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[1]Centre of Academic Primary Care, University of Aberdeen, Aberdeen, UK
[2]Norwich Medical School, University of East Anglia, Norwich, UK
[3]School of Nursing and Midwifery, University of East Anglia, Norwich, UK
[4]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada
[5]School of Health & Population Sciences, University of Birmingham, Birmingham, UK
[6]Thorpewood GP Surgery, Norwich, UK
[7]Sheringham Medical Practice, Norfolk, UK
[8]Great Yarmouth and Waveney Primary Care Trust, Norfolk, UK
[9]Castle GP Partnership, Norwich, UK

*Corresponding author

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Abstract

A pragmatic single-blind randomised controlled trial and economic evaluation of the use of leukotriene receptor antagonists in primary care at steps 2 and 3 of the national asthma guidelines (ELEVATE study)

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[1]Centre of Academic Primary Care, University of Aberdeen, Aberdeen, UK
[2]Norwich Medical School, University of East Anglia, Norwich, UK
[3]School of Nursing and Midwifery, University of East Anglia, Norwich, UK
[4]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada
[5]School of Health & Population Sciences, University of Birmingham, Birmingham, UK
[6]Thorpewood GP Surgery, Norwich, UK
[7]Sheringham Medical Practice, Norfolk, UK
[8]Great Yarmouth and Waveney Primary Care Trust, Norfolk, UK
[9]Castle GP Partnership, Norwich, UK

*Corresponding author david@respiratoryresearch.org

Objectives: To evaluate, under real-life practice conditions in UK primary care, asthma control and cost-effectiveness of commencing therapy with leukotriene antagonists compared with inhaled corticosteroids (ICSs) as initial controller therapy and compared with long-acting β_2-agonist as add-on therapy for patients with uncontrolled asthma already receiving ICS. Comparisons were made in terms of short-term efficacy (2 months) and longer-term effectiveness (2 years).

Design: The study comprised two randomised controlled trials, powered for equivalence. Incremental cost-effectiveness approaches were used to study health-economic outcomes utilising NHS and societal costs.

Setting: Study visits coincided with routine patient follow-up in the patients' own primary care practices by their normal health-care providers to obtain a 'real-life' setting.

Participants: Enrolled patients were aged 12–80 years, with asthma uncontrolled by (1) short-acting β_2-agonist or (2) ICS. Active smokers and patients with small impairment of lung function/other morbidities were included in the trial.

Interventions: Leukotriene antagonists were compared with ICS, as initial controller therapy, and with long-acting β_2-agonist, as add-on therapy to ICS.

Main outcome measures: The primary study outcome was the Mini Asthma Quality of Life Questionnaire (MiniAQLQ). An analysis of covariance was used, with treatment as a fixed effect, and baseline value as covariate, to analyse MiniAQLQ scores at 2 months (the primary time point), examining efficacy, and 2 years, as a measure of effectiveness, using an intention-to-treat approach.

Results: In total, 687 patients were randomised and 650 participants (95%) had evaluable data for the primary study outcome. *Comparing leukotriene antagonists with ICSs as initial controller therapy*: at 2 months, the MiniAQLQ scores met the equivalence criterion, with adjusted difference (95% CI) between leukotriene antagonist and ICS of –0.02 (–0.24 to 0.20). At 2 years, however, the 95% CIs excluded the threshold for equivalence of 0.3, favouring ICS [–0.11 (–0.35 to 0.13)]. No significant between-group differences were found in Asthma Control Questionnaire (ACQ) score at either 2 months [adjusted difference 0.01 (–0.20 to 0.22)] or 2 years [0.13 (–0.07 to 0.33)]. *Comparing leukotriene antagonist with long-acting β_2-agonist as add-on therapy to ICS*: at 2 months, the MiniAQLQ scores

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met the equivalence criterion [adjusted difference –0.10 (–0.29 to 0.10)], while at 2 years, the 95% CIs for MiniAQLQ score were marginally over the equivalence threshold, favouring long-acting β_2-agonist as add-on therapy [adjusted difference –0.11 (–0.32 to 0.11)]. There were no significant between-group differences in ACQ score [adjusted difference at 2 months 0.12 (–0.06 to 0.30), and at 2 years 0.04 (–0.15 to 0.22)]. Daily ICS dose did not differ between the two treatment groups. Analysis of cost-effectiveness revealed that participants receiving leukotriene antagonist had significantly higher NHS and societal costs at both 2 months and 2 years but the outcomes were not statistically significantly different. For patients receiving add-on therapy to ICS, no significant differences between leukotriene antagonist and long-acting β_2-agonist in NHS or societal cost were found at 2 months, but, after 2 years, participants receiving leukotriene antagonist had higher societal costs of borderline statistical significance.

