PLEASANT: Preventing and Lessening Exacerbations of Asthma in School-age children Associated with a New Term – a cluster randomised controlled trial and economic evaluation

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*National Institute for
Health Research*

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This report

Abstract

PLEASANT: Preventing and Lessening Exacerbations of Asthma in School-age children Associated with a New Term – a cluster randomised controlled trial and economic evaluation

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Background: Asthma episodes and deaths are known to be seasonal. A number of reports have shown peaks in asthma episodes in school-aged children associated with the return to school following the summer vacation. A fall in prescription collection in the month of August has been observed, and was associated with an increase in the number of unscheduled contacts after the return to school in September.

Objective: The primary objective of the study was to assess whether or not a NHS-delivered public health intervention reduces the September peak in unscheduled medical contacts.

Design: Cluster randomised trial, with the unit of randomisation being 142 NHS general practices, and trial-based economic evaluation.

Setting: Primary care.

Intervention: A letter sent ($n = 70$ practices) in July from their general practitioner (GP) to parents/carers of school-aged children with asthma to remind them of the importance of taking their medication, and to ensure that they have sufficient medication prior to the start of the new school year in September. The control group received usual care.

Main outcome measures: The primary outcome measure was the proportion of children aged 5–16 years who had an unscheduled medical contact in September 2013. Supporting end points included the proportion of children who collected prescriptions in August 2013 and unscheduled contacts through the following 12 months. Economic end points were quality-adjusted life-years (QALYs) gained and costs from an NHS and Personal Social Services perspective.

Results: There is no evidence of effect in terms of unscheduled contacts in September. Among children aged 5–16 years, the odds ratio (OR) was 1.09 [95% confidence interval (CI) 0.96 to 1.25] against the intervention. The intervention did increase the proportion of children collecting a prescription in August (OR 1.43, 95% CI 1.24 to 1.64) as well as scheduled contacts in the same month (OR 1.13, 95% CI 0.84 to 1.52). For the wider time intervals (September–December 2013 and September–August 2014), there is weak evidence of the intervention reducing unscheduled contacts. The intervention did not reduce unscheduled care in September, although it succeeded in increasing the proportion of children collecting prescriptions in August as well as having scheduled contacts in the same month. These unscheduled contacts in September could be a result of the intervention, as GPs may have wanted to see patients before issuing a prescription. The economic analysis estimated a high probability that the intervention was cost-saving, for baseline-adjusted costs, across both base-case and sensitivity analyses. There was no increase in QALYs.

Limitation: The use of routine data led to uncertainty in the coding of medical contacts. The uncertainty was mitigated by advice from a GP adjudication panel.

Conclusions: The intervention did not reduce unscheduled care in September, although it succeeded in increasing the proportion of children both collecting prescriptions and having scheduled contacts in August. After September there is weak evidence in favour of the intervention. The intervention had a favourable impact on costs but did not demonstrate any impact on QALYs. The results of the trial indicate that further work is required on assessing and understanding adherence, both in terms of using routine data to make quantitative assessments, and through additional qualitative interviews with key stakeholders such as practice nurses, GPs and a wider group of children with asthma.

Trial registration: Current Controlled Trials ISRCTN03000938.

Contents

CONTENTS

List of tables

List of figures

List of boxes

List of abbreviations

AQLQ	Asthma Quality of Life Questionnaire	ITT	intention to treat
ASS	asthma symptom score	MAGNETIC	MAGNEsium Trial In Children
BA	baseline adjusted	MeSH	medical subject heading
BCa	bias corrected and accelerated	NICE	National Institute for Health and Care Excellence
BTS	British Thoracic Society	NIHR	National Institute for Health Research
CI	confidence interval		
CONSORT	Consolidated Standards of Reporting Trials	OR	odds ratio
		PAHOM	Pediatric Asthma Health Outcome Measure
CPRD	Clinical Practice Research Datalink	PedsQL	Pediatric Quality of Life Inventory
CTRU	Clinical Trials Research Unit	PLEASANT	Preventing and Lessening Exacerbations of Asthma in School-age children Associated with a New Term
EoI	expression of interest		
EQ-5D	European Quality of Life-5 Dimensions		
EXALT	Evaluate Xolair for Asthma as Leading Treatment	PP	per protocol
		PPI	patient and public involvement
FEV_1	forced expiratory volume in the first second	PSS	Personal Social Services
		QALY	quality-adjusted life-year
GINA	Global Initiative for Asthma	RCT	randomised controlled trial
GOAL	Gaining Optimal Asthma ControL	SD	standard deviation
GP	general practitioner	SE	standard error
HRQoL	health-related quality of life	SIGN	Scottish Intercollegiate Guidelines Network
HTA	Health Technology Assessment		
HUI	Health Utilities Index	SOP	standard operating procedure
HUI-2	Health Utilities Index Mark 2	TMG	Trial Management Group
HUI-3	Health Utilities Index Mark 3	TSC	Trial Steering Committee
ICC	intraclass correlation	TTO	time trade-off
ICER	incremental cost-effectiveness ratio	VAS	visual analogue scale
ID	identification number	WTP	willingness to pay
IRR	incidence rate ratio		
ISSG	Information Specialists' Sub-Group		

Plain English summary

In the UK, the number of visits to the doctor by school-age children with asthma is high at the start of the new school term in September. During the summer holidays (i.e. in August), the number of visits is lower and the number of asthma prescriptions collected also falls.

We wondered whether or not a letter from the general practitioner to the parents or carers of children with asthma, reminding them to make sure that their children take their medication or to collect prescriptions, could help prevent the children from being poorly. It suggested that parents should ensure that their children's medication is up to date and that they take it for at least 2 weeks before the school return.

To see if the letter worked, we have undertaken a study in England and Wales. General practices were randomly assigned either to sending out the letter (70 practices) or to continue with care as usual (no letter, 72 practices) so that we could see if the letter had any effect.

We found there was an increase in the number prescriptions collected in August and medical contacts such as asthma reviews. These increased contacts did not follow through to reduce the numbers of children seeing their doctor or going to hospital in September, but there was evidence in October to December of reduced contacts. These reduced contacts meant there was evidence of the letter saving costs to the NHS.

General practitioners may wish to implement the intervention to increase prescriptions and scheduled contacts in August. Evidence from the trial suggests that this would not increase costs associated with the asthma management.

Scientific summary

Background

Asthma episodes and deaths are known to be seasonal. A number of reports have shown peaks in asthma episodes in school-aged children associated with the return to school following the summer vacation.

Children returning to school are exposed to a variety of novel respiratory insults, including allergens and viruses, at a time of changing climactic conditions. It has previously been shown that viral infection and allergen exposure in allergen-sensitised asthmatics are associated with increased hospital admissions for acute asthma.

In previous research by members of our team, a random sample of approximately 75,000 school-aged (5–16 years) children from England, Wales and Scotland, with a medical diagnosis of asthma, were obtained from general practices within the General Practice Research Database [now the Clinical Practice Research Datalink (CPRD)] to investigate the seasonal effect of asthma in a primary care setting. Age- (within 2 years) and sex-matched controls (i.e. no asthma diagnosis) from the same practices were also taken for comparisons.

This investigation confirmed the increase in unscheduled medical contacts in children with asthma throughout the year, and a regression analysis showed that children with asthma were approximately twice as likely as control children to have an unscheduled medical contact with their doctor around the time of the return to school.

In the same study it was found that in August, immediately preceding the return to school, there were 25% fewer prescriptions for inhaled corticosteroids than in July and September. Furthermore, patients who received a prescription for inhaled corticosteroids were less likely to have an unscheduled medical contact after the return to school.

Objectives

The aim of the study was to assess if a NHS-delivered public health intervention [a letter sent from the general practitioner (GP) to parents/carers of school-aged children with asthma] can reduce the number of unscheduled medical contacts after the school return.

The primary objective of the study was to assess whether or not the intervention reduces the September peak in unscheduled medical contacts.

Methods

The study was a cluster randomised trial to assess if a letter sent by a GP to the parents/carers of school-aged children with asthma, reminding them to take their medication, reduces the number of unscheduled medical contacts after return to school in September following the summer holiday. The unit of cluster was general practices. Site recruitment commenced in January 2013, with the intervention being delivered during the week commencing 29 July 2013. Data for the trial were collected via the CPRD.

The effectiveness of the intervention was assessed on the basis of prescription uptake prior to the school term and medical contacts thereafter. Analyses of medical contacts were defined in four overlapping time intervals:

1. September 2013 (the primary study period)
2. September–December 2013 (the extended study period)
3. September 2013–August 2014 (the 12-month study period)
4. September 2014 (the echo substudy).

The primary study period was 1–30 September 2013, as this was the period when the intervention was felt to be most likely be able to demonstrate an impact. The extended study period was 1 September– 31 December 2013, as asthma-related appointments are more frequent in these months. The full follow-up period was 12 calendar months from 1 September 2013 to 31 August 2014. There is also an echo (or follow-on) substudy period in September 2014 to see if the effect from September 2013 was maintained when there was no actual study intervention.

Prescription uptake and scheduled medical contacts such as asthma reviews were evaluated during three periods:

1. August 2013
2. August 2013–July 2014
3. August 2014 (the echo substudy).

The health economic analyses were based on a 12-month period from 1 August 2013 to 31 July 2014. The period starts 1 month earlier than the evaluation of medical contacts in order to incorporate the cost associated with delivering the intervention, including any increase in prescriptions or medical contacts in response to the intervention that occurred during August 2013.

The primary outcome was the proportion of patients who had an unscheduled medical contact in September 2013. The primary analysis population was the intention-to-treat (ITT) population among children aged between 5 and 16 years.

The secondary outcomes evaluated included the number of unscheduled medical contacts in September 2013, and the number and proportion of any medical contacts (scheduled and unscheduled) in the same time interval. The analyses of the same outcomes were repeated for the other time intervals.

The study was designed to detect a difference of 5% (30% vs. 25%) with 90% power and a two-sided significance level of 5%, with an intraclass correlation of 0.03 to account for clustering. Based on this, we estimated that we required 70 practices per arm. It was expected that the sample size of 140 practices would equate to approximately 14,000 school-aged children with asthma.

The proportion of children having a medical contact was analysed separately for each time period using logistic regression, in which the covariates were the individual's age, sex, number of contacts the previous September and the trial arm (intervention or control) as fixed effects, and the design/cluster effect of general practice as a random effect. The proportion of children having a prescription within each time period was analysed in the same manner.

The number of contacts, and the number of prescriptions, that each child had in each period were both analysed using a random-effects negative binomial model, in which the same covariates as above were included.

An economic evaluation was undertaken to estimate the cost-effectiveness of the intervention from an NHS and personal social services perspective. The population for the economic evaluation was defined as

school-aged children with asthma who are registered with a GP in England or Wales and, therefore, the analysis was based on the Preventing and Lessening Exacerbations of Asthma in School-age children Associated with a New Term (PLEASANT) study population. As the primary outcome for the PLEASANT study was restricted to those children aged 5–16 years, this age subgroup was used for the base-case cost-effectiveness analysis, with a subgroup analysis looking at children aged 4 years.

Setting

The setting was primary care, with the unit of cluster being general practices. Site eligibility required practices to be using the Vision IT software [INPS (In Practice Systems), London, UK] and to be part of CPRD. Site recruitment was conducted by CPRD and the National Institute for Health Research Primary Care Research Network.

Participants

Participants were school-aged children with asthma, aged between 4 and 16 years, who were registered with a GP.

Interventions

Sites were randomly allocated to either:

1. intervention group: sending out the letter
2. control group: standard care (no letter).

The intervention was a letter sent from a GP to the parents/carers of children with asthma, reminding them to maintain their children's medication, and to collect a prescription if they were running low. It also advised that, should their child have stopped their medication, it should be resumed as soon as possible.

The letter template was developed based on standard letters already used in general practice. The wording of the letter had input from the study team, which includes a GP, a health psychologist and a consultant respiratory paediatrician, and was also discussed in detail at two patient and public events that included school-aged children with asthma and their parents.

The intervention letters were sent out the week commencing 29 July 2013 to obviate the distraction of planning for family holidays, and yet left enough time for parents and children to renew prescriptions and gain benefit from the medication. The timing of the letter was decided following discussion with the patient and public involvement group.

Results

In the primary analysis, the proportion of individuals who had at least one unscheduled medical contact was 45.2% in the intervention arm, compared with 43.7% in the control arm [adjusted odds ratio (OR) 1.09, 95% confidence interval (CI) 0.96 to 1.25]. Similar results were observed across other subgroups, but with wider CIs in the under-fives subgroups, reflecting the smaller number of children. The difference was marginally greater for per-protocol than ITT analyses, and was marginally greater for children under 5 years old compared with those aged 5–16 years (ITT population). However, no statistically significant difference was seen in any of the ITT comparisons.

An objective with the PLEASANT study was that the intervention would increase the proportion of children who had a prescription in August 2013, as it was shown in the earlier research that not collecting a prescription was associated with unscheduled contacts in September. The intervention (letter) was associated with an increased uptake of prescriptions in the month of August 2013. Among children aged 5–16 years, 876 (16.5%) had at least one prescription, compared with 703 (12.6%) in the control group (adjusted OR 1.43, 95% CI 1.24 to 1.64); the total number of prescriptions was also higher (adjusted incidence rate ratio 1.31, 95% CI 1.17 to 1.48). Scheduled contacts made in August 2013 also increased (adjusted OR 1.13, 95% CI 0.84 to 1.52).

The increase in medical contacts in September may have been caused by GPs needing to see certain patients before giving a new prescription. Evidence to support this is the observation that for children who had collected a prescription within the last 3 months prior to the start of the study, there was no evidence of an increase in unscheduled contacts in September; 56.4% in the intervention arm compared with 56.8% in the control arm. For patients whose last prescription was 3–6 months prior to the start of the study, the excess was greater: 48.0% in the intervention arm against 42.9% in the control arm.

After September, there was evidence of a reduction in the mean number of unscheduled medical contacts. The difference was small and not statistically significant.

The reduction in the medical contacts was reflected in the economic analysis (which used data over a 12-month period from August 2013 to July 2014), which estimated that the intervention had a 96.3% probability of being cost-saving, with a mean cost saving of £36.07 per child in the base-case analysis for 5- to 16-year-olds when adjusting for baseline differences in costs between trial arms. There was no associated increase in quality-adjusted life-years (QALYs).

Conclusions

The intervention did not reduce unscheduled care in September, which was the primary end point. However, the intervention succeeded in increasing the proportion of children collecting a prescription in August, along with the proportion of children who had scheduled contacts in the same month.

Over a wider time interval, there is weak evidence that the intervention reduced unscheduled medical contacts. This is reflected in the health economic evaluation, which estimated a high probability that the intervention was cost-saving. There was no increase in QALYs associated with this cost reduction.

Trial registration

This trial is registered as ISRCTN03000938.

Funding

Chapter 1 Introduction

Asthma episodes and deaths are known to be seasonal.[1] A number of reports have shown peaks in asthma episodes in school-aged children associated with the return to school following the summer vacation.[2–10] These studies mainly report hospital admissions, although one study has reported peaks both in hospital admissions and in other medical contacts.[10]

Children returning to school are exposed to a variety of novel respiratory insults, including allergens and viruses, at a time of changing climactic conditions. It has previously been shown that viral infection and allergen exposure in allergen-sensitised asthmatics are associated with an increased risk of hospital admission for acute asthma. The same study demonstrated the protective effect of inhaled corticosteroids on acute asthma exacerbations in a paediatric asthma population.[11]

In previous research by members of our team, a random sample of approximately 75,000 school-aged (5–16 years) children from England, Wales and Scotland, with a medical diagnosis of asthma, were obtained from general practices within the General Practice Research Database [now the Clinical Practice Research Datalink (CPRD)[12]] to investigate the seasonal effect of asthma in a primary care setting. Age- (within 2 years) and sex-matched control patients (i.e. no asthma diagnosis) from the same practices were also sampled for comparison.[13]

This investigation confirmed the increase in unscheduled medical contacts in children with asthma throughout the year, and a regression analysis showed that children with asthma were approximately twice as likely as control children to have an unscheduled medical contact with their doctor around the time of return to school in September. If children with asthma were at a constant increased risk of medical contacts throughout the year, *Figure 1* would show a random scatter of the residuals in England.[13] However, around the time of return to school there is a pronounced positive increase in the value of residuals. A similar pattern was observed in Scotland but with an earlier peak, which can be attributed to school term starting 2 weeks earlier in Scotland than in England. These analyses indicate that, at this time, there is a greater than expected increase in the number of unscheduled contacts by children with asthma compared with control children.

We suggest that July and August are periods of reduced viral exposure (owing to reduced contact with other children because of the holidays) and reduced pollen (antigen) exposure for children with asthma.
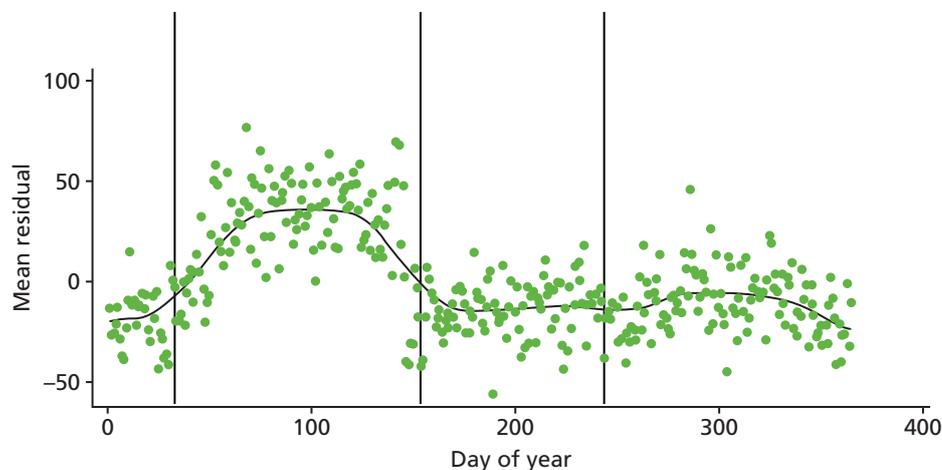
FIGURE 1 Mean residuals for excess medical contacts for children with asthma for over control children in England. The vertical lines represent, from left to right, 1 September, 1 January and 1 April.

The reduced exposures could be an explanation for the observed drop in prescriptions for inhaled steroids we found in August immediately preceding the return to school, with 25% fewer prescriptions in August than in July or September (*Figure 2*, taken from Julious *et al.*[13]) This drop in prescriptions precedes the viral challenge of a return to school. We further showed that patients who received a prescription for inhaled corticosteroids had, on average, 0.14 fewer contacts than those who did not receive an August prescription [England: 95% confidence interval (CI) 0.12 to 0.16 fewer contacts per patient; $p < 0.001$; Scotland: 95% CI 0.10 to 0.18 fewer contacts per patient; $p < 0.001$].

To interpret the figure of 0.14, imagine a hypothetical cohort of 200 children with asthma on inhaled corticosteroid, of whom 100 receive an August prescription and 100 do not. If the 100 patients with a

(a)

(b)
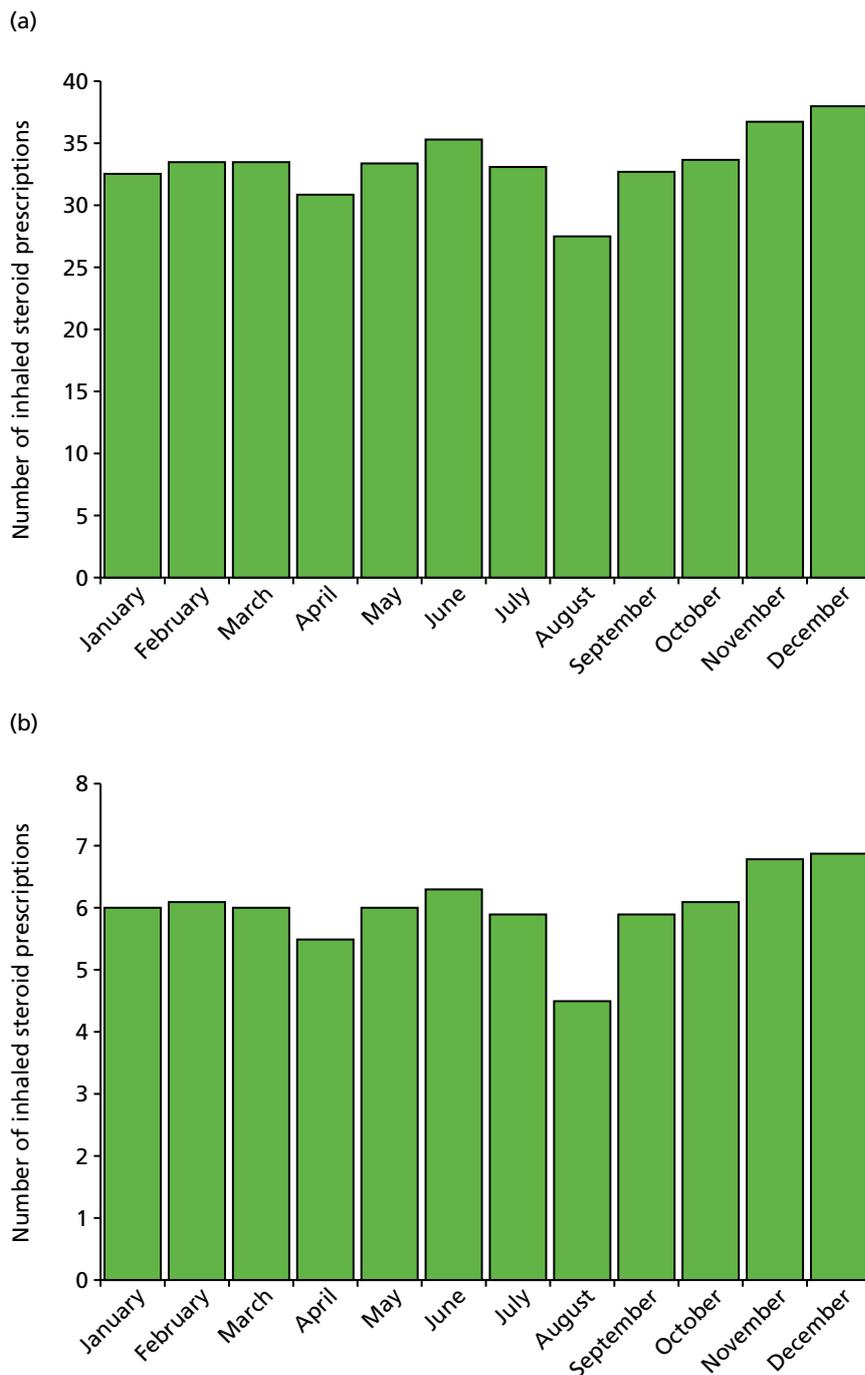
FIGURE 2 Average number of inhaled steroid prescriptions by month for (a) England and (b) Scotland.

prescription make a total of 50 unscheduled medical visits (0.5 mean visits/patient), then 64 unscheduled medical contacts would be made by those not receiving a prescription (0.64 mean visits/patient; difference 0.14). Therefore, for every 100 children with asthma on inhaled corticosteroids not receiving a prescription in August, there is an excess of 14 unscheduled medical contacts.

It is therefore possible that children who stop taking or reduce their inhaled corticosteroids over the summer months, and/or who run low on other medications and fail to restart them before the return to school, render themselves more vulnerable to an acute asthma exacerbation and unscheduled medical contacts.

The cost to the NHS of unplanned medical contacts is £36 for a general practitioner (GP) surgery contact, £121 for a GP home visit,[14] £59–142 for an emergency department contact if not admitted and £74–249 if admitted, and £385 for a non-elective short stay for asthma without complications.[15] The intervention/letter therefore has the potential to benefit the health and quality of life of children with asthma while also improving the effectiveness of NHS services by reducing NHS use in one of the busiest months of the year.

Research aims and objectives

The aim of the study was to assess if a NHS-delivered public health intervention (a letter sent from the GP to parents/carers of school-aged children with asthma) can reduce the number of unscheduled medical contacts after the school return.

The primary objective of the study was to assess whether or not the intervention reduces the September peak in unscheduled medical contacts.

Chapter 2 Methods

This report is concordant with the Consolidated Standards of Reporting Trials (CONSORT) statement extension for cluster randomised trials.[16]

Ethics approval and research governance

Ethics approval for the study was given by South Yorkshire Research Ethics Committee on 25 October 2012 (reference number 12/YH/04). NHS permissions to conduct the study were obtained for all the primary care trusts in England and health boards in Wales.

The trial was registered with the International Standard Randomised Controlled Trial Number ISRCTN03000938.

Trial design

The study was a cluster randomised trial[17] to assess if a letter sent by a GP to the parents/carers of school-aged children with asthma, reminding them to take their medication, reduces the number of unscheduled medical contacts after return to school following summer holiday in September. The unit of cluster was general practices; site recruitment commenced in January 2013, with the intervention being delivered during the week commencing 29 July 2013. Data for the trial were collected via the CPRD.

Clinical Practice Research Datalink

The CPRD GOLD is the world's largest validated computerised database of anonymised longitudinal medical records for primary care.[18] Records are derived from GP software systems and contain complete prescribing and coded diagnostic and clinical information, as well as information on tests requested, laboratory results and referrals made at or following on from each consultation.[19]

The CPRD is thus able to capture all medical contacts, from prescription request through to out-of-hours contacts, along with the reason for the contact. This therefore negated the need to request this information from the individual GP practices.

Settings and locations where the data were collected

The setting was primary care, with the unit of cluster being general practices. Site eligibility required practices to be using the Vision IT software [INPS (In Practice Systems), London, UK] and be part of CPRD. Site recruitment was conducted by CPRD and the National Institute for Health Research (NIHR) Primary Care Research Network.

Clinical Practice Research Datalink recruitment

Practice recruitment was carried out predominantly by CPRD. A practice recruitment pack, consisting of a detailed study information sheet and an expression of interest (EoI) form, was sent to all 433 practices contributing to CPRD in England and Wales at the time of recruitment. This was sent by post to the preferred contact at the practice as specified in CPRD's records for the practice. Non-responding practices were sent a reminder e-mail, followed by a second reminder e-mail and then final reminders by e-mail and

post. In addition to this, some practices were contacted by telephone, either by CPRD or by members of the study team at the Sheffield Clinical Trials Research Unit (CTRU).

Practices that wanted to take part in the study, or to decline participation, returned the completed EoI form, confirming or updating as necessary the information about the practice held by CPRD. Responses were tracked by CPRD to ensure practices that had expressed interest or declined to participate were not contacted again. The EoIs were then forwarded to the study team to contact practices and complete site set-up.

The details of the recruitment processes and contacts required to enrol GP practices have been published.[20]

National Institute for Health Research Primary Care Research Network

The Primary Care Research Network also advertised and invited recruitment to the trial. Eligibility criteria for general practices were that they were using Vision IT software and agree to be signed up to CPRD if they were not already. Completed EoIs were returned to the study team for follow-up and site set-up.

Site set-up

The study team contacted interested practices to complete site set-up; this was done via telephone or Skype™ (Microsoft Corporation, Redmond, WA, USA). Once set-up was complete and verbal consent obtained from the practice to participate, practice details were forwarded to the study statistician for randomisation. See *Randomisation and blinding* for details of randomisation.

Practices randomised to intervention group were sent GP packs that included the intervention letter template, which was added to practice headed paper, with procedures on confirming patient eligibility and instructions on the process and timing for delivery of the intervention via DocMail (www.cfhdocmail.com/; accessed 18 January 2016; CFH Docmail Ltd, Radstock, UK).

Practices randomised to the control group were to continue with care as usual; no other activity was required.

Participants and eligibility criteria

Participants were school-aged children with asthma, aged between 4 and 16 years, who were registered with a GP.

Inclusion criteria
Children were eligible if they:

- were aged between 4 and 16 years on 1 September 2013
- had a coded diagnosis of asthma
- had been prescribed asthma medication in the 12-month period from March 2012 to March 2013.

Exclusion criteria
Children were excluded if they:

- were aged 4 years or under on 1 September 2013 or 16 years or over on 31 August 2013
- were not considered appropriate for this intervention by their GP
- had asthma but were not receiving asthma medication
- had co-existing neoplastic disease.

The CPRD identified eligible participants based on pre-agreed diagnostic codes for asthma and the inclusion/exclusion criteria, which were subsequently screened by the GP to confirm inclusion. The list of diagnostic codes used by CPRD used for patient identification is available on the study Preventing and Lessening Exacerbations of Asthma in School-age children Associated with a New Term (PLEASANT) website: www.sheffield.ac.uk/scharr/sections/dts/ctru/pleasant/index (date last accessed 31 May 2016). When writing this report it became apparent that there was a discrepancy between the code list provided by the study team and the code list used by CPRD. The impact of this on the data extraction is discussed in *Changes to the data collection, data extraction and methods for allocation of data after the trial commenced, with reasons*.

Trial intervention

Sites were randomly allocated to:

1. intervention group: sending out the letter
2. control group: standard care (no letter).

For the intervention, a letter sent from a GP to the parents/carers of children with asthma reminding them to maintain their children's medication and collect a prescription if they are running low. It also advised that, should their child have stopped their medication, it should be resumed as soon as possible (see *Appendix 1*).

The letter template was developed based on standard letters already used in general practice. The wording of the letter had input from the study team, which includes a GP, health psychologist and consultant respiratory paediatrician, and was also discussed in detail at two patient and public events that included school-aged children with asthma and their parents.[21]

The intervention letters were sent out during the week commencing 29 July 2013 to obviate the distraction of planning for family holidays and yet left enough time for parents and children to renew prescriptions and gain benefit from the medication. The timing of the letter was decided following discussion with the patient and public involvement (PPI) group.[21]

Postal procedures

Practices were encouraged to use the DocMail service for sending the letters, which was done via a website to secure servers. This was done, first, to reduce practice burden and, second, to allow monitoring to confirm that the letters had been sent, the number of letters sent, and on which dates.

Practices that preferred not to use this method, and to arrange the posting themselves, were asked to confirm that the letters had been posted, the dates and the numbers sent.

Outcomes

The effectiveness of the intervention was assessed on the basis of prescription uptake prior to the school term and medical contacts thereafter. Analyses of medical contacts were defined in four overlapping time intervals:

1. September 2013 (the primary study period)
2. September to December 2013 (the extended study period)
3. September 2013 to August 2014 (the 12-month study period)
4. September 2014 (the echo substudy).

The primary study period spans from 1 to 30 September 2013, as this was the period when, prior to the start of the study, the intervention was considered most likely be able to demonstrate an impact. The extended study period was from 1 September to 31 December 2013, since asthma-related appointments are more frequent in these months. The full follow-up period was 12 calendar months from 1 September 2013 to 31 August 2014. There was also an echo (or follow-on) study period in September 2014 to see if the effect from September 2013 was maintained when there was no actual study intervention.

Prescription uptake and scheduled medical contacts were evaluated during three periods:

1. August 2013
2. August 2013 to July 2014
3. August 2014 (the echo substudy).

The health economic analyses were based on a 12-month period from 1 August 2013 to 31 July 2014. The period starts 1 month earlier than the evaluation of medical contacts in order to incorporate the cost associated with delivering the intervention including any increase in prescriptions or medical contacts in response to the intervention that occurred during August 2013.

Primary outcome
The primary outcome measure was the proportion of patients who had an unscheduled medical contact in September 2013. The primary analysis population was the intention-to-treat (ITT) population among children aged between 5 and 16 years, but was repeated for other subgroups (see *Analysis population* for more details).

Secondary outcomes
The following outcomes were evaluated:

1. medical contacts during the primary study period (September 2013):

   i. unscheduled medical contacts:

      – the proportion of patients who had an unscheduled medical contact
      – the number of unscheduled medical contacts.

   ii. unscheduled medical contact associated with a respiratory diagnosis:

      – the proportion of patients who had an unscheduled medical contact associated with a respiratory diagnosis
      – the number of unscheduled medical contacts associated with a respiratory diagnosis.

   iii. any medical contacts (scheduled or unscheduled):

      – the proportion of patients who had any medical contact
      – the number of medical contacts.

2. medical contacts during the extended study period (September to December 2013):

      – as for September 2013.

3. medical contacts during the 12-month study period (September 2013 to August 2014):

   i. unscheduled medical contacts:

      – the proportion of patients who had an unscheduled medical contact
      – the number of unscheduled medical contacts
      – the time to first unscheduled medical contact.

   ii. unscheduled medical contact associated with a respiratory diagnosis:

- the proportion of patients who had an unscheduled medical contact associated with a respiratory diagnosis
- the number of unscheduled medical contacts associated with a respiratory diagnosis
- the time to first unscheduled medical contact associated with a respiratory diagnosis.

   iii. any medical contacts (scheduled or unscheduled):

- the proportion of patients who had any medical contact
- the number of medical contacts
- the time to first medical contact.

4. medical contacts during the echo period (September 2014):

- as for September 2013.

5. prescriptions and scheduled contacts in the month of August 2013:

- the proportion of patients who had a scheduled medical contact (e.g. asthma review)
- the number of prescriptions for preventative medications.

6. scheduled contacts in the 12-month period from August 2013 to July 2014:

- the proportion of patients who had a scheduled medical contact (e.g. asthma review).

7. prescriptions and scheduled contacts in the month of August 2014:

- as for August 2013.

Changes to trial outcomes after the trial commenced, with reasons

An additional secondary outcome has been added to include data up to September 2014 to evaluate whether or not there was a carry-over effect into the following year. If the intervention were to increase prescription uptake and reduce unscheduled medical contacts in the original study period, it would be of interest to know whether or not the effect was repeated in the subsequent year without the need for a repeat intervention. As routinely collected data were used throughout the study, there was no cost associated with this extension. Therefore, the follow-up period was extended by 1 month. This was agreed by the Trial Steering Committee (TSC) and NIHR Health Technology Assessment (HTA) programme as a non-cost extension to the trial (see *Appendix 2*).

The non-cost extension also facilitated a survey of the GP practices that were in the intervention arm of the study to inform the health economic evaluation of the study by asking questions on resource use in the sending of the intervention letter.[22]

A second change concerned the analysis of adherence to medication. The planned statistical analysis defined the medical possession ratio as the total number of days of prescriptions in the last year. During the study it became clear that the CPRD data did not hold sufficient data to enable this analysis. The amount of medication dispensed (e.g. the number of inhalers) is captured usually, but the amount of medication required (e.g. the number of puffs an individual is required to take) is not. This information is required to calculate the medical possession ratio. For this reason, our planned analyses of adherence were not possible.

Data collection, data extraction and methods for allocation of data

Data were extracted from the December 2013 CPRD GOLD database build. Patients who were between 4 and 16 years of age on 1 September 2013 and currently registered at a participating practice were considered for inclusion. A Read Code list, supplied by the study team at the Sheffield CTRU, was applied to identify all patients who had a diagnosis code for asthma. The population was then limited to patients who had been prescribed an asthma medication in the 12-month period of March 2012 to March 2013 using a Multilex code list. Patients who had a Read Code indicating neoplastic disease were excluded. All data for the included patients were extracted from the database. In order to protect the identity of included patients, the patient and practice identification numbers (IDs) were pseudonymised by the research team at CPRD before the data were delivered to the CTRU. Read Code lists used for the data extraction are available on request and are also on the website of the PLEASANT study at the following address: www.sheffield.ac.uk/scharr/sections/dts/ctru/pleasant/index (accessed 31 May 2016).

Subsequent data extractions were done for the same patients on the April 2014, June 2014 and January 2015 builds in order to increase the length of follow-up.

Data handling

The primary data source was anonymised, and GP and NHS contacts extracted by the CPRD and forwarded to the CTRU via a password-protected zip file.

Every NHS service contact is coded by the general practice and captured within the practice database. These codes, which include diagnostic, consultation, prescription and test result codes, were used to enable allocation to either scheduled or unscheduled contact. This allocation was carried out by presenting a summary of the consultation codes, medcode descriptions and other tables used (as described in *Methods for allocation of data to scheduled/unscheduled contacts*) to an independent GP adjudication panel comprising three GPs. The GP adjudication panel reviewed the data and confirmed assumptions to use in order to code contacts as scheduled, unscheduled or not applicable (not relevant). Detail and definitions used for this coding are provided in the following section (see *Methods for allocation of data to scheduled/unscheduled contacts*).

The age for inclusion in the study is age as of 1 September 2013. Day of birth is missing for all children in the data set so there is no patient-identifiable information. For day of birth, the value '15' was used. If month of birth was also missing the value 'September' was used. The latter assumption was used because data provided by CPRD have been checked for meeting the eligibility criteria, and hence subjects with a missing month will be eligible with this month. All children with a missing month were born in the years 1997, 1998 and 1999. Thus assuming September, October, November or December for the missing months ensures that all subjects born in 1997 are included in the analysis.

Note that the data were provided by CPRD as anonymised to prevent the identification of the children and the practices in the study.

Given CPRD anonymisation of the practices, it was not possible to reconstruct the full disposition of some children. For example, in the present report, 5917 children are allocated to the intervention arm and 6262 to the control arm in 141 practices, which is based on the data extracted from the database for the analysis. In a different source (the original practice size listing used for the randomisation), 5907 subjects are allocated to the intervention and 6431 to the control in 142 practices (including one practice, with a size of 99, that subsequently withdrew its consent after randomisation – see *Recruitment and participant flow*). Owing to the blinding, it was not possible to fully describe the discrepancy in numbers of children.

A similar issue is found with subject allocation to the per-protocol (PP) population. Although it is possible to ascertain whether or not a subject is included in the PP population, because of blinding it was not possible to fully link to the reason (e.g. 'letter not sent' or 'letter sent late') without a little interpolation.

Detailed data management processes are set out in a data management plan. Data will be retained in accordance with the Data Protection Act 1998[23] and CTRU data management standard operating procedures (SOPs).

Methods for allocation of data to scheduled/unscheduled contacts

A scheduled contact was defined as any contact that is part of the planned care for the patient, for example an asthma review, a medical review, repeat prescription or immunisation. An unscheduled contact was defined as any contact not part of the patient's care plan that is either patient initiated or a result of illness.

To ensure that the allocation of scheduled and unscheduled contacts was robust, a GP Adjudication Panel comprising three independent GPs attended meetings to review the data blind to treatment. The GP Adjudication Panel reviewed the unique terms (17% of the unique terms were reviewed, which accounted for 90% of the data). During these meetings the GP Adjudication Panel devised the assumptions (i.e. rules) used to allocate to scheduled, unscheduled or not applicable (irrelevant) contacts. These assumptions were documented (see *Appendix 3*) and approved by the GP Adjudication Panel.

All types of 'consultation' are recorded within the data that CPRD provides; each consultation was considered a medical contact. Not all consultations are considered relevant to the study. One 'consultation' in the consultation table was considered one contact. All consultation data supplied are taken into account for the study, not just those that are asthma related. Only consultations that happened on or after 1 August were included.

Assumptions used to code records as scheduled, unscheduled or not applicable were based on a GP Adjudication Panel review of the clinical, immunisation, therapy, referral, and test and consultation data.

The 'medcode description' from the clinical data was used first, as it was felt that this table gave most description about the reason for the consultation. If contact type could not be determined by the 'medcode description', then clinical consultation was referenced.

Following the GP Adjudication Panel review of the medcode descriptions and clinical consultation types, in which over 90% of the data were reviewed (17% of the unique terms), clinical records were identified to be marked as scheduled (these include asthma annual review terms and other obvious types of planned appointments), unscheduled (e.g. examinations, emergency appointments), not applicable or unknown.

The clinical data contain more than one record per consultation and the same consultation ID can have more than one clinical contact type. For these clinical records, we assumed that unscheduled takes precedence (i.e. they are likely to have come in for an unscheduled visit but had a scheduled 'type' of procedure at the same time). Of all the contacts coded, a small proportion (2.27%, 10,011 of 440,429) could have been defined as both, based on the assumptions made about the clinical data.

Consultation data marked as unknown, based on the clinical data, as well as consultation data that did not link to clinical data, are coded based on immunisation, therapy, referral, and test and consultation data. If at least one match was found in the immunisation record, then the data were coded as scheduled. If at least one match was found with therapy (medication) data, then the data were coded as unscheduled. If the data matched with the test data as part of the routine asthma review, then they were coded as

scheduled. If they matched with test data of peak expiratory flow rate, then they were coded as unknown. Otherwise, a match with test data was coded as unscheduled.

Finally, contacts were coded on the consultation type in the consultation table, where follow-up/routine visits, repeat issue and medicine management were coded as scheduled; consultation types that indicated an emergency visit were coded as unscheduled; administrative-type consultation types were coded as not applicable; and those that were unclear, for example clinic, surgery consultation and other, were coded as unscheduled because of the likelihood that most scheduled consultation types would be clearly recorded. The process of allocation is detailed in *Appendix 3*.

Changes to the data collection, data extraction and methods for allocation of data after the trial commenced, with reasons

When reviewing the code lists used by CPRD to identify patients, after the study was completed and it was being reported, it became apparent that there was a discrepancy between the codes provided by the study team and the codes used by CPRD. The missing codes included some asthma, neoplasm and medication codes.

The clinicians on the Trial Management Group (TMG) reviewed the discrepancies between the codes used by CPRD and those provided by the study team. With reference to the omitted asthma codes, the clinical view was the codes were secondary codes and so there was no concern that children with asthma would have been missed. For the omitted neoplasm codes, the clinical view was that there was no concern as the codes were usually for adults and not children. However, there was a concern with the medication codes, which had been on the original code list but which were omitted from the CPRD extraction. This is of importance, as one of the inclusion criteria for the study was asthma medication prescribed in the previous 12 months. The clinical view was this may have resulted in fewer children having been identified as eligible for the trial than should have been if the correct, full list of product codes had been used. The views of the TMG, which were subsequently endorsed by the TSC, was that a further data extraction should be undertaken by the CPRD to quantify the effect of using the correct medication code list compared with the one used in error.

The CPRD undertook a review to identify the source of the problem and identified human error that was not picked up in their quality assurance. The CPRD has amended its documentation and quality assurance procedures to ensure that this type of human error is more readily identified and corrected at the time of the mistake.

In response to the request by the TSC, the set of product codes supplied by the study team was used by CPRD to identify those children with asthma who had received medication for asthma in the previous 12 months. This was done to estimate the magnitude of the impact upon the eligible patients. The CPRD conducted a post hoc analysis identifying children aged between 4 and 16 years, and still registered with a study practice, on 12 March 2013 using the April 2013 build of the CPRD GOLD database, utilising both lists of product codes. This date and database were chosen as they were the most recent versions documented to have been used for the identification of eligible patients for the trial. Owing to the human error, it is not possible to exactly extract the same data set as used in the PLEASANT study. However, it would give an estimate of the relative effect on the same size.

Using the CPRD list of medical codes, 10,753 children were identified, compared with 11,273 children identified using the full list of medical codes. This equates to an estimated 5% of children with asthma who potentially could have been in the trial but who were not. Thus, although this error has been identified, it was unlikely to have a major impact upon the trial.

The error is unfortunate, but CPRD has introduced procedures to prevent such an error from happening again.

