01	£762	76	£61.00	87	0.48
Treatment level²										
BTS/SIGN Step 2	£974	236				£522	113			
BTS/SIGN Step 3	£1,122	431	£148	426	0.72	£616	37	£64	99	0.55
BTS/SIGN Step 4	£1,113	153	£139	272	0.62	£864	68	£312	119	<0.05
Number of attacks										
0	£736	259				£356	19			
1-2	£1,138	262	£402	122	<0.05	£870	81	£514	78	<0.01
3-4	£2,302	588	£1,565	562	<0.01	£1,458	209	£1,102	213	<0.01
≥5	£2,188	434	£1,452	417	<0.01	£1,956	359	£1,600	355	<0.01
Adherence										
Not adherent (<70%)	£807	86				£709	55			
Adherent (≥70%)	£1,271	354	464	297	<0.05	£739	61	£30	83	0.72

¹p-value from GLM regression. SE: Standard Error. ²Treatment levels based on the British guidelines on the management of asthma.(23) British Thoracic Society (BTS); Scottish Intercollegiate Guidelines Network (SIGN)

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