Conclusions: The evidence suggests that leukotriene antagonists are unlikely to be a cost-effective alternative to ICSs, at 2005 prices, as initial asthma controller therapy at step 2. Leukotriene antagonists were clinically equivalent to ICS as initial controller therapy and to long-acting β_2-agonists as add-on to ICS in terms of QOL at 2 months; equivalence was not proven at 2 years. Future research should establish, in primary care, whether leukotriene antagonists will be more or less beneficial than ICSs alone or as an add-on to ICSs in treating patients with asthma who are also active smokers; determine why the ACQ correlates more poorly with economic outcomes of asthma than the Mini AQLQ and the European Quality of life-5 Dimensions questionnaire; and understand further the reasons why patients were switched from study medication when there was no real clinical indication to do so.

Trial registration: Current Controlled Trials ISRCTN99132811.

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List of abbreviations

%PPEF	per cent predicted peak expiratory flow
ACQ	Asthma Control Questionnaire
ATS	American Thoracic Society
BNF	*British National Formulary*
BTS	British Thoracic Society
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
EQ-5D	European Quality of life-5 Dimensions questionnaire
ERS	European Respiratory Society
FEV_1	forced expiratory volume in 1 second
GINA	Global Initiative For Asthma
GP	general practitioner
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICS	inhaled corticosteroid
INB	incremental net benefit
LABA	long-acting β_2-agonist
LTRA	leukotriene receptor antagonist
MiniAQLQ	Mini Asthma Quality of Life Questionnaire
mRQLQ	Mini Rhinitis Quality of Life Questionnaire
NHS	National Health Service
PCT	primary care trust
PEF	peak expiratory flow
PRN	*pro re nata* – as needed
RCP3	Royal College of Physicians three questions
QALY	quality-adjusted life-year
QOL	quality of life
SABA	short-acting β_2-agonist
SD	standard deviation

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

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Executive summary

Background

The role of leukotriene receptor antagonists is not clear for primary care asthma management of patients who are uncontrolled on short-acting β_2-agonists alone [British Thoracic Society (BTS) Guidelines step 2] or uncontrolled on low-dose inhaled corticosteroid (ICS) alone (BTS Guidelines step 3). Most clinical trials evaluating the role of leukotriene antagonists compared with conventional treatment (ICS as initial controller therapy at step 2, and long-acting β_2-agonist as add-on therapy to ICS at step 3) are short term in nature, are not representative of 'real-life' asthma populations and management in primary care, and do not include a full prospective cost evaluation.

Objective

The aim of our study was to evaluate, under real-life practice conditions in UK primary care, asthma-specific quality of life (QOL), markers of asthma control, and cost-effectiveness of commencing therapy with leukotriene antagonists compared with ICS as initial controller therapy and compared with long-acting β_2-agonist as add-on therapy for patients with uncontrolled asthma already receiving ICS. Comparisons were made in terms of short-term efficacy and longer-term effectiveness at 2 months and 2 years, respectively.

Methods

This study comprised two separate randomisations, thus two pragmatic randomised controlled trials, powered for equivalence, enrolling patients aged 12–80 years with asthma uncontrolled by (1) short-acting β_2-agonist (step 2) or (2) ICS (step 3) and a score of ≤ 6 points on the Mini Asthma Quality of Life Questionnaire (MiniAQLQ) (best score = 7) and/or ≥ 1 point on the Asthma Control Questionnaire (ACQ) (score of ≤ 0.75 denotes well-controlled asthma). Study visits were scheduled to coincide with routine patient follow-up as per usual care for asthma, and the study was conducted so as to minimally interfere with normal clinical practice. Health-care providers and patients were aware of treatment allocations, while study data collection and statistical analyses were blinded.

The primary study outcome was the MiniAQLQ, a validated disease-specific asthma QOL scale, chosen because it captures outcomes of relevance to patients and their primary care providers and reflects asthma control. An analysis of covariance was used, with treatment as a fixed effect, and baseline value as covariate, to analyse MiniAQLQ scores at 2 months (the primary time point), examining efficacy, and 2 years, as a measure of effectiveness, using an intention-to-treat approach. A 95% confidence interval (CI) for the difference between treatment mean scores was derived. While the minimum clinically important difference for the MiniAQLQ score is 0.5, we conservatively defined equivalence as a difference of 0.3; thus, 95% CI of less than ± 0.3.