Sample size

From previous research in the CPRD practice population, 30% of school-aged children with asthma had at least one unscheduled medical contact during the month of September.[13] We postulated that the intervention may reduce the number of children who have unscheduled medical contacts from 30% to 25% (i.e. an absolute reduction of 5%). The average practice size in the CPRD is 8294. Thus, we expected c. 100 school-aged children with asthma per practice (based on 12% of a practice being school-aged children and 11% of school-aged children having asthma). Therefore, to detect a difference of 5% with 90% power and two-sided significance level of 5%, and with an intraclass correlation (ICC) of 0.03 to account for clustering, we required 70 practices per arm. The sample size of 140 practices would equate to approximately 14,000 school-aged children with asthma.

Ukoumunne et al.[24] give estimates of ICCs for patients with respiratory symptoms in general practice. Based on the work of Ukoumunne et al., an ICC of 0.03 is a conservative estimate. The power of the study for ICCs of 0.01, 0.02, 0.03, 0.04 and 0.05 was 99.4%, 96.0%, 90.0%, 83.1% and 76.2%, respectively.

As a further sensitivity analysis, we investigated the effect of practices not sending out the letter as planned. Suppose 10 practices failed to send out the letter, these would still be included in the primary analysis under the ITT principle. However, the effect that could be observed would be reduced to 4.3%. Under the sample assumptions (ICC = 0.03, etc.), the power for the same sample size is reduced to 79.3%. This is a little under 80%, but it does demonstrate reasonable robustness to at least one deviation in the planned design.

Randomisation and blinding

Randomisation was at cluster (general practice) level, and was stratified by size of general practice (i.e. the 'list size'), to ensure that there was an equal sample size, in terms of number of school-aged children with asthma, in each arm of the trial. The randomisation sequence was generated by the main trial statistician based within the CTRU, and allocation concealment was ensured by restricting access to the two CTRU statisticians. The randomisation was undertaken by a statistician within the CTRU, in line with a study-specific randomisation plan. Once practices had agreed to participate, their identifier and list size were forwarded to the trial statisticians for randomisation to one of the two groups (intervention or usual care). The allocation was subsequently revealed to the study manager and research assistant.

The study team were unblinded throughout the study, but had no access to data until after a statistical analysis plan was developed, and had no influence on data capture. The GP Adjudication Panels did not have access to the randomisation group when reviewing the data.

Statistical methods

Analysis populations
Each of the outcomes listed in *Outcomes* were evaluated on each of the four subpopulations:

1. children aged 5–16 years (the primary analysis population)
2. children aged under 5 years
3. children aged 5–16 years with a prescription for steroid inhalers
4. children aged under 5 years with a prescription for steroid inhalers.

The choice of the 5–16 years age group as the primary analysis population is a result of the difficulty associated with making a diagnosis of asthma among children below this age.[25,26] Patients aged 4–5 years were analysed separately to those aged 5–16 years, as the diagnosis of asthma is more controversial in the

former age group; it is often not practical to measure variable airway obstruction below the age of 5 years, making diagnosis of asthma difficult.[25,26] The impact of the intervention in patients under 5 years will be compared with that seen in the main analysis to assess whether or not the intervention appears to benefit younger children. Additional analyses were restricted specifically to children who had received a prescription for steroid inhalers in the previous year, again undertaken separately for children aged 5–16 years and under 5 years.

Analyses of effectiveness were performed on both ITT and PP bases, with the ITT being primary. The health economic analyses were based on the PP population. ITT analyses included all practices for which data were obtained by study period. The PP analyses were the subset of children in the ITT analyses to whom the intervention was delivered as intended by the protocol. The two criteria for exclusion from PP analyses were:

1. Practices that did not send intervention letters as requested. In such cases, the entire practice data were excluded from the PP analyses.
2. Individual children who were not sent the intervention letter. GPs were given discretion to withhold the letter from any children they believed were unsuitable. In such cases, the individual was excluded from the PP analyses.

Analytical methods

The proportion of children having an unscheduled medical contact was analysed separately for each time period using logistic regression in which the covariates were the individual's age, sex, number of contacts the previous September and the trial arm (intervention or control) as fixed effects, and the design/cluster effect of general practice as a random effect. The proportion of children having a prescription within each time period was analysed in the same manner.

Both the number of unscheduled medical contacts made in each period by the children and the number of prescriptions ordered within a time period were analysed using a random-effects negative binomial model in which the same covariates as above were included.

Within each time period, the time to first medical contact was defined as the number of days from the start of school term to the date of first contact. If no contact was made in the period, the time was censored at the last date within the period. Analyses were conducted using Cox proportional hazards regression using a random-effects (or 'shared frailty') model to account for the clustering within each practice. The same covariates were used (i.e. age, sex, number of contacts the previous September and trial arm).

It should be noted that there was information on death status (no deaths were observed), but no information about the movement outside GPs or region.

Full details of the analyses are in the statistical analysis plan (see *Appendix 4*).

Patient and public involvement

Patient and public involvement throughout the trial
Patient and public involvement during the conduct of the study had two components: (1) PPI consultations, held in September 2012 and October 2015, that involved children with asthma and their parents; and (2) two parents were invited to be independent members of the TSC.

Patient and public involvement consultation events
The September 2012 PPI consultation[21] event was used to:

- Remind attendees of the purpose of the study and give feedback on outcome of the HTA programme application.

- Discuss the adherence of the children to their medication over the school holidays and subsequently since they have been back at school.
- Present the GP letter (trial intervention) that was discussed at a pre-funding PPI event in January 2011, to show how it has changed as a result of the previous consultation and to invite further discussion on how the wording of the letter could be improved.
- Invite comment on the design and end points to be used in the study and, in particular, on what, from their perspective, is a scheduled and unscheduled contact.
- Discuss plans for PPI throughout the study and invite interested parents onto the TSC.
- Discuss the ethics application and the rationale of the research team for how the ethics of the study are being addressed.
- Invite comment on the lay summary of the research ethics committee.
- Invite opinions on the study logo and the website.

The October 2015 PPI consultation[27] was used to:

- recap the reason for the trial
- discuss the findings and any implications
- obtain advice from the children and parents on the interpretation of the findings
- give children and parents an opportunity to discuss how the findings should best be disseminated
- provide details of the next steps for the research
- consider any future research.

For attending the consultation events, each child was given a £20 gift voucher and parents were paid travel expenses. Refreshments were also provided.[28]

Patient and public involvement members of the Trial Steering Committee
Two parents of children with asthma were invited onto the TSC. Payment for time was offered at a rate of £50 per meeting, plus travel expenses. A glossary of key research terms used in the study was provided and the study's PPI lead was available to meet with the parent members of the TSC before or after each meeting to discuss the agenda items and any issues of concern.

Trial oversight

Two committees were established to govern the conduct of the trial: the TMG and TSC.

All committees are governed by Sheffield CTRU SOPs. The TMG comprised the principal investigator, co-investigators and key staff within the CTRU. The role of the TMG was to implement all parts of the trial.

The TSC comprised an independent chairperson (GP), two independent members (academic GP and statistician), two lay members (parents of children with asthma), the principal investigator and key staff within the CTRU (as non-voting members). The role of the TSC was to provide supervision of the protocol; a statistical analysis plan; and to provide advice on, and monitor, the progress of the trial.

Safety assessments

The trial intervention aimed to optimise usual asthma care and improve adherence to medications already prescribed by the GP, thus reducing the potential exacerbation of asthma following return to school in September. Therefore, involvement in the trial was not expected to result in any adverse or serious adverse events arising from participation.

Any asthma complications relating to the health of the child were expected to be picked up by their GP or out-of-hours service and managed as per usual care. On advice from the TSC, no formal reporting procedures for adverse events or serious adverse events were put in place.

Practices randomised to the intervention were provided with a short template to report any incidents that they felt were related to the conduct of the trial.

Chapter 3 Trial results

Recruitment and participant flow

In total, 142 GP surgeries agreed to take part in the study (*Figure 3*).[20] Of these, one (a control group practice with 99 children with asthma) withdrew consent after the start of the study for the data to be extracted and stored by the CPRD (independent of the study); this practice was excluded from all analyses. In total, 70 practices (comprising 5917 individuals) were randomised to the intervention (letter) group and 71 practices (6262 individuals) to the control group.

Baseline characteristics

The descriptive statistics (age, sex and surgery size) of the 12,179 subjects included are given in *Tables 1* and *2*. Summaries reported are stratified by intervention type and overall.

An analysis has been undertaken on practice recruitment into the trial. For the practices recruited through CPRD, it was found that there was little difference in terms of the size of the practice.[20] It was also found that practices that have been involved in more research were more likely to be in the PLEASANT study, and that the more studies the practice had previously participated in, the greater the likelihood of entering the trial.

Number of participants and analysis subsets

Analyses were conducted using outcome data from four overlapping time periods and one baseline period. For each period, analyses were based only on practices that contributed data to the entirety of that period.

	January 2013	February 2013	March 2013	April 2013	May 2013	June 2013	July 2013
Predicted recruitment	10	34	58	82	106	130	140
Actual recruitment	10	31	46	67	98	124	142
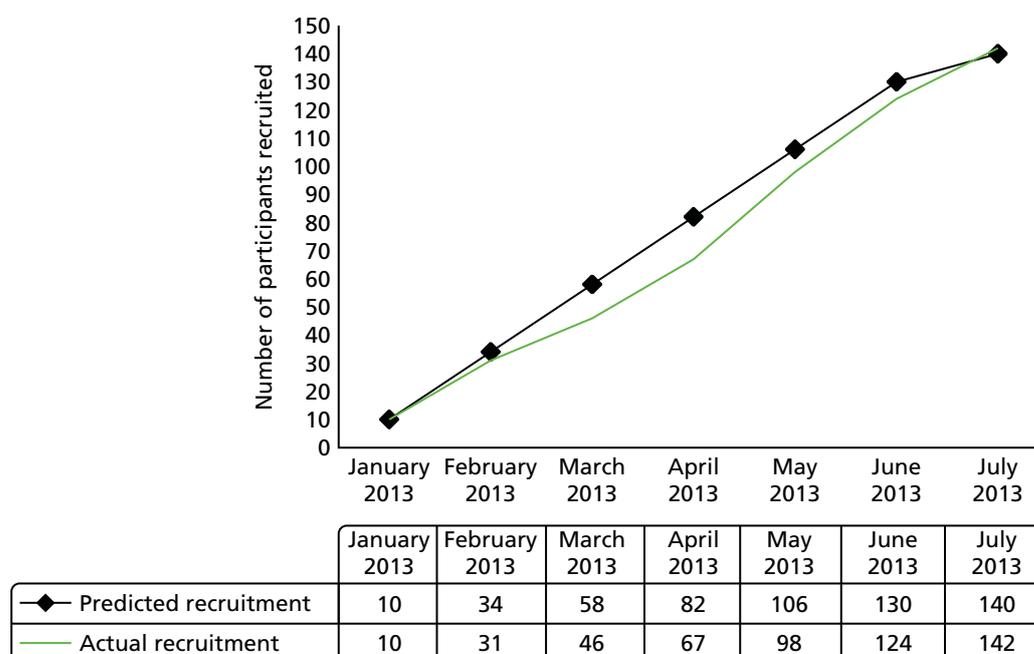
FIGURE 3 Participant recruitment curve.

TABLE 1 Descriptive statistics of patients[a]

| | Group | | |
| | Intervention (letter) | Control (no letter) | |
Statistic	(n = 5917)	(n = 6262)	Total (n = 12,179)
Sex, n (%)			
Male	3505 (59.24)	3749 (59.87)	7254 (59.56)
Female	2412 (40.76)	2513 (40.13)	4925 (40.44)
Age (years)			
Mean (SD)	10.51 (3.29)	10.55 (3.30)	10.53 (3.30)
Median (IQR)	10.80 (7.88–15.97)	10.89 (7.80–15.97)	10.89 (7.80–15.97)
Range	4.05–15.97	4.05–15.97	4.05–15.97

IQR, interquartile range; SD, standard deviation.
a Statistics produced at the subject level.

TABLE 2 Descriptive statistics of surgeries[a]

| | Practice group | | |
| | Intervention (letter) | Control (no letter) | |
Statistic	(n = 70)	(n = 71)	Total (n = 141)
Sample size (n)			
Mean (SD)	85 (44)	88 (SD 64)	86 (55)
Median (IQR)	80 (49–114)	75 (41–107)	76 (45–113)
Range	4–209	10–293	4–293

IQR, interquartile range; SD, standard deviation.
a Statistics produced at the surgery level.

In other words, if practices stopped submitting data to the CPRD before the end of a given follow-up period, they were excluded from all analyses for that time period.

Figure 4 shows the flow of subjects from the overall population (aged 4–16 years) to the main cohort (aged 5–16 years). Of the 456 practices invited, 433 were through the CPRD and 23 were through the primary care research network and joined the CPRD.[20]

Table 3 provides the number of practices and the number of individuals aged 5–16 years (the primary analysis population) included for each time period.

Adherence to protocol

Of the 70 intervention practices, two did not send letters to any of the patients identified and four sent the intervention out late, on 6, 8, 12 and 23 August. In addition, GPs were given discretion to withhold the letter from any children they believed were unsuitable candidates; among the remaining 64 practices (5222 individuals), letters were not sent to 786 children. These individuals were included in the primary ITT analyses but were excluded from the PP analyses.

GP practices approached
($n = 456$ practices)

Enrolment

Randomised
($n = 141$ practices;
$n = 12,179$ individuals)

Experimental

Control

Allocation

Allocated to intervention
($n = 70$ practices; $n = 5917$ individuals)
- Received allocated intervention
  ($n = 4436$ individuals)
- Did not receive allocated intervention as per protocol ($n = 1481$ individuals)
  ○ GP exclusions ($n = 786$ individuals)
  ○ Letter sent late or not at all
    ($n = 6$ practices; $n = 695$ individuals)

Allocated to intervention
($n = 71$ practices; $n = 6262$ individuals)
- Received allocated intervention ($n = 6262$)
- Did not receive allocated intervention ($n = 0$)

Follow-up

Discontinued intervention
- Withdrawal < 30 September 2014
  ($n = 13$ practices; $n = 1506$ individuals)

Discontinued intervention
- Withdrawal < 30 September 2014
  ($n = 18$ practices; $n = 1824$ individuals)

Analysis

Analysed (Experimental)

Prescription uptake and scheduled medical contacts		ITT	PP
	August 13	$N_P = 68$ $P_I = 5305$ $P_O = 612^{a,b}$	$N_P = 62$ $P_I = 4203$ $P_O = 1714^{a,b}$
	August 13– July 14	$N_P = 58$ $P_I = 4541$ $P_O = 764$	$N_P = 54$ $P_I = 3641$ $P_O = 562$
	August 14	$N_P = 58$ $P_I = 4541$ $P_O = 0$	$N_P = 54$ $P_I = 3641$ $P_O = 0$
All medical contacts	September 13	$N_P = 68$ $P_I = 5305$ $P_O = 612^{a,b}$	$N_P = 62$ $P_I = 4203$ $P_O = 1714^{a,b}$
	September– December 13	$N_P = 65$ $P_I = 5097$ $P_O = 208$	$N_P = 59$ $P_I = 4021$ $P_O = 182$
	September 13– August 14	$N_P = 58$ $P_I = 4541$ $P_O = 556$	$N_P = 54$ $P_I = 3641$ $P_O = 380$
	September 14	$N_P = 57$ $P_I = 4411$ $P_O = 130$	$N_P = 54$ $P_I = 3641$ $P_O = 0$

Analysed (Control)

Prescription uptake and scheduled medical contacts		ITT	PP
	August 13	$N_P = 69$ $P_I = 5586$ $P_O = 676^{b,c}$	$N_P = 69$ $P_I = 5586$ $P_O = 676^{b,c}$
	August 13– July 14	$N_P = 54$ $P_I = 4549$ $P_O = 1037$	$N_P = 54$ $P_I = 4549$ $P_O = 1037$
	August 14	$N_P = 54$ $P_I = 4549$ $P_O = 0$	$N_P = 54$ $P_I = 4549$ $P_O = 0$
All medical contacts	September 13	$N_P = 69$ $P_I = 5586$ $P_O = 676^{b,c}$	$N_P = 69$ $P_I = 5586$ $P_O = 676^{b,c}$
	September– December 13	$N_P = 67$ $P_I = 5384$ $P_O = 202$	$N_P = 67$ $P_I = 5384$ $P_O = 202$
	September 13– August 14	$N_P = 54$ $P_I = 4549$ $P_O = 835$	$N_P = 54$ $P_I = 4549$ $P_O = 835$
	September 14	$N_P = 53$ $P_I = 4438$ $P_O = 111$	$N_P = 53$ $P_I = 4438$ $P_O = 111$

FIGURE 4 The CONSORT diagram of the number of GP surgeries and individuals in the PLEASANT study. It is not a mistake that there are zero GP exclusions in the arm that did not send letters, as it is impossible for the GPs to exclude individuals from receiving letters when no one in that arm is receiving letters. a, In comparison to those in the experimental arm ($n = 5917$); b, in comparison to those in the control arm ($n = 6262$); and c, these figures include withdrawals and patients aged 4 years.

TABLE 3 Number of practices and individuals included within each time period

| Time period | Group | | | | |
| | Intervention | | Control | |
	Practices (*n*)	Individuals 5–16 years (*n*)	Practices (*n*)	Individuals 5–16 years (*n*)
Prescription uptake and scheduled medical contacts				
August 2013	68	5305	69	5586
August 2013–July 2014	58	4541	54	4549
August 2014	58	4541	54	4549
All medical contacts				
September 2013 (primary study period)	68	5305	69	5586
September–December 2013 (extended study period)	65	5097	67	5384
September 2013–August 2014 (12-month study period)	58	4541	54	4549
September 2014 (echo substudy)	57	4411	53	4438

Outcomes and estimation

Primary outcome

Unscheduled medical contacts in September 2013

The proportion of individuals with at least one unscheduled contact is summarised for each of the four populations (including the aforementioned primary analysis population) in *Figure 5*. Overall, 2399 individuals (45.2%) in the intervention arm had at least one unscheduled medical contact, compared with 2441 (43.7%) in the control arm [adjusted odds ratio (OR) 1.09, 95% CI 0.96 to 1.25]. The actual number of contacts was similar in the two groups, but there were 81 unscheduled contacts per 100 children in each arm [adjusted incidence rate ratio (IRR) 1.02, 95% CI 0.94 to 1.12]. Restricting the analyses to the PP population gave a similar (but slightly greater) increase in the effect sizes.

The ICC for the primary analysis was 2.6%, which was consistent with the ICC used for the sample size calculation.[29]

Similar results were observed for 5- to 16-year-old children who had been prescribed preventative steroids. Among children aged under 5 years, the differences were larger, and of borderline statistical significance, with the intervention being associated with more unscheduled visits for all subgroups. In all cases the effect among the PP population was greater than that observed in the ITT population.

The percentage of children aged 5–16 years who required one or more unscheduled contact between August and December 2013 is given in *Table 4*. The most immediate feature is the excess unscheduled contacts in August 2013, which is out of keeping both with the following months and with the equivalent figures in the previous year. Overall, the proportion of children making an unscheduled contact was higher in 2012 than in 2013, but only August (and to a lesser extent, September) 2013 showed a pronounced difference between the groups.

To further investigate the effect observed in *Table 4*, the analysis of unscheduled contacts by month was repeated (*Table 5*), but only for children who received preventative medication. The effects are similar to those observed in *Table 4*.
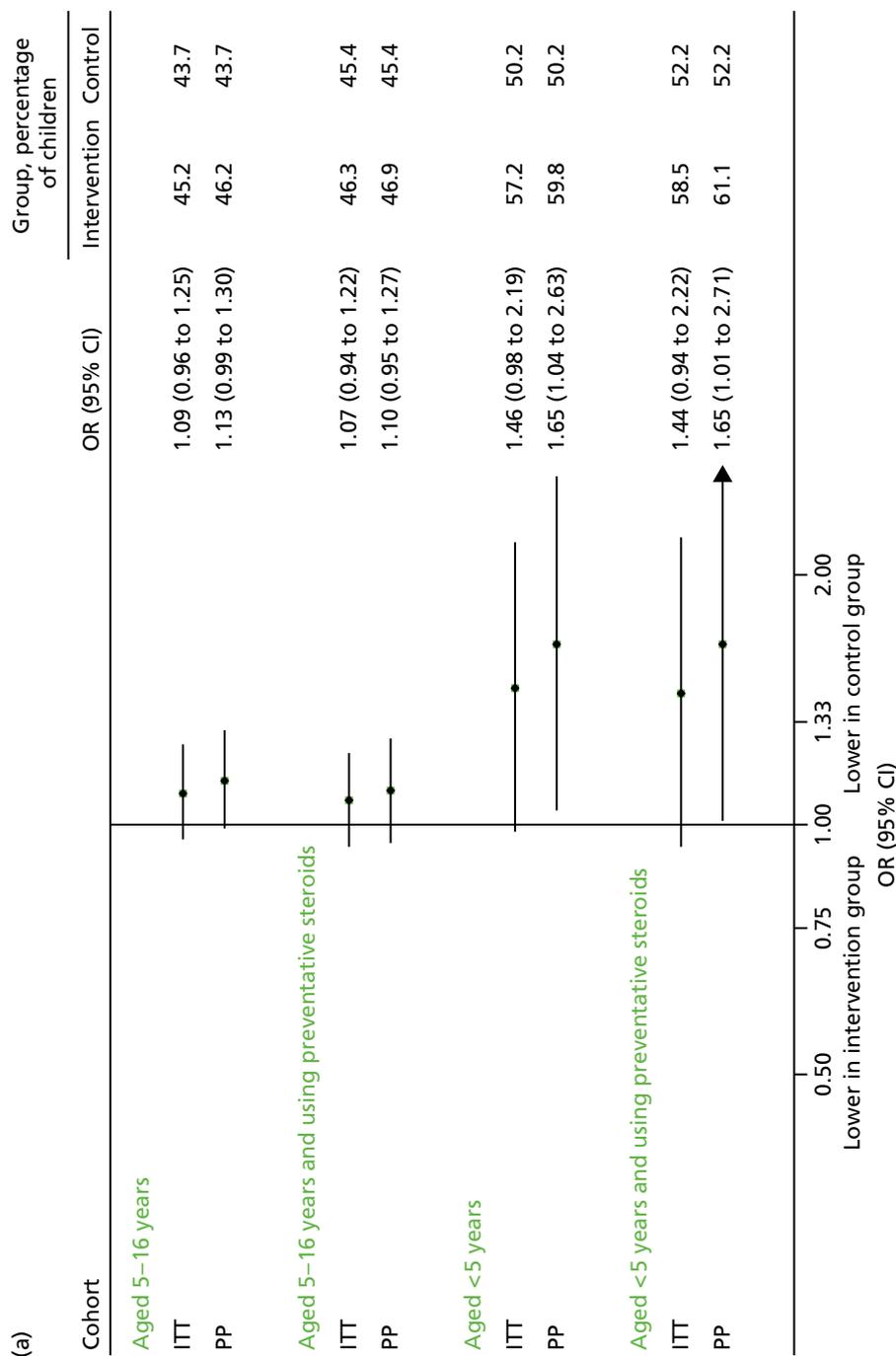
FIGURE 5 Unscheduled medical contacts in September 2013. (a) Number of children with one or more unscheduled contact; and (b) mean number of unscheduled contacts per child. (*continued*)

(b)

Cohort		IRR (95% CI)	Group, mean	
			Intervention	Control
Aged 5–16 years				
ITT		1.02 (0.94 to 1.12)	0.81	0.81
PP		1.03 (0.94 to 1.13)	0.82	0.81
Aged 5–16 years and using preventative steroids				
ITT		1.01 (0.92 to 1.10)	0.83	0.84
PP		1.01 (0.92 to 1.11)	0.83	0.84
Aged <5 years				
ITT		1.26 (0.98 to 1.63)	1.13	0.95
PP		1.36 (1.03 to 1.80)	1.21	0.95
Aged <5 years and using preventative steroids				
ITT		1.24 (0.96 to 1.60)	1.14	1.00
PP		1.35 (1.02 to 1.78)	1.23	1.00

0.67 0.75 1.00 1.33 1.50 1.75

Lower in intervention group   Lower in control group

IRR (95% CI)
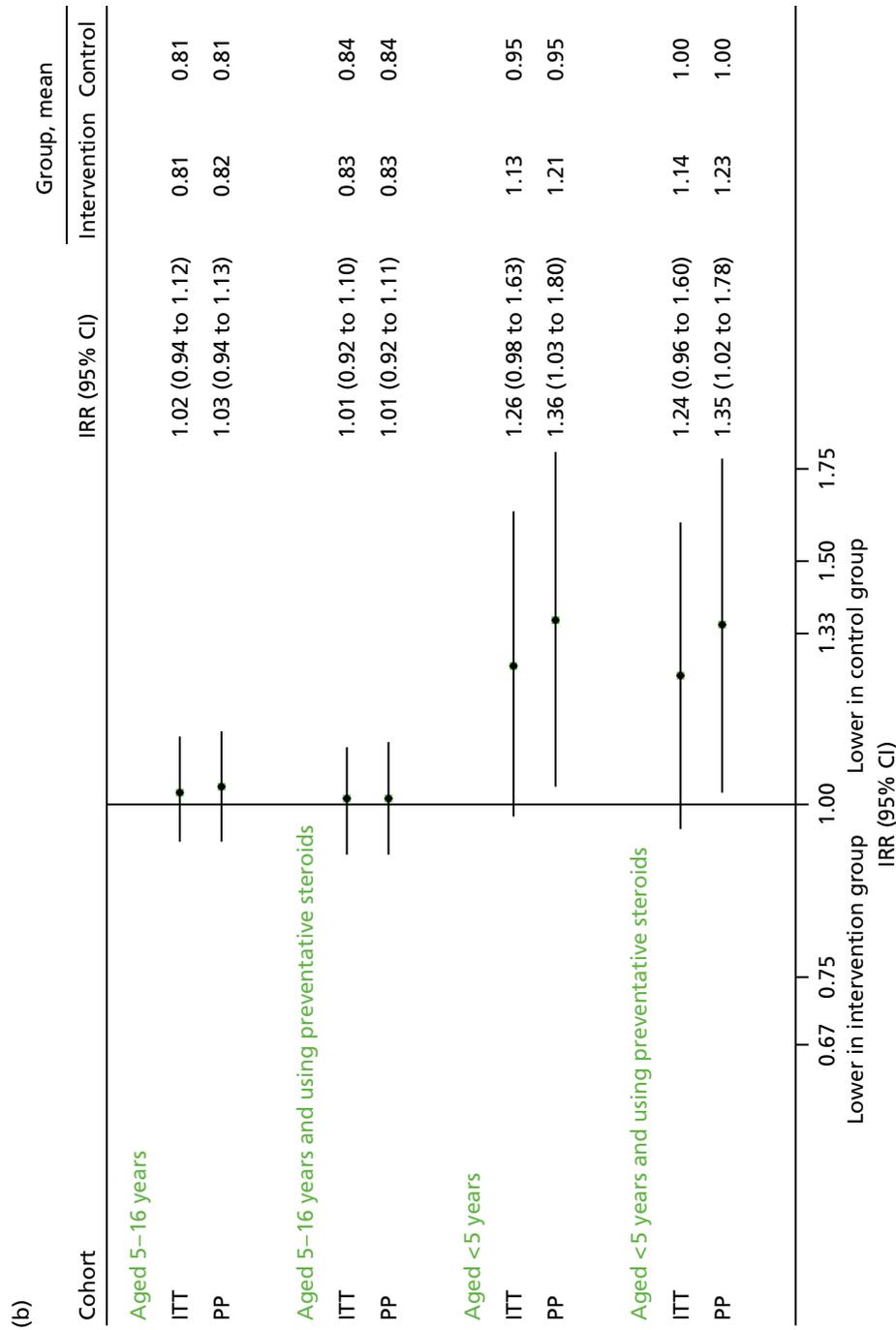
FIGURE 5 Unscheduled medical contacts in September 2013. (a) Number of children with one or more unscheduled contact; and (b) mean number of unscheduled contacts per child.

TABLE 4 Percentage of children aged 5–16 years who had at least one unscheduled contact

Month	2012 (preceding year)		2013 (intervention year)	
	Intervention (%)	Control (%)	Intervention (%)	Control (%)
August	41.8	41.0	41.1	34.4
September	47.4	48.2	45.2	43.7
October	51.4	50.0	44.5	45.8
November	51.5	50.1	43.7	44.3
December	49.0	49.1	42.2	41.8

TABLE 5 Percentage of children aged 5–16 years and using preventative medication who had at least one unscheduled contact

Month	2012 (preceding year)		2013 (intervention year)	
	Intervention (%)	Control (%)	Intervention (%)	Control (%)
August	41.9	41.3	39.0	34.1
September	47.8	48.9	43.2	41.5
October	52.0	52.0	42.7	43.5
November	52.1	50.9	41.5	40.5
December	49.9	50.0	39.9	38.5

In both *Tables 4* and *5*, after the initial increase in unscheduled contacts associated with the intervention in August and September there is a fall. The fact that there seems to be a reduction in contacts after September will be discussed further in *Chapter 3*, *Contacts in the extended post-intervention phase (September to December 2013)* and in *Health economic methods*.

In *Scheduled visits and steroid prescriptions in August 2013*, in the analysis of prescription data it will be highlighted how the intervention caused an increase in the proportion of prescriptions being collected. A likely explanation for the possible increase in August and September in the letter group is patients who have not collected a prescription in a while needing to see their GP before a new prescription could be given. This could be caused by patients wishing to see their GP or by the GP requiring an appointment with the patient before a prescription is given. The excess observed in August/September would therefore be, for some patients, a level of planned care that would then be reflected in the subsequent reductions in following months. To investigate this we have the results in *Table 6*.

The results in *Table 6* are the same data as in *Table 5* but broken down by when a patient last collected a prescription. There is little evidence of a difference in terms of the excess in unscheduled contacts in the letter arm in August. For children who last collected a prescription within the previous 3 months, 51.6% in the letter arm had an unscheduled contact in August, compared with 45.5% in the control arm, therefore 6.1% more children in the letter arm had a scheduled contact. For children who had collected a prescription within the previous 3–6 months, 38.5% in the letter arm had an unscheduled contact, compared with 34.5% in the control arm, which represents a 4.0% excess.

In September there does seem to be a difference in the proportion of children having an unscheduled contact according to when they last collected a prescription. If a prescription had been collected within 3 months, then in the letter arm 55.2% of children had an unscheduled contact in September, which is comparable to the 54.3% in the control arm. Conversely, if it was 3–6 months since the last prescription was collected, 42.1% of children had an unscheduled contact in the intervention arm, compared with just

TABLE 6 Percentage of children aged 5–16 years and using preventative medication who had at least one unscheduled contact broken down by when they had their last prescription in the 12 months prior to the start of the study

Month	Time period (%)							
	August–October 2012		November 2012– January 2013		February–April 2012		May–July 2013	
	Intervention (*n* = 385)	Control (*n* = 385)	Intervention (*n* = 645)	Control (*n* = 670)	Intervention (*n* = 738)	Control (*n* = 813)	Intervention (*n* = 1927)	Control (*n* = 2004)
August	29.2	24.9	30.4	28.9	38.5	34.5	51.6	45.5
September	35.5	30.8	35.9	37.3	42.1	39.7	55.2	54.3
October	31.3	33.6	33.5	41.2	37.4	41.8	58.6	56.4
November	33.4	24.2	33.0	36.7	40.0	37.7	54.1	53.0
December	30.8	25.6	34.3	34.1	36.0	36.5	53.2	50.3

39.7% in the control arm, which is an increase of 2.4%. Therefore, the effect in September seems to be greatest in children who had not collected a prescription recently.

One important thing to note is that when making the assessment of unscheduled contacts, we cannot determine whether the unscheduled contact is at the request of the patient or of the GP. This factor is important in the interpretation of the results in *Tables 4–6*.

Secondary outcomes

Scheduled visits and steroid prescriptions in August 2013
An objective of the PLEASANT study was that the intervention would increase the proportion of children who had a prescription in August 2013, which would follow through to an increase in medication usage and, thereby, a reduction in unscheduled medical contacts. Although the latter was not evident from the data in *Primary outcome*, and adherence could not be assessed, the intervention (letter) was associated with an increased uptake of prescriptions in the month of August 2013. Among children aged 5–16 years, 876 (16.5%) requested at least one prescription, compared with 703 (12.6%) in the control group (adjusted OR 1.43, 95% CI 1.24 to 1.64); the total number of prescriptions was also higher (adjusted IRR 1.31, 95% CI 1.17 to 1.48). These findings are displayed graphically in *Figure 6*.

Scheduled contacts made in August 2013 are displayed in *Figure 7*. The percentage of children with a scheduled medical contact was higher in the intervention group compared with the control group (see *Figure 7a*), but this was not statistically significant. The actual number of scheduled contacts were significantly increased in the intervention group (see *Figure 7b*).

Unscheduled medical contacts associated with respiratory diagnosis in September 2013
Unscheduled respiratory-related medical contacts are important, as these are the most sensitive outcome for determining whether or not the intervention is preventing episodes of asthma exacerbation. In absolute terms, however, these contribute only a small fraction of the total attendances (*Table 7*). Among the primary ITT analysis population of children aged between 5–16 years, a total of 513 subjects experienced at least one unscheduled respiratory-related contact across all practices, with slightly higher uptake in the intervention group. In the intervention group, 279 (5.3%) required at least one unscheduled respiratory related contact compared with 234 (4.2%) in the control group (adjusted OR 1.30, 95% CI 1.03 to 1.66). The percentages for other subgroups are presented in *Figure 8a*, and the total number in *Figure 8b*.

(a)

Cohort	OR (95% CI)	Group, percentage of children	
		Intervention	Control
Aged 5–16 years			
ITT	1.43 (1.24 to 1.64)	16.5	12.6
PP	1.52 (1.31 to 1.76)	17.5	12.6
Aged 5–16 years and using preventative steroids			
ITT	1.41 (1.23 to 1.63)	17.3	13.4
PP	1.48 (1.28 to 1.72)	18.1	13.4
Aged <5 years			
ITT	1.47 (0.93 to 2.33)	17.7	12.9
PP	1.75 (1.06 to 2.89)	20.1	12.9
Aged <5 years and using preventative steroids			
ITT	1.47 (0.93 to 2.34)	18.5	13.6
PP	1.72 (1.04 to 2.85)	20.6	13.6

0.50   0.75   1.00   1.33   2.00
OR (95% CI)
Lower in intervention group   Lower in control group

FIGURE 6 Uptake of steroid inhaler prescriptions, August 2013. (a) Number of children with one or more prescription; and (b) mean number of prescriptions. (*continued*)

(b)

Cohort	IRR (95% CI)	Group, mean	
		Intervention	Control
Aged 5–16 years			
ITT	1.31 (1.17 to 1.48)	0.17	0.13
PP	1.38 (1.22 to 1.56)	0.19	0.13
Aged 5–16 years and using preventative steroids			
ITT	1.30 (1.16 to 1.47)	0.18	0.14
PP	1.35 (1.20 to 1.53)	0.19	0.14
Aged <5 years			
ITT	1.43 (0.94 to 2.17)	0.18	0.13
PP	1.66 (1.06 to 2.58)	0.21	0.13
Aged <5 years and using preventative steroids			
ITT	1.43 (0.94 to 2.17)	0.19	0.14
PP	1.63 (1.05 to 2.54)	0.22	0.14

0.50   0.75   1.00   1.33   2.00

Lower in intervention group   Lower in control group

IRR (95% CI)

FIGURE 6 Uptake of steroid inhaler prescriptions, August 2013. (a) Number of children with one or more prescription; and (b) mean number of prescriptions.

FIGURE 7 Scheduled medical contacts in August 2013. (a) Number of children with one or more scheduled contact; and (b) mean number of scheduled contacts per child. (*continued*)

(b)
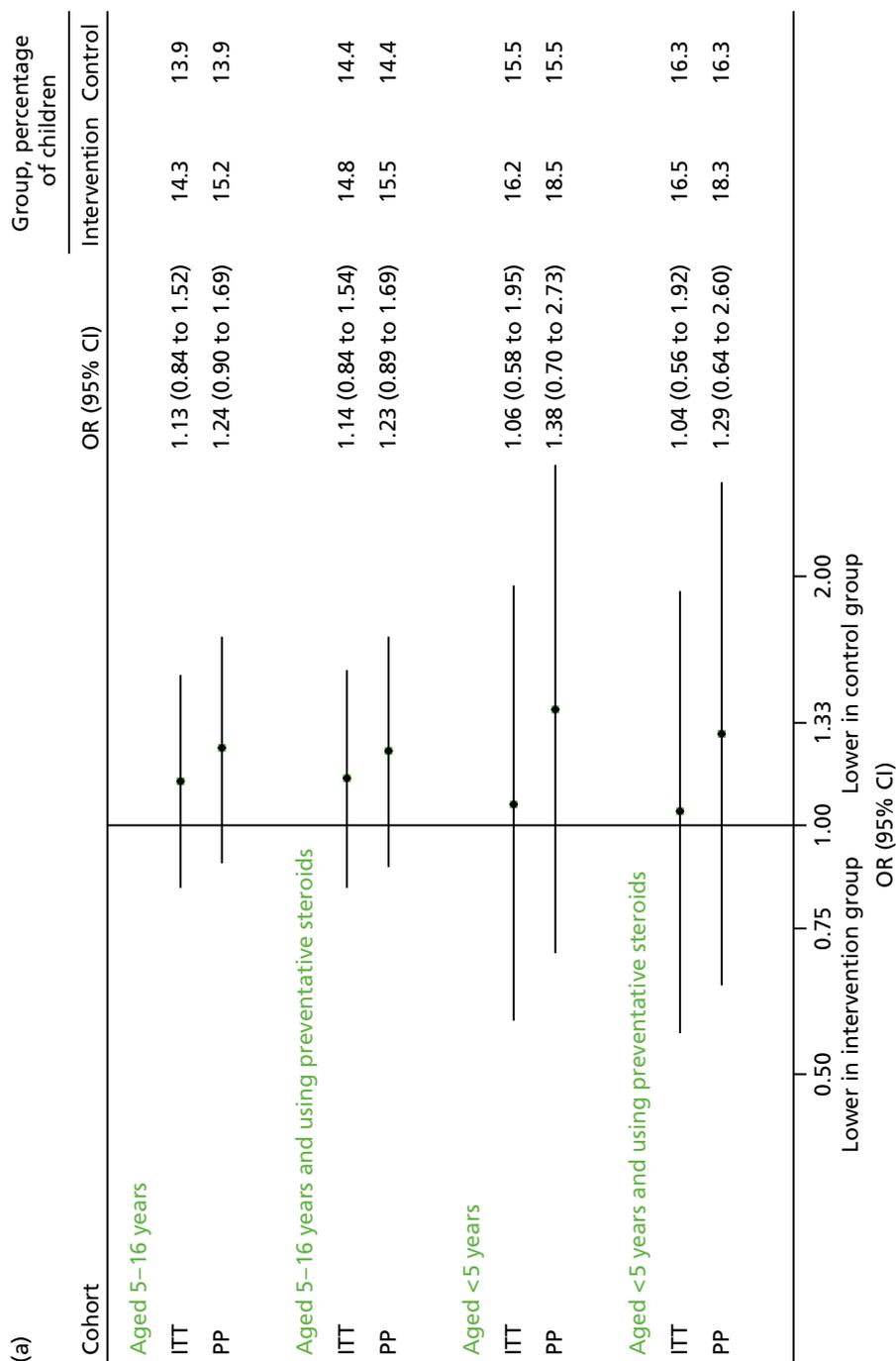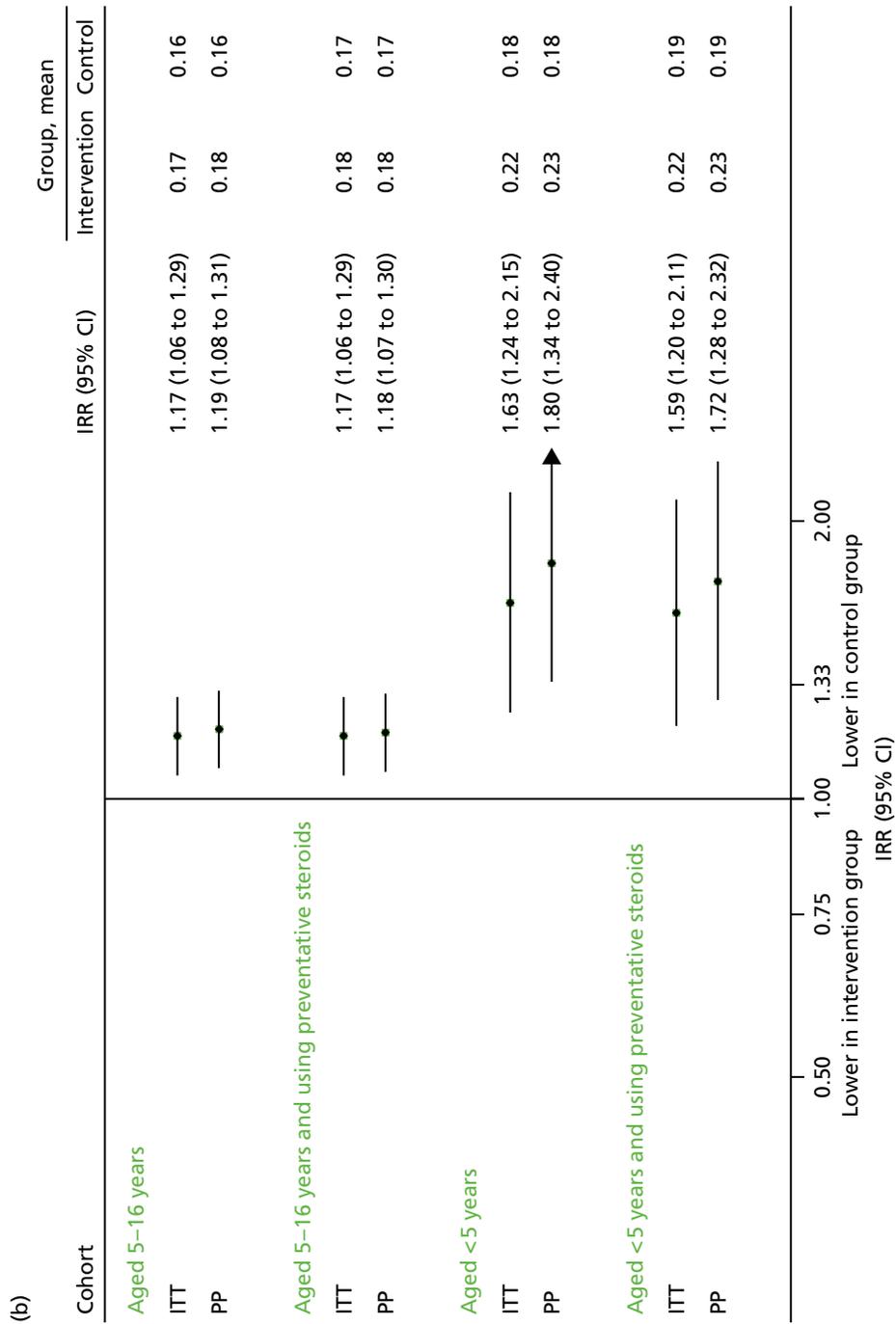
FIGURE 7 Scheduled medical contacts in August 2013. (a) Number of children with one or more scheduled contact; and (b) mean number of scheduled contacts per child.