Other outcome measures were two markers of asthma control: the validated ACQ, which evaluates symptoms of asthma and reliever treatment usage, and asthma exacerbations requiring oral steroid therapy or hospitalisation. Incremental cost-effectiveness approaches were used to study health-economic outcomes utilising NHS and societal costs with markers of disease control and disease-specific and generic health-related QOL [European Quality of life-5 Dimensions questionnaire (EQ-5D)], with calculation of quality-adjusted life-years (QALYs). Additional outcome measures included per cent predicted peak expiratory flow (%PPEF), Royal College of Physicians three (RCP3) asthma questions, Mini Rhinitis Quality of Life Questionnaire (mRQLQ), respiratory tract infections, and consultations for respiratory tract infection, and, for step 3 only, change in ICS dose.

Results

Six hundred and eighty-seven patients, recruited from 53 primary care practices, were randomised and 650 participants (95%) had evaluable data for the primary study outcome (145 leukotriene antagonist and 155 ICS for initial controller

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therapy, and 169 leukotriene antagonist and 181 long-acting β_2-agonist as add-on therapy to ICS). Of those receiving initial controller therapy, 51% were women; the mean age was 46 years and 22% were current smokers. Of those receiving add-on therapy, 63% were women; the mean age was 50 years and 17% were current smokers.

All treatments were associated with substantial mean improvements in outcome measures with no significant between-group differences in MiniAQLQ or ACQ score or QALYs gained at 2 months and 2 years.

Leukotriene antagonists compared with ICSs as initial controller therapy

At 2 months, the MiniAQLQ scores met our equivalence criterion, with adjusted difference (95% CI) between leukotriene antagonist and ICS of –0.02 (–0.24 to 0.20). At 2 years, however, the 95% CIs excluded the threshold for equivalence of 0.3, favouring ICS [–0.11 (–0.35 to 0.13)]. No significant between-group differences were found in ACQ score at either 2 months [adjusted difference 0.01 (–0.20 to 0.22)] or 2 years [0.13 (–0.07 to 0.33)]. The 95% CIs were well within the minimum clinically important difference of 0.5 for the ACQ. No significant differences between leukotriene antagonist and ICS were found for any other secondary end point at 2 months or 2 years, including the number of asthma exacerbations, %PPEF, RCP3 questions, mRQLQ, respiratory tract infections or respiratory tract infection consultations.

Leukotriene antagonist compared with long-acting β_2-agonist as add-on therapy to ICS

At 2 months, the MiniAQLQ scores met our equivalence criterion, with adjusted difference (95% CI) between leukotriene antagonist and long-acting β_2-agonist of –0.10 (–0.29 to 0.10). At 2 years, the 95% CIs for MiniAQLQ score were marginally over the equivalence threshold, favouring long-acting β_2-agonist as add-on therapy [adjusted difference at 2 years –0.11 (–0.32 to 0.11)]. However, there were no significant between-group differences in ACQ score at either 2 months [0.12 (–0.06 to 0.30)] or 2 years [0.04 (–0.15 to 0.22)]. Daily ICS dose did not differ between the two treatment groups. No significant differences were found in exacerbations, %PPEF, RCP3 questions, or mRQLQ, respiratory tract infections or respiratory tract infection consultations.

Cost-effectiveness results

Compared with those receiving ICS as initial controller therapy, participants receiving leukotriene antagonist had significantly higher NHS and societal costs at both time points. ICS numerically dominated leukotriene antagonist in terms of cost-effectiveness, although outcomes were not statistically significantly different.

For patients receiving add-on therapy to ICS, no significant differences between leukotriene antagonist and long-acting β_2-agonist in NHS or societal cost were found at 2 months, but, after 2 years, participants receiving leukotriene antagonist had higher societal costs of borderline statistical significance. The extra cost per extra QALY gained was £22,589 (2-year time horizon, societal perspective). Given a willingness to pay of £30,000 per QALY gained, there is a probability of between 51.6% and 54.6% that leukotriene antagonist is a cost-effective alternative to long-acting β_2-agonist as add-on therapy to ICS, depending on time horizon and perspective.