TABLE 7 Breakdown of contact types for children aged 5–16 years (ITT population)

| Allocation | Total, n | Contact | | | | | Respiratory-related | | | |
| | | All | | | | | | | | |
		Relevant (n)	Scheduled, n (%)	Unscheduled, n (%)	Unclassified (n)		Relevant (n)	Scheduled, n (%)	Unscheduled, n (%)	Unclassified (n)
September 2013										
Letter (n = 5305)	7480	5585	1306 (23.38)	4279 (76.62)	1895		682	374 (54.84)	308 (45.16)	34
No letter (n = 5586)	8400	6126	1591 (25.97)	4535 (74.03)	2274		748	492 (65.78)	256 (34.22)	39
September–December 2013										
Letter (n = 5097)	30,084	21,981	5745 (26.14)	16,236 (73.86)	8103		2833	1674 (59.09)	1159 (40.91)	181
No letter (n = 5384)	32,138	24,368	6504 (26.69)	17,864 (73.31)	7770		3027	1901 (62.80)	1126 (37.20)	151
September 2013–August 2014										
Letter (n = 4541)	71,126	52,330	11,089 (21.19)	41,241 (78.81)	18,796		6492	3909 (60.21)	2583 (39.79)	642
No letter (n = 4549)	72,175	54,962	12,344 (22.46)	42,618 (77.54)	17,213		6546	4134 (63.15)	2412 (36.85)	414
September 2014										
Letter (n = 4411)	6191	4590	1079 (23.51)	3511 (76.49)	1601		447	255 (57.05)	192 (42.95)	32
No letter (n = 4438)	6267	4629	1144 (24.71)	3485 (75.29)	1638		486	300 (61.73)	186 (38.27)	20

(a)

Cohort	OR (95% CI)		Group, percentage of children	
			Intervention	Control
Aged 5–16 years				
ITT	1.30 (1.03 to 1.66)		5.3	4.2
PP	1.28 (0.99 to 1.64)		5.1	4.2
Aged 5–16 years and using preventative steroids				
ITT	1.30 (1.02 to 1.66)		5.5	4.4
PP	1.25 (0.97 to 1.61)		5.2	4.4
Aged <5 years				
ITT	1.10 (0.48 to 2.52)		6.6	6.1
PP	1.30 (0.53 to 3.23)		7.6	6.1
Aged <5 years and using preventative steroids				
ITT	1.01 (0.43 to 2.40)		6.5	6.4
PP	1.27 (0.51 to 3.17)		7.8	6.4

0.50   0.75   1.00   1.33   2.00

Lower in intervention group   Lower in control group

OR (95% CI)

FIGURE 8 Unscheduled respiratory-related medical contacts in September 2013. (a) Number of children with one or more unscheduled respiratory-related contact; and (b) mean number of unscheduled respiratory-related contacts per child. (*continued*)

Cohort	IRR (95% CI)	Group, mean	
		Intervention	Control
Aged 5–16 years			
ITT	1.30 (1.02 to 1.66)	0.06	0.05
PP	1.25 (0.97 to 1.62)	0.06	0.05
Aged 5–16 years and using preventative steroids			
ITT	1.30 (1.01 to 1.66)	0.06	0.05
PP	1.23 (0.95 to 1.60)	0.06	0.05
Aged <5 years			
ITT	1.11 (0.52 to 2.36)	0.07	0.06
PP	1.30 (0.58 to 2.95)	0.08	0.06
Aged <5 years and using preventative steroids			
ITT	1.04 (0.48 to 2.26)	0.07	0.07
PP	1.27 (0.56 to 2.89)	0.08	0.07

IRR (95% CI): 0.50   0.75   1.00   1.33   2.00

Lower in intervention group | Lower in control group

(b)

**FIGURE 8** Unscheduled respiratory-related medical contacts in September 2013. (a) Number of children with one or more unscheduled respiratory-related contact; and (b) mean number of unscheduled respiratory-related contacts per child.

All medical contacts (scheduled and unscheduled) in September 2013

The total number of medical contacts (excluding those deemed irrelevant) is presented in *Figure 9*. In contrast to previous analyses, children in the intervention arm had fewer contacts, although, again, none of the comparisons was statistically significant. Among children aged 5–16 years, 57.8% of the intervention arm participants made one or more contact, compared with 58.4% of those in the control arm (adjusted OR 0.99, 95% CI 0.80 to 1.22). The total number of appointments per child was 1.05 in the intervention arm, compared with 1.10 in the control group (adjusted IRR 0.97, 95% CI 0.87 to 1.07). Similar findings were observed for children on preventative steroids. By contrast, an increase in contacts was observed among children under 5 years.

Contacts in the extended post-intervention phase (September–December 2013)

Data on medical contacts in the extended study period (September–December 2013) were available for 65 of the original 70 intervention practices and 67 of the 71 control practices. The results are presented in *Figures 10–12*. In some subgroups, a statistically significant excess of contacts was observed in the intervention group, although it should be noted that this could be because of the multiple outcomes and hypotheses tested.

The total number of unscheduled contacts is of particular relevance in the period September to December 2013. This includes the months (October to December) when the intervention arm seemed to reduce the number of contacts. It is this time interval that forms part of the health economic analysis, which analyses the total number of contacts rather than the percentage of children who required one.

The total number of contacts declined over the period from September to December. Although unscheduled respiratory-related contacts demonstrated a slight increase, the proportion of children aged 5–16 years requiring any medical contact remained higher in the intervention arm (although not statistically significant) for unscheduled contacts (see *Figure 10a*), unscheduled respiratory contacts (see *Figure 11a*) and all contacts (see *Figure 12a*). The overall number of contacts and the number of unscheduled was slightly reduced in the intervention arm (see *Figures 10b* and *12b*) for children aged 5–16 years, but not those aged under 5 years, for whom the number of unscheduled respiratory contacts was also higher (see *Figure 11b*). However, these differences were, generally, not statistically significant.

Contacts over 12 months (September 2013–August 2014)

Data on medical contacts in September 2013–August 2014 were available for 58 intervention practices and 54 control practices. The results are presented in *Figures 13–15*. The differences in percentages between the intervention and control groups were generally modest and not statistically significant on the ITT population, and differed according to the subgroups. For the primary population (the ITT among 5- to 16-year-olds), the number of unscheduled contacts was similar (see *Figure 13*) and respiratory contacts remained higher (see *Figure 14*), but overall, contacts were reduced (see *Figure 15*). The total number of contacts over the 12-month period was 11.5 per child in intervention group, compared with 12.1 in the control group, which equated to a 5% reduction overall (adjusted IRR 0.95, 95% CI 0.91 to 0.99). This analysis is particularly relevant to the economic analyses in the following section, which primarily considered the overall difference in resource costs between the groups and was largely based on this time period.

Echo substudy

The protocol was amended to include additional outcomes for the subsequent year. We refer to this as the 'echo substudy', the rationale of which was to assess whether or not any immediate intervention effect in 2013 was echoed the following year. A total of 110 practices (57 intervention and 53 control) contributed data to this time period.
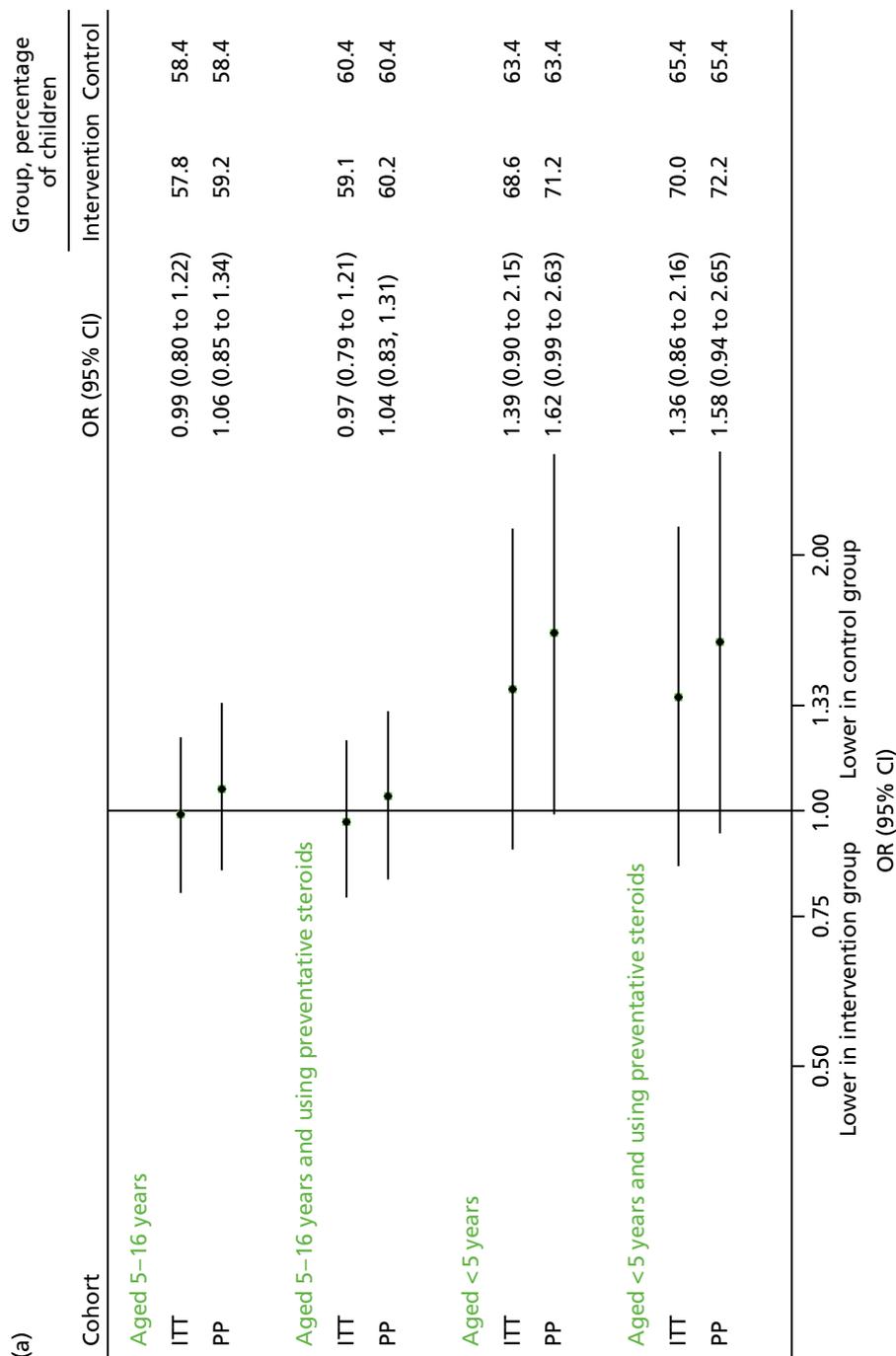
Cohort	OR (95% CI)	Group, percentage of children	
		Intervention	Control
Aged 5–16 years			
ITT	0.99 (0.80 to 1.22)	57.8	58.4
PP	1.06 (0.85 to 1.34)	59.2	58.4
Aged 5–16 years and using preventative steroids			
ITT	0.97 (0.79 to 1.21)	59.1	60.4
PP	1.04 (0.83, 1.31)	60.2	60.4
Aged <5 years			
ITT	1.39 (0.90 to 2.15)	68.6	63.4
PP	1.62 (0.99 to 2.63)	71.2	63.4
Aged <5 years and using preventative steroids			
ITT	1.36 (0.86 to 2.16)	70.0	65.4
PP	1.58 (0.94 to 2.65)	72.2	65.4

FIGURE 9 Total medical contacts in September 2013. (a) Number of children with one or more contacts; and (b) mean number of contacts per child. (*continued*)

FIGURE 9 Total medical contacts in September 2013. (a) Number of children with one or more contacts; and (b) mean number of contacts per child.

(a)

Cohort	OR (95% CI)	Group, percentage of children	
		Intervention	Control
Aged 5–16 years			
ITT	1.10 (0.96 to 1.26)	80.1	79.1
PP	1.24 (1.07 to 1.44)	82.2	79.1
Aged 5–16 years and using preventative steroids			
ITT	1.04 (0.90 to 1.21)	81.3	81.4
PP	1.16 (0.99 to 1.36)	83.1	81.4
Aged <5 years			
ITT	0.93 (0.56 to 1.56)	85.7	86.0
PP	1.42 (0.77 to 2.61)	90.5	86.0
Aged <5 years and using preventative steroids			
ITT	0.90 (0.52 to 1.58)	86.2	87.2
PP	1.37 (0.73 to 2.58)	90.9	87.2

0.33   0.50   0.75   1.00   1.33   2.00   3.00

OR (95% CI)

Lower in intervention group   Lower in control group

FIGURE 10 Unscheduled medical contacts in the period September–December 2013. (a) Number of children with one or more unscheduled contact; and (b) mean number of unscheduled contacts per child. (*continued*)

(b)

Cohort	IRR (95% CI)	Group, mean	
		Intervention	Control
Aged 5–16 years			
ITT	0.98 (0.93 to 1.04)	3.19	3.32
PP	1.01 (0.95 to 1.07)	3.27	3.32
Aged 5–16 years and using preventative steroids			
ITT	0.97 (0.92 to 1.03)	3.27	3.44
PP	0.99 (0.93 to 1.06)	3.33	3.44
Aged <5 years			
ITT	1.10 (0.94 to 1.28)	4.60	4.29
PP	1.15 (0.98 to 1.36)	4.97	4.29
Aged <5 years and using preventative steroids			
ITT	1.09 (0.93 to 1.28)	4.70	4.44
PP	1.14 (0.97 to 1.35)	5.04	4.44

0.75 0.80   0.90   1.00   1.11   1.25 1.33
Lower in intervention group   Lower in control group
IRR (95% CI)

FIGURE 10 Unscheduled medical contacts in the period September–December 2013. (a) Number of children with one or more unscheduled contact; and (b) mean number of unscheduled contacts per child.

FIGURE 11 Unscheduled medical contacts associated with a respiratory diagnosis in the period September–December 2013. (a) Number of children with one or more unscheduled respiratory-related contact; and (b) mean number of unscheduled respiratory-related contacts per child. (*continued*)

(b)

Cohort	IRR (95% CI)	Group, mean	
		Intervention	Control
Aged 5–16 years			
ITT	1.10 (0.95 to 1.27)	0.23	0.21
PP	1.11 (0.95 to 1.30)	0.23	0.21
Aged 5–16 years and using preventative steroids			
ITT	1.10 (0.95 to 1.28)	0.24	0.22
PP	1.10 (0.94 to 1.29)	0.23	0.22
Aged <5 years			
ITT	0.97 (0.67 to 1.42)	0.35	0.36
PP	1.07 (0.72 to 1.59)	0.40	0.36
Aged <5 years and using preventative steroids			
ITT	0.96 (0.66 to 1.40)	0.36	0.38
PP	1.06 (0.71 to 1.57)	0.41	0.38

0.67   0.75   1.00   1.33   1.50

Lower in intervention group   Lower in control group

IRR (95% CI)

FIGURE 11 Unscheduled medical contacts associated with a respiratory diagnosis in the period September–December 2013. (a) Number of children with one or more unscheduled respiratory-related contact; and (b) mean number of unscheduled respiratory-related contacts per child.

(a)

Cohort	OR (95% CI)	Group, percentage of children	
		Intervention	Control
Aged 5–16 years			
ITT	1.06 (0.89 to 1.27)	89.3	88.4
PP	1.28 (1.06 to 1.55)	91.4	88.4
Aged 5–16 years and using preventative steroids			
ITT	0.98 (0.81 to 1.19)	90.4	90.5
PP	1.17 (0.95 to 1.43)	92.1	90.5
Aged <5 years			
ITT	0.97 (0.52 to 1.81)	92.1	90.7
PP	1.87 (0.86 to 4.03)	96.6	90.7
Aged <5 years and using preventative steroids			
ITT	0.93 (0.47 to 1.86)	92.5	91.7
PP	1.78 (0.80 to 3.96)	96.6	91.7

FIGURE 12 All medical contacts in September–December 2013. (a) Number of children with one or more contact; and (b) mean number of contacts per child. (*continued*)

(b)

Cohort	IRR (95% CI)	Group, mean	
		Intervention	Control
Aged 5–16 years			
ITT	0.95 (0.90 to 1.02)	4.31	4.53
PP	0.99 (0.93 to 1.05)	4.49	4.53
Aged 5–16 years and using preventative steroids			
ITT	0.95 (0.89 to 1.01)	4.43	4.70
PP	0.98 (0.92 to 1.04)	4.59	4.70
Aged <5 years			
ITT	1.09 (0.94 to 1.26)	5.92	5.66
PP	1.14 (0.97 to 1.33)	6.32	5.66
Aged <5 years and using preventative steroids			
ITT	1.08 (0.93 to 1.26)	6.07	5.86
PP	1.12 (0.96 to 1.31)	6.41	5.86

0.75 0.80 0.90 1.00 1.11 1.25 1.33

Lower in intervention group Lower in control group

IRR (95% CI)

FIGURE 12 All medical contacts in September–December 2013. (a) Number of children with one or more contact; and (b) mean number of contacts per child.

FIGURE 13 Unscheduled medical contacts from September 2013 to August 2014. (a) Number of children with one or more unscheduled contact; and (b) mean number of unscheduled contacts per child. (*continued*)

(b)

Cohort	IRR (95% CI)	Group, mean	
		Intervention	Control
Aged 5–16 years			
ITT	0.97 (0.93 to 1.02)	9.08	9.37
PP	0.99 (0.95 to 1.04)	9.31	9.37
Aged 5–16 years and using preventative steroids			
ITT	0.98 (0.92 to 1.04)	9.31	9.71
PP	1.00 (0.94 to 1.06)	9.47	9.71
Aged <5 years			
ITT	1.12 (0.98 to 1.28)	11.83	10.60
PP	1.20 (1.04 to 1.39)	13.14	10.60
Aged <5 years and using preventative steroids			
ITT	1.09 (0.96 to 1.24)	12.11	10.87
PP	1.15 (1.00 to 1.33)	13.27	10.87

0.75 0.80   0.90   1.00   1.11   1.25 1.33

Lower in intervention group   IRR (95% CI)   Lower in control group
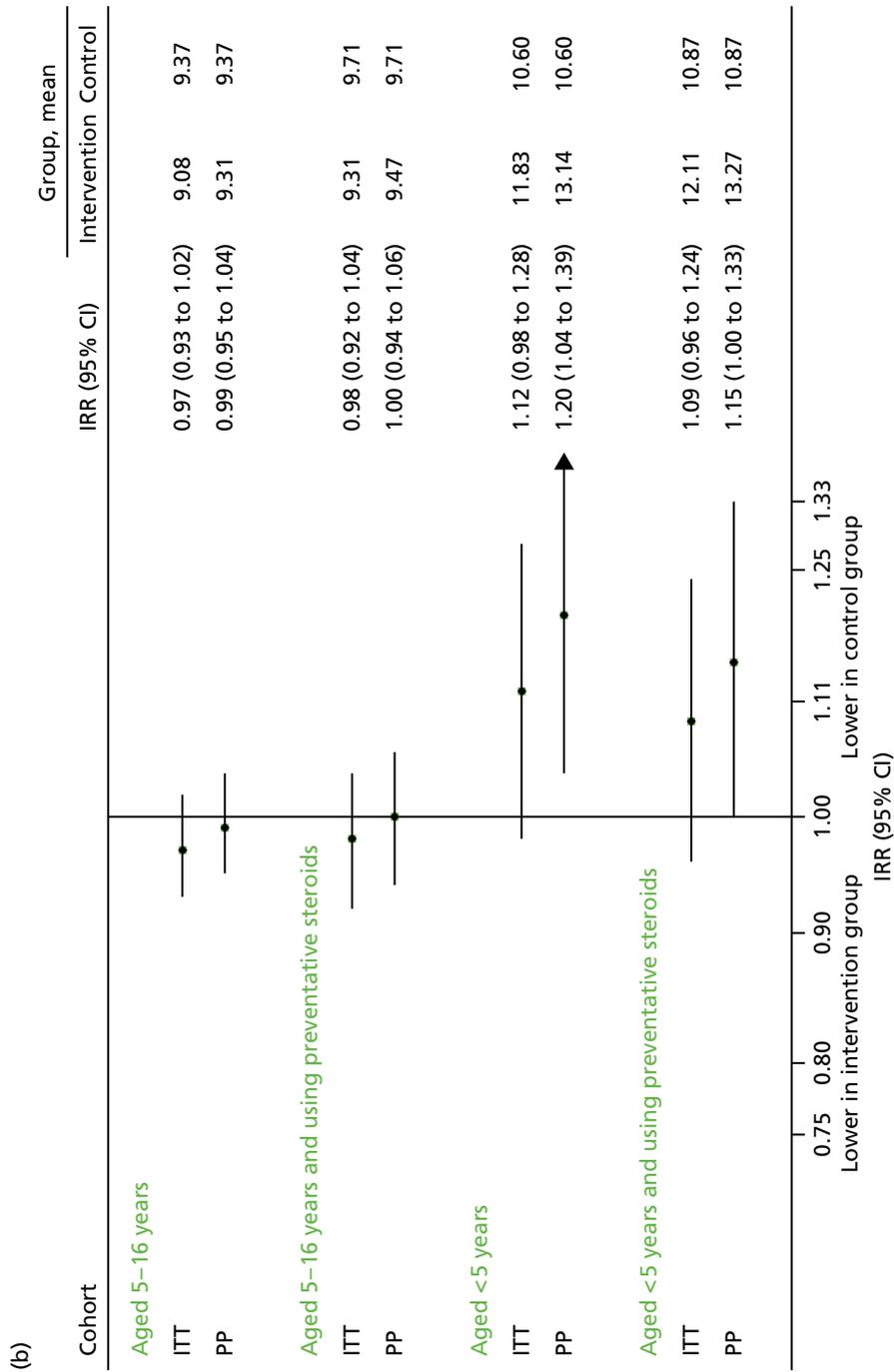
FIGURE 13 Unscheduled medical contacts from September 2013 to August 2014. (a) Number of children with one or more unscheduled contact; and (b) mean number of unscheduled contacts per child.

FIGURE 14 Unscheduled medical contacts associated with a respiratory diagnosis from September 2013 to August 2014. (a) Number of children with one or more unscheduled respiratory contact; and (b) mean number of unscheduled respiratory contacts per child. (*continued*)

(b)

Cohort	IRR (95% CI)		Group, mean	
			Intervention	Control
Aged 5–16 years				
ITT	1.04 (0.90 to 1.20)		0.57	0.53
PP	1.05 (0.91 to 1.22)		0.57	0.53
Aged 5–16 years and using preventative steroids				
ITT	1.06 (0.92 to 1.23)		0.59	0.55
PP	1.07 (0.91 to 1.24)		0.58	0.55
Aged <5 years				
ITT	1.08 (0.82 to 1.42)		0.83	0.83
PP	1.24 (0.92 to 1.68)		0.98	0.83
Aged <5 years and using preventative steroids				
ITT	1.10 (0.84 to 1.43)		0.85	0.85
PP	1.24 (0.93 to 1.64)		1.00	0.85

0.67   0.75   1.00   1.33   1.50
Lower in intervention group   Lower in control group
IRR (95% CI)

FIGURE 14 Unscheduled medical contacts associated with a respiratory diagnosis from September 2013 to August 2014. (a) Number of children with one or more unscheduled respiratory contact; and (b) mean number of unscheduled respiratory contacts per child.

(a)

Cohort	OR (95% CI)		Group, percentage of children	
			Intervention	Control
Aged 5–16 years				
ITT	0.89 (0.71 to 1.12)		96.6	96.4
PP	1.05 (0.82 to 1.34)		97.3	96.4
Aged 5–16 years and using preventative steroids				
ITT	0.81 (0.64 to 1.01)		97.1	97.3
PP	0.94 (0.74 to 1.20)		97.6	97.3
Aged <5 years				
ITT	0.56 (0.24 to 1.28)		95.4	95.7
PP	1.18 (0.35 to 3.97)		98.8	95.7
Aged <5 years and using preventative steroids				
ITT	0.54 (0.23 to 1.25)		95.6	96.0
PP	1.12 (0.34 to 3.75)		98.7	96.0

0.33　0.50　0.75　1.00　1.33　2.00　3.00

Lower in intervention group ← OR (95% CI) → Lower in control group

FIGURE 15 All medical contacts from September 2013 to August 2014. (a) Number of children with one or more contact; and (b) mean number of contacts per child. (*continued*)

(b)

Cohort	IRR (95% CI)	Group, mean	
		Intervention	Control
Aged 5–16 years			
ITT	0.95 (0.91 to 0.99)	11.52	12.08
PP	0.97 (0.93 to 1.02)	11.86	12.08
Aged 5–16 years and using preventative steroids			
ITT	0.96 (0.90 to 1.02)	11.82	12.53
PP	0.98 (0.92 to 1.05)	12.08	12.53
Aged <5 years			
ITT	1.09 (0.96 to 1.23)	14.56	13.31
PP	1.16 (1.01 to 1.33)	15.93	13.31
Aged <5 years and using preventative steroids			
ITT	1.06 (0.94 to 1.20)	14.90	13.68
PP	1.11 (0.97 to 1.27)	16.10	13.68

IRR (95% CI)

0.75 0.80 0.90 1.00 1.11 1.25 1.33

Lower in intervention group   Lower in control group

FIGURE 15 All medical contacts from September 2013 to August 2014. (a) Number of children with one or more contact; and (b) mean number of contacts per child.

In a survey of the practices in the intervention it was found that, of those that responded, 54% (13 out of 24 responding practices) had sent out the intervention again in 2014.[22] This would also contribute to an echo effect

Steroid prescriptions and scheduled contacts in the echo substudy (August 2014)

Although the increase in prescriptions found in 2013 was not as marked in 2014, the under-fives subgroup (i.e. children who were now aged under 6 years) did demonstrate an increase overall in terms of prescription uptake. These findings are displayed graphically in *Figure 16*. Unexpectedly, the proportion of children making at least one scheduled contact was lower in the intervention arm (*Figure 17a*). However, this association disappeared when evaluating the total number of scheduled medical contacts (see *Figure 17b*).

Contacts in the echo substudy (September 2014)

The findings were similar to those of September 2013. Unscheduled contacts, unscheduled respiratory-related contacts and scheduled contacts were all marginally higher in the intervention group (*Figures 18–20*), although the size of the difference was more modest than that observed in the previous year.

Time to first unscheduled contact

The time to first unscheduled and respiratory-related unscheduled contacts are presented in *Figure 21* (September 2013) and *Figure 22* (September–December 2013). Consistent with the number of contacts as previously demonstrated, the intervention group tended to make their first contact earlier than the control group. As the majority of contacts were unscheduled, the time to first contact of any type was similar to the time to first unscheduled contact.
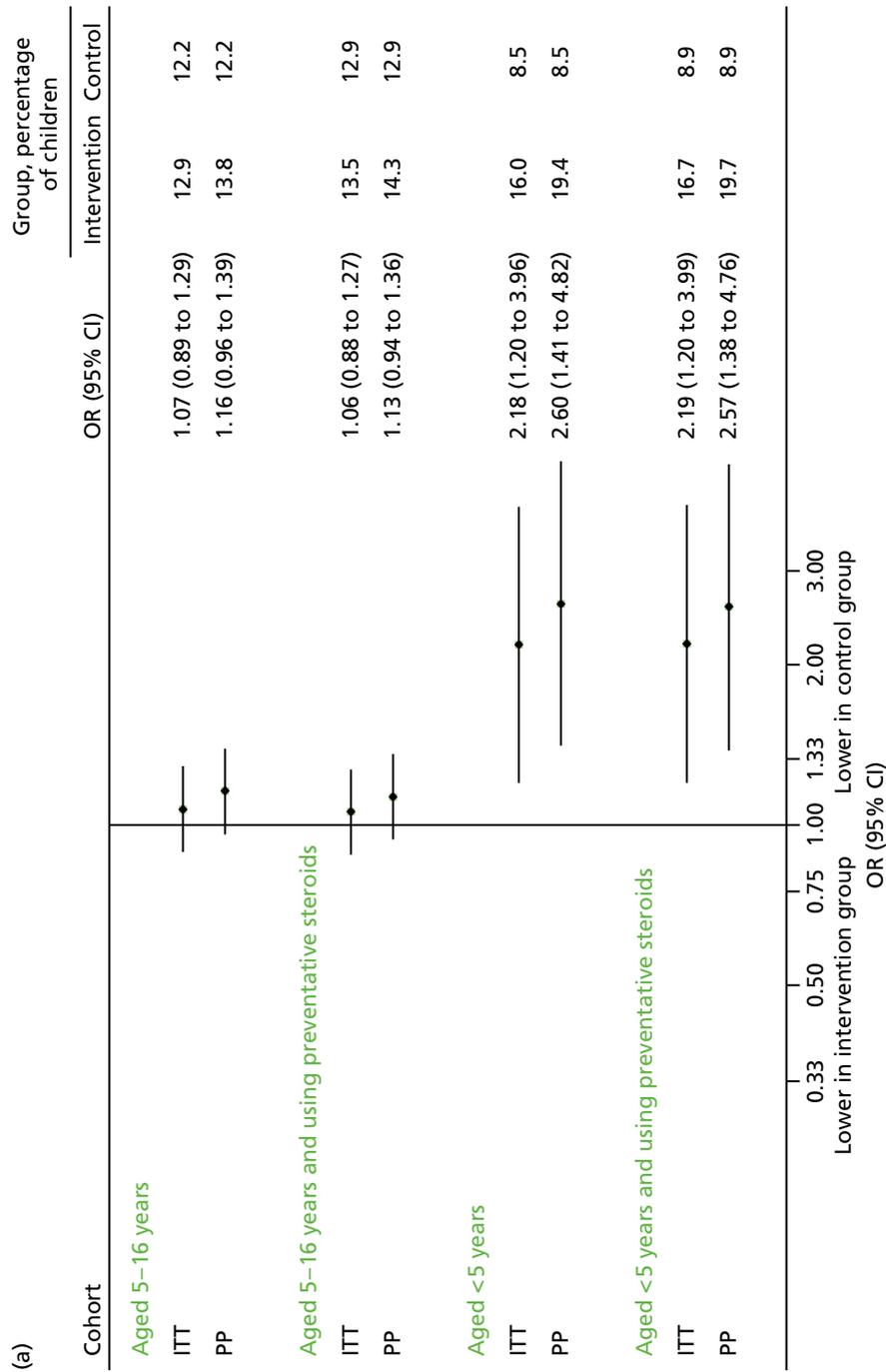
(a)

Cohort	OR (95% CI)		Group, percentage of children	
			Intervention	Control
Aged 5–16 years				
ITT	1.07 (0.89 to 1.29)		12.9	12.2
PP	1.16 (0.96 to 1.39)		13.8	12.2
Aged 5–16 years and using preventative steroids				
ITT	1.06 (0.88 to 1.27)		13.5	12.9
PP	1.13 (0.94 to 1.36)		14.3	12.9
Aged <5 years				
ITT	2.18 (1.20 to 3.96)		16.0	8.5
PP	2.60 (1.41 to 4.82)		19.4	8.5
Aged <5 years and using preventative steroids				
ITT	2.19 (1.20 to 3.99)		16.7	8.9
PP	2.57 (1.38 to 4.76)		19.7	8.9

0.33   0.50   0.75   1.00   1.33   2.00   3.00
Lower in intervention group   Lower in control group
OR (95% CI)

FIGURE 16 Uptake of steroid inhaler prescriptions in August 2014. (a) Number of children with one or more prescriptions; and (b) mean number of prescriptions. (*continued*)
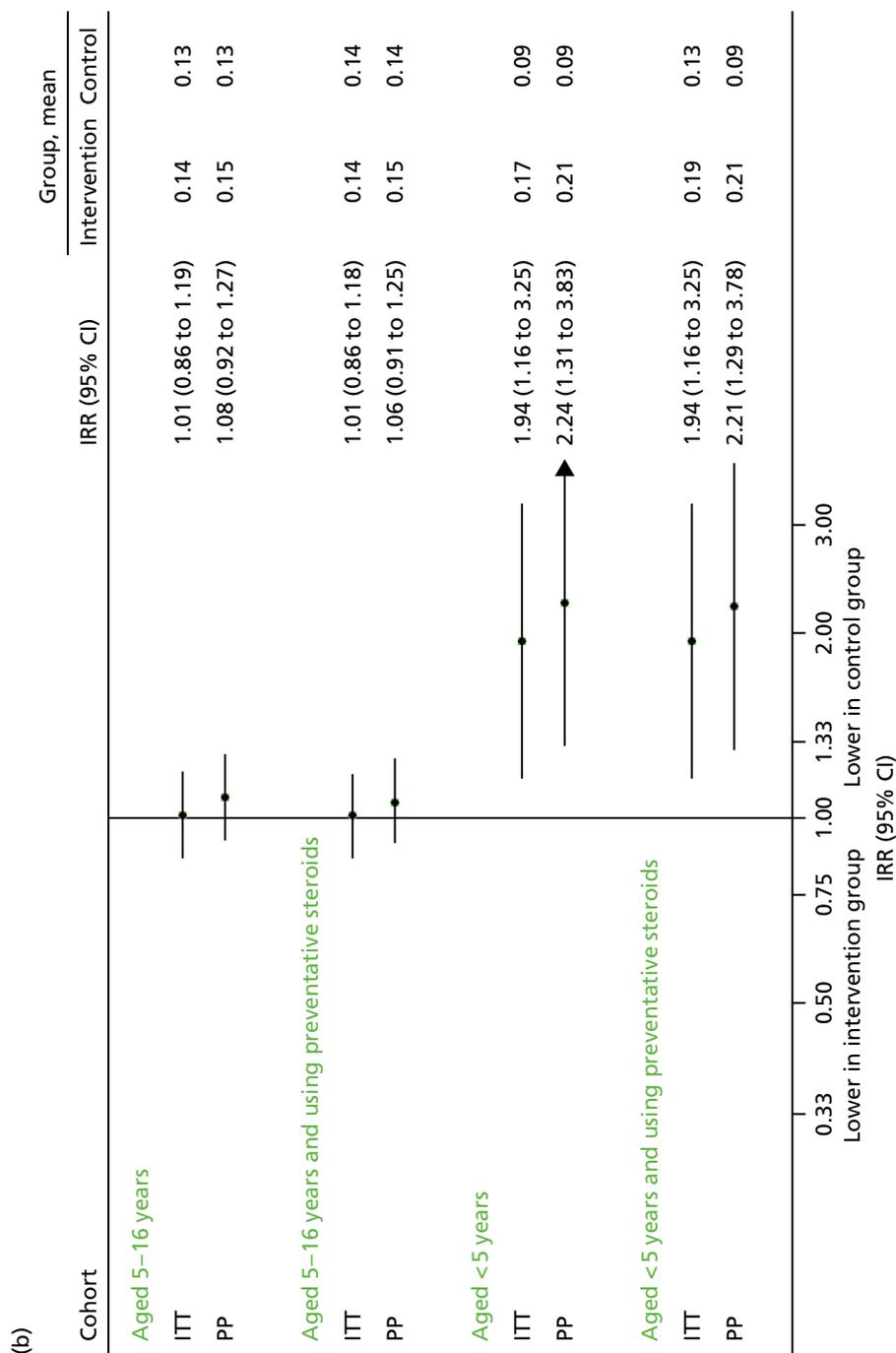
FIGURE 16 Uptake of steroid inhaler prescriptions in August 2014. (a) Number of children with one or more prescriptions; and (b) mean number of prescriptions.
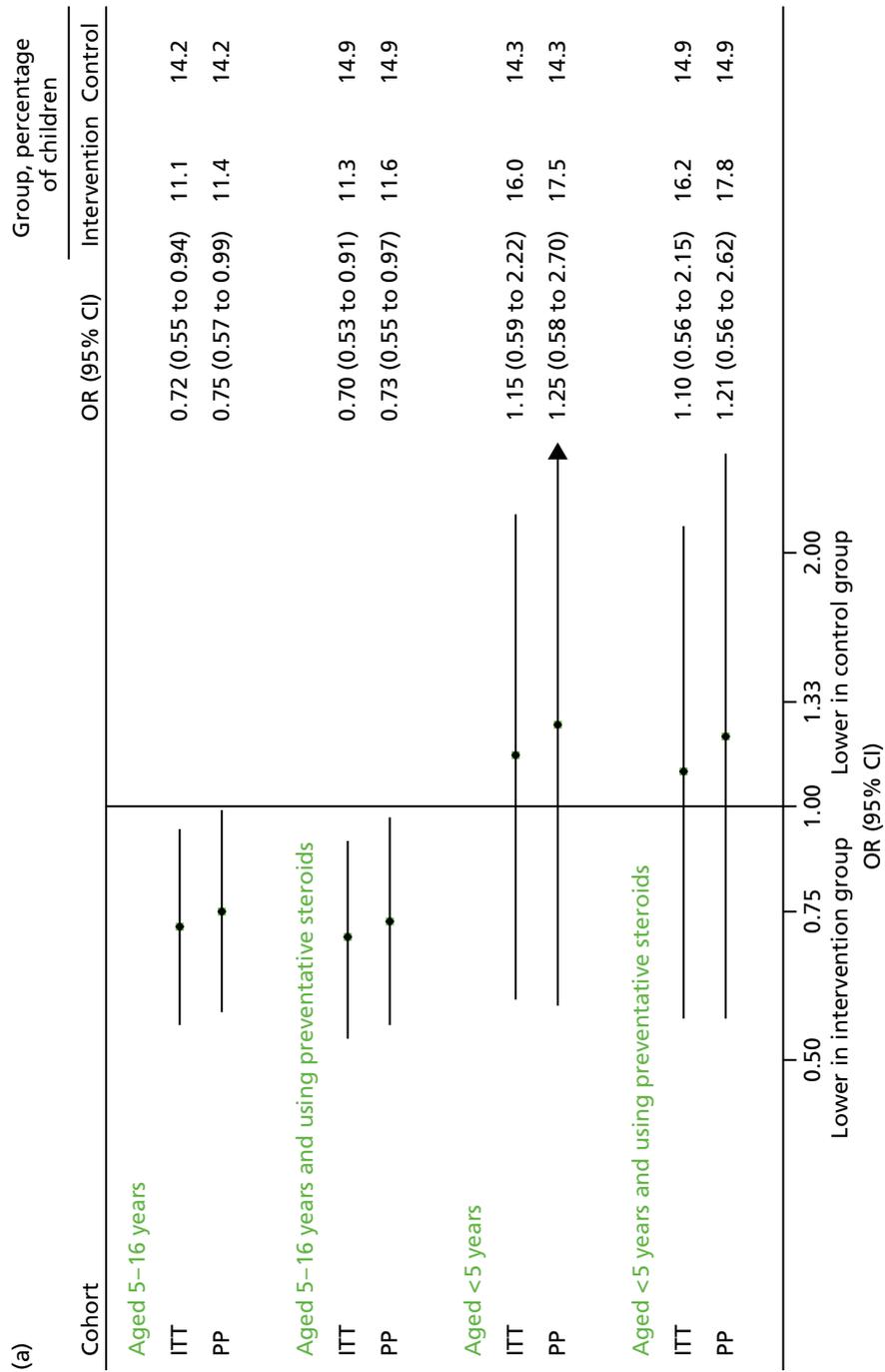
FIGURE 17 Scheduled contacts in August 2014. (a) Number of children with one or more contact; and (b) number of contacts per child. (*continued*)

FIGURE 17 Scheduled contacts in August 2014. (a) Number of children with one or more contact; and (b) number of contacts per child.