The broad inclusion criteria for this study meant that active smokers, those with smaller impairments of lung function and patients with other comorbidities, who are typically excluded from clinical trials, were included in our study population. The conduct of this study in patients' own primary care practices by their normal health-care providers retained the 'real-life' setting, thereby enabling the generalisability of our results to primary care. This also resulted in extremely low dropouts from the study, which contrasts strongly with most published randomised trials in respiratory disease. A limitation of this study is that by 2 years many patients were switched from initial randomised therapy to alternate therapy due to a range of factors, including practice protocols for inhalers and chlorofluorocarbon transition. We speculate that another factor may be the shorter durations of drug supplies in those randomised to leukotriene antagonist and resulting greater review, providing greater opportunities to change therapy.

Conclusions

Results of this pragmatic trial in UK primary care were equivalent with regard to asthma-specific

QoL (MiniAQLQ) at 2 months after commencing controller therapy with leukotriene antagonist or ICS (step 2 of the BTS guidelines). Our equivalence criterion for MiniAQLQ was not met at 2 years; however, there were no statistically significant differences between treatment groups at this time. There were no differences in asthma control measures (ACQ score and exacerbations) at 2 months or 2 years; thus, any possible advantage of one over the other appears to be clinically unimportant. All treatments were associated with substantial mean improvements, which may, at least in part, have been due to regression to the mean or treatment effects. At 2005 UK prices of leukotriene antagonist and ICS, leukotriene antagonist was not a cost-effective alternative to inhaled corticosteroid at step 2.

Results of add-on therapy with leukotriene antagonist or long-acting β_2-agonist for patients with uncontrolled asthma already receiving ICS (step 3) were equivalent at 2 months (step 3 of the BTS guidelines), and at 2 years almost met our equivalence criterion. There were no significant differences between treatment groups in ACQ score or exacerbations. Leukotriene antagonist was of borderline cost-effectiveness compared with long-acting β_2-agonist.

Implications for health care

The evidence suggests that, while any advantage of one treatment over the other appears to be clinically unimportant, leukotriene antagonists are unlikely to be a cost-effective alternative to ICSs, at 2005 prices, as initial asthma controller therapy at step 2. In addition, the evidence suggests that leukotriene antagonists may be clinically equivalent to long-acting β_2-agonists as add-on to ICSs in terms of QOL as well as secondary measures, and, furthermore, suggests that leukotriene antagonists could be repositioned as an equal alternative to long-acting β_2-agonists at step 3 of the BTS guidelines.

When generic leukotriene antagonist formulations become available in the next few years their cost-effectiveness as an alternative to ICS may justify further evaluation, particularly in the subgroup of patients with limited impairment of lung function, those newly diagnosed with asthma to minimise inhaler education and those with fears about inhalers or inhaled steroids.

Recommendations for research

- Establish, in primary care, whether leukotriene antagonists will be more or less beneficial than ICSs alone or as an add-on to ICSs in treating patients with asthma who are also active smokers.
- Determine why the ACQ correlates more poorly with economic outcomes of asthma than the MiniAQLQ and EQ-5D.
- Understand further the reasons why patients were switched from study medication when there was no real clinical indication to do so and examine ways to minimise this happening in future pragmatic primary care-based clinical trials.

Trial registration

This trial is registered as ISRCTN99132811.

Funding

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Chapter 1
Introduction

Scientific background

Asthma is a condition of the bronchial airways, characterised by airway hyper-responsiveness (or airway irritability) and reversible airway obstruction. In 2002, an estimated 3 million people, or 5% of the UK population, had asthma.[1,2] Asthma is caused by chronic inflammation of the small, or bronchial, airways. This inflammation causes the production of mucus, oedema formation, and nerve end exposure, and leads to an increase in airway hyper-responsiveness. Increased airway hyper-responsiveness causes narrowing of the airways (or bronchoconstriction), which may lead to coughing, wheezing, chest tightness and shortness of breath. In asthma, airway bronchoconstriction can be substantially reversed with a short-acting β_2-agonist or reliever medication.