(a)

Cohort	OR (95% CI)	Group, percentage of children	
		Intervention	Control
Aged 5–16 years			
ITT	1.13 (0.99 to 1.30)	43.6	41.1
PP	1.17 (1.02 to 1.35)	44.4	41.1
Aged 5–16 years and using preventative steroids			
ITT	1.60 (0.85 to 3.03)	44.6	42.3
PP	1.81 (0.96 to 3.42)	45.1	42.3
Aged <5 years			
ITT	1.33 (0.85 to 2.10)	48.3	42.5
PP	1.47 (0.90 to 2.41)	51.9	42.5
Aged <5 years and using preventative steroids			
ITT	1.83 (0.98 to 3.42)	50.0	43.0
PP	2.00 (1.05 to 3.79)	52.9	43.0

0.33   0.50   0.75   1.00   1.33   2.00   3.00

Lower in intervention group   Lower in control group

OR (95% CI)
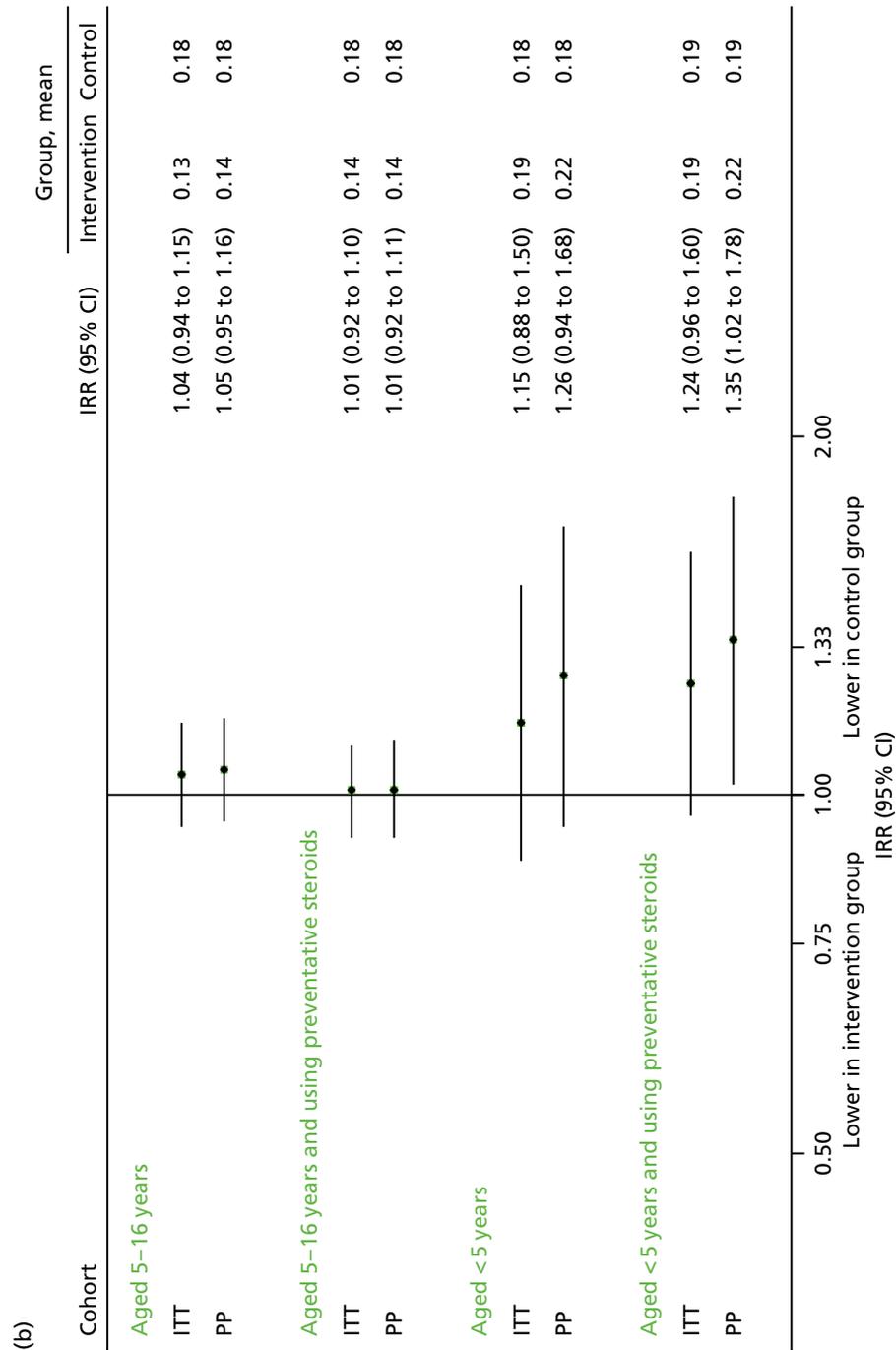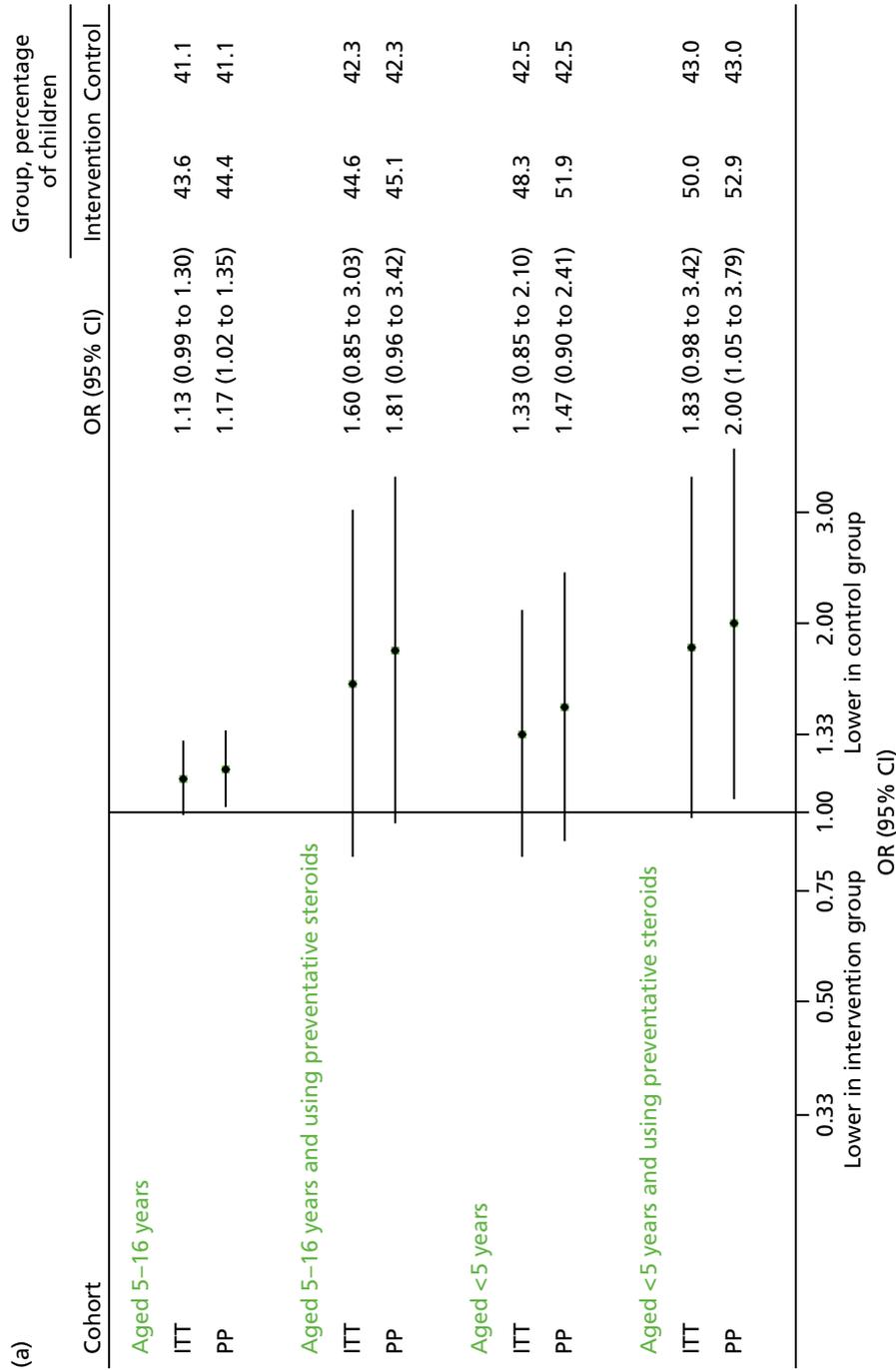
FIGURE 18 Unscheduled medical contacts in September 2014. (a) Number of children with one or more unscheduled contact; and (b) mean number of unscheduled contacts per child. (*continued*)

**FIGURE 18** Unscheduled medical contacts in September 2014. (a) Number of children with one or more unscheduled contact; and (b) mean number of unscheduled contacts per child.

(a)

| Cohort	OR (95% CI)	Group, percentage of children	
		Intervention	Control
Aged 5–16 years			
ITT	1.07 (0.82 to 1.40)	4.1	3.9
PP	1.15 (0.87 to 1.53)	4.4	3.9
Aged 5–16 years and using preventative steroids			
ITT	1.16 (0.80 to 1.67)	4.2	4.1
PP	1.26 (0.87 to 1.84)	4.4	4.1
Aged <5 years			
ITT	2.77 (0.66 to 11.69)	4.3	1.6
PP	2.73 (0.65 to 11.52)	4.4	1.6
Aged <5 years and using preventative steroids			
ITT	2.77 (0.29 to 26.74)	4.5	1.7
PP	2.66 (0.55 to 12.71)	4.5	1.7

0.33 0.50 0.75 1.00 1.33 2.00 3.00

Lower in intervention group   Lower in control group

OR (95% CI)
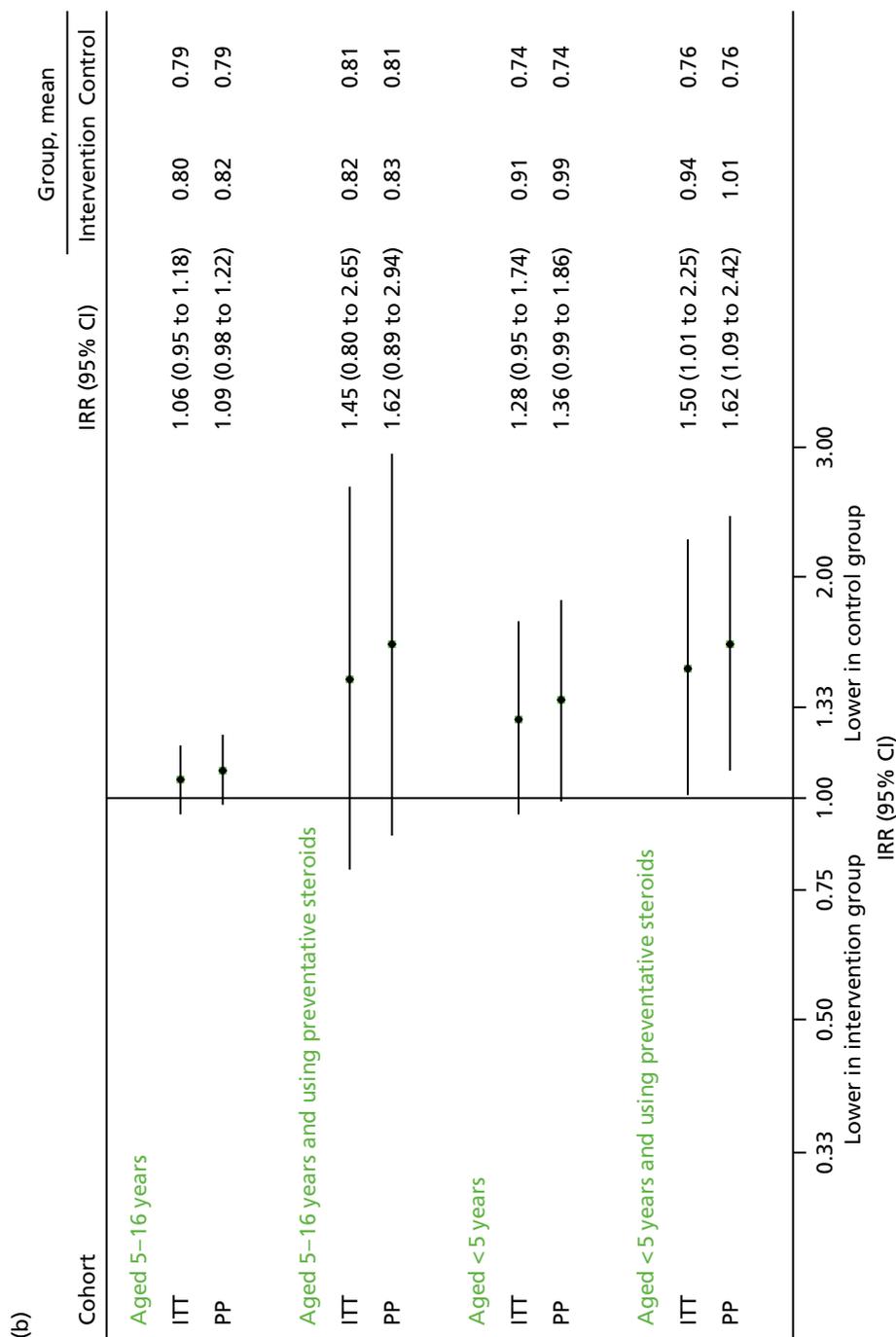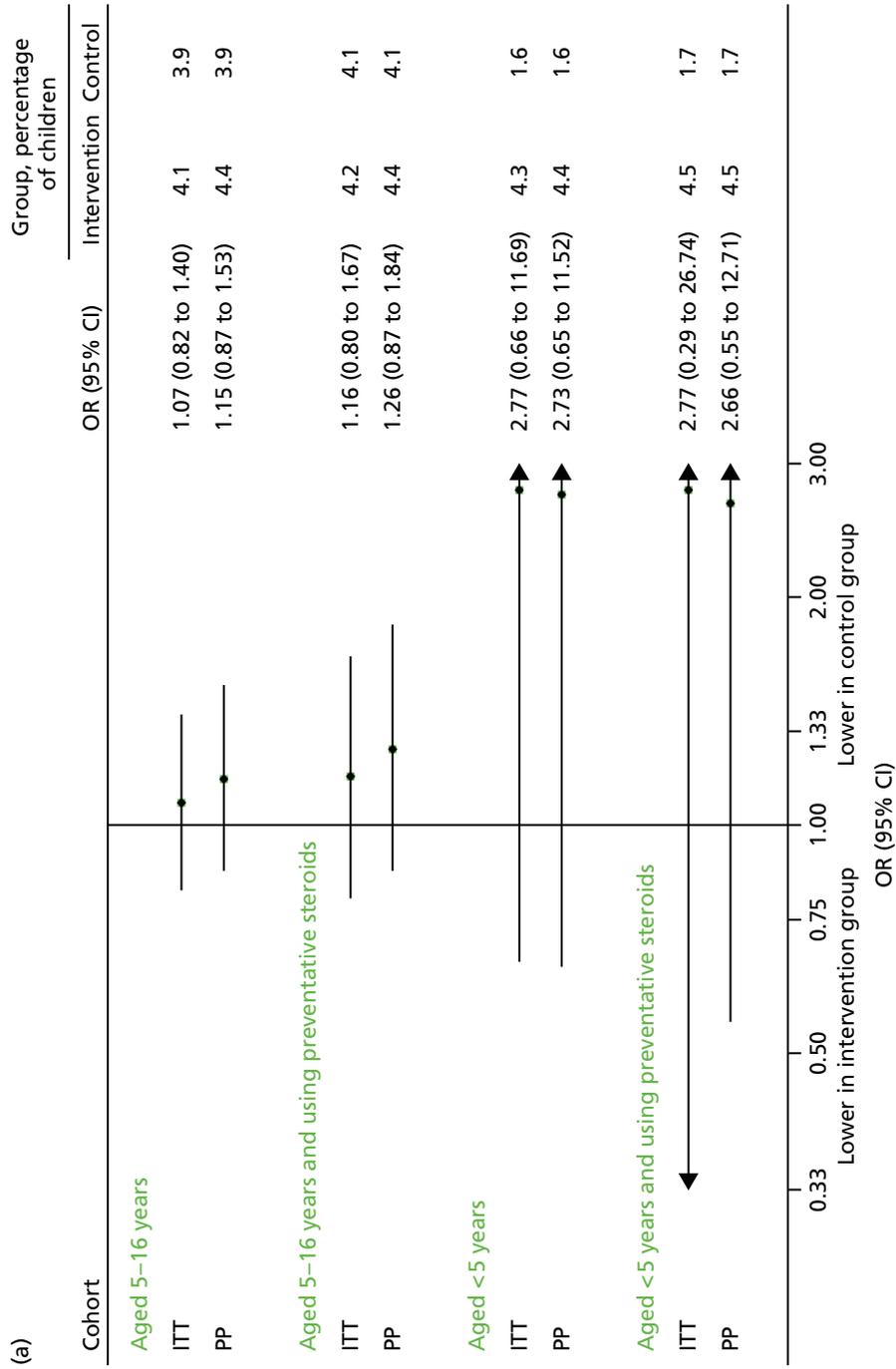
FIGURE 19 Unscheduled respiratory-related medical contacts in September 2014. (a) Number of children with one or more unscheduled contact; and (b) mean number of unscheduled contacts per child. (*continued*)

FIGURE 19 Unscheduled respiratory-related medical contacts in September 2014. (a) Number of children with one or more unscheduled contact; and (b) mean number of unscheduled contacts per child.

(a)

Cohort	OR (95% CI)	Group, percentage of children	
		Intervention	Control
Aged 5–16 years			
ITT	1.13 (0.94 to 1.34)	56.2	53.0
PP	1.19 (0.99 to 1.44)	57.6	53.0
Aged 5–16 years and using preventative steroids			
ITT	1.65 (0.80 to 3.37)	57.4	54.6
PP	1.86 (0.91 to 3.81)	58.6	54.6
Aged <5 years			
ITT	1.46 (0.94 to 2.28)	61.6	53.2
PP	1.68 (1.01 to 2.78)	66.3	53.2
Aged <5 years and using preventative steroids			
ITT	2.44 (1.19 to 5.00)	63.8	53.7
PP	2.71 (1.28 to 5.72)	67.5	53.7

0.33 0.50 0.75 1.00 1.33 2.00 3.00

Lower in intervention group   Lower in control group

OR (95% CI)
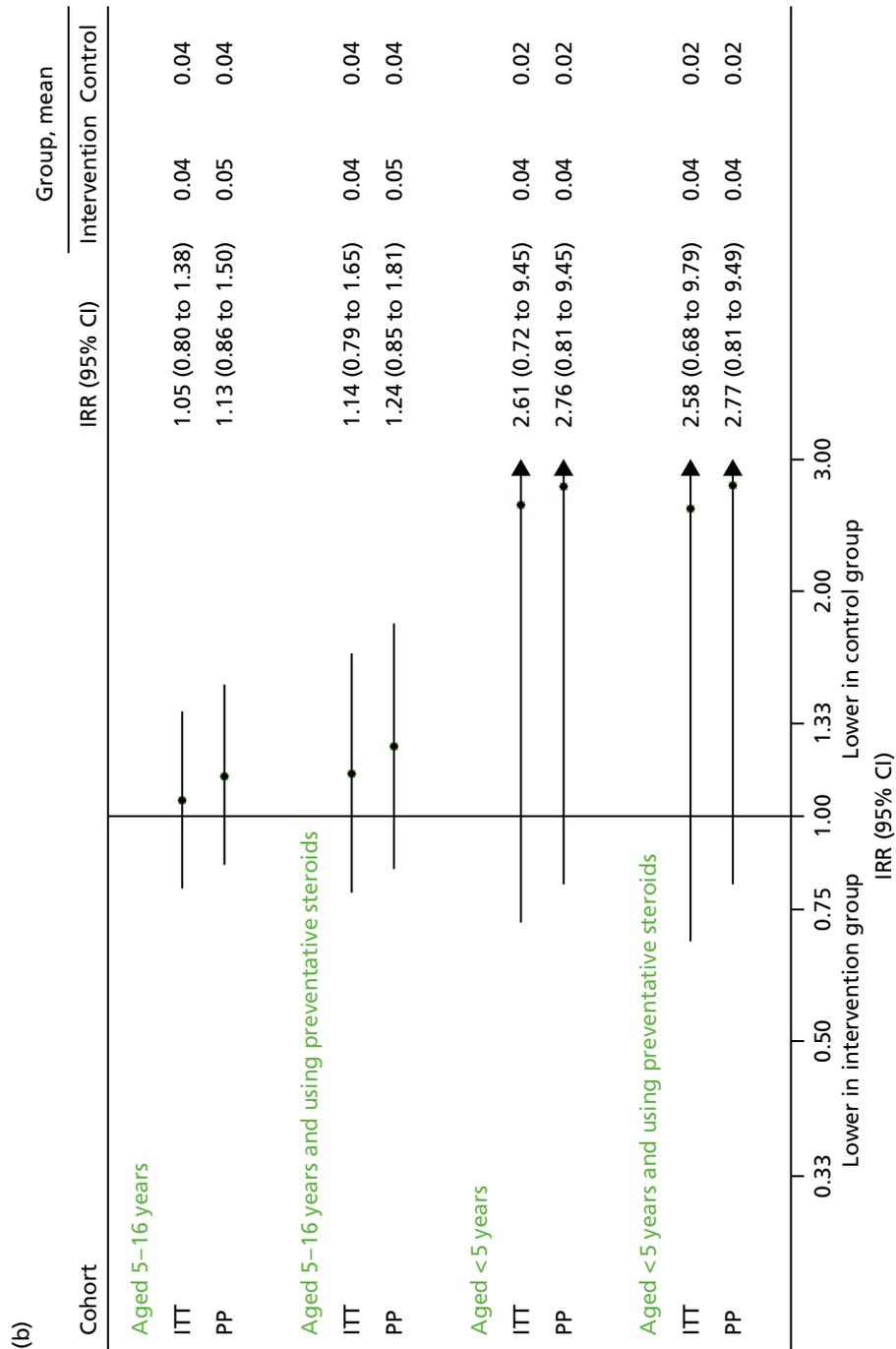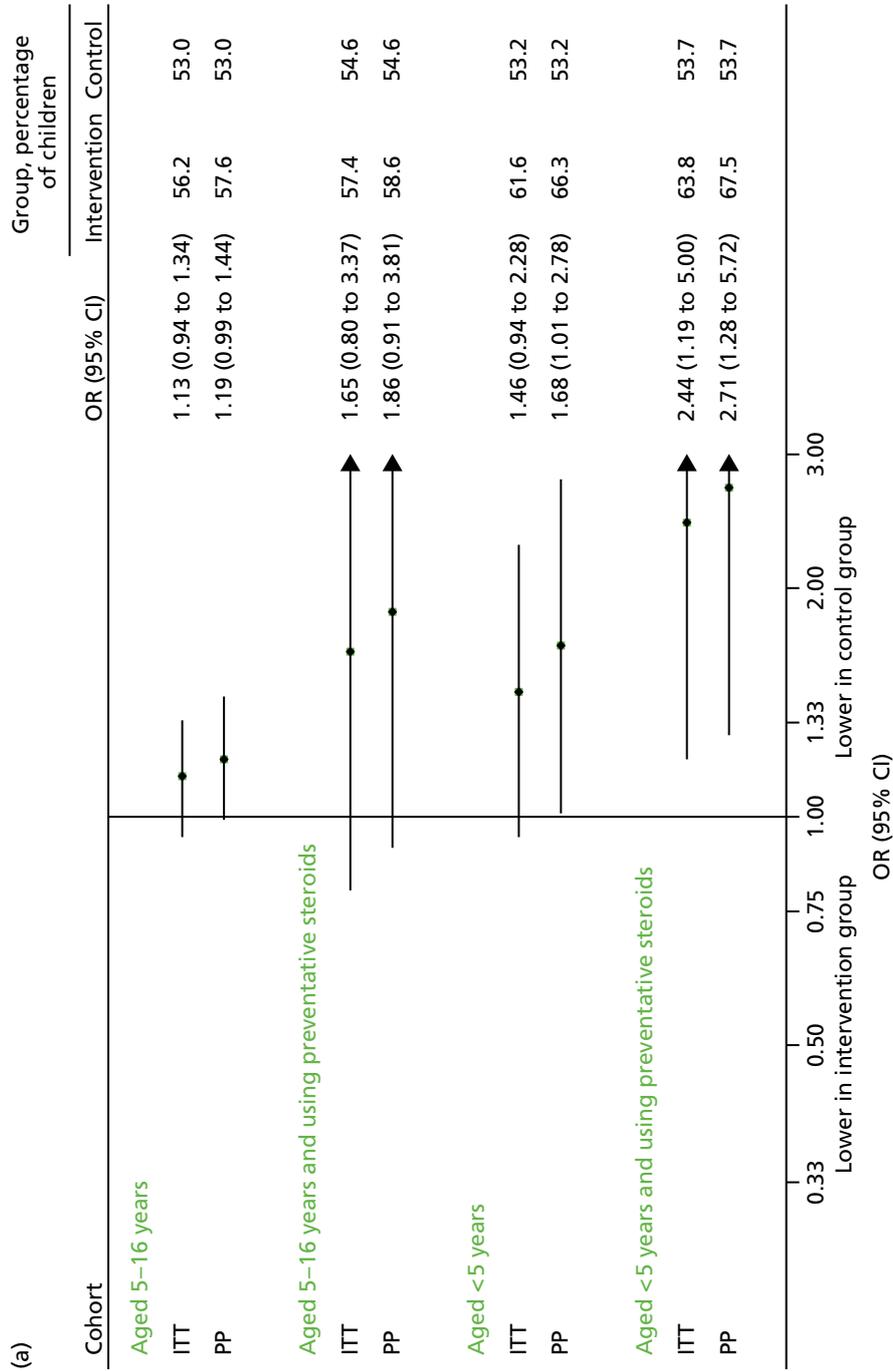
FIGURE 20 All medical contacts in September 2014. (a) Number of children with one or more contact; and (b) mean number of contacts per child. (*continued*)

**FIGURE 20** All medical contacts in September 2014. (a) Number of children with one or more contact; and (b) mean number of contacts per child.

(a)

Cohort	Hazard ratio (95% CI)	Group, percentage of children	
		Intervention	Control
Aged 5–16 years			
ITT	1.06 (0.96 to 1.16)	45.2	43.7
PP	1.08 (0.98 to 1.19)	46.2	43.7
Aged 5–16 years and using preventative steroids			
ITT	1.04 (0.94 to 1.14)	46.3	45.4
PP	1.05 (0.95 to 1.17)	46.9	45.4
Aged <5 years			
ITT	1.24 (0.95 to 1.61)	57.2	50.2
PP	1.27 (0.96 to 1.69)	59.8	50.2
Aged <5 years and using preventative steroids			
ITT	1.21 (0.92 to 1.60)	58.5	52.2
PP	1.25 (0.93 to 1.68)	61.1	52.2

0.80   0.90   1.00   1.11   1.25   1.50

Earlier in control group   Earlier in intervention group

Hazard ratio (95% CI)

FIGURE 21 Time to first contact in September 2013. (a) First unscheduled contact; and (b) first respiratory-related unscheduled contact. (*continued*)

Cohort	Hazard ratio (95% CI)	Group, percentage of children	
		Intervention	Control
Aged 5–16 years			
ITT	1.30 (1.03 to 1.64)	5.3	4.2
PP	1.26 (0.99 to 1.61)	5.1	4.2
Aged 5–16 years and using preventative steroids			
ITT	1.17 (0.97 to 1.42)	5.5	4.4
PP	1.16 (0.95 to 1.41)	5.2	4.4
Aged <5 years			
ITT	1.08 (0.51 to 2.29)	6.6	6.1
PP	1.27 (0.56 to 2.86)	7.6	6.1
Aged <5 years and using preventative steroids			
ITT	1.00 (0.46 to 2.17)	6.5	6.4
PP	1.23 (0.55 to 2.79)	7.8	6.4

FIGURE 21 Time to first contact in September 2013. (a) First unscheduled contact; and (b) first respiratory-related unscheduled contact.

(a)

Cohort	Hazard ratio (95% CI)	Group, percentage of children	
		Intervention	Control
Aged 5–16 years			
ITT	1.05 (0.94 to 1.17)	80.1	79.1
PP	1.10 (0.98 to 1.24)	82.2	79.1
Aged 5–16 years and using preventative steroids			
ITT	1.03 (0.95 to 1.11)	81.3	81.4
PP	1.07 (0.98 to 1.15)	83.1	81.4
Aged <5 years			
ITT	1.14 (0.92 to 1.42)	85.7	86.0
PP	1.25 (1.01 to 1.55)	90.5	86.0
Aged <5 years and using preventative steroids			
ITT	1.13 (0.89 to 1.42)	86.2	87.2
PP	1.22 (0.98 to 1.53)	90.9	87.2

Hazard ratio (95% CI)

0.80 0.90 1.00 1.11 1.25 1.50

Earlier in control group   Earlier in intervention group

FIGURE 22 Time to first contact in September–December 2013. (a) First unscheduled contact; and (b) first respiratory-related unscheduled contact. (*continued*)

(b) Cohort	Hazard ratio (95% CI)	Group, percentage of children	
		Intervention	Control
Aged 5–16 years			
ITT	1.13 (0.97 to 1.33)	18.4	16.7
PP	1.16 (0.98 to 1.37)	18.7	16.7
Aged 5–16 years and using preventative steroids			
ITT	1.11 (0.98 to 1.26)	19.2	17.4
PP	1.12 (0.99 to 1.28)	19.2	17.4
Aged <5 years			
ITT	0.85 (0.58 to 1.25)	23.8	26.0
PP	0.96 (0.64 to 1.44)	26.8	26.0
Aged <5 years and using preventative steroids			
ITT	0.83 (0.56 to 1.22)	24.4	27.1
PP	0.93 (0.61 to 1.42)	27.4	27.1

Hazard ratio (95% CI)

Earlier in control group   Earlier in intervention group

0.50   0.80   1.00   1.25   1.50   2.00

FIGURE 22 Time to first contact in September–December 2013. (a) First unscheduled contact; and (b) first respiratory-related unscheduled contact.

Chapter 4 Health economics

Health economic methods

Background

Asthma exacerbations in school-aged children have the potential to result in a reduction in health-related quality of life (HRQoL) for the child and additional NHS resource use in either primary or secondary care if the child presents with symptoms of an acute exacerbation. As the aim of the letter is to reduce the incidence of asthma exacerbations associated with the new school term, the intervention has the potential to result in both an improvement in HRQoL for children and cost savings for the NHS. There is, however, an initial upfront cost of delivering the letter intervention, and those resources could be used to implement other initiatives within the NHS. It was therefore important to consider not only whether the intervention is clinically effective for the individual patient, but also whether or not adopting the letter intervention across the NHS would be a cost-effective use of resources.

Overview

An economic evaluation was undertaken to compare the incremental cost per quality-adjusted life-year (QALY) of the reminder letter compared with standard care. The population for the economic evaluation was defined as school-aged children with asthma who are registered with a GP in England or Wales, and therefore the analysis was based on the PLEASANT study population. As the primary outcome for the PLEASANT study was restricted to those children aged 5–16 years, we have used this age subgroup for the base-case cost-effectiveness analysis, and have done a subgroup analysis looking at children aged 4 years. The perspective of the analysis was that of the NHS and Personal Social Services (PSS), although, as the intervention is not expected to have any impact on PSS resource use, no costs for PSS were included in the analysis. Both primary and secondary care NHS costs were included. We considered the benefits, measured in QALYs, for the individual children included in the study and did not include any benefits falling on parents, carers or other family members. The time horizon was 1 year from the intervention and, therefore, no discounting was applied.

Unscheduled and scheduled contacts in the year following intervention were included in the economic analysis to capture any change in health-care resource use in response to the letter. Prescriptions in the year following the intervention for asthma medications used in the management of chronic asthma and asthma medications used in the treatment of acute exacerbations were included to establish if the cost of prescriptions had increased in response to the letter intervention. It was considered necessary to include costs in the year following intervention rather than just in the first 4 months to distinguish between an increase in the number of scheduled contacts and a change in the timing of the scheduled contacts.

The cost of the letter intervention was included for intervention practices with no cost included for practices in the control arm, as standard care was assumed to be the same in both intervention and control practices.

Measure of effectiveness for economic evaluation

Owing to the design of the trial, no data were collected directly from patients and, therefore, it was not possible to directly determine the number, severity or duration of any acute asthma exacerbations associated with the new school term. It was therefore necessary to estimate the number of asthma exacerbations experienced from the routine data collected by the CPRD. As a single exacerbation may be associated with more than one unscheduled contact, we needed to define the number of exacerbations based on the pattern of unscheduled contacts. To do this, we split the 4-month follow-up period into 1-week intervals, and assumed that the patient was having an exacerbation in any week that included an

unscheduled contact of any type. The intervention was assumed not to have any impact on exacerbations after December.

Resource use

Data on the number and type of medical contacts in the intervention and control arms were collected through the CPRD. As patients may present with multiple problems at a single contact, and the reason for the contact is not always accurately coded, we have not restricted our analysis to respiratory-related contacts. Although not all scheduled contacts in children with asthma will be related to their asthma management, it is reasonable to expect that the number of contacts for other reasons will not differ between the trial arms. We have therefore assumed in our analysis that any difference in the number of scheduled or unscheduled contacts between the intervention and comparator arms is related to the intervention.

For primary care contacts, the staff mix and duration of staff contact for each type of primary care contact was estimated by clinical experts (clinicians on the TMG). For some unscheduled surgery visits and emergency consultations, the estimates of resource use were stratified according to the severity of acute exacerbation. The percentage having moderate, severe or life-threatening exacerbations was based on clinical opinion and is shown in *Table 8*. The resource use estimates for primary care contacts are summarised in *Tables 9* and *10*.

Data were also obtained from the CPRD on the number of prescriptions for medications used in the management of chronic asthma and for medications used to treat acute exacerbations. A list of relevant drugs was prepared in consultation with clinical experts, and these are shown in *Table 11*. The list of antibiotics was restricted to those commonly used to treat respiratory infections associated with asthma exacerbations in children. Although some drugs are used in the management of both chronic and acute symptoms, they have been included in *Table 11* under their primary use, but this has no implication for the cost-effectiveness analysis, as drugs used for both indications are included in the total cost.

Information on the staff time required to deliver the letter intervention was based on the survey of participating practices,[22] which included questions regarding the staff members involved and the duration of time required to complete the various tasks necessary to deliver the letter intervention across the eligible population within a single practice. Resource-use data from the survey are summarised in *Table 12*. The survey was undertaken as part of a no-cost extension of the trial (see *Appendix 2*).

Unit costs

For primary care contacts, the unit costs for scheduled and unscheduled patient contacts were taken from *Unit Costs of Health and Social Care 2014*,[30] and these are summarised in *Tables 9* and *10*. The Department

TABLE 8 Distribution of asthma severity by setting (estimated by clinical advisors)

Setting	Exacerbation type	Percentage
GP surgery	Moderate asthma	70
	Severe asthma	25
	Life-threatening asthma	5
Emergency department	Moderate asthma	20
	Severe asthma	50
	Life-threatening asthma	30
Hospital	Severe asthma	60
	Life-threatening asthma	40

TABLE 9 Costing data for unscheduled surgery visit/emergency consultation

Scenario for exacerbation type	Staff (ratio)	Duration (minutes)	Costs		Weighted average of provider cost[a]	Proportion of cases presented at surgery
			GP	Nurse		
(1) Moderate asthma						
Contact with GP	PN or GP (20 : 80)	15	£58.50	£13.25	£49.45	0.70
(2) Severe asthma						0.25
Cost components						
Seeing and diagnosing patients	GP	5	£19.50		£19.50	
Administration of medications	PN or GP (10 : 1)	15	£58.50	£13.25	£17.36	
Monitoring patient	PN or GP (10 : 1)	5	£19.50	£4.42	£5.79	
Total cost					£42.65	
(3) Life-threatening asthma						
Cost components						
Stabilise and monitor patient until ambulance arrives	PN and GP	5	£19.50	£4.42	£23.92	0.05
Unit cost of an unscheduled visit					£46.47[b]	

PN, practice nurse; PSSRU, Personal Social Services Research Unit.
a Costs were estimated as weighted average of GP and nurse costs.
b Weighted average of unscheduled surgery costs associated with moderate, severe and life-threatening asthma calculated using the proportions shown in *Table 8*.
Notes
Source: PSSRU.[30]
Duration, staff and proportion of cases presented at surgery were estimated by clinical advisor. GP costs were estimated by clinical advisor. GP costs were based on £3.90 per minute of patient contact, practice nurse costs were based on £53 per hour (face-to-face contact) including qualifications.

TABLE 10 Costing data for primary care contacts (other than unscheduled surgery visits/emergency consultations)

Scenario for exacerbation type	Staff (ratio)	Range of duration (minutes)	Average duration (minutes)	Costs			Weighted average of provider cost
				GP[a]	Nurse[b]	Administrator[c]	
Unscheduled clinic review	PN	15–30	22.5	–	£19.88	–	£19.88
Acute visit	GP	10–15	12.5	£48.75	–	–	£48.75
Third-party consultation[d]	NA	–	–	–	–	–	£212.00
Unscheduled home visit	GP	15–30	22.5	£87.75	–	–	£87.75
Unscheduled phone consultation	PN : GP (10 : 1)	–	5	£19.50	£4.42	–	£5.79
Scheduled phone consultation	PN : GP (10 : 1)	–	2	£7.80	£1.77	–	£2.32
Scheduled surgery consultation	PN : GP (2 : 8)	10–15	12.5	£48.75	£11.04	–	£41.21
Scheduled clinic review	PN	–	30	£26.50	–	–	–
Medication management	PN : GP (25 : 75)	–	GP, 2; PN, 5	£7.80	£4.42	–	£6.95
Administration	Administrative staff	–	0.5	–	–	£0.11	£0.11
Results recording	Administrative staff	–	0.5	–	–	£0.11	£0.11

N/A, not applicable; PN, practice nurse.
a £3.90 per minute of patient contact.[30]
b £53 per hour of face-to-face contact time including qualification costs.[30]
c £12.44 per hour.[31]
d Reference cost 258: paediatric respiratory medicine consultant-led non-admitted face-to-face attendance, follow-up.[32]

TABLE 11 Average cost per prescription for drugs included in the economic analysis

Drug class	Drug or unique combination of drugs	Average cost per prescription[a] (unit cost × mean number of units)
Drugs used primarily in the management of chronic asthma[b]		
Inhaled beta-2 agonist	Salbutamol[b]	£2.33
	Salmeterol	£34.66
	Formoterol fumarate	£27.16
	Terbutaline	£8.64
Inhaled corticosteroids	Beclometasone dipropionate	£6.71
	Budesonide	£14.29
	Fluticasone	£9.32

TABLE 11 Average cost per prescription for drugs included in the economic analysis (*continued*)

Drug class	Drug or unique combination of drugs	Average cost per prescription[a] (unit cost × mean number of units)
Leukotriene receptor antagonists	Montelukast[c]	£4.85
	Zafirlukast	£20.80
Theophylline	Modified-release oral theophylline (aminophylline/theophylline)	£5.42
Cromoglicic acid and related therapy	Sodium cromoglycate	Not prescribed within the data set
	Nedocromil sodium	£34.94
Combination inhalers	Beclometasone dipropionate/formoterol fumarate dihydrate	£32.25
	Budesonide/formoterol fumarate dihydrate	£44.27
	Fluticasone propionate/formoterol fumarate	£30.48
	Fluticasone propionate/salmeterol xinafoate	£32.64
Drugs used primarily in the management of acute asthma exacerbations		
Antimuscarinic bronchodilators	Ipratropium bromide	£6.43
Oral corticosteroids[d]	Oral prednisolone	£26.68
Drugs used in the treatment of respiratory infections associated with asthma exacerbations		
Broad-spectrum penicillins	Amoxicillin	£1.40
	Co-amoxiclav	£4.85
Macrolides	Clarithromycin	£12.95
	Erythromycin	£7.61
Cephalosporins	Cefaclor	£5.68
	Cefradine	Not prescribed within the data set
	Cefalexin	£2.22

a Derived by combining information on the quantity prescribed and the list price.[33]

TABLE 12 Resource use, unit costs and total costs for letter intervention

Activity, cost or staff member	Staff					Average cost	
	Practice manager	Administrative staff	GP	Practice nurse	Research nurse	Per practice[a]	Per patient[a]
Unit cost per hour for different staff members[b]	£30.42	£14.15	£80.00	£0.42	£30.42	–	–
Resource use and average cost per task *Database search*							
Time per practice (minutes)	40	29	38	–	–	–	–
Percentage of staff involved (%)	38	46	17	–	–	–	–
Weighted mean cost across staff						£19.03	£0.22

TABLE 12 Resource use, unit costs and total costs for letter intervention (*continued*)

Activity, cost or staff member	Staff					Average cost	
	Practice manager	Administrative staff	GP	Practice nurse	Research nurse	Per practice[a]	Per patient[a]
Checklist generated by search							
Mean time per 10 patients (minutes)	6	9	6	7	10	–	–
Percentage of staff involved (%)	30	13	39	13	4	–	–
Weighted mean cost across staff						£44.31	£0.51
Mail-out process							
Mail-out by DocMail							
Time per practice (minutes)	36	26	–	–	–	–	–
Percentage of staff involved (%)	47	53	–	–	–	–	–
Weighted mean cost across staff types						£11.92	£0.14
Mail-out by other process							
Mean time per 10 patients (minutes)	15	13	–	–	–	–	–
Percentage of staff involved (%)	14	86	–	–	–	–	–
Weighted mean cost across staff						£31.21	£0.36
DocMail cost per letter/cost of postage plus materials for other mail-out process						£33.69	£0.39
Average across DocMail and other mail-out processes (67% DocMail and 33% other)						£18.34	£0.21
Total						£115.38	£1.34

a Assuming 86 patients per practice.
b National institute for Health Research.[31]

of Health's reference costs[32] were used for secondary care contacts, and these are summarised in *Tables 13* and *14*. Drug costs were taken from the *British National Formulary for Children August 2015*.[33] The average cost per prescription (see *Table 11*) was calculated by combining data on the pack size (e.g. inhaler containing 200 doses), the number of doses prescribed (e.g. 200 inhalations or one inhaler) and the unit cost for each item. When more than 10 different preparations of the same drug were prescribed across the whole data set, we have applied the average unit cost, weighted by frequency, from the 10 most commonly prescribed preparations. Unit costs for the staff time associated with delivering the intervention were based on the national costing template from the NIHR Primary Care Research Network's *Clinical Research Network Industry Costing Template*.[31] Unit costs for materials and postage were based on commercial costs for DocMail.[34] The total average cost per patient was estimated by combining data on resource use, with the unit costs as shown in *Table 12*.

Health outcomes

Owing to the design of the trial, no data were collected directly from patients and, therefore, it was not possible to obtain direct estimates of health utility for the enrolled patients. Instead, these were obtained indirectly from the estimated number of asthma exacerbations. Children experiencing an exacerbation were assumed to have a utility decrement for the week of exacerbation, which was defined as any week containing one or more unscheduled contacts.

TABLE 13 Unit costs for emergency department attendances by severity of asthma exacerbation

Exacerbation type	Code	Healthcare Resource Group	Investigations	Treatment	Unit cost[a]
Moderate asthma presenting to emergency department	VB09Z	Emergency Medicine, category 1 investigation with category 1–2 treatment (type 1 non-admitted)	None	i.v. cannula, guidance advice, inhalers, oral prednisolone	£102
Severe asthma presenting to emergency department	VB06Z	Emergency medicine, category 1 investigation with category 3–4 treatment (type 1 non-admitted)	Capillary blood gas	Administration of drug via spacer or nebuliser, supplemental oxygen, oral prednisolone	£128
Life-threatening asthma presenting to emergency department	VB43Z	Emergency medicine, category 2 investigation with category 4 treatment (type 1 non-admitted)	Capillary blood gas, chest radiography	Nebulisation, guidance advice, vital signs monitoring, radiograph review, CPAP, supplemental oxygen, administration of infusion or subcutaneous drug	£224
Weighted average for all emergency department attendances					£152

CPAP, continuous positive airway pressure; i.v. intravenous.
a Sourced from the *National Schedule of Reference Costs 2013–14: NHS Trusts and NHS Foundation Trusts*.[32]

TABLE 14 Unit costs of hospital admission

Reference cost details	Frequency[a]	Unit cost[b]
PD12C: Non-elective short stay: paediatric asthma or wheezing, with a CC score of 0	15,159	£559
PD12B: Non-elective short stay: paediatric asthma or wheezing, with a CC score of 1–3	8390	£579
PD12A: Non-elective short stay: paediatric asthma or wheezing, with a CC score of ≥ 4	392	£572
Weighted average across all non-elective short-stay admissions		£566

CC, complications or comorbidities.
a Frequency has been based on activity recorded for the Healthcare Resource Group within the national schedule of reference costs.
b Sourced from the *National Schedule of Reference Costs 2013–14: NHS Trusts and NHS Foundation Trusts*.[32]

A systematic review of HRQoL data in children with asthma was conducted to identify appropriate sources of data for patients with and without an exacerbation. Selection of utility data to use in the economic analysis was based on (1) quality of the study, (2) the relevance of utility data to the population and health states in the PLEASANT study and (3) the extent to which the measurement method was in accordance with the National Institute for Health and Care Excellence (NICE) reference case.

The systematic review found that there was a lack of relevant and high-quality data on the impact of exacerbations on HRQoL for school-aged children. Many of the studies in children did not estimate the impact of exacerbation or used a less suitable measure of HRQoL, such as direct valuation or subjective mapping from disease states to HRQoL. However, data were available for adults on the impact of exacerbations estimated using NICE's preferred instrument, the European Quality of Life-5 Dimensions (EQ-5D).[35] We considered that the estimates for exacerbations in adults may underestimate the degree of utility loss in children with a severe or life-threatening acute exacerbation during the period of hospitalisation, so alternative estimates that were considered to provide an upper limit on the utility decrement attributable to exacerbation in children were explored in a sensitivity analysis. The systematic

review and rationale for selection of model inputs is further detailed in *Appendix 5* and the data applied in the model are summarised in *Table 15*.

The QALYs accrued per patient in the 4 months following the intervention (from 1 September to 31 December) were estimated using the area under the curve method. We assumed that the intervention would have no impact on QALYs gained outside this 4-month period. We have also assumed that the intervention had no impact on mortality.