Untreated chronic inflammation in the airways may lead, in some individuals, to structural changes (or airway remodelling), irreversible bronchoconstriction and persistent symptoms. The recognition that airway inflammation is present even in patients with mild asthma has led to a shift towards introducing anti-inflammatory therapy earlier in the management of asthma,[2,3] with increased prescribing of inhaled corticosteroids[4,5] in patients requiring daily use of a short-acting β_2-agonist [step 2 of British Thoracic Society (BTS) Asthma Guidelines].[4,5] However, while there is some evidence of reduced morbidity, many patients with asthma still have considerable symptoms and lifestyle limitation.[6] Possible reasons for this include lack of disease recognition, poor adherence to inhaled steroids, poor inhaler technique, untreated rhinitis, smoking, and an inability of inhaled steroids alone to fully control asthma, with an increasing emphasis on the role of adding additional therapy to inhaled steroids rather than routinely increasing inhaled steroid dose. As a result these patients end up being treated at step 3 of the BTS Asthma Guidelines.[4]

Efficacy studies of antiasthma therapies have traditionally used measures of airways function, such as spirometry [forced expiratory volume in 1 second (FEV_1)][7,8] and domiciliary peak expiratory flow (PEF),[7] or measures of airway hyper-reactivity, such as methacholine bronchial challenge testing,[9–12] to demonstrate therapeutic effectiveness. While these measures provide objective information on airway function, they provide no information on patient perceived effectiveness of an asthma treatment or asthma control. Indeed, the 'real-life' control of asthma is now regularly assessed in terms of changes in patient-reported quality of life (QOL), symptoms, exacerbations and rescue medication use. As the correlation is often poor between objective measures of airway function (e.g. domiciliary PEF) and measures of asthma control, international guidelines encourage the collection of measures of both airway function and disease control.[5]

Anti-inflammatory treatments with the potential to treat mild to moderate asthma are inhaled corticosteroids and leukotriene receptor antagonists. Corticosteroids work by suppressing the production of inflammatory mediators by airway epithelial and smooth muscle cells, endothelial cells and fibroblasts.[13] However, inhaled steroids have been shown to have limited impact on suppressing the production or release of the cysteinyl leukotrienes LTC_4, LTD_4 and LTE_4, biologically active mediators derived from arachidonic acid, which collectively account for the biological activity known as slow-reacting substance of anaphylaxis.[14,15] These leukotrienes mediate many responses that are associated with asthma, including mucus production, decreased mucociliary clearance, changes in vascular permeability, inflammatory cell influx and smooth muscle contraction.[16] Thus, leukotriene receptor antagonists that act to reduce the production or block the action of leukotrienes may be important in asthma management and complementary to inhaled corticosteroids.

Leukotriene receptor antagonists

Montelukast and zafirlukast are orally active, potent selective leukotriene $CysLT_1$ receptor antagonists. The safety and tolerability of both of these leukotriene antagonists are well established.[17,18] Compared with placebo they

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have been shown to improve airway function and symptoms, and decrease short-acting β_2-agonist use.[19–21] They also inhibit early- and late-phase bronchoconstriction that is induced by inhaled allergen,[22,23] and attenuate exercise-induced bronchoconstriction at a level at least comparable to long-acting β_2-agonist.[24] Montelukast has also been shown to decrease sputum and peripheral blood eosinophil levels.[25] Results from adult Phase III clinical studies demonstrate that, compared with placebo, montelukast[21] and zafirlukast[19] improve FEV_1, daytime symptoms, total daily β_2-agonist use, nocturnal asthma, morning and evening PEF, asthma-specific QOL, patient and investigator global evaluations, and asthma exacerbation rate in patients using short-acting β_2-agonist only. Other studies have demonstrated the additive effects of montelukast in patients taking inhaled steroids.[26] Additionally, results from a chronic exercise study demonstrate the ability of montelukast to attenuate exercise-induced bronchoconstriction at the end of the dosing interval over a 12-week period without loss of effect[27] and a comparable effect to long-acting β_2-agonist.[24] Montelukast also reduces blood[21] and sputum eosinophils.[25]

Leukotriene antagonists could potentially be used at step 2 or step 3 of the asthma guidelines. At step 2, leukotriene antagonists would be used as an alternative to inhaled steroids, while at step 3 leukotriene antagonists would be used as an alternative to long-acting β_2-agonists as add-on therapy to inhaled steroids in patients who are not controlled on inhaled steroids alone.

Recent studies evaluating the use of montelukast or zafirlukast against inhaled steroids at step 2 suggest that leukotriene antagonists are inferior to inhaled steroids in short-term double-blind double-dummy studies and in patients with significant asthma severity. In a meta-analysis, Ducharme[28] reported that patients randomised to a leukotriene antagonist had a 60% increased risk of exacerbation compared with a patient receiving 400 µg of the inhaled steroid beclometasone dipropionate. Those randomised to inhaled steroid had a significantly increased FEV_1 compared with leukotriene antagonist. However, Israel *et al.*[29] reported that although 400 µg beclometasone significantly improved FEV_1 compared with montelukast, they found no significant difference in the number of exacerbations, possibly indicating that leukotriene antagonists may confer benefits in asthma control which are equivalent to those of inhaled steroids.