Analysis

The health economics analysis was restricted to the PP patient group for whom CPRD data were available over the period of analysis (1 August 2012 to 31 July 2014). The PP patient group was used, as these are

TABLE 15 Health state utility values to be applied in the economic evaluation

Health state	Health utility value	Description of state from source study	Measurement	Source
Base-case scenario				
No exacerbation	0.96 (SD 0.07)	Average baseline utility across children (*n* = 27) aged 7–18 years with GINA severity stage I to III receiving standard outpatient care in the Netherlands as part of the control arm of a RCT	EQ-5D child version (filled out by parent for children aged < 12 years). UK adult TTO valuation set	Willems *et al.*[36]
Exacerbation not requiring hospitalisation (including those managed in the emergency department)	−0.10 relative to no exacerbation	Adult patients enrolled in a prospective observational study who have moderate or severe asthma (BTS/SIGN stage 4/5) at baseline and who have experienced one exacerbation requiring oral steroid treatment (without hospitalisation) in the previous 4 weeks (*n* = 22)	EQ-5D UK adult valuation set	LLoyd *et al.*[37]
Exacerbation requiring hospitalisation	−0.20 relative to no exacerbation	Adult patients enrolled in a prospective observational study who have moderate or severe asthma (BTS/SIGN stage 4/5) at baseline who have experienced one exacerbation requiring hospitalisation in the previous 4 weeks (*n* = 5)	EQ-5D UK adult valuation set	LLoyd *et al.*[37]
Sensitivity analysis				
No exacerbation	As per base case	As per base case	As per base case	As per base case
Any exacerbation	−0.216 relative to no exacerbation	Patients aged over 12 years (including adults) enrolled in the GOAL study[38] who experienced an exacerbation (defined as deterioration in asthma requiring treatment with an oral corticosteroid, or an emergency department visit or hospitalisation)	AQLQ values mapped to EQ-5D (valuation set not stated)	Briggs *et al.*[38]

AQLQ, Asthma Quality of Life Questionnaire; BTS, British Thoracic Society; GINA, Global Initiative for Asthma; GOAL, Gaining Optimal Asthma ControL; RCT, randomised controlled trial; SD, standard deviation; SIGN, Scottish Intercollegiate Guidelines Network; TTO, time trade-off.

the patients who actually received the intervention and for whom resource use information was available within the CPRD for the time period of interest and, therefore, this group better predicts the costs and benefits of implementing the intervention in clinical practice. The average cost per patient was calculated by combining the resource use estimates with unit costs. This resource use is based on all 'tasks' recorded in the CPRD data set, which could be face-to-face contacts (surgery visits), non-face-to-face contacts (e.g. telephone calls) or general administrative tasks (i.e. recording letters sent to the surgery). In addition to reporting the average cost per patient, we have also reported the breakdown of costs of intervention costs, scheduled contacts, unscheduled contacts, prescriptions for chronic asthma management and treatment of acute exacerbations. This breakdown is reported by mean value and distribution statistics [for number of tasks, the mean, standard deviation (SD) and range are reported; for costs, the mean, 95% CIs, median and range are reported]. The mean number of acute exacerbations per patient has been reported in addition to the average QALYs accrued per patient. A statistically significant difference in resource use or costs was assessed by using the *t*-test assuming unequal variance (because of the unequal sample sizes between the letter intervention and no-letter groups). Statistical significance is defined as a *p*-value below 0.05 when describing statistical significance associated with 95% CIs for the outcomes of the economic evaluation. We have defined statistical significance as $p < 0.1$ when assessing baseline imbalances.

Quality-adjusted life-years were calculated for the 4-month post-intervention time period, and costs were calculated for 1 year post intervention. Utilities were assigned using a Markov assumption, whereby the 4-month post-intervention time period was split into 17 1-week time periods and one 3-day period (accounting for the 122 days from 1 September to 31 December). It was assumed that, if an unscheduled contact occurred within any particular week, a utility decrement for exacerbation was applied dependent on the type of contact (see *Table 16*). The utility decrement for an exacerbation resulting in hospitalisation overruled a non-hospital-related exacerbation utility value such that the most severe utility decrement for a given exacerbation week was applied to the whole week. QALYs were calculated using the area under the curve method[39] based on the assumed exacerbation time period using *Equation 1*:

$$q_{jti} = \frac{(u_{j(t-1)i} + U_{jti})}{2}\delta_t, \tag{1}$$

where u is the utility score, i denotes an individual and t is time so that at baseline $t = 0$. For each group j [$j = 0$ for the no-letter group (control) and $j = 1$ for the letter group (intervention)], the consecutive time measures are added, averaged and then rescaled (δ) for the percentage of a year that t and $t-1$ cover, which in this case was 0.019 (7 days in a week divided by 365.25 days in year) for the 17 1-week time periods and 0.008 (3 days divided by 365.25 days in year) for the last 3 days in December. The total QALYs (Q) for the 4-month estimation period (T) was the summation of the utility values at all 18 time points starting at $t = 1$, the first week period, such that

$$Q_{ji} = \sum_{t=1}^{T} q_{jti}. \tag{2}$$

Patient costs were adjusted by 1-year baseline costs [baseline adjusted (BA)] using bootstrapped ordinary least squares regression models (1000 replications) with 1-year baseline costs and intervention group as covariates in the model, as recommended by van Asselt *et al.*[40] Non-parametric bootstrapped estimation was employed for unadjusted patient costs and QALYs, also using 1000 replications. Clustering at the practice level with random effects was accounted for in the bootstrapped analysis. Unadjusted (observed) and adjusted (BA, accounting for baseline costs) results are reported for mean and incremental values as well as the bootstrapped standard error (SE), and bias corrected and accelerated (BCa) 95% CIs[41] for all post-bootstrap estimations. For the BA mean cost estimations (not the BA incremental results), the reported SE are the delta method SEs, which are appropriate for adjusted/transformed cost approximations,[42] and normal 95% CIs. The main structural uncertainty analyses in reference to sensitivity analysis and subgroup analysis are summarised in *Table 16*.

TABLE 16 Summary of sensitivity analysis and subgroup analysis

Model aspect varied	Base-case scenario	Sensitivity scenarios	Rationale
Unit cost for contact types defined as 'other'	Unit cost of £0.11, assuming that 'other' are undefined administrative tasks	Pooled weighted unit cost of £45.58 based on the recorded resource use for all contacts and associated unit costs excluding 'other' tasks	It is uncertain if these 'other' consultation types are administrative
Duration of period used to define exacerbation	1 week	3 days 2 weeks	The average duration of symptoms for an exacerbation is uncertain
Utility values for exacerbation	–0.1 for non-hospital and –0.2 for hospitalisation following exacerbation	–0.216 relative to no exacerbation	The utility decrement relative to no exacerbation is uncertain
Type of contacts included	All contacts regardless of whether or not they are respiratory related	Respiratory-related contacts	Contacts coded as respiratory related are more likely to be affected by the intervention but a large proportion of contacts could not be coded as respiratory or non-respiratory related
QALY and cost estimation period	QALYs estimated for 4 months and costs for 1 year post intervention	QALY estimated for 4 months and costs for 5 months post intervention	To assess the shorter-term (5-month) cost implications of the intervention
Age of population receiving intervention	Children aged 5–16 years	Children aged < 5 years	To assess the cost-effectiveness of the intervention for children aged < 5 years

Health economic results

Descriptive statistics of number of exacerbations, resource use and unit costs

A total of 8190 patients (letter group, $n = 3641$; no-letter group, $n = 4549$) were defined as being a part of the PP patient group and had data available over the analysis period of 1 August 2012 until 31 July 2014; it is these 8190 patients who were the focus of the health economic analysis. A summary of the number of exacerbations per patient, as well as resource use and associated costs per patient by classified resource use type (i.e. scheduled or unscheduled), prescription costs and overall costs, is presented in *Table 17*. A detailed summary of patient resource use and associated costs by task, as reported in the CPRD data set (reported in alphabetical order based on the task type), is presented in *Table 18* (A–H; i.e. 'acute visit' to 'hospital admission') *Table 19* (L–O; i.e. 'letters from outpatient' to 'out-of-hours practice') and *Table 20* (R–W; i.e. 'radiology result' to 'walk-in centre').

The estimated number of exacerbations for the 4-month QALY estimation period (that period for which a utility decrement was attached to these exacerbations) is dependent on the assumed period of exacerbation, which was 1 week for the base-case analysis (the period of exacerbation was varied to 3 days or 2 weeks as part of the sensitivity analysis). The mean number of exacerbations per patient, as presented in *Table 17*, was not statistically significantly different between the letter and no-letter groups for this 4-month period (2.50 vs. 2.41, respectively; $p = 0.078$). These results suggest that over the 4-month period, on average, patients in the letter group spent 2.5 weeks in an exacerbated state and the patients in the no-letter group spent just under 2.5 (2.41) weeks in an exacerbated state.

The resource use and associated cost results, as presented in *Table 17*, suggest that those patients in the no-letter (control) group had more scheduled tasks over the 12-month post-intervention period than the

TABLE 17 Mean number of exacerbations for 4 months and resource use and cost for 12 months post intervention per patient by intervention group

Variable and statistics	Variable type	Group		Significant difference (p-value)
		Intervention	Control	
Mean number of exacerbations,[a] mean (SD), range	Number of exacerbations when exacerbation period was 1 week	2.50 (2.19), 0–14	2.41 (2.19), 0–16	0.078
Number of tasks,[b] mean (SD), range	Scheduled tasks	2.60 (2.72), 0–22	2.69 (2.85), 0–30	0.130
	Unscheduled tasks	9.39 (8.32), 0–73	9.36 (9.22), 0–101	0.867
	'Not relevant' tasks	4.17 (4.79), 0–45	3.75 (4.73), 0–60	< 0.001
	Total number of tasks[c]	16.16 (13.30), 0–120	15.80 (14.42), 0–163	0.249
Mean costs, mean (95% CI), median (range)	Scheduled tasks	£169 (£158 to £181), £27 (£0–3857)	£173 (£163 to £183), £41 (£0–3839)	0.623
	Unscheduled tasks	£266 (£255 to 277), £146 (£0–4661)	£283 (£272 to 294), £186 (£0–8010)	0.030
	'Not relevant' tasks	£204 (£191 to £217), £1 (£0–£6149)	£205 (£193 to £218), £1 (£0–£7675)	0.915
	Total task cost[d]	£639 (£612 to £667), £342 (£0–£8829)	£662 (£636 to £688), £358 (£0–13,411)	0.251
	Prescriptions	£55 (£52 to £59), £20 (£0–849)	£49 (£47 to £52), £16 (£0–789)	0.003
	Total task and prescription cost[e]	£695 (£666 to £723), £402 (£0–8921)	£711 (£684 to £738), £412 (£0–13,484)	0.420
	Intervention	£1.34	£0	–
	Overall resource use cost[f]	£696 (£668 to 3725), £403 (£1–8922)	£711 (£684 to £738), £412 (£0–13,484)	0.460

a Number of exacerbations' is dependent on the assumed period of exacerbation, that is, 1 week. Therefore, for the letter group, for example, there was a mean number of 2.5 exacerbations (2.5 weeks spent in an exacerbated state) over the assessed 4-month period for which a utility value was attached.
b The mean number of tasks is provided to give descriptive information about the number of tasks per patient that were included in the costing analysis, and for which a utility decrement could have been attached (unscheduled tasks only). These figures should not be interpreted in relation to the more detailed clinical analysis focused on unscheduled events.
c Total number of tasks = the number of scheduled tasks plus the number of unscheduled tasks plus the number of 'not relevant' tasks per patient.
d Total task cost = the cost for scheduled tasks plus the cost for unscheduled tasks plus the cost for 'not relevant' tasks per patient.
e Total task and prescription cost = total task cost plus the cost for the prescriptions per patient.
f Overall resource use cost = the total task and prescription costs plus the cost of the intervention per patient.

letter (intervention) group (2.69 vs. 2.60 tasks, respectively; $p = 0.130$), but the difference was not statistically significant. The cost for scheduled tasks was also higher on average for the no-letter group, but was not statistically significantly different (£169 for letter vs. £173 for no letter; $p = 0.623$). The reverse was true for those tasks that were classified as 'not relevant'. These 'not relevant' tasks were not classified as either 'scheduled' or 'unscheduled' but were included in the economic analysis as part of the resource use and cost estimations. The letter group had statistically significant more 'not relevant' tasks than the no-letter group (mean number of tasks of 4.17 for letter vs. 3.75 for no letter; $p < 0.001$), but again this did not translate into statistically significant different costs associated with these tasks (£204 for letter vs. £205 for no letter; $p = 0.915$). There was no statistically significant difference in the number of unscheduled tasks between groups ($p = 0.867$). There was a statistically significant lower mean cost for unscheduled tasks in the letter group (£266 for letter vs. £283 for no letter; $p = 0.030$). There was no statistically

TABLE 18 Patient resource use and cost by task for 12 months post intervention by intervention group (ordered alphabetically: A–H)

Resource use (n = 8190)	Group						Statistical significant difference in resource use (and costs[a]) between intervention groups (p-value)
	Intervention (n = 3641)			Control (n = 4549)			
	Number of resource users (% study group), mean number of tasks per resource user (SD, range)	Mean cost per patient (95% CI; median)	Mean cost per resource user (95% CI; median, range)	Number of resource users (% study group), mean number of tasks per resource user (SD, range)	Mean cost per patient (95% CI; median)	Mean cost per resource user (95% CI; median, range)	
Acute visit	7 (0.19), 1 (0, 1–1)	£0.09 (£0.02 to £0.16; £0)	£48.75 (£48.75 to £48.75; £48.75, £48.75–48.75)	13 (0.29), 1 (0, 1–1)	£0.14 (£0.06 to £0.21; £0)	£48.75 (£48.75 to £48.75; £48.75, £48.75–48.75)	0.384
Administration	3078 (84.54), 4.7 (4.35, 1–52)	£0.44 (£0.42 to £0.45; £0.33)	£0.52 (£0.50 to £0.53; £0.39, £0.11–5.72)	3565 (78.37), 4.25 (4.19, 1–86)	£0.37 (£0.35 to £0.38; 0.22)	£0.47 (£0.45 to £0.48; £0.33, £0.11–9.46)	< 0.001
Casualty attendance	51 (1.4), 1.33 (0.77, 1–4)	£2.84 (£1.95 to £3.73; £0)	£202.67 (£169.92 to £235.41; £152.00, £152.00–608.00)	6 (0.13), 1.5 (0.55, 1–2)	£0.30 (£0.05 to £0.55; £0)	£228.00 (£140.63 to £315.37; £228.00, £152.00–304.00)	< 0.001
Children's home visit	0 (0), . (.,–.)	£0 (£0 to £0; £0)	. (–; ., –.)	1 (0.02), 1 (., 1–1)	£0.02 (–£0.02 to £0.06; £0)	£87.75 (.–; £87.75; £87.75–87.75)	0.317
Clinic	804 (22.08), 2.24 (1.73, 1–22)	£9.83 (£9.03 to £10.62; £0)	£44.51 (£42.13 to £46.89; £39.76, £19.88–437.36)	851 (18.71), 1.9 (1.44, 1–16)	£7.07 (£6.51 to £7.63; £0)	£37.77 (£35.85 to £39.70; £19.88, £19.88–318.08)	< 0.001
Co-op surgery consultation	0 (0). . (.,–.)	£0 (£0 to £0; £0)	. (–; ., –.)	40 (0.88), 1.48 (0.85, 1–5)	£2.75 (£1.77 to £3.73; £0)	£312.70 (£255.28 to £370.12; £212.00, £212.00–1060.00)	< 0.001
Co-op telephone advice	0 (0). . (.,–.)	£0 (£0 to £0; £0)	. (–; ., –.)	34 (0.75), 1.41 (0.92, 1–5)	£0.06 (£0.04 to £0.09; £0)	£8.17 (£6.31 to £10.04; £5.79, £5.79–28.95)	< 0.001
Discharge details	56 (1.54), 2.2 (4.02, 1–31)	£0 (£0 to £0.01; £0)	£0.24 (£0.12 to £0.36; £0.11, £0.11–3.41)	90 (1.98), 1.63 (1.13, 1–6)	£0 (£0 to £0; £0)	£0.18 (£0.15 to £0.21; £0.11, £0.11–0.66)	0.886
Emergency consultation	160 (4.39), 1.63 (1.22, 1–8)	£3.33 (£2.7 to £3.97; £0)	£75.8 (£66.94 to £84.67; £46.47, £46.47–371.76)	243 (5.34), 1.7 (1.34, 1–11)	£4.22 (£3.55 to £4.88; £0)	£78.98 (£71.11 to £86.85; £46.47, £46.47–511.17)	0.058
Follow-up/routine visit	0 (0). . (.,–.)	£0 (£0 to £0; £0)	. (–; ., –.)	6 (0.13), 1.5 (0.84, 1–3)	£0.08 (£0.01 to £0.16; £0)	£63.57 (£28.61 to £98.52; £46.47, £41.21–123.63)	0.029 (0.027)

Resource use (n = 8190)	Group						Statistical significant difference in resource use (and costs[a]) between intervention groups (p-value)
	Intervention (n = 3641)			Control (n = 4549)			
	Number of resource users (% study group), mean number of tasks per resource user (SD, range)	Mean cost per patient (95% CI; median)	Mean cost per resource user (95% CI; median, range)	Number of resource users (% study group), mean number of tasks per resource user (SD, range)	Mean cost per patient (95% CI; median)	Mean cost per resource user (95% CI; median, range)	
Home visit	10 (0.27), 1.1 (0.32, 1–2)	£0.27 (£0.09 to £0.44; £0)	£96.53 (£76.67 to £116.38; £87.75, £87.75–175.5)	12 (0.26), 1.92 (1.73, 1–6)	£0.44 (£0.11 to £0.78; £0)	£168.19 (£71.74 to £264.63; £87.75, £87.75–526.5)	0.348
Hospital admission	10 (0.27), 2 (1.49, 1–5)	£3.11 (£0.75 to £5.47; £0)	£1132 (£528.42 to £1735.58; £566, £566–2830)	0 (0), . (., .–)	£0 (£0 to £0; £0)	(.–; ., .–)	0.01

a　Costs were applied to resource use using the CPRD-defined resource use parameters presented in *Tables 18–20*; therefore, the cost is proportional to the amount of resource use and the *p*-value is the same for the difference in costs and resource use. There are instances in which an unscheduled and a scheduled cost were applied to the resource use, and so the *p*-value is not the same, in which case the *p*-value for the cost is provided in the parentheses if the *p*-value is different from that for the difference in resource use.

Note

A missing value is depicted by a '.' if there are either zero observations or just one observation, where for the latter a '.' is used to describe the unknown uncertainty around the point estimates instead of a value for the SD or 95% CI when there is only one observation.

TABLE 19 Patient resource use and cost by task for 12 months post intervention by intervention group (ordered alphabetically: L–O)

Resource use (n = 8190)	Group						Statistical significant difference in resource use (and costs[a]) between intervention groups (p-value)
	Intervention (n = 3641)			Control (n = 4549)			
	Number of resource users (% study group), mean number of tasks per resource user (SD, range)	Mean cost per patient (95% CI; median)	Mean cost per resource user (95% CI; median, range)	Number of resource users (% study group), mean number of tasks per resource user (SD, range)	Mean cost per patient (£) (95% CI; median)	Mean cost per resource user (£) (95% CI; median, range)	
Letter from outpatients	168 (4.61), 1.96 (2.08, 1–15)	£0.01 (£0.01 to £0.01; £0)	£0.22 (£0.18 to £0.25; £0.11, £0.11–1.65)	122 (2.68), 1.45 (0.98, 1–9)	£0 (£0 to £0.01; £0)	£0.16 (£0.14 to £0.18; £0.11, £0.11–0.99)	< 0.001
Mail from patient	10 (0.27), 2.8 (1.69, 1–5)	£0 (£0 to £0; £0)	£0.31 (£0.18 to £0.44; £0.28, £0.11–0.55)	3 (0.07), 1 (0, 1–1)	£0 (£0 to £0; £0)	£0.11 (£0.11 to £0.11; £0.11, £0.11–0.11)	0.013
Mail to patient	1098 (30.16), 1.83 (1.18, 1–7)	£0.06 (£0.06 to £0.06; £0)	£0.20 (£0.19 to £0.21; £0.11, £0.11–0.77)	1362 (29.94), 1.94 (1.41, 1–15)	£0.06 (£0.06 to £0.07; £0)	£0.21 (£0.20 to £0.22; £0.11, £0.11–1.65)	0.253
Medicine management	250 (6.87), 1.42 (0.88, 1–6)	£0.68 (£0.58 to £0.77; £0)	£9.87 (£9.11 to £10.63; £6.95, £6.95–41.7)	363 (7.98), 2.24 (2.42, 1–20)	£1.24 (£1.06 to £1.43; £0)	£15.58 (£13.85 to £17.32; £6.95, £6.95–139)	< 0.001
Minor injury service	3 (0.08), 1 (0, 1–1)	£0.04 (−£0.01 to £0.08; £0)	£46.47 (£46.47 to £46.47; £46.47, £46.47–£46.47)	3 (0.07), 1 (0, 1–1)	£0.03 (£0 to £0.07; £0)	£46.47 (£46.47 to £46.47; £46.47, £46.47–46.47)	0.787
NHS Direct report	0 (0), . (., .–.)	£0 (£0 to £0; £0)	. (.–.; ., .–.)	1 (0.02), 1 (., 1–1)	£0 (£0 to £0; £0)	£0.11 (.–.; £0.11, £0.11–0.11)	0.317
Other	1946 (53.45), 4.05 (4.5, 1–44)	£0.24 (£0.22 to £0.25; 0.11)	£0.45 (£0.42 to £0.47; £0.33, £0.11–4.84)	2053 (45.13), 3.39 (3.81, 1–35)	£0.17 (£0.16 to £0.18; 0)	£0.37 (£0.35 to £0.39; £0.22, £0.11–3.85)	< 0.001
Out-of-hours non-practice	424 (11.65), 1.68 (1.17, 1–10)	£9.07 (£8.06 to £10.08; £0)	£77.92 (£72.75 to £83.10; £46.47, £46.47–464.70)	419 (9.21), 1.65 (1.31, 1–14)	£7.08 (£6.24 to £7.92; £0)	£76.86 (£71.02 to £82.69; £46.47, £46.47–650.58)	0.003
Out-of-hours practice	0 (0), . (., .–.)	£0 (£0 to £0; £0)	. (.–.; ., .–.)	9 (0.2), 1.22 (0.67, 1–3)	£0.11 (£0.03 to £0.19; £0)	£56.8 (£32.98 to £80.61; £46.47, £46.47–139.41)	0.008

a Costs were applied to resource use using the CPRD-defined resource use parameters presented in *Tables 18–20*; therefore, the cost is proportional to the amount of resource use and the *p*-value is the same for the difference in costs and resource use. There are instances where an unscheduled and a scheduled cost were applied to the resource use, and so the *p*-value is not the same, in which case the *p*-value for the cost is provided in the parentheses if the *p*-value is different from that for the difference in resource use.

Note

A missing value is depicted by a '.' if there are either zero observations or just one observation, where for the latter a '.' is used to describe the unknown uncertainty around the point estimates instead of a value for the SD or 95% CI when there is only one observation.

TABLE 20 Patient resource use and cost by task for 12 months post intervention by intervention group (ordered alphabetically: R–W)

Resource use (n = 8190)	Group						Significant difference in resource use (and costs') between intervention groups (p-value)
	Intervention (n = 3641)			Control (n = 4549)			
	Number of resource users (% study group), mean number of tasks per resource user (SD, range)	Mean cost per patient (95% CI; median)	Mean cost per resource user (95% CI; median, range)	Number of resource users (% study group), mean number of tasks per resource user (SD, range)	Mean cost per patient (95% CI; median)	Mean cost per resource user (95% CI; median; range)	
Radiology result	1 (0.03), 1 (, 1–1)	£0 (£0 to £0; £0)	£0.11 (–; £0.11, £0.11–0.11)	0 (0), . (., –.)	£0 (£0 to £0; £0)	£0 (£0 to £0; £0, £0–0)	0.317
Referral letter	30 (0.82), 1.23 (0.63, 1–3)	£0 (£0 to £0; £0)	£0.14 (£0.11 to £0.16; £0.11, £0.11–0.33)	5 (0.11), 1 (0, 1–1)	£0 (£0 to £0; £0)	£0.11 (£0.11 to £0.11; £0.11, £0.11–0.11)	< 0.001
Repeat issue	1786 (49.05), 4.23 (3.95, 1–30)	£0.23 (£0.22 to £0.24; £0)	£0.47 (£0.45 to £0.49; £0.33, £0.11–3.30)	2293 (50.41), 4.28 (4.51, 1–53)	£0.24 (£0.23 to £0.25; £0.11)	£0.47 (£0.45 to £0.49; £0.33, £0.11–5.83)	0.307
Residential home visit	2 (0.05), 1 (0, 1–1)	£0.05 (–£0.02 to £0.12; £0)	£87.75 (£87.75 to £87.75; £87.75, £87.75–87.75)	4 (0.09), 1 (0, 1–1)	£0.08 (£0 to £0.15; £0)	£87.75 (£87.75 to £87.75; £87.75, £87.75–87.75)	0.574
Results recording	656 (18.02), 2.88 (2.79, 1–28)	£0.06 (£0.05 to £0.06; £0)	£0.32 (£0.29 to £0.34; £0.22, £0.11–3.08)	839 (18.44), 3.02 (3.43, 1–38)	£0.06 (£0.06 to £0.07; £0)	£0.33 (£0.31 to £0.36; £0.22, £0.11–4.18)	0.324
Surgery consultation	2948 (80.97), 3.95 (3.45, 1–35)	£145.96 (£140.79 to £151.13; £92.94)	£180.28 (£174.56 to £186.00; £139.41, £41.21–1615.93)	3762 (82.7), 4.62 (4.61, 1–70)	£174.21 (£168.15 to £180.27; £128.89)	£210.66 (£203.89 to £217.43; £139.41, £41.21–3247.64)	< 0.001
Telephone call from a patient	239 (6.56), 1.42 (1.07, 1–10)	£0.51 (£0.43 to £0.59; £0)	£7.76 (£7.05 to £8.47; £5.79, £2.32–50.96)	450 (9.89), 1.7 (1.7, 1–17)	£0.92 (£0.80 to £1.04; £0)	£9.3 (£8.43 to £10.17; £5.79, £2.32–94.96)	< 0.001
Telephone call to a patient	321 (8.82), 1.66 (1.56, 1–14)	£0.76 (£0.65 to £0.87; £0)	£8.62 (£7.74 to £9.5; £5.79, £2.32–74.12)	663 (14.57), 2.01 (2.86, 1–52)	£1.54 (£1.34 to £1.74; £0)	£10.56 (£9.38 to £11.75; £5.79, £2.32–276.79)	< 0.001
Third-party consultation	2118 (58.17), 3.73 (3.92, 1–40)	£460.04 (£435.87 to £484.21; £212)	£790.85 (£755.45 to £826.24; £424.00, £212–8480)	2599 (57.13), 3.79 (4.12, 1–53)	£458.72 (£436.31 to £481.13; £212.00)	£802.89 (£769.27 to £836.51; £424, £212–11,236)	0.937
Triage	359 (9.86), 2.33 (2.25, 1–21)	£1.27 (£1.09 to £1.45; £0)	£12.92 (£11.61 to £14.22; £5.79, £2.32–121.59)	640 (14.07), 2.27 (1.92, 1–18)	£1.76 (£1.59 to £1.93; £0)	£12.51 (£11.70–£13.31; £8.11, £2.32–90.34)	< 0.001

TABLE 20 Patient resource use and cost by task for 12 months post intervention by intervention group (ordered alphabetically: R–W) (*continued*)

Resource use (n = 8190)	Group			Control (n = 4549)			Significant difference in resource use (and costs[a]) between intervention groups (p-value)
	Intervention (n = 3641)						
	Number of resource users (% study group), mean number of tasks per resource user (SD, range)	Mean cost per patient (95% CI; median)	Mean cost per resource user (95% CI; median, range)	Number of resource users (% study group), mean number of tasks per resource user (SD, range)	Mean cost per patient (95% CI; median)	Mean cost per resource user (95% CI; median; range)	
Twilight visit	1 (0.03), 1 (., 1–1)	£0.01 (–£0.01 to £0.04; £0)	£46.47 (.–; £46.47, £46.47–46.47)	1 (0.02), 1 (., 1–1)	£0.01 (–£0.01 to £0.03; £0)	£46.47 (.–; £46.47, £46.47–46.47)	0.876
Walk-in centre	28 (0.77), 1.46 (0.88, 1–5)	£0.52 (£0.30 to £0.75; £0)	£68.05 (£52.17 to £83.92; £46.47, £46.47–232.35)	0 (0), . (.,.–)	£0 (£0 to £0; £0)	. (.–; ., .–)	< 0.001

a Costs were applied to resource use using the CPRD-defined resource use parameters presented in *Tables 18–20*; therefore, the cost is proportional to the amount of resource use and the *p*-value is the same for the difference in costs and resource use. There are instances where an unscheduled and a scheduled cost were applied to the resource use, and so the *p*-value is not the same, in which case the *p*-value for the cost is provided in the parentheses if the *p*-value is different from that for the difference in resource use.

Note
A missing value is depicted by a '.' if there are either zero observations or just one observation, where for the latter a '.' is used to describe the unknown uncertainty around the point estimates instead of a value for the SD or 95% CI when there is only one observation.

significant difference between the letter and no-letter groups in either the overall number of tasks ($p = 0.249$) or associated costs ($p = 0.251$).

The results presented in *Tables 18–20* suggest that there were some statistically significant ($p < 0.001$) differences in the types of tasks and associated costs that defined the patients' resource use over the 12-month post-intervention time period between the letter and no-letter groups. For example, the no-letter group had a statistically significant lower number of casualty attendances [51 (1.40%) people from the letter group had a casualty attendance, compared with 6 (0.13%) from the no-letter group]. This resulted in a statistically significant mean higher cost of £2.84 vs. £0.30 for the letter compared with the no-letter group (see *Table 18*). Tasks such as 'co-op surgery consultation', 'co-op telephone advice' and 'follow-up/routine visit' were mainly associated with the no-letter group, with no recorded entry of these tasks for the letter group (see *Table 18*). Surgery consultations occurred statistically significantly more often in the no-letter group, which translated into a statistically significantly higher mean cost per patient associated with these tasks of £174 for the no-letter group compared with £146 for the letter group (see *Table 20*).

Tasks recorded as 'other' occurred statistically significantly more often in the letter group than in the no-letter group, with 53.5% of the letter group having a recorded 'other' task, compared with 45.1% in the no-letter group. Among patients for whom an 'other' task was recorded (defined as 'resource users'), the number of tasks defined as 'other' was higher in the letter group than in the no-letter group (on average, 4.1 tasks per patient in the letter group compared with 3.4 tasks per patient in the no-letter group). This resulted in a statistically significant higher mean cost of £0.24 for the letter group compared with £0.17 for the no-letter group. Although this difference is very small when a unit cost of £0.11 is assigned to this 'other' task, larger unit costs being assigned to 'other' tasks could have an impact on the cost-effectiveness of the letter group, as tasks classified as 'other' occur significantly more often for this group (this aspect has been assessed as part of the sensitivity analysis; see *Table 16*).

The costs associated with prescriptions were statistically significantly different ($p = 0.003$) between groups, with the mean cost for prescriptions being approximately £55 for the letter group and £49 for the no-letter group, for the 12-month post-intervention period.

Although there appears to be a pattern of resource use and associated costs between the letter and no-letter group, this did not translate into significantly different costs between the groups as a whole (see *Table 17*).

Mean and incremental costs and quality-adjusted life-years from main, adjusted and sensitivity analyses

The mean, SE and 95% CI for costs and QALYs by intervention (letter) and control group (no letter) are presented in *Table 21*; the incremental results (mean difference for the intervention group minus control group and distribution statistics) are presented in *Table 22*. BA results are presented alongside the unadjusted results. It should be noted that there was a statistically significant difference ($p < 0.1$) in overall costs at baseline (12 months before intervention) between the trial arms (these baseline results are presented in *Appendix 10*, *Table 40*).

For the main unadjusted analysis, the mean observed cost and number of QALYs gained was £696.24 and 0.31594, respectively, in the letter group and £710.98 and 0.31611, respectively, in the no-letter group. For the BA main analysis, the adjusted mean costs were £684.39 and £720.46 for the letter and no-letter groups, respectively. From these results, it can been seen that the baseline adjustment had an important effect on the cost results. The influence of the baseline adjustment on the cost results is discussed further in *Strengths and weaknesses of the economic analysis*.

As presented in *Table 22* for the main analysis, the incremental QALY loss for the letter group was 0.00017, with a cost saving of £14.74 or £36.07 for the unadjusted and adjusted cost analysis, respectively. These mean point estimates were surrounded by large amounts of uncertainty. For example,

TABLE 21 Mean and distribution statistics by cost and QALY per patient for main analysis, adjusted analysis, sensitivity analysis and subgroup analysis

Analysis	Letter (yes/no)	Cost			QALYs		
		Mean	SE	95% CI[a]	Mean	SE	95% CI[a]
Main	Yes	£696.24	£23.11	£649.31 to £740.98	0.31594	0.00013	0.31567 to 0.31619
	No	£710.98	£20.81	£670.07 to £752.73	0.31611	0.00012	0.31585 to 0.31631
BA main	Yes	£684.39	£17.08	£650.93 to £717.86	0.31594	0.00013	0.31567 to 0.31619
	No	£720.46	£12.33	£696.29 to £744.64	0.31611	0.00012	0.31585 to 0.31631
Sensitivity analysis: 'other' unit cost							
Cost	Yes	£794.72	£27.19	£747.51 to £853.65	0.31594	0.00013	0.31567 to 0.31619
	No	£780.53	£24.07	£733.49 to £826.41	0.31611	0.00012	0.31585 to 0.31631
BA cost	Yes	£770.99	£18.74	£734.26 to £807.72	0.31594	0.00013	0.31567 to 0.31619
	No	£799.52	£13.91	£772.26 to £826.79	0.31611	0.00012	0.31585 to 0.31631
Sensitivity analysis: duration of exacerbation							
3 days	Yes	£696.24	£23.11	£649.31 to £740.98	0.31843	0.00006	0.31830 to 0.31855
	No	£710.98	£20.81	£670.07 to £752.73	0.31848	0.00006	0.31835 to 0.31858
BA 3 days	Yes	£684.39	£17.08	£650.93 to £717.86	0.31843	0.00006	0.31830 to 0.31855
	No	£720.46	£12.33	£696.29 to £744.64	0.31848	0.00006	0.31835 to 0.31858
2 weeks	Yes	£696.24	£23.11	£649.31 to £740.98	0.31236	0.00022	0.31190 to 0.31276
	No	£710.98	£20.81	£670.07 to £752.73	0.31270	0.00020	0.31226 to 0.31304
BA 2 weeks	Yes	£684.39	£17.08	£650.93 to £717.86	0.31236	0.00022	0.31190 to 0.31276
	No	£720.46	£12.33	£696.29 to £744.64	0.31270	0.00020	0.31226 to 0.31304
Sensitivity analysis: utility of exacerbation							
Utility	Yes	£696.24	£23.11	£649.31 to £740.98	0.31048	0.00028	0.30989 to 0.31100
	No	£710.98	£20.81	£670.07 to £752.73	0.31083	0.00025	0.31028 to 0.31126
BA utility	Yes	£684.39	£17.08	£650.93 to £717.86	0.31048	0.00028	0.30989 to 0.31100
	No	£720.46	£12.33	£696.29 to £744.64	0.31083	0.00025	0.31028 to 0.31126
Sensitivity analysis: type of contacts							
Respiratory	Yes	£123.17	£4.98	£114.10 to £133.39	0.31999	0.00004	0.31992 to 0.32006
	No	£120.76	£6.87	£108.90 to £136.88	0.32007	0.00003	0.32001 to 0.32013
BA respiratory	Yes	£119.02	£3.17	£112.80 to £125.23	0.31999	0.00004	0.31992 to 0.32006
	No	£124.08	£3.17	£114.42 to £133.74	0.32007	0.00003	0.32001 to 0.32013
Sensitivity analysis: cost estimation period							
5 months	Yes	£322.70	£9.64	£303.47 to £341.75	0.31594	0.00013	0.31567 to 0.31619
	No	£318.96	£11.15	£298.17 to £340.84	0.31611	0.00012	0.31585 to 0.31631
BA 5 months	Yes	£317.17	£7.03	£303.40 to £330.94	0.31594	0.00013	0.31567 to 0.31619
	No	£323.38	£7.13	£309.40 to £337.35	0.31611	0.00012	0.31585 to 0.31631
Subgroup analysis: under-fives							
Under-fives	Yes	£1006.21	£120.73	£798.09 to £1289.15	0.31397	0.00049	0.31285 to 0.31485
	No	£809.30	£53.23	£722.15 to £932.29	0.31500	0.00038	0.31407 to 0.31561
BA under-fives	Yes	£906.71	£67.80	£773.82 to £1039.59	0.31397	0.00049	0.31285 to 0.31485
	No	£871.01	£50.85	£771.35 to £970.67	0.31500	0.00038	0.31407 to 0.31561

a All unadjusted SE are bias corrected and 95% CIs are BCa based on estimates post bootstrap; however, adjusted SE are delta method SEs and 95% CIs are normal 95% CIs.

TABLE 22 Summary of incremental results by cost and QALY per patient for the main analysis, adjusted analysis and sensitivity analysis and subgroup analysis

Analysis (1 – 0)[a]	Cost			QALYs		
	Difference in means	SE	BCa 95% CI	Difference in means	SE	BCa 95% CI
Main	–£14.74	£31.25	–£75.86 to £45.19	–0.00017	0.00018	–0.00051 to 0.00018
BA main	–£36.07	£21.10	–£77.11 to £9.67	–0.00017	0.00018	–0.00051 to 0.00018
Sensitivity analysis: 'other' unit cost						
Cost	£14.19	£36.86	–£56.22 to £95.34	–0.00017	0.00018	–0.00051 to 0.00018
BA cost	–£28.53	£23.64	–£72.74 to £20.18	–0.00017	0.00018	–0.00051 to 0.00018
Sensitivity analysis: duration of exacerbation						
3 days	–£14.74	£31.25	–£75.86 to £45.19	–0.00005	0.00009	–0.00022 to 0.00012
BA 3 days	–£36.07	£21.10	–£77.11 to £9.67	–0.00005	0.00009	–0.00022 to 0.00012
2 weeks	–£14.74	£31.25	–£75.86 to £45.19	–0.00034	0.00030	–0.00093 to 0.00025
BA 2 weeks	–£36.07	£21.10	–£77.11 to £9.67	–0.00034	0.00030	–0.00093 to 0.00025
Sensitivity analysis: utility of exacerbation						
Utility	–£14.74	£31.25	–£75.86 to £45.19	–0.00035	0.00038	–0.00109 to 0.00039
BA utility	–£36.07	£21.10	–£77.11 to £9.67	–0.00035	0.00038	–0.00109 to 0.00039
Sensitivity analysis: type of contacts						
Respiratory	£2.41	£8.65	–£17.58 to £17.26	–0.00008	0.00005	–0.00017 to 0.00001
BA respiratory	–£5.06	£5.98	–£18.51 to £5.87	–0.00008	0.00005	–0.00017 to 0.00001
Sensitivity analysis: cost estimation period						
5 months	£3.74	£14.78	–£25.68 to £32.47	–0.00017	0.00018	–0.00051 to 0.00018
BA 5 months	–£6.21	£10.04	–£25.73 to £14.54	–0.00017	0.00018	–0.00051 to 0.00018
Subgroup analysis: under-fives						
Under-fives	£196.91	£132.94	–£47.60 to £466.99	–0.00102	0.00062	–0.00221 to 0.00020
BA under-fives	£35.69	£85.30	–£137.40 to £195.31	–0.00102	0.00062	–0.00221 to 0.00020

a Incremental results are the letter group (1) minus the no-letter group (0).

the uncertainty around the incremental adjusted main analysis of a mean cost saving of £36.07 was a SE of £21.10 and 95% CI ranging from a cost saving of £77.11 up to an additional cost of £9.67. For the main analysis (QALY loss of 0.00017), the SE for the incremental QALY was 0.00018 and the 95% CI ranged from a QALY loss of 0.00051 up to a QALY gain of 0.00018.

In the sensitivity analyses using BA costs, the letter was always shown to result in a mean cost saving, although the difference never achieved statistical significance. However, in the sensitivity analyses using the observed unadjusted costs, the letter resulted in an additional cost on average, albeit still non-statistically significant, in all of the sensitivity analyses in which costs were affected. For the under-fives subgroup analysis, a cost increase was identified in the unadjusted and adjusted analyses of £196.11 and £35.69 per person, respectively. In general, for the adjusted analysis, the letter group was shown to be cost-saving at the mean point estimate for the main and sensitivity analysis.

Across the main, sensitivity and subgroup analyses, a QALY loss was observed for the mean point estimates ranging from a QALY loss of 0.00005 when the period of exacerbation was reduced from 1 week to 3 days up to 0.00102 in the under-fives subgroup analysis. All incremental and mean point QALY estimates were surrounded by large amounts of uncertainty, as presented in *Tables 21* and *22*.

In general, the letter intervention was found to be cost-saving, but less effective than no letter at the mean point estimate. However, all QALY and costs estimates were surrounded by large amounts of uncertainty. In order to give these results some context based on a hypothetical population of 100,000 people, the mean point estimates from the adjusted main analysis suggest that by implementing the letter intervention, 17 QALYs would have to be traded against a cost saving of £3,607,000 by decision-makers if the letter was implemented for 1 year, but with 95% confidence that the intervention may result in a loss of up to 51 QALYs or a gain of up to 18 QALYs and in a cost saving of up to £7,711,000 or an additional cost of up to £967,000.

Summary of key results from the cost-effectiveness, sensitivity and subgroup analyses

The cost-effectiveness analysis found that there is considerable uncertainty regarding the impact of the letter intervention on both benefits to patients and costs falling on the NHS. Although the adjusted base-case analysis showed a mean cost saving of £36.07 per patient and a mean QALY loss of 0.00017, the CIs around each were wide and did not demonstrate significantly significant differences. The differences in costs and QALYs from the bootstrapped analysis can also be visually interpreted from the cost-effectiveness planes for the unadjusted and adjusted main analyses as presented in *Figures 23* and *24*, respectively. While the intervention was cost-saving in 96.3% of samples, it also resulted in a QALY loss in
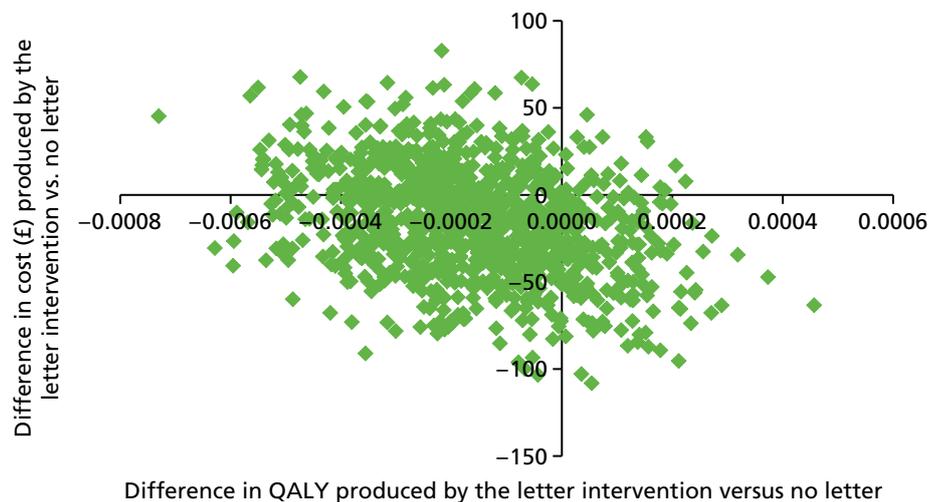
FIGURE 23 Cost-effectiveness plane for the letter intervention vs. no letter from the main analysis.
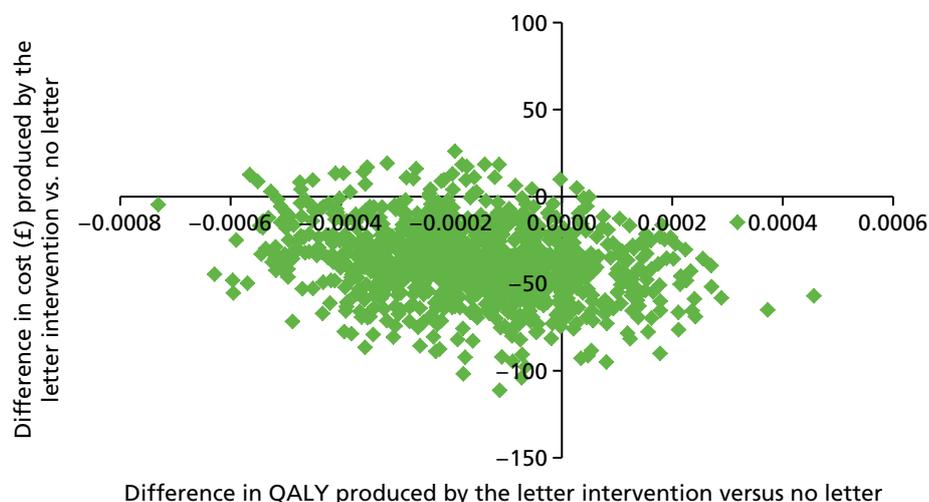
FIGURE 24 Cost-effectiveness plane for the letter intervention vs. no letter from the BA main analysis.

82.9% of samples (*Table 23* and *Figure 24*). Overall, the intervention was found to be cost-effective in 93.8% of samples when valuing a QALY at £20,000 (see *Table 23* and the cost-effectiveness acceptability curve for the unadjusted and adjusted main analysis in *Figure 25*).

The very small QALY loss means that the incremental cost-effectiveness ratio (ICER) is very large for all the analyses. For example, for the adjusted main analysis, the ICER based on the mean point estimates was £597,103 (SE from the bootstrapped estimations: £187,787) per QALY, which is the ICER for the cost savings per QALY forgone, rather than the slightly more common cost per QALY gained associated with reported ICERs. The intervention was dominated (the letter intervention was more costly and less effective

TABLE 23 Mean (SE) ICER, percentage of ICERs in each quadrant of the cost-effectiveness plane, and probability of cost-effectiveness for main analysis, adjusted analysis and sensitivity analysis

Analysis (1–0)[a]	Mean (SE) ICER[b] [£/QALY]	ICERs by cost-effectiveness plane quadrant (%)				Percentages of cost-effectiveness at $\lambda <$ willingness to pay (%)	
		South-east	South-west	North-east	North-west	$\lambda < £0$	$\lambda < £20,000$
Main	88,733 (114,126)	14.6	52.7	2.5	30.2	67.3	63.1
BA main	597,103 (187,787)	17.0	79.3	0.1	3.6	96.3	93.8
Sensitivity analysis: 'other' unit cost							
Cost	Dominated	11.6	26.6	5.5	56.3	38.2	34.6
BA cost	171,716 (167,195)	16.7	73.5	0.4	9.4	90.2	86.5
Sensitivity analysis: duration of exacerbation							
3 days	279,489 (288,070)	23.5	43.8	4.3	28.4	67.3	66.0
BA 3 days	683,777 (314,408)	27.6	68.7	0.2	3.5	96.3	95.5
2 weeks	43,121 (112,808)	11.6	55.7	1.8	30.9	67.3	59.9
BA 2 weeks	105,496 (156,183)	13.3	83.0	0.1	3.6	96.3	90.3
Sensitivity analysis: utility of exacerbation							
Utility	41,607 (53,125)	14.9	52.4	2.6	30.1	67.3	59.9
BA utility	101,793 (91,714)	17.4	78.9	0.1	3.6	96.3	89.8
Sensitivity analysis: type of contacts							
Respiratory	Dominated	2.0	35.5	1.9	60.6	37.5	32.5
BA respiratory	65,020 (22,731)	3.4	76.2	0.5	19.9	79.6	70.7
Sensitivity analysis: cost estimation period							
5 months	Dominated	11.7	29.3	5.4	53.6	41.0	34.2
BA 5 months	37,358 (45,190)	16.1	58.9	1.0	24.0	75.0	62.4
Subgroup analysis: under-fives							
Under-fives	Dominated	1.4	4.2	2.6	91.8	5.6	4.5
BA under-fives	Dominated	2.8	30.6	1.2	65.4	33.4	26.3

Cost-effectiveness plane quadrants are south-east (less costly, more effective), south-west (less costly, less effective), north-east (more costly, more effective) and north-west (more costly, less effective).
a   Incremental results are the letter group (1) minus the no-letter group (0).
b   Negative ICERs can indicate an intervention is either dominant (mean ICER in south-east quadrant) or dominated (mean ICER in north-west quadrant); negative ICERs are not reported, but are instead replaced with a definition of the intervention being dominant or dominated by the control.
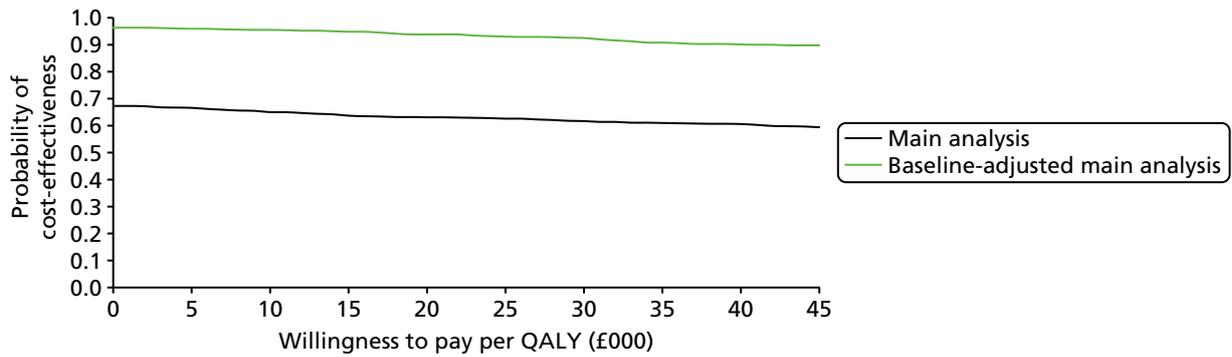
FIGURE 25 Cost-effectiveness acceptability curve for the letter intervention vs. no letter. Note that this graph demonstrates the probability of cost-effectiveness at a range of decision-maker ceiling willingness-to-pay values for the letter intervention from the main analysis (unadjusted) and the baseline cost-adjusted main analysis.

than no letter at the mean point estimate) when the 'other' unit cost was assigned a pooled weighted cost, when accounting for only 'respiratory'-related contacts, when restricting the analysis to 5 months after intervention, and in the under-fives subgroup analysis; however, this was for the unadjusted analysis and the intervention was not dominated in the adjusted analysis except in the subgroup analysis. No ICER could be defined as dominant (a scenario in which the letter intervention would be cost-saving and more effective at the mean point estimate) as a result of this analysis. These ICERs are suggestive of an intervention that would be generally deemed not cost-effective if effectiveness (QALY gain) was important for decision-makers.

The sensitivity analyses showed that the cost-effectiveness results were sensitive to the assumptions regarding the costing of 'other' contacts, the duration and utility decrement assigned to a period of exacerbation, the types of contact included in the analysis, as well as the period of cost-estimation and whether or not the focus was on 5- to 16-year-olds or under-5-year-olds. The probability of cost-effectiveness in the adjusted analysis for the 5- to 16-year-olds, however, generally remained above 62% at a willingness-to-pay (WTP) threshold (λ) of £20,000 and above 75% when focused on the cost savings (rather than effectiveness; WTP threshold of £0) of the intervention. The probability of cost-effectiveness in the adjusted analysis for the under 5 years of age was 26.3% ($\lambda < £20,000$) or 33.4% ($\lambda < £0$). It should also be noted, however, that none of the sensitivity analyses demonstrated a significant difference in QALYs or costs, so the overall conclusion is that there is considerable uncertainty around the cost-effectiveness of the letter intervention.

Although there appears to be some discordance between the cost-effectiveness results and the trial's primary clinical outcome of proportion of children having an unscheduled contact in September, the cost-effectiveness results are consistent with the mean contacts per child endpoints, particularly over the wider time interval.

Chapter 5 Discussion

Main findings

Previous work has shown an increase in the number of unscheduled medical contacts by children in autumn months (September to December), which may be a result of the start of the new school term.[13] By sending a letter in July to remind children (and their parents) of the importance of using their inhaler, it was hypothesised that the increase may be averted. More specifically, the hope was that a reminder letter would lead to a greater uptake of inhaler prescriptions in August, that this, in turn, would also lead to an increased adherence and, finally, that fewer unscheduled medical appointments would be required.

There is evidence of an impact on the first part of this pathway, as the intervention group demonstrated a higher uptake of prescriptions in August 2013. There was also an increase in scheduled contacts in the same month in this group. The data are not available to confirm actual medicine use (as quantified by the medicine possession ratio), and so it is unclear whether or not the increased uptake also translated into increased use.

The primary end point was unscheduled medical contacts in September 2013, which coincided with the start of the new school term. There was no evidence of a reduction in the intervention group, but the finding of a greater number of unscheduled medical contacts (albeit not statistically significant) is unexpected. We can offer three potential explanations for this.

First, a repeat prescription request may not be dispensed without a review in situations in which the child has not received a prescription for several months, or in which the parent wishes to discuss the advantages and/or disadvantages of recommencing treatment that the child has stopped some months before. This in turn may be classified as an unscheduled contact in the coding algorithm that we used to define contacts as unscheduled. The evidence to support this is the large increase in unscheduled contacts in the intervention group in August (relative to the control group). In addition, it seems the longer the time since a patient last collected a prescription, the higher the likelihood of an unscheduled contact in September in the intervention group. This implies that patients with more troublesome asthma may be more likely to have collected a prescription recently; conversely, patients who have not collected a prescription recently may have stopped their preventative medication and may be seeing their GP to check whether or not it is still necessary.

Second, the letter may have acted inadvertently as a trigger to contact the practice in relation to an unrelated medical issue they had been meaning to discuss, which may increase the number of contacts in the short term.

Third, and finally, the data collected at the time may be equivocal in the coding of the contact, leading us to incorrectly adjudicate certain contacts as unscheduled when the contact was scheduled, a limitation of routine data that we will return to in the next section; this is a factor that is important for this intervention, which did increase scheduled contacts in the first instance.

Despite the increase in unscheduled contacts in September, both the total number of contacts per child (i.e. scheduled plus unscheduled) and unscheduled contacts were lower in the intervention group than in the control over the extended study period (September–December 2013) and the full year (September 2013–August 2014). Although the effects were not statistically significantly, the minimal cost associated with the intervention meant that the intervention was found to have a high probability of being cost-saving overall. The economic analysis (which used data over a 12-month period from August 2013 to July 2014) estimated a mean cost saving across the base case of £36.07 per child and 96.3% probability that the intervention is cost-saving. By contrast, the cost-effectiveness results are suggestive of an intervention that would be

generally deemed not cost-effective if effectiveness (QALY gain) was important for decision-makers, as it also resulted in a QALY loss in 82.9% of samples and a mean loss of 0.00017 QALYs.

The small effects observed could be because of the strength of the link between prescription uptake and unscheduled medical contacts. Around 5–6% more children received a prescription for asthma medication in August 2013, a difference that, while substantial, may not be sufficient to achieve the postulated 5% reduction in unscheduled medical contacts that the study was planned to detect. On the other hand, it could be that the increased prescription uptake could have reduced the severity (and days off school), which we could not detect from routine health-care data.

Strengths and weaknesses

Strengths and weaknesses of the trial
The primary strength of the trial is its simple and generalisable design, incorporating an intervention that could be delivered within general practices with minimal cost. The intervention comprised a short letter, delivered at the start of the school summer holidays, reminding children of the importance of adhering to their asthma medication. The trial demonstrated that doing so increased the number of children both requesting a repeat asthma prescription and having a scheduled medical contact (such as an asthma review) in August without an associated increase in cost. Nevertheless, as noted above [see *Secondary outcomes*, *Contacts over 12 months (September 2013 to August 2014)*], there was (at best) limited evidence that this translated into an overall reduction of medical contacts.

We believe the risk of methodological bias is low in this study. The designation of contacts as 'scheduled', 'unscheduled' and 'irrelevant' was based on an independent adjudication panel comprising experienced GPs who were blinded to treatment group.

The main limitations of the trial were those imposed by the use of routinely collected data as the sole data source. The issues with using routine data are fairly obvious; data that are collected primarily as a record of medical care may not contain the information needed for a subsequent research question. For the outcomes evaluated within this trial, there was considerable uncertainty around the adjudication of some of the contacts as scheduled, unscheduled or irrelevant. Many of the contacts were coded 'other' or otherwise ambiguous, and the GP Adjudication Panel advised that this probably reflected the limited time available to GPs when summarising the appointment. There were 34,947 such contacts in the data set, out of 440,429 contacts (109,352 of which were deemed irrelevant). Even if adjudication of all contacts was feasible, however, some of more detailed fields are withheld as per CPRD policy, with the (understandable) reason being to safeguard potentially identifiable details contained therein. As a general issue, this highlights the tension between research ethics and individual rights, which arises in the use of routine data for research. On the advice of the GP Adjudication Panel, these contacts were coded as unscheduled.

We note that the use of routine data was a strength in some regards. First and foremost, using routine data substantially reduced the cost of the trial and allowed us to study a relatively large cohort of children. It is also the only appropriate way to assess the impact of a population-level intervention. If patients were recruited to a trial of the effect of receiving (or not) a letter, the very process of recruitment would have been an intervention. It should also be noted that this is the first large-scale trial of its type using routine CPRD data as the sole source data: issues that arose in the course of this trial may be abated on future trials as researchers and data providers become more familiar with the practical considerations involved in the process of data collation, transfer, recoding and analysis. Some specific examples encountered here are that practices may withdraw from being with CPRD; that prespecified coding for contacts are often not used; and that some fields are withheld for reasons of data confidentiality. The extent of these had not been appreciated or accounted for at the design stage of this trial.

The push for the use of routine data in clinical evaluation seems likely to continue, and it is important that researchers have appropriate expectations of what is, and what is not, realistic and achievable, when using these repositories. Practices leaving the CPRD is a particular issue for studies that have a long-term follow-up as the primary analysis.

Over the course of the study period, 28 practices stopped contributing data to the CPRD as a result of switching practice computer systems. At the time of the conclusion of the study period, the CPRD was only able to collect research-usable data from practices using the Vision IT computer system. It should be noted, however, that the CPRD is working towards being able to collect research data from GP practices using computer systems other than Vision. Once this work is complete, it should be the case that practices switching from one computer system to another will be able to continue their participation in trials and studies.

In retrospect, qualitative interviews with key stakeholders, including practice nurses and GPs, as well as a larger group of children with asthma, may have added a different dimension in both the development and (suggested) implementation of the intervention.

Strengths and weaknesses of the economic analysis

As with the clinical evaluation, the main limitation of the economic analysis is that it relied solely on routine data available within the CPRD database. We therefore had to infer the number of exacerbations experienced by patients, as well as the duration and severity of those exacerbations, from data on health-care resource use, which required several assumptions. For example, we assumed that any week including one or more unscheduled health care contacts was an exacerbation week. Under this assumption, two unscheduled contacts occurring 2 days apart may count as 1 or 2 weeks of exacerbation depending on whether or not they fall within the same calendar week. This adds further uncertainty to the QALY estimates that is not quantified within the CIs provided by the bootstrap analysis.

The use in the study of routine data also meant that we had to rely on published estimates for the impact of asthma exacerbations on children rather than measuring HRQoL in the patients themselves. This was problematic, as there was a lack of relevant and high-quality data on the impact of exacerbations on HRQoL for school-aged children. As a result, we decided to use data from adults in the base-case analysis, but this may not accurately reflect the impact of exacerbations on HRQoL in children, as their experiences of asthma may differ from those of adults.

Although the CPRD provides comprehensive data on resource use for the costing analysis, a number of assumptions were needed to classify all the health-care contacts as either scheduled or unscheduled. We also had difficulty classifying contacts as respiratory related or not, with a large proportion (38%) remaining unclassified. For this reason, in the costing analysis we included all contacts, whether they could be classified as respiratory related or not. As the intervention is not expected to have any effect on non-respiratory-related contacts, our analysis assumes that any difference between the intervention and comparator arms was a result of a change in respiratory-related contacts. The inclusion of these unrelated contacts in the costing analysis is likely to have made it harder to detect whether or not there was a true difference in respiratory-related contacts. We also found that a significant proportion of contacts (10%) were coded as consultation type 'other', which does not provide a clear indication of the activity involved. We therefore had to make an assumption regarding the type of activity that might be coded this way. Our sensitivity analysis found that making alternative assumptions regarding contacts coded as 'other' made some difference to the likelihood that the intervention was cost-effective, further supporting our conclusions that the cost-effectiveness of the letter intervention remains uncertain.

The data recorded in the CPRD on the duration of the consultation and the staff members involved in each consultation were not considered to be robust enough to use for calculating unit costs. Therefore, in calculating the unit costs for different types of consultation, we had to make assumptions using advice from our clinical experts regarding the likely staff mix and duration of contact. We also had to make assumptions regarding the likely severity of asthma exacerbations presenting in primary and secondary care.

The costing analysis for prescriptions was also problematic, as many of the drugs used in the management of asthma are available as a large number of different preparations, each with a unique product code. For example, for salbutamol inhalers alone, 17 unique products were prescribed within the data set. To keep the prescription cost analysis manageable, we estimated the cost per prescription for the 10 most commonly prescribed products for each drug. However, this approximation is not expected to have significantly biased the cost-effectiveness analysis because the absolute cost of most products prescribed in the management of asthma is low. We did find that the cost of prescriptions was significantly higher in the year overall for the letter arm, but this was more than offset by cost savings for other activity, resulting in a statistically non-significant cost-saving for letter compared with no letter overall.

The analysis takes an NHS and PSS perspective for costs and considers the benefits falling on patients themselves. Although this is the perspective preferred by NICE,[35] it excludes the broader impact of asthma exacerbations on the children themselves, such as reduced educational opportunities due to missed schooling. It also excludes any impact on parents and carers, such as time off work when children are not fit enough to attend school.

A strength of this analysis was the ability to control for baseline costs in the BA economic analysis, which is an important aspect for consideration based on the allocation of patients (and their associated resource use patterns) to the control and intervention arms of the trial. Although it was shown in *Table 17* that there was no statistically significant difference in overall resource use or costs between the trial arms for the 12 months post intervention, there was a statistically significant ($p < 0.1$) difference in overall costs at baseline (12 months before intervention) between the trial arms (these baseline results are presented in *Appendix 10*, *Table 40*). There are four reasons why the baseline resource use and costs are important for the BA economic analysis results and their interpretation:

1. A strong predictor of future resource use is past resource use, and it may be more difficult to influence the resource use habits of high resource users (who are also referred to as frequent attenders in the empirical literature) and, therefore, the patients in the letter group may have been less influenced by the intervention than those in the no-letter group may have been if they were allocated to receive the letter.
2. The letter intervention was allocated to a group of higher resource users, and this is not accounted for in the unadjusted economic analysis, which accounts only for the incremental difference in costs at the 12-month follow-up. Therefore, the costs of the letter group were already naturally higher in the letter group, which has an effect on the assessment of the incremental 12-month follow-up costs in this economic evaluation.
3. In relation to points 1 and 2, high resource users are, by nature, able to have larger changes in resource use and costs than low resource users, which will influence the incremental difference between groups when focusing on incremental differences at follow-up (in terms of costs) if these high resource users are allocated more to one arm of the trial than the other (e.g. reducing the resource use patterns of healthier patients with low resource use using an intervention will potentially have a much smaller change than the potential change if the intervention successfully altered the resource use patterns of unhealthier patients who are high resource users).
4. The higher resource use and costs could actually have been a result of improved (or just more) resource use recording at the practices allocated to the letter intervention group (note that allocation was at the practice level, rather than the patient level), which would have resulted in artificially higher costs and resource use in the letter group.

For the purpose of discussion, it is unclear which of the aforementioned points may have contributed to the statistically significantly higher resource use and costs for the letter group at baseline; however, whatever the reason for the difference in costs and resource use between the letter and no-letter group at baseline and post intervention, this aspect was controlled for in the BA economic analysis. Therefore, there is reason to consider that the results from the BA economic analysis may be a better representation of the potential economic benefit of the letter intervention than the unadjusted (observed) economic analysis.

In this report, both results have been presented in order to allow decision-makers to account for both sets of results when judging the cost-effectiveness of this intervention; however, without the BA results, the intervention would seem less cost-effective than it actually may be in practice.

Patient and public involvement input on the trial results

The children and parents fed back that they felt that the saving per individual as a result of the intervention was an important finding from the study.[27] Their feedback was that this should be emphasised more in the reporting of the result. We had the children and parents involved throughout, but this input was from October 2015.

A key point that came from the feedback was the question of whether the results would have been different if the study had been conducted over a 3-year period rather than 1 year. The parents felt that if the letter was something they expected each summer it could help in their planning for the start of the school year.

The trial in context: other studies and differences in results

We have not identified any other studies that have examined the economic benefits of a simple postal intervention in asthma patients and, therefore, it is difficult to compare our results with those of existing published studies. Yong and Shafie[43] have published a systematic review that looked more broadly at non-pharmacological interventions aiming to improve asthma management. The interventions included by Yong and Shafie varied from educational and self-management interventions to environmental interventions. While the PLEASANT study intervention letter could be considered a simple form of patient education, the educational interventions included by Yong and Shafie were all more intensive, and the population was not restricted to school-aged children, making comparisons difficult. However, the broader evidence reviewed by Yong and Shafie suggests that non-pharmacological interventions that aim to improve individuals' management of their asthma have the potential to be cost-effective.

Meaning of the study and implications for clinicians or policy-makers

The intervention in the PLEASANT study caused an increase in prescription collection in August, as well as an increase in scheduled medical contacts. It also had the effect of increasing medical contacts in August and September. After September, there was evidence of a fall in medical contacts, which, although not statistically significant, did follow through in the economic analysis to give a high probability of the intervention being cost-saving.

The increase in prescriptions and scheduled contacts in August could lead to individual GP practices wishing to implement the intervention. Evidence from the trial suggests that this would not increase overall costs associated with the asthma management, and may improve scheduled care. However, the evidence from the PLEASANT study is not sufficient to support a general recommendation for all GP practices.

Recommendations for future research

An objective of the study was to increase the take-up of prescriptions in August, as well as the adherence of children with asthma to taking their medications. The study was not able to assess the latter aspect.

Using routine data has many advantages in terms of trial efficiency in assessing public health or population-level interventions or in the assessment of proven interventions in real-world settings.

Our analysis of the PLEASANT study data set suggests that further work is required to determine how to assess adherence using such data.

A suggested refinement for future trials using routine data could be the inclusion of a prompt for clinicians to answer study-related questions for patients in the study. For example, if patients enrolled in the study were to be given a specific study code, then clinicians, when having a consultation with such patients, could be automatically presented with a template for reporting key data during the study period. For the PLEASANT study, this would involve asking the clinician one simple question: whether the appointment was scheduled or not (and perhaps, second, if this was a respiratory-related consultation).

An additional point would be to emphasise to clinicians the importance of ensuring that the routinely collected patient data needed for the trial are complete, for example, in the PLEASANT study, prescription data to assess adherence. This could be done through a system prompt.

An investigation of the intervention on emergency contacts (such as out of hours, walk-in centres and emergency departments) would be of interest.

Future research in assessing interventions to improve adherence in school-aged children with asthma could include additional qualitative interviews with key stakeholders such as practice nurses, GPs and a wider group of children with asthma.

A study estimating the impact of asthma exacerbations on school-aged children, using a preference-based measure of HRQoL that has been validated for use in children, would be useful to inform future cost-effectiveness analyses.

Chapter 6 Conclusions

The intervention did not reduce unscheduled care in September, which was the primary end point. However, the intervention succeeded in increasing the proportion of children who collected a prescription in August, along with the proportion of children who had scheduled contacts in the same month.

Over a wider time interval, there is weak evidence that the intervention may have reduced medical contacts. This is reflected in the health economic evaluation, which, overall, showed that the intervention had a high probability of giving a cost saving. However, there was no associated increase in QALYs.

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Data sharing statement

Access to patient-level data is provided by the CPRD for health research purposes and is dependent on approval of a study protocol by the Medicines and Healthcare products Regulatory Agency Independent Scientific Advisory Committee. More information on the Independent Scientific Advisory Committee and the protocol submission process can be found at www.cprd.com/isac (date accessed 30 May 2016).

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Appendix 1 Trial intervention

GP letterhead

<Address line 1>

<Address line 2>

<Address line 3>

<Address line 4>

<Insert Date>

Dear Parent

Please read this important letter regarding your child's asthma

It is really important that your child continues to take their asthma medication during the summer holidays. Returning to school is a time when asthma can get worse and make children and young people with asthma poorly. This may be due to contact with infections at the start of the new school year.

To reduce the chances of getting poorly when they return to school, your child should continue to take their asthma medication as prescribed by their GP or practice nurse. If your child has stopped taking their medication over the summer holidays it is important to start it again as soon as possible. If they are short of medication, or you are not sure of the proper dose, please get in touch with the practice.

Yours sincerely

<Name of Doctor>

Appendix 2 Changes to protocol

TABLE 24 Changes to the protocol

Changes to protocol	Outcome	Research ethics committee approval date	Approved by
Protocol version 2 (14 May 2015): this version included an additional secondary outcome to include data up to September 2014, to see if the effect from September 2013 is maintained when there is no study intervention, thus extending the follow-up period by 1 month (see *Chapter 2*, *Changes to the data collection, data extraction and methods for allocation of data after the trial commenced, with reasons*)	Agreed as a 2-month, non-cost contact variation by the HTA programme on 2 February 2015	25 May 2014	National Research Ethics Service Committee Yorkshire & The Humber – South Yorkshire

Appendix 3 Data management process: allocation of medical contacts and follow-up data

All types of 'consultation' are recorded within the data that the CPRD provides. For the purpose of this study, each consultation is considered a medical contact, but not all consultations are considered relevant to the study. According to the protocol, a scheduled contact is any contact that is part of the planned care for the patient, for example an asthma review, a medical review, repeat prescription or immunisation. An unscheduled contact is any unplanned contact that is either patient initiated or is a result of illness.

Details of how this has been applied and other assumptions to propose the allocation of medical contacts as 'scheduled' and 'unscheduled' are described in this appendix.

Data received from the Clinical Practice Research Datalink

Initial test data set received 10 May 2013.

First baseline data set received 19 December 2013.

Second baseline data set received 3 February 2014.

Third baseline data set received 13 July 2014.

Baseline and follow-up data set received 19 January 2015.

Clinical Practice Research Datalink data

Data from the consultation, clinical, immunisation, test, referral and therapy tables from the CPRD Gold Data dictionary were used.

Overview

Figure 26 shows a very broad overview of how the data have been processed and the number of records. Full details of assumptions are now described.

General assumptions

One 'consultation' (based on the combination of patient ID, practice ID and consultation ID) in the consultation table is considered one contact.

All consultation data supplied, not just those that are asthma related, are taken into account for the study.

Only consultations that happened on or after 1 August 2012 are included.

Assumptions used to code records as scheduled or unscheduled (contact type) are based on clinical, immunisation, therapy, referral, test and consultation data.
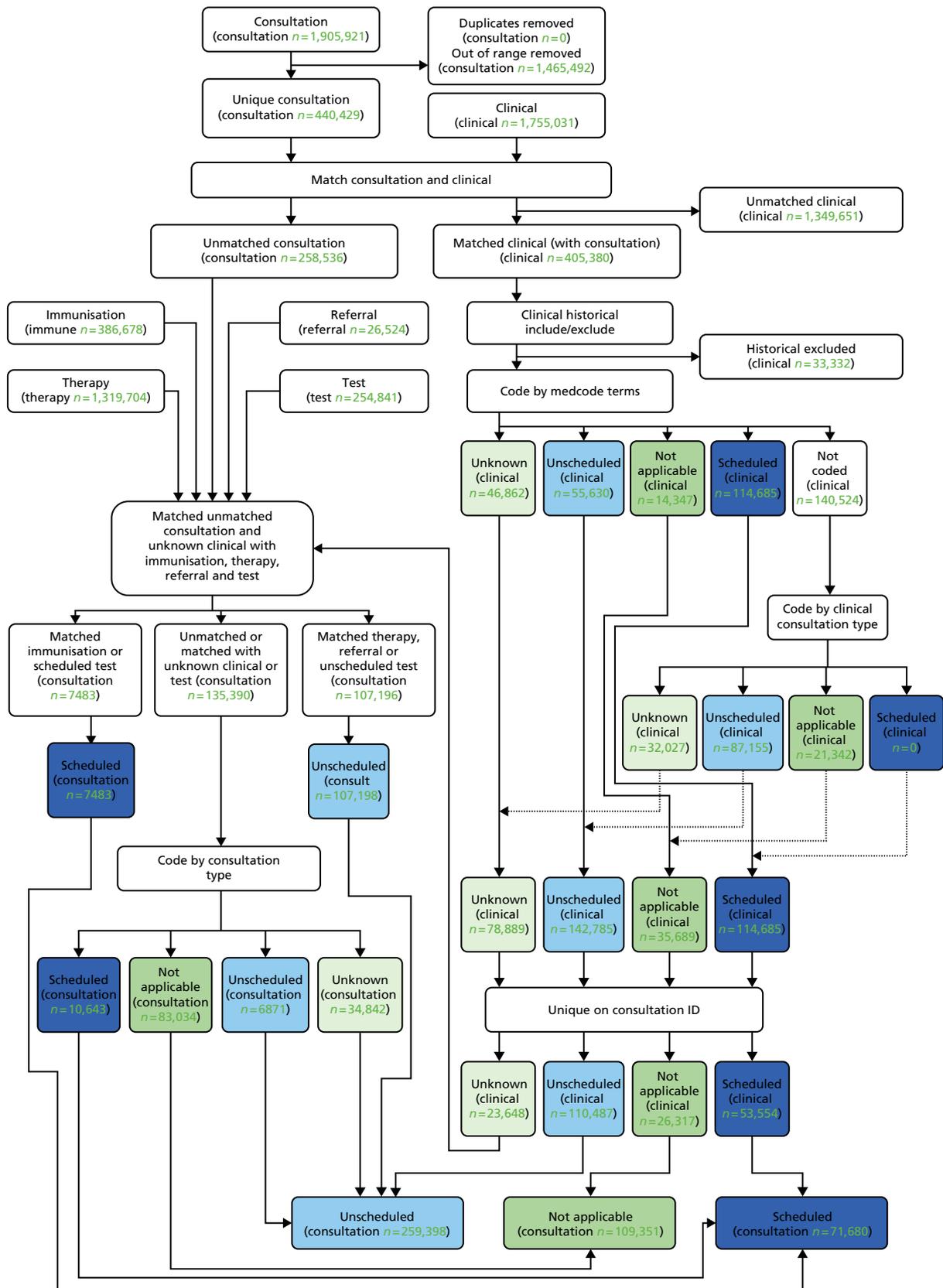
FIGURE 26 Decision tree showing an overview of how medical contacts have been allocated.

Records with unmatched event dates

Each consultation record is supplied with an event date; this event date does not always match the event date recorded for that consultation within the other tables. This is most likely a result of information entered into the database historically. Those contacts within the clinical table were included if they were relevant and unlikely to be duplicated (see *Inclusion of 'unmatched/historical' data* section for more details). All immunisation, therapy, referral and test records that did not match the event date supplied in the consultation data were excluded.

Clinical data

Clinical data are linked to consultation data, and all matched records are included.

Inclusion of 'unmatched/historical' data

If the event date does not match but the clinical event date is within the dates of interest (i.e. from 1 August 2012 to 30 September 2014), then those records that are both relevant and unlikely to be duplicated are included. The decision on which records to include was made by the GP Adjudication Panel after reviewing the most common unique terms (10% of the terms, which covered 88% of the data). The most common 10 terms and the decision of whether or not to include them is shown in *Table 25* for information; rules based on this review were used to decide whether or not to include the 12% of data not reviewed, for example 'if it contains seen it is relevant and unlikely to be duplicated'.

Summary of coding using clinical data

The records included are used to determine scheduled or unscheduled contacts based on 'medcode description'; the clinical data references Pegasus medical data using the field 'medcode' to get 'medcode description'. If contact types cannot be determined by 'medcode description', then clinical consultation type 'constype' (consultation type) is referenced.

Following GP Adjudication Panel review of the medcode descriptions, in which over 90% of the data were reviewed (17% of the unique terms), clinical records to be marked as scheduled, unscheduled, not

TABLE 25 Inclusion of 'unmatched/historical' data

Medcode_desc	Records	Flag
Seen in paediatric clinic	5214	Relevant and unlikely to be duplicated
Seen in hospital casualty	4863	Relevant and unlikely to be duplicated
Letter received	2901	Irrelevant
Letter encounter	2654	Irrelevant
Administration	2167	Irrelevant
Seen in orthopaedic clinic	1699	Relevant and unlikely to be duplicated
Letter from consultant	1587	Likely to be duplicated
Letter from specialist	1488	Likely to be duplicated
Discharge summary	1479	Likely to be duplicated
Asthma	1398	Likely to be duplicated

applicable or unknown were identified based on terms (see *Boxes 1–4* and *Tables 26* and *27* for examples; full details are available on request). Based on this review, rules to apply to the data were also determined (see *Table 26*). Finally, decisions on how to code the remaining records based on the clinical consultation type were made (see *Table 27*).

Conflicting clinical contact types

Clinical data contain more than one record per consultation. In some cases, the same consultation ID can have more than one clinical contact type. For these clinical records, we assume that unscheduled takes precedence (i.e. they are likely to have come in for an unscheduled visit but had a scheduled 'type' of procedure at the same time) over all other contact types; that scheduled takes precedence over not applicable and unknown; and that unknown takes precedence over not applicable.

Clinical to consultation

The code assigned in accordance with clinical contact type as described above is linked to the consultation data.

Consultation data marked as 'unknown' based on the clinical data as well as consultation data that did not link to clinical data are coded based on immunisation, therapy, referral, test and consultation data as described in the following sections.

BOX 1 Clinical records: scheduled

Medcode_desc

Administration of medication under patient group direction.

Administration of medication under patient-specific direction.

Antimalarial drug prophylaxis.

Asthma annual review.

Asthma causes daytime symptoms once or twice per month.

Asthma causes daytime symptoms once or twice per week.

Asthma causes daytime symptoms most days.

Asthma causes night-time symptoms once or twice per month.

Asthma causes symptoms most nights.

Asthma causes night waking.

Asthma control questionnaire.

BOX 2 Clinical records: unscheduled

Medcode_desc

Abdomen examined – NAD.

Abdominal examination – NAD.

Breast examination.

CVS examination.

CVS examined – NAD.

Ear examination – normal.

Emergency appointment.

Examination of cardiovascular system.

Examination of digestive system.

Examination of abdomen.

BOX 3 Clinical records: not applicable

Medcode_desc

[V]Healthy person accompanying sick person.

Advice to GP to change patient medication.

Did not attend – no reason.

Discharged from hospital.

Discharged from accident and emergency.

Discharged from inpatient care.

Drug not collected – no reason.

Employment milestones.

Failed encounter.

Failed encounter – message left on answer machine.

BOX 4 Clinical records: unknown

Medcode_desc

[V]Issue of repeat prescription.

Advice.

Asthma.

Asthma medication review.

Asthma monitoring due.

Asthma NOS.

Bronchial asthma.

Change in asthma management plan.

Clinical management plan agreed.

Family history.

TABLE 26 Medcode description rules coding

Medcode description	Rule
Letter rule	If contains 'letter' then scheduled, unless it contains 'referral'; in that case not applicable
Pain/inflamed/sore rule	If contains 'pain', 'inflamed' or 'sore', then unscheduled
Asthma trigger rule	If contains 'asthma trigger' then scheduled, unless it contains 'infection'; then unscheduled
Immunisation/ vaccination rule	If does not contain 'letter' and contains 'immunisation', 'immunisats', 'imm', 'vacc' or 'vaccination', then scheduled, unless it contains 'flu', 'Influenza', 'advice', 'not consent', 'declined' or 'requires'; in that case 'unknown'
Exam/examination rule	If contains 'exam' or 'examination', then unscheduled, unless it contains 'chest', 'respiratory', 'lung', 'breath', 'foot' or 'eye'; then scheduled
Asthma management plan rule	If contains 'asthma management plan' then scheduled, unless it also contains 'change' or 'step up'; in that case unknown
Referral rule	If contains 'referral' then not applicable, unless it contains 'a and e', 'accident and emergency' or 'admission'; in that case unscheduled
Blank rule	If blank, then unscheduled
DNA rule	If contains 'did not attend' or 'DNA', then not applicable
Failed encounter rule	If contains 'failed encounter', then not applicable
Lloyd George rule	If contains 'Lloyd George', then not applicable
Seen rule	If contains 'seen', scheduled, unless it contains 'accident', 'emergency', 'out of hours', 'GP', 'A&E', 'rota', 'primary care centre', 'patient call', 'triage', 'co-op', 'coop', 'co op', 'walk in', 'ooh', 'injury', 'on call', 'home visit', 'urgent', 'surgery', 'doctor', in which case unscheduled
Out-of-hours rule	If contains 'out of hours', then unscheduled
Emergency rule	If contains 'emergency', then unscheduled
Discharge report	If contains 'discharge report', then unscheduled

DNA, did not attend.

TABLE 27 Clinical consultation type coding

Clinical consultation type	Code as
Administration	Not applicable
Symptom	Unscheduled
Diagnosis	Unscheduled
Intervention	Unscheduled
Management	Unscheduled
Presenting complaint	Unscheduled
Examination	Unknown

Immunisation data

Uncoded consultation data are matched against immunisation data; if at least one match is found in the immunisation record, then these are marked as 'scheduled'.

Therapy

Those that do not match with immunisation data are linked to medication data. If at least one match is found, they are marked as 'unscheduled'.

Referral

Those that do not match with immunisation or therapy data are linked to referral data. If at least one match is found, they are marked as 'unscheduled'.

Test

Those that are still uncoded are linked to test. If linked to test it is coded as either 'scheduled', 'unknown' or 'unscheduled' based on a review of the data. In general, if the test is part of the routine asthma review, then it is coded as 'scheduled'; if it is testing peak expiratory flow rate then it is coded as 'unknown'. Otherwise, it is coded as 'unscheduled' (full details are available on request).

When a consultation links to more than one record, the same rules of precedence apply as outlined in the *Conflicting clinical contact types* section.

Consultation data

For consultation data that are still 'unknown', 'unlinked' and, therefore, uncoded, consultation type is used to determine whether it is scheduled, unscheduled or not applicable (see *Table 28* for a summary; full details are available on request). In this way, all contacts will now be coded as either 'scheduled', 'unscheduled' or 'not applicable'.

TABLE 28 Consultation type coding

Consultation type	Coded as
Follow-up/routine visit	Scheduled
Repeat issue	
Community clinic	
Medicine management	
If the consultation is about out-of-hours visits, telephone calls, acute visits, inpatient/hospital admission, accident and emergency attendance, triage, home/hotel visit, walk-in centre, co-op surgery or injury	Unscheduled
Clinic	Unscheduled (it is assumed that most scheduled consultation types will be clearly recorded)
Surgery consultation	
Other	
If the consultation type is 'Data not entered', or if it is about correspondence, reports, administration, nursing/residential home visits, test results or non-consultation data	Not applicable

Emergency contacts

In addition to coding as scheduled, unscheduled and not applicable, some consultation types from the consultation table were coded as emergency (*Table 29*).

TABLE 29 Emergency contact codes

Code	Consultation type	Relevant medical contact?	Unscheduled/scheduled	Emergency
2	Night visit, deputising service	Yes	Unscheduled	Yes
4	Night visit, local rota	Yes	Unscheduled	Yes
6	Night visit, practice	Yes	Unscheduled	Yes
7	Out of hours, practice	Yes	Unscheduled	Yes
8	Out of hours, non-practice	Yes	Unscheduled	Yes
11	Acute visit	Yes	Unscheduled	Yes
18	Emergency consultation	Yes	Unscheduled	Yes
20	Casualty attendance	Yes	Unscheduled	Yes
23	Hospital admission	Yes	Unscheduled	Yes
24	Children's home visit	Yes	Unscheduled	Yes
27	Home visit	Yes	Unscheduled	Yes
28	Hotel visit	Yes	Unscheduled	Yes
32	Twilight visit	Yes	Unscheduled	Yes
34	Walk-in centre	Yes	Unscheduled	Yes
37	Co-op home visit	Yes	Unscheduled	Yes
50	Night visit	Yes	Unscheduled	Yes

Appendix 4 Statistical analysis plan

Project Title: The PLEASANT Study

(Preventing and Lessening Exacerbations of Asthma in School-age children Associated with a New Term)

A cluster randomised controlled trial investigating the effect of a postal intervention in reducing unscheduled medical contacts in school age children following returning to school.

Statistical Analysis Plan

Version 1.1.0

Authored by

_____   ___/___/_____

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List of abbreviations used

AE	Adverse Event
AFT	Accelerated Failure Time
CI	Confidence Interval
CPRD	Clinical Practice Research Datalink
CTRU	Clinical Trials Research Unit
GP	General Practitioner
HTA	Health Technology Assessment
ICC	Intra-Class Correlation
ITT	Intent-To-Treat
MPR	Medicine Possessions Ratio
NHS	National Health Service
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
UoS	University of Sheffield

1.1.1 Introduction, study design and key trial objectives

1.1.1.1 Study outline

The PLEASANT study is a parallel group, cluster randomised controlled trial that will compare a postal intervention to standard care in children aged 4-16 with previous diagnoses of asthma; 70 General Practices (GPs) will be randomised to each arm, and patients from these GPs will receive the appropriate intervention.