In patients with unstable asthma currently receiving an inhaled steroid, the addition of montelukast or zafirlukast leads to clinically important improvements in airway function, asthma exacerbations, attacks and symptoms, as reviewed by Currie and McLaughlin.[30] All inhaled steroids have debilitating side effects; although these are largely associated with high doses, local side effects appear to be more common at lower doses than previously recognised.[31] Indeed guidelines advocate tapering inhaled steroids to the minimum effective dose.[4,5] Although neither montelukast nor zafirlukast is licensed for steroid sparing (i.e. minimising the dose of inhaled steroid), Lofdahl *et al.*,[32] Price *et al.*[33] and Riccioni *et al.*[34] have reported some evidence that this may be possible.

Two recent meta-analyses have examined the effects of leukotriene antagonists as add-on therapy to inhaled steroids.[35,36] Ducharme *et al.*,[35] compared the effects of adding leukotriene antagonist versus long-acting β_2-agonist to inhaled steroid therapy in trials of 28 days or longer, and found a 17% lower risk of asthma exacerbation with add-on long-acting β_2-agonist: 38 patients receiving inhaled steroid had to be treated for 48 weeks with add-on long-acting β_2-agonist rather than add-on leukotriene antagonist to prevent one exacerbation. Lung function, symptoms and the use of rescue short-acting β_2-agonist were also better with long-acting β_2-agonist. The authors note that while the internal validity of their findings is supported by the homogeneity of studied patients and trials, the external validity or generalisability of their findings is an issue.[35] Indeed, a limitation of the majority of the studies performed to date is that they are not 'real world', and do not necessarily reflect the issues of poorer compliance and adherence to inhaled medications compared with oral medications observed in primary care. They also rarely take a true intention-to-treat approach with patients who cease study therapies and drop out of the study at that point.[37]

The second systematic review (pooling of data by meta-analyses performed when feasible) looked only at studies of ≥12 weeks' duration that compared montelukast as add-on to inhaled steroid with inhaled steroid monotherapy or with salmeterol as add-on to inhaled steroid.[36] Compared with inhaled steroid monotherapy, add-on montelukast to inhaled steroid improved control of mild to moderate asthma. Compared with add-on salmeterol, add-on montelukast to inhaled steroid was less effective with regard

to most clinical outcomes in the medium term; however, over 48 weeks the proportions of patients with ≥ 1 exacerbation were similar, as were hospitalisation and emergency treatment rates. The rate of serious adverse events over 48 weeks was significantly higher with add-on salmeterol; thus, montelukast may have a better long-term safety profile.[36]

At the time of commissioning this study, the data regarding the cost-effectiveness of leukotriene antagonists in primary care were limited. In one primary care centre, a prospective audit of outcomes and cost associated with montelukast suggested that as an add-on option in patients at step 3, there might be significant clinical benefits at little additional cost.[38] Recent studies have suggested that, at step 2 of the asthma guidelines, use of a leukotriene antagonist compared with an inhaled steroid is associated with higher health-care resource utilisation.[39] However, this study did not evaluate clinical outcomes or patient reported measures of disease control.

Hypotheses

In older children and adult patients with chronic asthma, initiation of a leukotriene receptor antagonist will provide, at no greater cost to the National Health Service (NHS) and patients, clinical improvements in QOL and other important asthma parameters that are at least equal to the alternative treatment options of inhaled corticosteroid at step 2 and adding a long-acting β_2-agonist at step 3. This study was designed as two separate, but concurrent, equivalence trials to determine whether a leukotriene antagonist is an equal choice to inhaled steroid as monotherapy, and to long-acting β_2-agonist as add-on therapy, for a real-world population of patients with perhaps milder asthma and who are less likely to adhere to therapy than those enrolled in classical clinical trials.

Rationale for this study

Need for cost-effectiveness data

In response to growing pressure on health-care budgets, and the availability of a choice of different therapeutic interventions for many diseases, evidence on the relative value for money of new or different therapeutic interventions is becoming increasingly important. In recognition of this, the UK Department of Health has provided guidelines to encourage the evaluation of therapeutic interventions from an economic perspective, in parallel with traditional investigations into efficacy and safety.[40] Indeed the UK National Institute for Health and Clinical Excellence (NICE), established in 1999, evaluates medicines (new and current) for use within the NHS by reviewing both clinical and economic evidence.