This statistical analysis plan is written in conjunction with the International Conference on Harmonisation topic E9 (Statistical principles for clinical trials), applicable standard operating procedures from the Sheffield Clinical Trials Research Unit (CTRU) and trial documents referenced in section 4.

This trial is funded by the National Health Service (NHS) Health Technology Assessment (HTA).

1.1.2 Outcome measures

1.1.2.1 Primary outcome measure

- The proportion of patients aged between 5-16 who have an unscheduled medical contact in September

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1.1.2.2 Secondary outcome measures

- The proportion of patients who have an unscheduled medical contact in the period September – December

- The total number of medical contacts (scheduled and unscheduled) per patient in September and in the period September – December

- The time to first unscheduled medical contact in September and in the period September – December

- The proportion of patients who have a medical contact (either scheduled or unscheduled) in September and in the period September – December

- The total number of medical contacts (scheduled and unscheduled) per patient in September and in the period September – December

- The time to first medical contact in September and in the period September – December

- The proportion of patients who have an unscheduled medical contact in September and in the period September – December associated with a respiratory diagnosis

- The number of unscheduled medical contacts per patient in September and in the period September – December associated with a respiratory diagnosis

- The time to first unscheduled medical contact associated with a respiratory diagnosis in September and in the period September – December

- The number of prescriptions per patient in the month of August

- The number of prescriptions in the 12 months following the intervention

- The proportion of patients who have a scheduled medical contact (for example asthma review) in August

- The proportion of patients who have a scheduled medical contact (for example Asthma review) in the 12 months following the intervention.

All above analyses will be undertaken and reported twice: once on patients under the age of 5 and once on patients aged between 5 and 16. This is because asthma is difficult to diagnose in children below this age[1-2].

1.1.2.3 Sample size

From previous research in the CPRD practice population 30% of school age asthmatic children had at least one unscheduled medical contact within the month of September13. We postulate that the intervention may reduce the number of children who have unscheduled medical contacts from 30% to 25% (i.e. an absolute reduction of 5%). We would have an effect size of 5%. The average practice size in the CPRD is 8,294. We thus anticipate circa 100 school age asthmatic patients per practice (based on 12% of a practice being school age children and 11% of school age children having asthma). Hence, to detect a difference of 5% with 90% power and two sided significance level of 5%, with an intra-class correlation (ICC) of 0.03 to account for clustering we require 70 practices per arm. The sample size of 140 practices would equate to approximately 14,000 school age asthmatic patients.

Ukoumunne et al[3] give estimates of ICCs for patients with respiratory symptoms in General Practice. Based on the work of Ukoumunne et al an ICC of 0.03 is a conservative estimate. The power of the study for ICCs of 0.01, 0.02, 0.03, 0.04 and 0.05 is respectively 99.4, 96.0, 90.0, 83.1 and 76.2%

As a further sensitivity analysis we investigated the effect of practices not sending out the letter as planned. Suppose 10 practices failed to send out the letter, these would still be included in the primary analysis under the intent to treat principle. However, the effect that could be observed would be reduced to 4.3%. Under the sample assumptions (ICC=0.03 etc) the power for the same sample size is reduced to 79.3%. This is a little under 80% but it does demonstrate that the study is reasonably robust to at least one deviation in the planned design.

1.1.2.4 Randomisation

The study is a cluster randomised trial; 70 general practices (GPs) undertaking the intervention and 70 control practices of "usual care". The randomisation will be stratified by size of GP to ensure that there is an equal sample size – in terms of number of school age asthmatic children – in each arm of the trial. Practices will be randomised to one of the two arms after they have agreed to participate. The randomisation will be carried out by the University of Sheffield (UoS) Clinical Trials Research Unit (CTRU) using a randomisation plan developed prior to the beginning of the trial.

1.1.2.5 Interim analyses and study committees

Two committees will be established to govern the conduct of the study:

1. Trial Management Group (TMG)
2. Trial Steering Committee (TSC)

All committees are governed by Sheffield CTRU standard operating procedures. The TMG consists of the Principal Investigator, co-investigators and key staff within the CTRU. The role of the TMG is to implement all parts of the trial.

The TSC consists of the Principal Investigator, key staff within the CTRU (as non-voting members), an independent chair and two independent members (including a statistician) and 2 lay members. The roles of the TSC are to provide supervision of the protocol and statistical analysis plan, provide advice on and monitor progress of the trial.

No formal interim analyses are required in the study.

1.1.3 Data sources, data evaluability and analysis populations

1.1.3.1 Data sources

The data for this study will be collected and managed by the Clinical Practice Research Datalink (CPRD), a computerised database of anonymised longitudinal medical records from primary care. The CPRD are able to capture all medical contacts along with the reason for the contact.

The PLEASANT study team at CTRU will request and collect the appropriate data from CPRD at three time points:

1. Baseline
2. 1 month post intervention
3. 12 months post intervention

The data requested from CPRD will include, for each patient:

- Age
- Gender
- Anonymised General Practice identifier
- The date of each appointment
- The type of medical contact for each appointment

- The diagnosis given for each appointment
- Any prescriptions given as a result of an appointment.

1.1.4 Data evaluability

Upon receiving the data from CPRD, CTRU will handle and prepare the data for statistical analysis. This includes forwarding data pertaining to the nature of each appointment to an adjudication panel for their review, who will in turn define appointments as being either scheduled or unscheduled. The CTRU will also merge treatment allocation data with CPRD data and calculate the number of appointments for each patient.

Detailed data management and data quality issues will be set out in a data management plan. Data will be retained in accordance with the Data Protection Act 1998 and CTRU data management Standard Operating Procedures (SOPs).

All source documents and data will be retained for a period of at least 5 years following the end of the trial.

1.1.5 Analysis populations

The analysis populations will be as follows:

Intent To Treat (ITT)	All randomised patients identified through the extraction identified by the CPRD.
Per protocol (PP)	The subset of the ITT who belong to a practice which complies to the protocol, meet the inclusion/exclusion criteria and whom the GPs did not exclude from receiving the intervention.

All analyses will be performed on both study populations.

There are three study periods to be analysed. The primary analysis will be undertaken on the primary study period; secondary analyses will use all three stages.

Primary study period	1st September 2013 – 30th September 2013
Extended study period	1st September 2013 – 31st December 2013
Follow-up period	1st September 2013 – 31st August 2014

1.1.6　Outline of analyses

1.1.6.1　General considerations

Summaries of continuous variables will comprise the sample size used and either:

i.　mean, standard deviation, minimum and maximum, or

ii.　median, inter-quartile range, minimum and maximum

as appropriate for the distributional form of the data. Summaries of categorical variables will comprise the sample size used, and the number and percentage of observations in each category.

1.1.6.2　Levels of statistical significance and adjustment for multiplicity

The PLEASANT study was designed and planned using a 2-sided significance level of 5%. All analyses will be undertaken using this level of significance. As there is only one primary outcome and no interim analysis, adjustment for multiplicity is unnecessary. However adjustments will be made for the multitude of secondary outcomes. Conservative Bonferroni corrections will be made to the raw P-values and where possible k-fold cross-validation will be performed by using a leave-one-out approach.

1.1.6.3　Rules for derived variables

The number of appointments for each patient will be calculated after the panel has determined whether appointments were scheduled or unscheduled. The numbers of each will then be summed (for both the primary and extended study periods). There are instances where no medical code has been used to record the type of medical contact and instead free-form text has been entered. Such entries will always be unscheduled (because scheduled contacts are recorded so that GPs are remunerated) but it is impossible to determine the nature of the contact and therefore whether it is respiratory related or not. The number of each contact type, in terms of "relevant"/"irrelevant", "scheduled"/"unscheduled"/"unknown" and "respiratory related"/"not respiratory related"/"indeterminable" will be reported.

The proportion of patients with unscheduled medical contacts in September 2013 will be analysed using a derived variable. Any patients who have had one or more unscheduled medical contacts in this period will be coded as '1', while those who have had zero unscheduled medical contacts in this period will be coded as '0'. This binary variable will then be used as the dependent variable in the analysis. This will be done for all outcomes involving a proportion of patients.

1.1.7 Disposition

The following summary will be presented for all practices and patients:

- Centre disposition: the number and percentage of practices included in each analysis population with reason for exclusion

- Patient disposition: the number and percentage of patients included in each analysis population with reason for exclusion

The following summary will be presented for the ITT:

- Data completeness: the number of patients with complete data for key parameters by treatment group

- Data completeness by practice: the number of patients with complete data for key parameters by practice.

1.1.8 Demographics and baseline characteristics

The following summaries will be presented:

- Demographics: age; gender; practice; number of asthma admissions in September 2012, the period 1st September – 31st December 2012 and the period 1st September 2012 – 31st August 2013 (scheduled, unscheduled and both combined); time to first medical contact in September and the period 1st September – 31st December 2012 (scheduled, unscheduled and both combined).

1.1.9   Efficacy

1.1.9.1 Primary outcome

The primary outcome will be analysed by intent to treat among patients aged 5-16 as of 1ˢᵗ September 2012. The primary endpoint (the proportion of patients who have an unscheduled medical contact in September) will be analysed by logistic regression in which the fixed covariates will include the individual's age, gender, number of contacts the previous September, and trial arm; GP will be included as a random effect to account for the effect of clustering by practice.

The following outputs will be presented for the ITT and PP:

- The number of unscheduled medical contacts in September 2013

- The proportion of patients having unscheduled medical contacts in September 2013

- The results of the logistic regression modelling for the primary outcome, summarising the effect of all covariates fitted in the model.

1.1.10 Secondary outcomes

1.1.10.1 Proportion of patients with medical contacts

For analysis of secondary outcomes involving proportions of patients in both the extended period of September-December 2013, September2-13-August 2014 and September 2014 , the same approach will be used as for the primary outcome. Similar covariates will be included in the analysis, ensuring that the baseline variable matches the outcome variable. For example, when analysing the proportion of patients who have an unscheduled medical contact in the period September – December 2013 associated with a respiratory diagnosis, the baseline covariate will be the number of contacts in the previous September – December 2012 associated with a respiratory diagnosis.

1.1.10.2 Number of patients with medical contacts

For outcomes involving numbers of medical appointments or prescriptions the intervention will be analysed in an analogous approach to those involving proportions. A random effects negative binomial model will be fitted, including the same covariates as above.

1.1.10.3 Time to first medical contact

Analyses involving the time to first medical contact will all be analysed using a random effects ("shared frailty") regression model including the same covariates as described previously. Due to the expected high prevalence of ties (i.e. the same time to first contact) the Efron method for handling ties will be used.

1.1.11 Number of Prescriptions

The number of prescriptions per patient in August 2013 and in the 12 months following the intervention will also be summarised and analysed under a negative binomial random effects regression model.

1.1.11.1 Scheduled contacts

The proportion of patients who have a scheduled medical contact (e.g. asthma review) in August 2013 and in the 12 months following the intervention will be analysed using a logistic random effects regression model.

1.1.12 Testing assumptions of statistical analyses

The primary outcome will be analysed using a random effects logistic regression model. This modelling technique is very robust and makes very few assumptions. The same applies for the secondary analyses involving proportional dependent variables. The Hosmer-Lemeshow test will be used to test the goodness of fit for these models.

The secondary analyses involving number of events will be analysed using random effects negative binomial regression. Similarly to above, this method is very flexible and does not rely on assumptions.

Analyses involving time-to-event data will be analysed using random effects "shared frailty" Cox regression. The key assumption underlying this analysis method is that the hazard in one group (or one level for a continuous covariate) is a constant multiple of that in another group (level). This will be tested by fitting an interaction term between time and treatment arm: if the hazard ratio is constant, this term will be non-significant. If the hazard ratio is found to be non-constant over time the outcome will instead be analysed using Accelerated Failure Time (AFT), with goodness of fit assessed by Q-Q plots[4]. If the assumptions underlying this method are not met, residual mean survival methods will be used[5].

1.1.13 Compliance

Compliance will be based on whether or not practices comply with the intervention i.e. whether they send out the letter. To check for differences between complying and non-complying practices the demographics for each population will be. Tables displaying outcome data will also be reported split by compliance.

1.1.14 Economic analyses

Economic analyses will be included in a separate document.

1.1.15 Analysis of non-adherence

In order to identify patients who are non-adherent to regular asthma treatments the medicine possessions ratio (MPR) for each participant will be calculated as the following:

$$MPR = 100 \times \frac{\text{Number of days of medicine prescribed in last 12 months}}{365}$$

This will be calculated at baseline (the year prior to the intervention) and at follow-up (the year following the intervention). Patients with an MPR of under 80% will be classed as 'non-adherent' to medicine.

The MPR will be calculated for preventative medications only, using prescription information. The analysis will be undertaken only on patients who have a single medication which remains the same over both baseline and follow-up; patients prescribed more than one preventative medication or who switch medications between periods will be excluded from this analysis.

Informal analysis will take place to ensure that the MPRs are independent across treatment arms at baseline and also independent across time points in the control group. This will comprise histograms of the MPR and summary statistics.

The main analysis of MPR will test whether the intervention changes MPR. This will be done in two ways:

1. A test for change in proportion of patients classed as non-adherent before and after the intervention in control and intervention arms.

2. Testing the difference in change in MPR before and after the intervention between the control and intervention arms.

A separate subgroup analysis will investigate whether patients who are classed as non-adherent at baseline respond differently to the intervention to those who are classed as adherent.

1. Paired t-test, intervention group only, comparing difference between baseline and follow-up for adherent vs non-adherent.

1.1.16 References

1.1.16.1 Trial Documents

Trial Protocol (version 1.6, 25/09/2012)

1.1.16.2 Other References

1. British Thoracic Society / Scottish Intercollegiate Guideline Network. British Guideline on the Management of Asthma: A national clinical guideline. Jan 2012.

2. Bush A. Diagnosis of asthma in children under five. Primary Care Respiratory Journal. 2007;16(1):7-15

3. Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC and Burney PJG. Methods for evaluating area-wide and organisation-based interventions in health and health care: a systematic review. Health Technology Assessment 1999; Vol. 3: No. 5.

4. Bradburn MJ, Clark TG, Love SB and DG Altman DG. Survival Analysis Part III: Multivariate data analysis – choosing a model and assessing its adequacy and fit. British Journal of Cancer (2003) 89, 605–611.

5. Royston P and Parmar MKB. The use of restricted mean survival time to analyse randomized clinical trials data when the proportional hazards assumption is in doubt. Statistics in Medicine 2011; 30: 2409-2421.

Appendix 5 Systematic review of health-related quality of life data to inform health economic analysis

This review aimed to identify preference-based utility values for asthma day-to-day symptoms (baseline utility) and asthma exacerbation.

Scoping

A scoping search was conducted to establish the likely quantity and relevance of published literature. This was done by searching MEDLINE and The Cochrane Library (Cochrane Database of Systematic Review, HTA database and NHS Economic Evaluation Database) using a limited number of population terms in addition to a search filter for quality of life. It was found that there was a lack of utility data derived from EQ-5D in children with asthma. Although EQ-5D is the preferred outcome measure, the standard version of EQ-5D is not designed to be used with children. EQ-5D-Youth is available for children and adolescents, but there is not yet a validated UK tariff. In view of this, the NICE reference case states to use other validated preference-based measures developed for children, but does not specify the preferred quality-of-life instrument.[35] Therefore, a broad approach was taken in the search to identify utility values derived from EQ-5D, as well as other preference-based measures. EQ-5D values estimated from mapping studies were also considered.

Search strategy

Search terms

Both free text and medical subject headings (MeSH) pertaining to children, asthma and asthma exacerbation were used in the search (see *Appendix 6*). The InterTASC Information Specialists' Sub-Group (ISSG) search filter was used to filter studies that report HRQoL (see *Appendix 7*). The filter was adapted to include a newly developed preference-based measure for children, Child Health Utility Index 9D,[44] as well as other preference-based measures in asthmatic children, such as Asthma Symptom Utility Index. Full search terms for this review are presented *Appendices 6* and *7*.

Search limit

The search was not limited by language, publication type, publication dates or study design, with the aim of increasing sensitivity.

Sources searched

The following clinical and economic databases were searched:

- MEDLINE (via Ovid) (In-Process & Other Non-Indexed Citations) (1946 to 5 July 2014)
- The Cochrane Library (includes Cochrane Database of Systematic Review, NHS Economic Evaluation Database and HTA database) (up to 5 July 2014)
- EMBASE (1974 to 5 July 2014)
- EconLit (1886 to 5 July 2014)
- School of Health and Related Research (ScHARR) Health Utilities Database (up to 5 July 2014).

In addition to the electronic database search, reference lists of the retrieved papers were screened for relevant papers.

Inclusion and exclusion criteria

The inclusion and exclusion criteria for the review are summarised in *Table 30*. Systematic reviews and protocols were not included, but were used to identify relevant papers. Modelling studies were examined to determine the source of utility values used. Modelling studies that described utility data not reported elsewhere were included in the review.

Selection of studies

In the first stage of study selection, titles and abstracts of the searched results were screened against the inclusion/exclusion criteria. Full articles were assessed if titles and abstracts were unclear. All studies identified at titles and abstracts were further screened at full text. The studies were screened by a single reviewer.

Quality assessment

Quality assessment of articles in this review followed the criteria (sample size, number loss at follow-up and handling of missing data) recommended by Papaioannou *et al.*[45] in the Decision Support Unit Technical Support Document on the identification, review and synthesis of health state utility values from the literature.

Data extraction

Data extracted comprised characteristics of study population, study design and details of outcome measurements (descriptive system, tariff used, method of valuation, time of measurement, mean utility data and other relevant measures).

TABLE 30 Review inclusion and exclusion criteria

Criteria	Inclusion	Exclusion
Population	• Children with asthma • Population with mixed age groups but including some children	• Asthmatic patients aged ≥ 18 years • Non-asthma patients
Intervention		• Studies presenting utility data as utility changes associated with a particular intervention
Outcomes	• Utility values from preference-based measures	• Non-preference-based utility scores unless mapping to EQ-5D was performed • Studies that did not publish utility data
Publication type		• Qualitative study • Letters • Editorials • Case reports/case series • Systematic review • Protocols
Language/others	• English-language published papers	• Non-English-language published papers

Selection of utility data for use in the economic analysis

Selection of utility data to use in the economic analysis was based on (1) quality of the study; (2) the relevance of utility data to the population and health states in the PLEASANT study; and (3) the extent to which the measurement method was in accordance with the NICE reference case.

Results of systematic review of health-related quality-of-life data

A total of 927 studies were retrieved from the database search and reference tracking. After removal of duplicates, 683 studies were screened at titles and abstract. A total of 659 studies were excluded at this stage (see *Appendix 8*). Subsequently, 24 papers were screened at full text and 10 papers were excluded, with reasons given in *Appendix 9*. Finally, 14 papers were included in this review. *Figure 27* shows the search process of this review.

Study characteristics for the included studies are summarised in *Table 31*. The study populations are summarised in *Table 32* and methods used to measure HRQoL are summarised in *Table 33*. Details regarding study quality are provided in *Table 34*. Details regarding the suitability of the studies for use in the economic model, based on the criteria described above, are provided in *Table 35*.
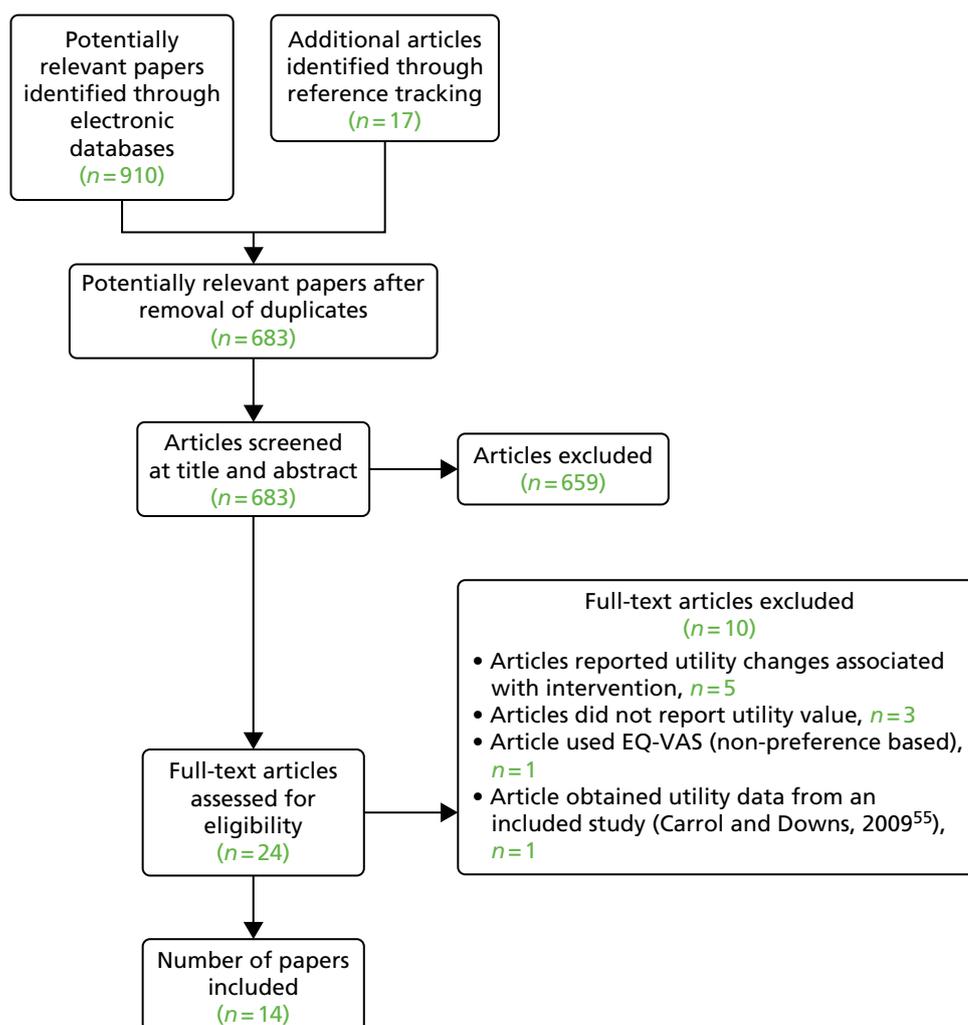

FIGURE 27 Flow diagram of search process. EQ-VAS, EuroQol Visual Analogue Scale.

TABLE 31 Characteristics of included studies

Number	First author, year	Country	Study design	Total participants	Duration	Intervention	Control	Primary outcome
1	Willems et al., 2007[36]	The Netherlands	Economic evaluation alongside a RCT	109 (56 aged under 18 years)	1 year	Nurse-led telemonitoring	Usual care	Cost per QALY
2	Powell et al., 2013[46]	UK	Multicentre, double-blind RCT	508 children	1 month	Nebulised magnesium sulphate	Usual care	Asthma severity score 1 hour after treatment
3	Price et al., 2011[47]	UK	Single-blind RCT, pragmatic	687 (mixed age group, 12–80 years)	2 years	Leukotriene receptor antagonist (step 2), as above plus ICS (step 3)	ICS (step 2), ICS + LABA (step 3)	Changes in Mini-AQLQ
4	Brusselle et al., 2009[48]	Belgium	Cohort	158 (mixed age group)	1 year	Omalizumab	N/A (single-arm study)	Clinical effectiveness (asthma symptoms, lung function, HRQoL) and safety of omalizumab
5	Chiou et al., 2005[49]	USA	Outcome measure was used in the baseline assessment of a RCT	Utility measurement was performed on a sample of 72 children from the RCT	Baseline utility measurement	Environmental intervention	Placebo	HRQoL
6	Mittmann et al., 1999[50]	Canada	Cross-sectional survey	17,626 household residents of which 229 had asthma	Cross-sectional	None	None	HRQoL
7	Juniper et al., 1997[51]	Canada	Cohort	52 children	9 weeks	None	None	Validity of outcome measures in children
8	Norman et al., 2013[52]	UK	Decision model, EQ-5D data from the EXALT study used for day-to-day symptoms. Literature-based estimate used for exacerbation	EXALT: 404 (mixed age group)	EXALT: 36 weeks	Omalizumab and usual care	Usual care	Cost per QALY

Number	First author, year	Country	Study design	Total participants	Duration	Intervention	Control	Primary outcome
9	Briggs et al., 2006[38]	Multinational	Economic evaluation of GOAL (multinational, double-blind RCT), CSM data from the GOAL study were mapped onto EQ-5D	GOAL: 3416 (mixed age group)	GOAL: 1 year, model as weekly event	Salmeterol/fluticasone	Fluticasone	Cost per QALY
10	Doull et al., 2007[53]	Multinational	Decision model, CSM data from GOAL (multinational, double-blind, RCT) were mapped onto EQ-5D	GOAL: 3416 (mixed age group)	GOAL: 1 year, model as weekly event	Salmeterol/fluticasone	Fluticasone	Cost per QALY
11	Rodríguez-Martínez et al., 2013[54]	Spain	Decision model (Markov), utility values were derived from a utility valuation survey	76 parents were involved in the survey	Utility measured at one time point	Budesonide, fluticasone, ciclesonide	Beclomethasone dipropionate	Cost per QALY
12	Carroll and Downs, 2009[55]	USA	Cross-sectional	4016 parents, each valued 3 of 29 health states (≈415 valuations per health state)	Duration of recruitment: 2 years. HRQoL measurement was performed at a time point	None	None	Utility values
13	Brown et al., 2007[56]	Multinational	Decision model (Markov), CSM data from the ETOPA study (open-label trial) were mapped onto EQ-5D	ETOPA: 312 (mixed age group)	1 year	Omalizumab and BSC	BSC	Cost per QALY
14	Gerald et al., 2010[57]	USA	Decision model (decision tree and Markov)	Utility data based on study by Chiou et al.[49]	Time horizon: 1 year, cycle length: 1 day	Four school-based asthma screening strategies	Status quo	Cost per QALY

AQLQ, Asthma Quality of Life Questionnaire; BSC, best supportive care; CSM, condition-specific measure; EXALT, Evaluate Xolair for Asthma as Leading Treatment; GOAL, Gaining Optimal Asthma ControL; LABA, long-acting β₂-agonist; N/A, not applicable; RCT, randomised controlled trial.

TABLE 32 Population of included studies

First author, year	Disease type	Severity/stage	Age (years)	Male sex	Ethnicity
Willems et al., 2007[36]	Mild to moderate asthma managed in outpatient care	GINA stages I–III, mean FEV_1% predicted for children: 96.5 (SD 8.4) for intervention and 99.4 (SD 11.3) for control	7–18 strata. Intervention, mean 10.57 (SD 2.1); control, mean 10.85 (SD 2.3)	Intervention, 72.4%; control, 55.6%	Not reported
Powell et al., 2013[46]	Acute asthma	Severe acute asthma (BTS/SIGN definition)	Median 4.0 (IQR 3.0–7.0), range 2–16	58%	Not reported
Price et al., 2011[47]	Poorly controlled asthma at BTS/SIGN step 2 or 3	ACQ ≥ 1 or Mini-AQLQ ≤ 6	Step 2, mean 44.74 (SD 16.49); step 3, mean 50.02 (SD 15.93); range 12–80	Step 2, 162 (49.7%); step 3, 136 (37.7%)	98% Caucasian
Brusselle et al., 2009[48]	Poorly controlled severe persistent allergic asthma on ICS/LABA (GINA definition)	Mean FEV_1% <80% predicted, day and night symptoms, ≥ two exacerbations (requiring systematic steroid, emergency department or hospitalisations) in past 2 years	Mean 48.17 (SD 17.18), range 12–83	73 (46.2%)	94.9% Caucasian
Chiou et al., 2005[49]	Diagnosed asthma	Mild to severe	Age group: 7–8, 37.5%; 9–10, 34.7%, 11–12, 27.8%	Not reported	White (15.3%), Asian (40.3%) and African American (29.2%)
Mittmann et al., 1999[50]	Asthma generally	Not reported	Not reported. 10.5% (n = 1847) of total respondents were under 19 years	8058 (45.7%), but data were not stratified to age	Caucasian
Juniper et al., 1997[51]	Symptomatic asthma	Mean FEV_1% predicted: 85 ± 16.6. No previous exacerbation in past 2 weeks	Mean 12 (SD 3.1), range 7–17	30 (57.7%)	Majority Caucasian
Norman et al., 2013[52]	Poorly controlled severe persistent allergic asthma on high-dose ICS and LABA with > one severe exacerbation in previous year and FEV_1 <80% predicted	BTS/SIGN ≥ step 4 EXALT: FEV_1 40–80% predicted: > one severe exacerbation within previous year	EXALT: mean across both arms 44.7, range 12–75 (only five patients under 18 years)	EXALT: 141 (35.2%)	Not reported
Briggs et al., 2006[38]	Diagnosed asthma (≥ 6 months), no use of LABA or oral β_2-agonists in previous 2 weeks	Uncontrolled, mean FEV_1% predicted: ranged from 76 to 79	SFC: stratum 1, mean 36.1 (SD 15.6); stratum 2, mean 40.4 (SD 16.4), stratum 3; mean 44.1 (SD 15.9) FC: stratum 1, mean 36.4 (SD 15.6); stratum 2, mean 40.3 (SD 16.6); stratum 3, mean 42.7 (SD 15.7)	42%	Not reported

First author, year	Disease type	Severity/stage	Age (years)	Male sex	Ethnicity
Doull et al., 2007[53]	Diagnosed asthma (≥ 6 months), no use of LABA or oral β_2-agonists in previous 2 weeks	Uncontrolled, mean FEV_1% predicted: ranged from 76 to 79	SFC: stratum 1, mean 36.1 (SD 15.6); stratum 2, mean 40.4 (SD 16.4); stratum 3, mean 44.1 (SD 15.9) FC: stratum 1, mean 36.4 (SD 15.6); stratum 2, mean 40.3 (SD 16.6); stratum 3, mean 42.7 (SD 15.7)	42%	Not reported
Rodríguez-Martínez et al., 2013[54]	Persistent asthma	Mild to moderate	Not reported	Not reported	Caucasian
Carroll and Downs, 2009[55]	Persistent asthma	Mild to severe	Not reported	1982 (49%) (sex of parent's child)	African American (48%) and Caucasian (47%)
Brown et al., 2007[56]	Poorly controlled severe persistent allergic asthma despite high-dose ICS and LABA	Subgroup of severe patients from ETOPA included	For whole ETOPA trial: omalizumab, mean 37.5 (range 12–73); best supportive care, mean 39.3 (range 12–71)	For whole ETOPA trial: omalizumab and best supportive care, 58 (28.2%); best supportive care 34 (32.1%)	Caucasian
Gerald et al., 2010[57]	Asthma symptom-free day, symptom days, exacerbation recovery days, emergency department visits, and hospitalisation days	Intermittent, mild, moderate, severe	Utility data based on study by Chiou et al.[49]	Utility data based on study by Chiou et al.[49]	Utility data based on study by Chiou et al.[49]

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; BTS, British Thoracic Society; EXALT, Evaluate Xolair for Asthma as Leading Treatment; FC, fluticasone propionate; FEV_1, forced expiratory volume in the first second; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; IQR, interquartile ratio; LABA, long-acting β_2-agonist; SFC, salmeterol/fluticasone propionate; SIGN, Scottish Intercollegiate Guidelines Network.

TABLE 33 Outcome measurement and utility values in each study

First author, year	Descriptive system	Type	Descriptive measure filled by	Population in valuation	Valuation method	When HRQoL data were obtained	Utility estimates, mean (SD)	Other HRQoL measures
Willems et al., 2007[36]	EQ-5D (child version)	Generic	Carer (age < 12 years), ≥ 12 years by patient	Adult UK tariff	TTO	Baseline, 4 months, 8 months and 12 months	7–18 years strata at baseline: usual care, 0.96 (0.07); telemonitoring, 0.92 (0.20)	PAQLQ
Powell et al., 2013[46]	EQ-5D	Generic	Carer of children age between 5 and 16 years	Adult UK tariff	TTO	1 month post exacerbation	Exacerbation: 0.52 (based on mean ASS of 5.8 mapped to EQ-5D 22222); 1 month: magnesium group, 0.86 (0.04); standard care, 0.88 (0.04)	PedsQL™
Price et al., 2011[47]	EQ-5D	Generic	Patient	Adult UK tariff	TTO	2 months and 2 years	Step 2 at baseline: intervention, 0.795 (0.245); control 0.830 (0.195); Step 3 baseline: intervention, 0.780 (0.237); control 0.772 (0.234)	Mini AQLQ, asthma control questionnaire
Brusselle et al., 2009[48]	EQ-5D	Generic	Patient	Belgian tariff	VAS	Baseline, 52 weeks	At baseline: 0.54 (0.24)	AQLQ
Chiou et al., 2005[49]	PAHOM	Population-specific measure	Patient	Adults valuing for children	VAS, SG	Single time point	General asthma (VAS 0.7, converted SG 0.83)	None
Mittmann et al., 1999[50]	HUI-3	Generic	Participant was interviewed by telephone or in person	HUI-2 (Canada algorithm) 293 parents of school children	VAS, SG	Single time point	12–19 years: 0.90 (0.12)	None
Juniper et al., 1997[51]	HUI (interviewer version)	Generic	Children	HUI-2 (Canada algorithm) 293 parents of school children	VAS, SG	Baseline, week 5 and week 9	At baseline: 0.89 (SD 0.09) (range 0.67–1.00)	PAQLQ, feeling thermometer, direct valuation via SG
Norman et al., 2013[52]	EQ-5D	Generic	Patients	Not stated	Not stated	31 weeks	31 weeks: standard care, 0.719 (0.026); omalizumab, 0.767 (0.02)	AQLQ
Briggs et al., 2006[38]	Mapped EQ-5D from AQLQ	Mapping of CSM to EQ-5D	Patient	Valuation population not reported	Valuation method not reported	Baseline, 12, 24, 36 and 52 weeks	Totally controlled: 0.946 (SE 0.011); Well controlled: 0.900 (SE 0.011); Not well controlled: 0.842 (SE 0.011); Exacerbation: 0.729 (SE 0.013)	AQLQ

First author, year	Descriptive system	Type	Descriptive measure filled by	Population in valuation	Valuation method	When HRQoL data were obtained	Utility estimates, mean (SD)	Other HRQoL measures
Doull et al., 2007[53]	Mapped EQ-5D from AQLQ	Mapping of CSM to EQ-5D	Patient	Valuation population not reported	Valuation method not reported	Baseline, 12, 24, 36, and 52 weeks	Symptom free: 0.97 (0.014); With symptoms: 0.85 (0.015)	AQLQ
Rodríguez-Martínez et al., 2013[54]	Direct valuation using vignettes	Direct valuation	N/A	Parents	SG	Single time point	No symptoms, 0.989; symptom no exacerbation, 0.705; and asthma exacerbation (0.275)	None
Carroll and Downs, 2009[55]	Direct valuation using vignettes	Direct valuation	N/A	Parents	TTO, SG	Single time point	SG: mild intermittent, 0.91 (0.18); mild persistent, 0.90 (0.18); moderate persistent, 0.88 (0.18); severe persistent asthma, 0.83 (0.21); 10-day hospitalisation, 0.94 (0.14) TTO: mild intermittent, mild persistent, 0.91 (0.17); moderate persistent, 0.91 (0.15); severe persistent asthma, 0.85 (0.20); 10-day hospitalisation, 0.95 (0.15)	None
Brown et al., 2007[56]	Mapped EQ-5D from mini AQLQ	Mapping of CSM to EQ-5D	Patient	UK adult tariff for EQ-5D	TTO for EQ-5D	Baseline and 52 weeks	Daily symptoms, baseline: best supportive care, 0.62; omalizumab, 0.58; Daily symptoms, week 52: best supportive care, 0.65; omalizumab, 0.82	Mini AQLQ
Gerald et al., 2010[57]	PAHOM	Population-specific measure	N/A (utility data for modelled states were estimated by averaging utility values of PAHOM states)	PAHOM: adults valuing for children	VAS, SG	N/A	Asthma symptom-free day, 1.0 (range 0.98–1.0); symptomatic, 0.90 (range 0.84–0.96); recovery, 0.70 (range 0.64–0.76); emergency department, 0.43 (range 0.37–0.049); hospitalisation, 0.06 (range 0.01–0.11)	None

AQLQ, Asthma Quality of Life Questionnaire; ASS, asthma symptom score; CSM, condition-specific measure; EQ-5D, EuroQol-5 Dimension Questionnaire; EXALT, Evaluate Xolair for Asthma as Leading Treatment; HUI, Health Utilities Index; HUI-2, Health Utilities Index Mark 2; HUI-3, Health Utilities Index Mark 3; N/A, not applicable; PAHOM, Pediatric Asthma Health Outcome Measure; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; PedsQL, Pediatric Quality of Life Inventory; SG, subgroup analysis; TTO, time trade-off; VAS, visual analogue scale.

TABLE 34 Quality assessments of included papers

First author, year	Sample size	Number loss at follow-up	Methods of handling missing data
Willems et al., 2007[36]	109 (mixed age group)	7/109 (four children)	Data imputation by using mean for baseline score, interpolation between scores and last value carried forward
Powell et al., 2013[46]	508 children	Postal survey response rate: 45%. 228 completed PedsQL™. 89 patients aged over 5 years completed EQ-5D questionnaires (46 in magnesium arm and 43 in placebo)	Multiple imputation by chained equations was used to impute missing data. In under-fives the EQ-5D scores were estimated by mapping from the PedsQL™ scores. EQ-5D scores at time of exacerbation were mapped subjectively from ASSs
Price et al., 2011[47]	687 (mixed age group)	Step 2: 20/326 excluded post randomisation, 13/306 loss to follow-up, but 300/306 had some data post randomisation Step 3: 9/361 excluded post randomisation, 12/352 were lost to follow-up, but 350/352 had some data post randomisation	Complete data in 218/683 patients (32%), data available for ≥ 10 out of 13 items: 514/683 (75%). 19% missing visit 2 EQ-5D data. Complete-case analysis presented. In addition, imputed case presented using Rubin's multiple imputation
Brusselle et al., 2009[48]	158 (mixed age group)	Only 126 of 158 patients had baseline EQ-5D values and only 67 had EQ-5D data at 1 year	Not reported
Chiou et al., 2005[49]	72 children	Not applicable	Not reported
Mittmann et al., 1999[50]	17,626 household residents, of whom 229 had asthma	Not relevant as cross-sectional data	Not reported
Juniper et al., 1997[51]	52 children	None	Complete data sets provided for all patients
Norman et al., 2013[52]	EXALT: 404 (mixed age group)	EQ-5D scores available for 318 (79%) at 31 weeks	Not reported
Briggs et al., 2006[38]	GOAL: 3416 (mixed age group)	526 withdrawals, including 111 lost to follow-up. Reasons were adverse events, withdrawal of consent, protocol violation, ineligible for study, data that could not be analysed (n = 117)	Not reported
Doull et al., 2007[53]	GOAL: 3416 (mixed age group)	526 withdrawals, including 111 lost to follow-up. Reasons were adverse events, withdrawal of consent, protocol violation, ineligible for study, data that could not be analysed (n = 117)	Not reported
Rodríguez-Martínez et al., 2013[54]	76 parents	Not reported	Not reported
Carroll and Downs, 2009[55]	4016 parents, 29 diseases	Not reported	Not reported
Brown et al., 2007[56]	ETOPA: 312 (mixed age group)	Not reported	Imputation method for patient prematurely withdrawn. Event with zero duration was assigned if patient did not experience any event after 7 days of discontinuation
Gerald et al., 2010[57]	Utility data based on study by Chiou et al.[49]	Utility data based on study by Chiou et al.[49]	Utility data based on study by Chiou et al.[49]

ASS, asthma symptom score; EXALT, Evaluate Xolair for Asthma as Leading Treatment; GOAL, Gaining Optimal Asthma ControL; PedsQL™, Pediatric Quality of Life Inventory.

TABLE 35 Relevance of studies to the PLEASANT study analysis and the NICE reference case

First author, year	Relevance of population	Relevance of health states	Instrument	Measured from	Tariff	Valuation method	Applicability issues
Willems et al., 2007[36]	Stratified into adults and children	Baseline utility for mild to moderate asthma patients	EQ-5D	Carer or children (≥ 12 years)	Adult UK tariff	TTO	EQ-5D from non-UK population
Powell et al., 2013[46]	Young children	Utility of severe acute asthma and post exacerbation	EQ-5D for post exacerbation. For acute exacerbation, EQ-5D states were mapped to ASSs	Carer or children (≥ 5 years)	Adult UK tariff	TTO	EQ-5D are preferred, but subjective mapping was used to estimate EQ-5D from ASS during exacerbation
Price et al., 2011[47]	Mixed age (above 12 years, mean age of 44.7 years in step 2, 50 years in step 3	Baseline utility (uncontrolled asthma) by intervention arm, utility changes due to intervention	EQ-5D	Patient	Adult UK tariff	TTO	Utility decrement for exacerbations not reported
Brusselle et al., 2009[48]	Population is constrained to patients with severe asthma of long duration, older population (mean age 48 years), allergic and on maintenance steroids	Baseline utility of population with uncontrolled severe allergic asthma	EQ-5D	Patient	Belgian tariff	VAS	Utility decrement for exacerbations not reported. None UK. Tariff VAS not TTO
Chiou et al., 2005[49]	Children with diagnosed asthma of at least mild persistent severity	Utility of asthma generally, score stratified by severity	PAHOM	Children	Adult preference	VAS, SG (converted from VAS)	Utility decrement for exacerbations not reported
Mittmann et al., 1999[50]	Stratified by age 12–19 years	Utility of asthma generally	HUI-3	Patient	HUI-2 (Canadian algorithm)	VAS, SG	Utility decrement for exacerbations not reported
Juniper et al., 1997[51]	Children population, symptomatic asthma, with no exacerbation in past 2 weeks, FEV$_1$ > 80% predicted	Baseline utility in general asthma	HUI	Children	HUI-2 (Canadian algorithm)	VAS, SG	Utility decrement for exacerbations not reported
Norman et al., 2013[52]	Poorly controlled severe persistent allergic asthma	Utility of day to day symptoms (not exacerbation)	EQ-5D	Patients	Not stated	Not stated	Utility decrement for exacerbations not derived from this study (literature-based estimates used)

continued

TABLE 35 Relevance of studies to the PLEASANT study analysis and the NICE reference case (*continued*)

First author, year	Relevance of population	Relevance of health states	Instrument	Measured from	Tariff	Valuation method	Applicability issues
Briggs et al., 2006[38]	Mean age > 30 years, mean FEV₁ <80% predicted, utility adjusted in regression to UK population, population treated with inhaled fluticasone or salmeterol/fluticasone	Relevant health states: totally controlled, well controlled, not well controlled, without exacerbation and exacerbation	Mapped EQ-5D from AQLQ	Patient	Not reported	Not reported	Used an unpublished mapping algorithm and insufficient details reported to assess validity mapping method
Doull et al., 2007[53]	Mean age > 30, mean FEV₁ <80% predicted, utility adjusted in regression to UK population, population treated with inhaled fluticasone or salmeterol/fluticasone	Health states were less relevant than those used by Briggs et al.[38] as the exacerbation state was combined with other symptomatic states	Mapped EQ-5D from AQLQ	Patient	Not reported	Not reported	Used an unpublished mapping algorithm and insufficient details reported to assess validity mapping method
Rodriguez-Martinez et al., 2013[54]	Parents answering for children	Health states were no symptoms, suboptimal control, no exacerbation and asthma exacerbation	Direct valuation	Parents	No	SG	Direct valuation of clinical vignettes does not meet the NICE reference case
Carroll and Downs, 2009[55]	Carer valuing for children aged between 0 and 18 years	Utility data for different asthma severity	Direct valuation	Parents	No	TTO, SG	Direct valuation of clinical vignettes does not meet the NICE reference case
Brown et al., 2007[56]	Poorly controlled allergic, severe asthma with mean age of 37.5–39.3 years	Utility for day to day symptoms at baseline and 1 year	Mapped EQ-5D from mini-AQLQ	Patient	UK adult tariff for EQ-5D	TTO for EQ-5D	Utility decrement for exacerbations not derived from this study (literature-based estimates used)
Gerald et al., 2010[57]	Cohort of school children with asthma	Reported health states related to asthma exacerbations	PAHOM	Estimated based on children's characteristics	PAHOM derived from adult preferences	VAS, SG (SG converted from VAS)	Health states were subjectively mapped to PAHOM state

AQLQ, Asthma Quality of Life Questionnaire; ASS, asthma symptom score; FEV₁, forced expiratory volume in the first second; HUI, Health Utilities Index; HUI-2, Health Utilities Index Mark 2; HUI-3, Health Utilities Index Mark 3; PAHOM, Pediatric Asthma Health Outcome Measure; SG, subgroup analysis; TTO, time trade-off; VAS, visual analogue scale.