Asthma is a condition for which economic evaluation of therapeutic interventions is particularly relevant; the prevalence is high, with reported treatment prevalence rates for the UK ranging from 2% to 5% for adults and up to 10% for school-aged children,[1] and a range of different therapeutic interventions are available.[4] The high-prevalence chronic nature of the disease, along with the range of therapeutic interventions, make the management of asthma a considerable financial burden on the NHS.[41] However, published investigations into the costs of asthma management either have focused on isolated components of treatment, such as specific medications, or have used limited retrospective data for estimates of health-care utilisation.[41–45] Only minimal information is available on the 'real-world' cost of asthma management, including costs to primary and secondary care, the patient, and the indirect cost of lost productivity to the economy.

Leukotriene receptor antagonists could potentially be used at both steps 2 and 3 of the asthma guidelines.[4,5] Although leukotriene antagonists are more expensive to prescribe, in terms of drug acquisition costs, than low-dose inhaled steroids (~£24 per 28 days versus ~£8 per 28 days, respectively[46]), and although less effective in terms of objective measures of lung function, they appear to produce comparable overall asthma control[29] and are associated with superior adherence.[37,47] Leukotriene antagonists may therefore result in significant health gain and savings in other areas of health and patient costs, which might justify additional prescribing costs. There is some evidence from long-term trials that this may be the case.[48] However, markers of cost-effectiveness in asthma clinical trials have included cost per asthma-free day or cost to achieve a given improvement in lung function.[49] Outcomes such as asthma-free days and improvement in lung function are good clinical measures. However, the latter is not necessarily correlated with meaningful changes in overall QOL for the patient, and the former does not cover all aspects of health-related QOL that may be of relevance to the patient. More appropriate markers are required.

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The purpose of this study was to compare the long-term effectiveness and total cost of asthma management to the NHS, patients and society in two groups of patients – one group receiving leukotriene antagonist and the other group receiving the most effective evidence-based alternatives at step 2 (inhaled steroid) and step 3 (long-acting β_2-agonist). It is important to provide a convincing investigation of the cost-effectiveness of prescribing leukotriene antagonists. To this end, we proposed a long-term study, taking the wider costs of asthma management into account, to be conducted in a manner reflecting real clinical practice. The primary efficacy variable for this study was the validated Juniper disease-specific asthma QOL scale – the Mini Asthma Quality of Life Questionnaire (MiniAQLQ).[50] This was chosen because it captures outcomes of relevance to patients and their primary caregivers, thus reflecting 'real life'. We regarded a difference of > 0.3 in MiniAQLQ score as a meaningful difference because although 0.5 has been regarded in individuals as a minimum clinically important difference,[51] many studies, even versus placebo, have found smaller differences of 0.3–0.4[21] to be associated with clinical benefit. Therefore, we have opted for this more conservative figure for a population difference.

Evaluation of effectiveness at step 2 of asthma guidelines

Many patients are not fully controlled by inhaled steroids, due to a mixture of lack of complete clinical effectiveness and poor adherence with regular treatment. Alternative treatments for inhaled steroids, such as the leukotriene receptor antagonists zafirlukast and montelukast, may have a role, with some studies suggesting fairly similar overall asthma control and proportion of responders to inhaled steroids,[52,53] greater patient preference[54] and higher adherence rates.[55]

At the time of designing and commissioning of this study, UK guidelines for the management of asthma in older children and adults (written in 1995) did not propose a clear role for leukotriene antagonists.[56] However, the latest Global Initiative For Asthma (GINA)/World Health Organization and UK guidelines suggest they may be used at step 2 as an alternative to inhaled steroids.[4,5]

Evaluation of effectiveness at step 3 of asthma guidelines

Many patients taking inhaled steroids continue to have symptoms, reduced asthma-specific QOL and excessive relief treatment use, and thus require additional treatment.[57] BTS and GINA guidelines suggest two options: increasing the dose of inhaled steroid or adding a long-acting β_2-agonist.[4,5] However, some view the safety, tolerability and compliance with high doses of inhaled steroids with some concern,[5,58,59] and most studies suggest that adding a long-acting β_2-agonist may be most likely to be clinically effective.[60,61]

Adding in a leukotriene antagonist may be useful at this step for two reasons (1) steroids do not appear to suppress leukotriene production[14,15] and (2) montelukast and zafirlukast have both been shown to give add-on benefit to inhaled steroid.[26,30] Leukotriene antagonists may enable inhaled steroid tapering and thus maintenance on a lower dose of inhaled steroid.[32]