Six studies included UK patients,[38,46,47,52,53,56] three of which were multinational studies.[38,53,56] Three papers were from the USA,[49,55,57] two were based in Canada[50,51] and one each was from the Netherlands,[36] Belgium[48] and Spain.[54] Only the studies by Juniper et al.,[51] Chiou et al.[49] and Powell et al.[46] directly measured HRQoL in populations confined to children. Chiou et al.[49] recruited children aged between 7 and 12 years with diagnosed asthma of at least mild persistent severity, while Juniper et al.[51] studied children with symptomatic asthma with a mean age of 12 years (range 7–17 years) and Powell et al.[46] included children aged between 2 and 16 years with acute severe asthma. Two studies, by Rodríguez-Martínez et al.[54] and Carroll and Downs,[55] elicited preferences from parents regarding health states in children. Other studies comprised populations with mixed age groups. Of these, the studies by Mittmann et al.[50] and Willems et al.[36] presented HRQoL data stratified by age.

The populations in the included studies differed in asthma severity and characteristics. Five studies measured HRQoL using EQ-5D.[36,46–48,52] Other studies used outcome measurements, such as the Pediatric Asthma Health Outcome Measure (PAHOM) ($n = 2$) and Health Utilities Index Mark 2 (HUI-2) ($n = 1$) and Mark 3 (HUI-3) ($n = 1$). Direct valuation using vignettes was used in two studies. This review also included three modelling studies,[38,53,56] which estimated EQ-5D data from mapping exercises.

The EQ-5D is a generic preference-based measure in which the descriptive systems consist of five dimensions: mobility, depression/anxiety, self-care, usual activities, pain and discomfort. Each dimension has three levels of severity, and this gives rise to 243 possible health states described by the EQ-5D. In the UK, scoring of EQ-5D was based on time trade-off (TTO) in a representative sample of 2997 adults administered using York Measurement and Valuation of Health TTO protocol. Public preferences were obtained for 43 health states and regression was used to model data for the remaining health states. Utility score from the algorithm was anchored at '1' for perfect health and '0' for a state equivalent to death.[58]

Willems et al.,[36] Price et al.[47] and Powell et al.[46] were randomised controlled trials (RCTs) that elicited an EQ-5D index score using UK preferences, whereas the EQ-5D score in a cohort study by Brusselle et al.[48] was based on the Belgian tariff. Norman et al.[52] was a modelling study that used EQ-5D data collected from the Evaluate Xolair for Asthma as Leading Treatment (EXALT) trial. The tariff used in the EXALT study is not described by Norman et al.,[52] but the data are described as being consistent with the NICE reference case, suggesting that the UK TTO valuation set was used.

In the MAGNEsium Trial In Children (MAGNETIC), Powell et al.[46] included a population of children ($n = 508$) with severe acute exacerbations, as defined by British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN). The MAGNETIC was a prospective, double-blind, multicentre RCT in the UK, designed to compare efficacy of nebulised magnesium sulphate with usual care. EQ-5D and Paediatric Quality of Life Inventory (PedsQL™) postal questionnaires were collected at 1 month post exacerbation. EQ-5D data were obtained for children aged ≥ 5 years and were filled out by parents as proxy, while PedsQL™ were obtained for all children and were self-completed if children were over 5 years. Respondents were asked to recall events in the previous 4 weeks while filling out the outcome measures. The adult UK tariff was applied to EQ-5D to obtain utility value for each child. Utility values for patients under 5 years were estimated through mapping between EQ-5D and PedsQL™. In this study, baseline EQ-5D data during exacerbation were not collected for ethical reasons. Therefore, asthma symptom scores (ASSs) at exacerbation were mapped to EQ-5D based on experts' opinions. The expert team comprised a paediatric consultant and two respiratory nurses who routinely treated asthmatic paediatric patients. An EQ-5D health state of 11111 was assigned to ASSs of 1–3 in the base case, while ASSs of 4–6 and 7–9 were mapped to EQ-5D health states of 22222 and 33333, respectively. In our opinion, the subjective nature of this mapping between ASS and EQ-5D was considered to make the EQ-5D scores estimated at the time of exacerbation very uncertain. Furthermore, these data would be relevant only to the subgroup of patients who have severe acute exacerbations requiring treatment in secondary care, as this was the population recruited into the MAGNETIC. This study was blinded to patients, health-care providers and outcome analysts. Therefore, it had low risk of performance and detection bias. However, the study was subjected to risk of attrition bias due to the low response rate of EQ-5D questionnaires. The authors addressed this limitation by using a

mapping function to estimate EQ-5D data for those with PedsQL™ data. This was based on the subset of patients for whom both PedQL and EQ-5D data were available. Following mapping estimations, a total of 218 EQ-5D data were available for analysis for the outcome 1 month after exacerbation.

Price et al.[47] included patients in the UK aged between 12 and 80 years with poorly controlled asthma at BTS/SIGN treatment step 2 or 3. The mean age of patients was 44.74 years (SD 16.49 years) at step 2 and 50.02 years (SD 15.93 years) at step 3. In step 2 patients, a leukotriene receptor antagonist was compared with inhaled corticosteroid. In step 3 patients who were already receiving inhaled corticosteroid, a leukotriene receptor antagonist was compared with a long-acting β_2-agonist. EQ-5D data were directly measured from patients and were presented by treatment steps and interventions at baseline, 2 months and 2 years. Utility values were estimated using UK preferences. This RCT had a high retention rate, with 5–10% loss to follow-up. A large proportion (75%) of patients presented with less than four missing data, and missing data were handled using multiple imputation. This single-blind RCT ($n = 687$) was robust, with large sample size, low risk of attrition bias and measured outcomes with EQ-5D. However, utility data presented were not stratified by age nor related to asthma exacerbations. Therefore, these data lack applicability to the PLEASANT trial and the health states modelled.

Willems et al.[36] used UK preferences to estimate utility scores for asthmatic patients in the Netherlands. Populations comprised adults ($n = 53$) and children ($n = 56$) with mild to moderate asthma [Global Initiative for Asthma (GINA) states I–III]. EQ-5D questionnaires were filled by carers for children under 12 years and self-completed for those aged ≥ 12 years. There were only four children lost to follow-up, and various imputation techniques were applied. Missing baseline scores were imputed with mean scores. Quality of life scores at baseline (usual care 0.96, nurse monitoring 0.92) were consistent with the good lung function of the study's population [mean forced expiratory volume in the first second (FEV_1) above 90% predicted]. However, these results were elicited from a non-UK population, but did use a UK valuation set. Willems et al.[36] did not examine the utility decrement in exacerbation.

Brusselle et al.[48] conducted a 1-year cohort study ($n = 158$) to determine the efficacy and safety of omalizumab by looking at changes from baseline in a single-arm study. The mean age of the population studied was 48.17 years (SD 17.18 years) and age ranged from 12 to 83 years. Patients included had poorly controlled severe allergic asthma ($FEV_1 < 80\%$ predicted) and past history of exacerbations. The Belgian tariff was applied to the collected EQ-5D data at baseline and 1 year. Only 126 of 158 patients had baseline EQ-5D values, and only 67 had EQ-5D data at 1 year. Handling of missing data, however, was not reported. This tariff was obtained from public preferences in Belgium using the visual analogue scale (VAS) valuation method.[59] However, valuation using VAS is not a choice-based method. In the UK, NICE expressed a preference of using TTO as the valuation method, and, in the absence of TTO, other choice-based methods such as subgroup analysis are preferred over VAS.[60] Therefore, utility data estimated from this study do not meet the NICE requirement of using a choice-based valuation method.

Two USA-based studies, by Chiou et al.[49] and Gerald et al.,[57] used PAHOM, an asthma-specific preference-based measure designed for children. It consists of a descriptive system with three dimensions: symptoms, emotions and activity. The symptoms dimension is classified to three levels of severity, while emotions and activity are dichotomous choices to indicate presence or absence of problems. Unlike EQ-5D with a recall period of 1 day, respondents are asked to describe health states for the past 7 days using PAHOM. The utility value of a health state is calculated as the average utility values over 7 days. Preference weights for PAHOM were elicited from 114 adults in Seattle, WA, USA, who responded for children. Subgroup analysis and VAS were used to value health states. As not all health states were valued using subgroup analysis, because of cognitive burden, VAS values were transformed into subgroup analysis values using relative risk attitude equation.[49]

Chiou et al.[49] measured utility value in 72 children (aged 7–12 years) with diagnosed asthma of at least mild persistent severity as 0.83 (converted subgroup analysis value). Chiou et al.[49] also reported mean VAS and subgroup analysis values for patients according to asthma severity, with subgroup analysis values of

0.79 for mild or no symptoms, 0.70 for moderate and 0.28 for severe. A limitation of this study was the small sample size, which may have affected the accuracy and validity of results, particularly for the estimates stratified by severity. Values stratified by presence or absence of exacerbation were not reported.

Gerald et al.[57] performed a modelling study on different screening strategies for asthma. A decision tree and Markov models for a cohort of children were constructed. The Markov model consists of five health states: asthma symptom-free day, symptom days, exacerbation recovery days, emergency department visits and hospitalisation days. The utility value for each health state was derived using PAHOM. PAHOM states were allocated to the modelled health states. When several PAHOM states could describe a modelled health state, utility values of the relevant states were averaged to estimate a single utility value. For example, three or four PAHOM states were thought to characterise 'symptom days' in the model. The utility values of these states were averaged to derive utility value for 'symptom days'. The authors highlighted that this approach may fail to capture valuation of 'symptom days' accurately. In our opinion, the subjective nature of this mapping from modelled health states to PAHOM states reduces the robustness of these utility estimates. In addition, a general concern regarding PAHOM was that this measure was not validated for its psychometric properties. Furthermore, validation of the relative risk attitude equation used to derive subgroup analysis values was not performed.[49]

Two Canadian-based observational studies used the Health Utilities Index (HUI) as an outcome measure. Juniper et al.[51] studied the minimum skills required by children to complete outcome measurements unassisted. The Paediatric Asthma Quality of Life Questionnaire, Feeling Thermometer, HUI and direct valuation were administered to 52 children aged 7–17 years (mean 12 years) with symptomatic asthma (mean FEV_1 85% predicted). The HUI-2 Canadian tariff was applied to obtain utility value. The mean HUI baseline value for asthma was reported as 0.89 (SD 0.09).

The six-dimensional version of HUI-2 is a common generic outcome measure in children. Each dimension has 3–5 levels, allowing 8000 unique health states to be defined. The HUI-2 tariff was estimated from a sample of 293 parents of school children in Ontario, Canada. Valuations were performed using VAS and three health states were valued with VAS and subgroup analysis. A power function was then derived to map VAS values to subgroup analysis values, and multiattribute utility theory was used to derive the valuation functions.[58]

Mittmann et al.[50] conducted a cross-sectional study to measure HRQoL of 20 chronic diseases. The HUI-3 was administered through interview to 17,626 household residents ($\geq$ 12 years) in Canada. HUI-3 is an adapted version of HUI-2 with additional dimensions and levels. HUI-3 weights were elicited from a random sample of adults ($n = 504$) in Ontario, Canada. In this study, however, the HUI-2 scoring algorithm was used for HUI-3 data. The mean HUI score reported for children (aged 12–19 years) with asthma was similar to that reported by Juniper et al.[51]

In measuring and valuing children's health, NICE is less clear on the preferred instrument, but advises use of a standardised and validated preference-based measure designed for children. Although HUI is an example of an instrument that meets the mentioned criteria, the HUI data from these studies may not be valid, as the study designs lack rigour. First, the small sample size ($n = 52$) recruited by Juniper et al.[51] may introduce inaccuracy to the results. Second, HUI-3 data were inappropriately scored in the study by Mittmann et al.[50] and utility scores estimated were deemed to be provisional by the authors. Furthermore, neither of these studies reported the utility decrement attributable to asthma exacerbation.

Four modelling studies performed mapping to estimate EQ-5D values. Brown et al.[56] and Norman et al.[52] constructed Markov models to evaluate the cost-effectiveness of omalizumab in addition to standard care. Norman et al.[52] used EQ-5D scores measured in the EXALT study for day-to-day asthma symptoms. The EXALT study was an open-label RCT, comprising 404 patients in the UK (age range from 12 to 75 years) with poorly controlled severe allergic asthma (FEV_1 < 80% predicted). Utility for day-to-day symptoms (by treatment arm) was estimated from EQ-5D scores recorded in the EXALT study.

Norman *et al.*[52] also conducted a systematic review of HRQoL literature to identify HRQoL data of relevance to both adult and paediatric populations. In their base-case analysis they used data from Lloyd *et al.*,[37] a study conducted in an adult population that provides estimates of the health utility decrement (loss) associated with exacerbations requiring oral steroid treatment and exacerbations requiring hospitalisation. The decrement was measured by comparing baseline EQ-5D values with those reported at 4 weeks for patients who did and did not experience exacerbations during that 4-week period. They cited another study by Steuten *et al.*,[61] which also provided utility values for exacerbations in an adult population. However, this study collected data at 3- to 6-month intervals, which could make it harder to detect the relationship between short-term exacerbations and health utility than the 4-week interval used by Lloyd *et al.*[37]

Brown *et al.*[56] used a published algorithm by Tsuchiya *et al.*[62] to map the mini-Asthma Quality of Life Questionnaire (AQLQ) scores from the ETOPA trial onto the EQ-5D. The ETOPA trial was a multinational open-label trial that recruited 312 patients aged between 12 and 73 years (mean > 35 years) with poorly controlled allergic asthma (mean FEV_1 < 73% predicted).[63] (Note that Brown *et al.*[56] used data from the subgroup of ETOPA patients with severe disease, but baseline characteristics are not described for this subgroup, so *Table 32* provides characteristics for the ETOPA trial as a whole.) The AQLQ scores were mapped to EQ-5D for patients separated by disease state and responder status. The mapping algorithm used by Brown *et al.*[56] was derived from a RCT of 3000 adults in the UK with a wide range of asthma.[62] In the RCT used to generate the mapping algorithm, both EQ-5D and AQLQ were collected.[64] Domains in EQ-5D were found to overlap with those in AQLQ, with correlations between 0.56 and 0.65. Six main mapping models and two supplementary models were derived using the regression method and were validated using an external data set. However, these mapping functions were associated with large marginal errors, and should be considered only as second best to direct elicitation of EQ-5D data.[58]

In the economic modelling study by Brown *et al.*,[56] literature-based estimates were used to model the decrement associated with exacerbations, as the authors stated that the ETOPA trial collected insufficient patient quality-of-life data during exacerbations. The literature-based estimates cited by Brown *et al.*[56] appear to be from an earlier publication[65] of the study by Lloyd *et al.*[37]

The modelling studies by Briggs *et al.*[38] and Doull *et al.*[53] mapped AQLQ scores from the 52-week Gaining Optimal Asthma ControL (GOAL) trial onto EQ-5D values. The GOAL study was a multinational double-blind RCT designed to evaluate efficacy of a combination of fluticasone/salmeterol compared with fluticasone in terms of asthma control. The GOAL study comprised 3416 patients (mean age > 35 years; range 12–80 years) with uncontrolled asthma (mean FEV_1 < 80% predicted) from 44 countries.[66] Asthma control in the GOAL trial was classified as totally controlled, well controlled, not well controlled or exacerbation requiring oral steroid or secondary care by Briggs *et al.*[38] using the GINA definition. As the GOAL trial collected only AQLQ data, a mapping function obtained through personal communication with Macran and Kind (no further details of this communication provided by Briggs *et al.*[38]) was used to transform AQLQ scores to EQ-5D values. Subsequently, the utility value for each asthma control health state was derived using regression. In the regression model, a UK indicator was added as a dummy variable to adjust for a UK specific-population. The dependent variable was the utility value, whereas asthma control and the UK indicator were the independent variables. Both independent variables were found to be significant predictors of quality of life. The quality-of-life data from this study are of relevance to the PLEASANT trial. However, the mapping function used in the analysis by Briggs *et al.*[38] was inadequately described by the authors, and a published article providing more details could not be identified from searches. Therefore, an assessment of mapping performance was not possible.

Doull *et al.*[53] adapted the analysis by Briggs *et al.*,[38] and reclassified asthma control to 'symptom free' and 'with symptoms'. Totally controlled asthma was classified as 'symptom free', while other states were classified as 'with symptoms'. The weekly utility in the 'with symptom' state was equivalent to the weighted average of the weekly utility in well controlled, not well controlled and exacerbation health states from Briggs *et al.*[38] Regression was used to estimate the relationship between asthma control and quality of life, when quality of life was obtained by mapping AQLQ scores to EQ-5D. Asthma control and

the UK indicator were entered into the model as the independent variables, while weekly utility was entered as the dependent variable. Subsequently, utility for the 'with symptoms' and the 'symptoms-free' health states were estimated from the regression coefficients. As utility data in this study were adapted from Briggs et al.,[38] which mapped AQLQ scores to EQ-5D using the mapping function by Macran and Kind, the validity of mapped data was likewise not assessable.

The method used in Carroll and Downs[55] and Rodríguez-Martínez et al.[54] involved valuation of hypothetical health states by parents. Parents were asked to value health states described in vignettes by imagining their children affected by those states. Descriptions in vignettes, however, differed across studies. Rodríguez-Martínez et al.[54] developed asthma-specific vignettes based on PAHOM,[49] and these were validated by expert opinions, whereas Carroll and Downs[55] developed general descriptions of 29 health states with the inclusion of time as a factor. Rodriguez-Martinez et al.[54] requested parents (n = 76) to value vignettes using subgroup analysis, while Carroll and Downs[55] used subgroup analysis and TTO methods in a sample of 4016 parents (Note that each parent valued only three of a potential 29 states providing around 415 values per state.) Neither study constructed vignettes based on rigorous methods such as a focus group. The lack of standardised descriptive systems of vignettes and different valuation methods also resulted in a lack of comparability of results between studies. In addition, vignettes are limited to specific descriptions of a condition, and may not fully reflect all experiences of a patient. Therefore, vignettes do not meet the NICE reference case and are considered of little value in economic evaluation.[60] In view of the various limitations associated with vignettes, utility values from Carroll and Downs[55] and Rodríguez-Martínez et al.[54] were not considered suitable for use in the PLEASANT study economic analysis.

Health state utility values used in the analysis

The utility values used in the economic evaluation by Briggs et al.[38] appear to be particularly relevant to our proposed model structure, as they are reported for relevant health states, including an exacerbation state, and have been estimated from a trial population that included some children. However, the mapping algorithm used to convert from the condition-specific HRQoL measure (AQLQ) to the EQ-5D utility score is not from a published source, and is not described in detail, making it difficult to assess its validity. However, if the values reported by Briggs et al.[38] are taken at face value, they provide an estimate of the utility loss for exacerbation versus total asthma control of –0.216 (SE 0.007). It is possible that some patients do not have total asthma control in the absence of an exacerbation and the difference between the utility values for the exacerbation state and the not well controlled states is smaller, at –0.112. The data from Briggs et al.[38] suggest that the utility decrement for exacerbation in the average patient is likely to fall in the range –0.112 to – 0.216. The utility decrements provided by Lloyd et al.[37] from an adult population are –0.1 and –0.2 for exacerbations requiring oral steroids and exacerbations requiring hospitalisation, respectively. It therefore appears that there is reasonable agreement between the values reported by Briggs et al.[38] and Lloyd et al.[37]

We accept that the estimates provided by Briggs et al.[38] and Lloyd et al.[37] probably underestimate the degree of utility loss in children with a severe or life-threatening acute exacerbation during the period of hospitalisation. This is because the utility values were not measured during the acute exacerbation period itself. In the MAGNETIC, which estimated utility scores in children attending EDs with severe acute asthma, the utility was estimated to be reduced from a baseline of 0.88 to 0.516 during the initial acute period, giving a utility decrement of 0.364. However, in the MAGNETIC, this more severe utility decrement was only applied until hospital discharge, with the average length of hospital stay being 1 day. If we apply a decrement of 0.364 for 1 day and assume a loss of 0.2 in the remaining 6 days, the average utility loss over the whole week of exacerbation (–0.22) would be similar to that reported by Briggs et al.[38]

Given the uncertainty regarding the mapping algorithm used by Briggs et al.,[38] and the previous use of data from Lloyd et al.[37] in a number of published economic evaluations, we decided to use the data from Lloyd et al.[37] in the base-case analysis. The data from Briggs et al.[38] have been explored in a sensitivity analysis using the difference between the total control state and the exacerbation state (–0.216) to

estimate the quality-of-life decrement from exacerbations. This sensitivity analysis is considered to provide an upper limit on the utility decrement attributable to exacerbation.

For patients without an exacerbation, we have taken the baseline utility score for the control arm of the study by Willems *et al.*,[36] as this provides an estimate based on the child version of the EQ-5D valued using the adult UK TTO valuation set. The population was Dutch children aged 7–18 years with a GINA severity stage I–III receiving standard outpatient care. The value applied to patients without an exacerbation will affect the calculation of absolute QALYs in each trial arm, but does not affect the estimation of incremental QALY gain that goes into the cost-effectiveness ratio. Therefore, the selection of this data source is less critical than that used to determine the decrement attributable to exacerbations. The data that have been applied in the model are summarised in *Health outcomes*.

Appendix 6 Full search strategy

TABLE 36 Full search strategy

Search database	Search terms
MEDLINE/EMBASE	1. exp child/ 2. exp adolescent/ 3. (adolescen$ or teenager$ or teen$ or preteen$ or pre-teen$ or young$ or youth or young one$ or paediat$ or pediat$ or child$ or "young people").ti,ab. 4. 1 or 2 or 3 5. exp asthma/ 6. (asthma$ or (asthma$ adj exacerbate$) or "asthma exacerbation").ti,ab. 7. 5 or 6 8. 4 and 7 9. quality adjusted life year/ 10. quality adjusted life.tw. 11. (qaly$ or qald$ or qale$ or qtime$).tw. 12. disability adjusted life.tw. 13. daly$.tw. 14. health status indicators/ 15. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. 16. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. 17. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. 18. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. 19. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. 20. (euroqol or euro qol or eq5d or eq 5d).tw. 21. (eq5d child$ or eq 5d child$ or eq5d-youth or eq-5d-y or EuroQol 5D- Youth or EQ-5D Youth or eq 5d youth).ti,ab. 22. (chu-9d or chu9d or Child Health Utility Index 9D).tw. 23. (asui or Asthma Symptom Utility Index).tw. 24. (hql or hqol or h qol or hrqol or hr qol).tw. 25. (hye or hyes).tw. 26. health$ year$ equivalent$.tw. 27. health utilit$.tw. 28. (hui or hui1 or hui2 or hui3).tw. 29. disutili$.tw. 30. rosser.tw. 31. quality of wellbeing.tw. 32. qwb.tw. 33. willingness to pay.tw. 34. standard gamble$.tw. 35. time trade off.tw. 36. time tradeoff.tw. 37. tto.tw. 38. (preference-based or preference based).tw. 39. or/9–39 40. 8 and 40
The Cochrane Library (Cochrane Database of Systematic Review, HTA and the NHS Economic Evaluation Database)	#1 MeSH descriptor: [Child] explode all trees #2 MeSH descriptor: [Adolescent] explode all trees #3 (adolescen* or teenager* or teen* or preteen* or pre-teen* or young* or youth or young one* or paediat* or pediat* or child* or 'young people'): ti,ab #4 #1 or #2 or #3 #5 MeSH descriptor: [Asthma] explode all trees #6 (asthma* or (asthma*adj exacerbate*) or 'asthma exacerbation'):ti,ab

TABLE 36 Full search strategy (*continued*)

Search database	Search terms
	#7 #5 or #6
	#8 #4 and #7
	#9 MeSH descriptor: [Quality-Adjusted Life Years] explode all trees
	#10 quality adjusted life:ti,ab
	#11 (qaly* or qald* or qale* or qtime*):ti,ab
	#12 'disability adjusted life':ti,ab
	#13 daly*:ti,ab
	#14 MeSH descriptor: [Health Status Indicators] explode all trees
	#15 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six):ti,ab
	#16 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six):ti,ab
	#17 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve):ti,ab
	#18 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen):ti,ab
	#19 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty):ti,ab
	#20 (euroqol or euro qol or eq5d or eq 5d):ti,ab
	#21 (eq5d child* or eq 5d child* or eq5d-youth or eq-5d-y or EuroQol 5D- Youth or EQ-5D Youth or eq 5d youth):ti,ab
	#22 (chu-9d or chu9d or Child Health Utility Index 9D)
	#23 ('aql-5d' or 'Asthma Quality of Life Utility Index- 5d' or 'Asthma Quality of Life Utility Index- 5 dimension'):ti,ab
	#24 (asui or 'Asthma Symptom Utility Index'):ti,ab
	#25 (hql or hqol or h qol or hrqol or hr qol):ti,ab
	#26 (hye or hyes):ti,ab
	#27 health* year* equivalent*:ti,ab
	#28 health utilit*:ti,ab
	#29 (hui or hui1 or hui2 or hui3):ti,ab
	#30 disutili*:ti,ab
	#31 rosser:ti,ab
	#32 quality of wellbeing:ti,ab
	#33 qwb:ti,ab
	#34 willingness to pay:ti,ab
	#35 standard gamble*:ti,ab
	#36 time trade off:ti,ab
	#37 time tradeoff:ti,ab
	#38 tto:ti,ab
	#39 ('preference-based' or 'preference based'):ti,ab
	#40 or/9–39
	#41 #8 and #40 in Cochrane Reviews (Reviews and Protocols), Other Reviews, Technology Assessments and Economic Evaluations
School of Health and Related Research (ScHARR) Health Utilities Database	1. asthma* or (asthma*adj exacerbate*) or 'asthma exacerbation'/Any field
EconLit	1. (adolescen$ or teenager$ or teen$ or preteen$ or pre-teen$ or young$ or youth or young one$ or paediat$ or pediat$ or child$ or "young people").ti,ab.
	2. (asthma$ or (asthma$ adj exacerbate$) or "asthma exacerbation").ti,ab.
	3. 1 and 2
	4. quality adjusted life.tw.
	5. (qaly$ or qald$ or qale$ or qtime$).tw.
	6. disability adjusted life.tw.
	7. daly$.tw.
	8. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
	9. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
	10. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
	11. (euroqol or euro qol or eq5d or eq 5d).tw.

TABLE 36 Full search strategy (*continued*)

Search database	Search terms
	12. (eq5d child$ version or eq 5d child$ version or eq5d-youth or eq-5d-y).tw.
	13. (chu-9d or chu9d or Child Health Utility Index 9D).tw.
	14. (aql-5d or Asthma Quality of Life Utility Index- 5d or Asthma Quality of Life Utility Index- 5 dimension).tw.
	15. (hql or hqol or h qol or hrqol or hr qol).tw.
	16. (hye or hyes).tw.
	17. health$ year$ equivalent$.tw.
	18. health utilit$.tw.
	19. (hui or hui1 or hui2 or hui3).tw.
	20. disutili$.tw.
	21. rosser.tw.
	22. quality of wellbeing.tw.
	23. qwb.tw.
	24. willingness to pay.tw.
	25. standard gamble$.tw.
	26. time trade off.tw.
	27. time tradeoff.tw.
	28. tto.tw.
	29. (preference-based or preference based).tw.
	30. or/4–29
	31. 3 and 30

Appendix 7 Quality-of-life filter

TABLE 37 Quality of life filter

Source/database	Filter
Original quality of life (ISSG): MEDLINE/EMBASE	1. value of life/ 2. quality adjusted life year/ 3. quality adjusted life.tw 4. (qaly$ or qald$ or qale$ or qtime$).tw 5. disability adjusted life.tw 6. daly$.tw 7. health status indicators/ 8. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw 9. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw 10. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw 11. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw 12. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw 13. (euroqol or euro qol or eq5d or eq 5d).tw 14. (hql or hqol or h qol or hrqol or hr qol).tw 15. (hye or hyes).tw 16. health$ year$ equivalent$.tw 17. health utilit$.tw 18. (hui or hui1 or hui2 or hui3).tw 19. disutili$.tw 20. rosser.tw 21. quality of wellbeing.tw 22. quality of wellbeing.tw 23. qwb.tw 24. willingness to pay.tw 25. standard gamble$.tw 26. time trade off.tw 27. time tradeoff.tw 28. tto.tw 29. or/1–28
(A) Adapted quality of life (ISSG): MEDLINE/EMBASE	1. quality-adjusted life-year/ 2. quality-adjusted life.tw. 3. (qaly$ or qald$ or qale$ or qtime$).tw. 4. disability adjusted life.tw. 5. daly$.tw. 6. health status indicators/ 7. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. 8. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. 9. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. 10. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. 11. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. 12. (euroqol or euro qol or eq5d or eq 5d).tw. 13. (eq5d child* or eq 5d child* or eq5d-youth or eq-5d-y or EuroQol 5D- Youth or EQ-5D Youth or eq 5d youth).ti,ab. 14. (chu-9d or chu9d or Child Health Utility Index 9D).tw.

TABLE 37 Quality of life filter (*continued*)

Source/database	Filter
	15. (aql-5d or Asthma Quality of Life Utility Index- 5d or Asthma Quality of Life Utility Index- 5 dimension).tw. 16. (asui or Asthma Symptom Utility Index).tw. 17. (hql or hqol or h qol or hrqol or hr qol).tw. 18. (hye or hyes).tw. 19. health$ year$ equivalent$.tw. 20. health utilit$.tw. 21. (hui or hui1 or hui2 or hui3).tw. 22. disutili$.tw. 23. rosser.tw. 24. quality of wellbeing.tw. 25. qwb.tw. 26. willingness to pay.tw. 27. standard gamble$.tw. 28. time trade off.tw. 29. time tradeoff.tw. 30. tto.tw. 31. (preference-based or preference based).tw. 32. or/1–31
(B) Adapted quality of life (ISSG): Cochrane. QOL FILTER – 4 July 2014	#1 MeSH descriptor: [Quality-Adjusted Life-years] explode all trees #2 quality-adjusted life:ti,ab #3 (qaly* or qald* or qale* or qtime*):ti,ab #4 'disability adjusted life':ti,ab #5 daly*:ti,ab #6 MeSH descriptor: [Health Status Indicators] explode all trees #7 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six):ti,ab #8 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six):ti,ab #9 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve):ti,ab #10 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen):ti,ab #11 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty):ti,ab #12 (euroqol or euro qol or eq5d or eq 5d):ti,ab #13 (eq5d child* or eq 5d child* or eq5d-youth or eq-5d-y or EuroQol 5D- Youth or EQ-5D Youth or eq 5d youth):ti,ab #14 (chu-9d or chu9d or Child Health Utility Index 9D) #15 ('aql-5d' or 'Asthma Quality of Life Utility Index- 5d' or 'Asthma Quality of Life Utility Index- 5 dimension'):ti,ab #16 (asui or 'Asthma Symptom Utility Index'):ti,ab #17 (hql or hqol or h qol or hrqol or hr qol):ti,ab #18 (hye or hyes):ti,ab #19 health* year* equivalent*:ti,ab #20 health utilit*:ti,ab #21 (hui or hui1 or hui2 or hui3):ti,ab #22 disutili*:ti,ab #23 rosser:ti,ab #24 quality of wellbeing:ti,ab #25 qwb:ti,ab #26 willingness to pay:ti,ab #27 standard gamble*:ti,ab #28 time trade off:ti,ab #29 time tradeoff:ti,ab #30 tto:ti,ab #31 ('preference-based' or 'preference based'):ti,ab #32 or/1–31

Appendix 8 Reasons for exclusion at titles and abstracts

TABLE 38 Reasons for exclusion at titles and abstracts

Reasons	Number of studies excluded
Aged ≥ 18 years	175
Did not publish utility data	197
Non-asthma population	87
Non-English papers	8
Non-preference-based/non-utility measure	158
Publication types	34
Total	659

Appendix 9 Reasons for exclusion at full texts

TABLE 39 Reasons for exclusion at full texts

Study	Reasons for exclusion
Janse A, Sinnema G, Uiterwaal C, Kimpen J, Gemke R. Quality of life in chronic illness: perceptions of parents and paediatricians. *Arch Dis Child* 2005;**90**:486–91	Used HUI-3, but did not report utility data. Results were presented as percentage similarity in outcome measurements between physician and parents
Mo F, Choi BC, Li FC, Merrick J. Using Health Utility Index (HUI) for measuring the impact on health-related quality of Life (HRQL) among individuals with chronic diseases. *Sci World J* 2004;**4**:746–57	Used HUI-3, but did not report utility data. Results were presented as graphical differences of quality of life between diseases
Willems DC, Joore MA, Nieman FH, Severens JL, Wouters EF, Hendriks JJ. Using EQ-5D in children with asthma, rheumatic disorders, diabetes, and speech/language and/or hearing disorders. *Int J Technol Assess Health Care* 2009;**25**:391–9	Used EQ-5D, but did not report utility data. Results were presented as EQ-5D interclass coefficients and Spearman coefficients between outcome measures
Burstrom K, Svartengren M, Egmar AC. Testing a Swedish child-friendly pilot version of the EQ-5D instrument – initial results. *Eur J Public Health* 2011;**21**:178–83	Used direct valuation using EQ-VAS as outcome measure (non-preference based) in Swedish children
Finnell SM, Carroll AE, Downs SM. Application of classic utilities to published pediatric cost-utility studies. *Acad Pediatr* 2012;**12**:219–28	Utility data were obtained from an included study by Carroll and Downs[55]
Brodtkorb TH, Zetterstrom O, Tinghog G. Cost-effectiveness of clean air administered to the breathing zone in allergic asthma. *Clin Respir J* 2010;**4**:104–10	Utility data were presented as utility changes associated with intervention
Meadows A, Kaambwa B, Novielli N, Huissoon A, Fry-Smith A, Meads C, *et al.* A systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis. *Health Technol Assess* 2013;**17**(27)	
Smith LJ, Holbrook JT, Wise R, Blumenthal M, Dozor AJ, Mastronarde J, *et al.* Dietary intake of soy genistein is associated with lung function in patients with asthma. *J Asthma* 2004;**41**:833–43	
Wilson EC, Price D, Musgrave SD, Sims EJ, Shepstone L, Murdoch J, *et al.* Cost effectiveness of leukotriene receptor antagonists versus long-acting beta-2 agonists as add-on therapy to inhaled corticosteroids for asthma: a pragmatic trial. *PharmacoEconomics* 2010;**28**:597–608	
Wilson EC, Sims EJ, Musgrave SD, Shepstone L, Blyth A, Murdoch J, *et al.* Cost effectiveness of leukotriene receptor antagonists versus inhaled corticosteroids for initial asthma controller therapy: a pragmatic trial. *PharmacoEconomics* 2010;**28**:585–95	

Appendix 10 Baseline (12 months pre intervention) and post-intervention (12 months) resource use and costs per patient

TABLE 40 Resource use and cost for baseline (12 months pre intervention) and post intervention (12 months) per patient by intervention group

Statistics	Resource-use type	Baseline (12 months pre intervention)			Post intervention (12 months)		
		Intervention	Control	Significant difference (*p*-value)	Intervention	Control	Significant differences (*p*-value)
Mean number of tasks,[a] SD (range)	Scheduled tasks	2.77 (2.63, 0–29)	2.74 (2.69, 0–36)	0.583	2.60 (2.72, 0–22)	2.69 (2.85, 0–30)	0.130
	Unscheduled tasks	10.53 (8.03, 0–79)	10.44 (8.67, 0–127)	0.610	9.39 (8.32, 0–73)	9.36 (9.22, 0–101)	0.867
	'Not relevant' tasks	4.31 (4.48, 0–52)	3.97 (4.54, 0–60)	< 0.001	4.17 (4.79, 0–45)	3.75 (4.73, 0–60)	< 0.001
	Total tasks[b]	17.61 (12.47, 0–115)	17.14 (13.38, 0–168)	0.102	16.16 (13.3, 0–120)	15.8 (14.42, 0–163)	0.249
Mean costs (95% CI; median, range)	Scheduled tasks	£178 (£167 to £190; £41, £0–3871)	£160 (£150 to £169; £41, £0–5554)	0.015	£169 (£158 to £181; £27, £0–3857)	£173 (£163 to £183; £41, £0–3839)	0.623
	Unscheduled tasks	£305 (£295 to £316; £208, £0–3181)	£315 (£305 to £326; £212, £0–4027)	0.198	£266 (£255 to £277; £146, £0–4661)	£283 (£272 to £294; £186, £0–8010)	0.030
	'Not relevant' tasks	£215 (£202 to £228; £1, £0–5727)	£197 (£186 to £209; £1, £0–4111)	0.045	£204 (£191 to £217; £1, £0–6149)	£205 (£193 to £218; £1, £0–£7675)	0.915
	Total cost[c]	£699 (£672 to £725; £435, £0–8597)	£672 (£649 to £696; £408, £0–8919)	0.147	£639 (£612 to £667; £342, £0–8829)	£662 (£636 to £688; £358, £0–13,411)	0.251
	Prescriptions	£62 (£59 to £66; £27, £0–1141)	£55 (£52 to £57; £20, £0–808)	< 0.001	£55 (£52 to £59; £20, £0–849)	£49 (£47 to 52, £16; £0–789)	0.003
	Total task and prescription cost[d]	£761 (£734 to £789; £498, £0–8622)	£727 (£703 to £751; £468, £0–8997)	0.069	£695 (£666 to £723; £402, £0–8921)	£711 (£684 to £738; £412, £0–13484)	0.420

a The mean number of tasks is provided to give descriptive information about the number of tasks per patient that were included in the costing analysis and for which a utility decrement could have been attached (unscheduled tasks only). These figures should not be interpreted in relation to the more detailed clinical analysis focused on unscheduled events.
b Total number of tasks = the number of scheduled tasks *plus* the number of unscheduled tasks *plus* the number of 'not relevant' tasks per patient.
c Total task cost = the cost for scheduled tasks *plus* the cost for unscheduled tasks *plus* the cost for 'not relevant' tasks per patient.
d Total task and prescription cost = total task cost *plus* the cost for the prescriptions per patient.
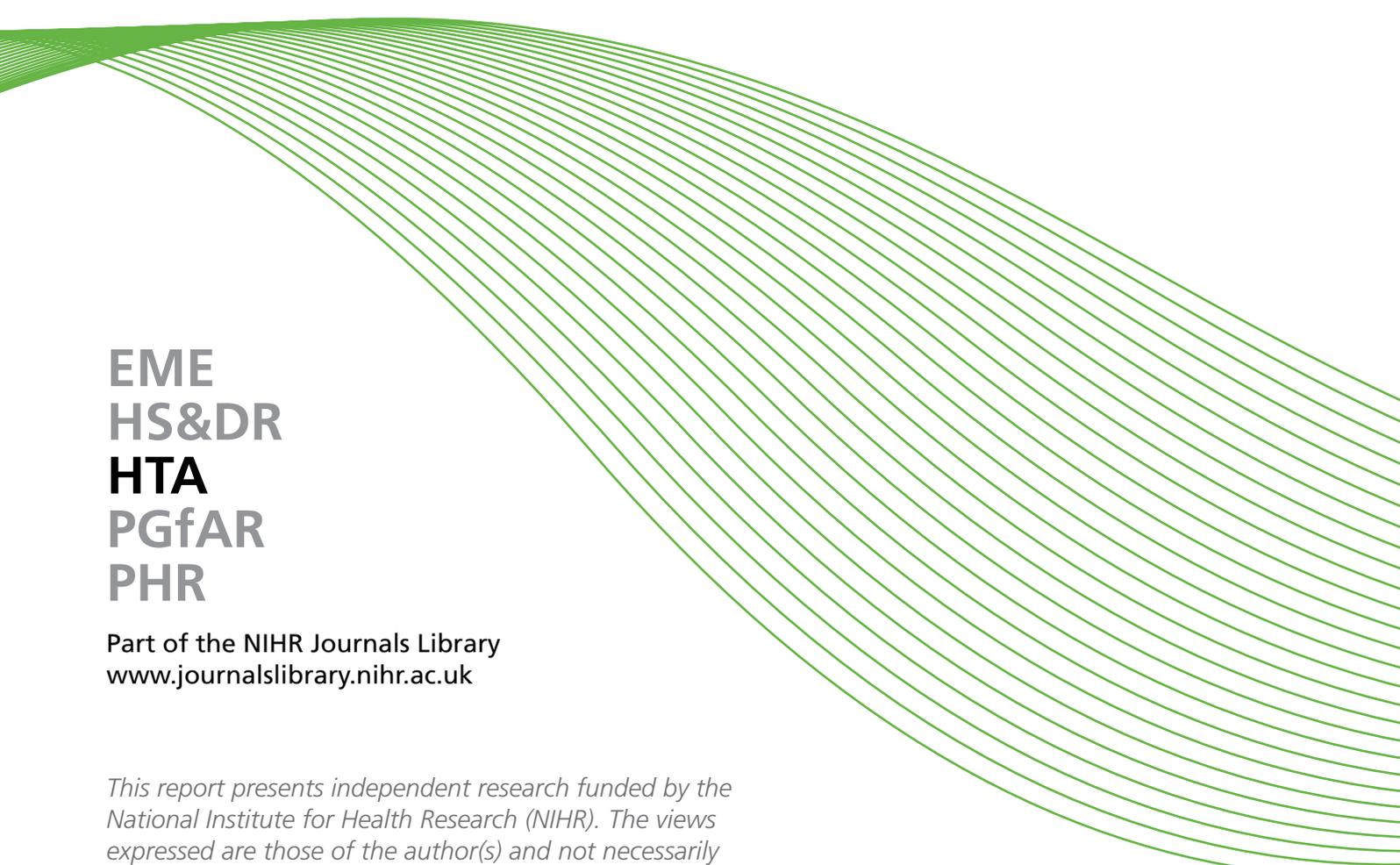
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