Chapter 2
Methods

This study comprised two separate randomisations, thus two pragmatic randomised controlled trials, powered for equivalence, comparing leukotriene antagonists with (1) inhaled steroids for patients initiating controller therapy at step 2 and (2) long-acting β_2-agonists on a background of inhaled steroids for patients at step 3 of the asthma guidelines with regard to disease-specific QOL and resource use in the short term (2 months) and the long term (2 years) on an intention-to-treat basis. The trials were conducted with minimal interference with routine clinical care to evaluate real-life outcomes for patients with asthma in general practice. Patients and health-care providers were not blinded to treatment allocations; however, data collection and statistical analyses were blinded.

The study was reviewed and approved by the Eastern Multi Centre Research Ethics Committee (Ref. 00/5/13) and local (research consortia and primary care trust) ethical and research governance committees, and was conducted in accordance with appropriate research guidelines.

Participants

In the BTS *British Guideline on the Management of Asthma*[4] the therapy of patients from the age of 6 years upwards follows the same strategy as for adults, except for alterations in dosage ranges to adjust for differences in body mass. Since exactly the same strategy is used across the age range of older children and adults, the findings of studies will have greater generalisability if they enrol patients from that entire range. Owing to limitations of validity of the MiniAQLQ and the Asthma Control Questionnaire (ACQ),[62] we were unable to study children below the age of 12 but did allow children over this age, as well as adults of all ages, to be included to maximise generalisability of the study findings.

In the initial design of the study, participant recruitment was to be by primary care practice staff, as they conducted acute and routine respiratory care visits, identifying patients who met the entry criteria, informing them of the study and, if appropriate, consenting and enrolling them into the study. However, recruitment by this strategy was slower than originally anticipated owing to changes in clinical practice resulting from delays in study funding and changes in national asthma guidelines. The protocol and the process of identification of eligible patients were therefore modified, as described below, to allow prospective identification of possible study participants. All patients entering the study met the same eligibility criteria and follow-up was identical.

Further recruitment into the study was via a three-stage process.

Recruitment stage 1

Patients aged 12–80 years, attending 53 participating primary care (or general) practices in Norfolk, Suffolk, Essex, Cambridgeshire, Bedfordshire, Hampshire and Dorset, in the UK, who had received a prescription of short-acting β_2-agonist in the previous 2 years, were invited, by letter, to provide data allowing eligibility for the studies to be determined. Patients were asked to provide information on their current asthma status and inhaler usage. The case notes of patients whose asthma status was consistent with eligibility in the study were reviewed by practice and study staff against the following eligibility criteria.

Inclusion criteria

- Capable of understanding the study and study procedures (and parent/guardian's capability of understanding the study and study procedures for patients aged under 16 years).
- Patient had a diagnosis of asthma [defined as (1) documented reversibility after inhaled short-acting β_2-agonist *and/or* (2) PEF variability on PEF diary *and/or* (3) physician-diagnosed asthma *and/or* (4) physician diagnosis of asthma plus history of response to treatment].
- *Step 2 trial* Patient was not currently receiving, and had not received, inhaled steroid or leukotriene antagonist within the previous 12 weeks.

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- *Step 3 trial* (1) Patient had received inhaled steroid for at least the last 12 weeks, as ascertained from prescribing records and patient self-report and (2) had not received a long-acting β_2-agonist or leukotriene antagonist in the previous 12 weeks.

Exclusion criteria

- Patient had participated in a clinical trial involving an investigational or marketed drug within 90 days.
- Patients had received a substantial change in antiasthma medication within the previous 12 weeks.
- Patient was a current, or recent past, abuser (within past 3 years) of alcohol or illicit drugs.
- Patient had any other active, acute or chronic pulmonary disorder or unresolved respiratory infection within previous 12 weeks.
- Patient had a history of any illness that was considered to be immediately life threatening, would pose restriction on participation or successful completion of the study or would be put at risk by any study drugs (e.g. allergy to leukotriene antagonist).
- Patient had received systemic, intramuscular or intra-articular corticosteroids within the previous 2 weeks (artificial baseline).

Patients who met those entry criteria that could be assessed by a records review in their general practice were invited for a screening visit (visit 1 – see *Figure 1* and *Table 1*). All patients had at least 24 hours to review the patient information sheet prior to attending the visit. Patients attending for at least visit 1 will, from here on, be referred to as 'participants'.

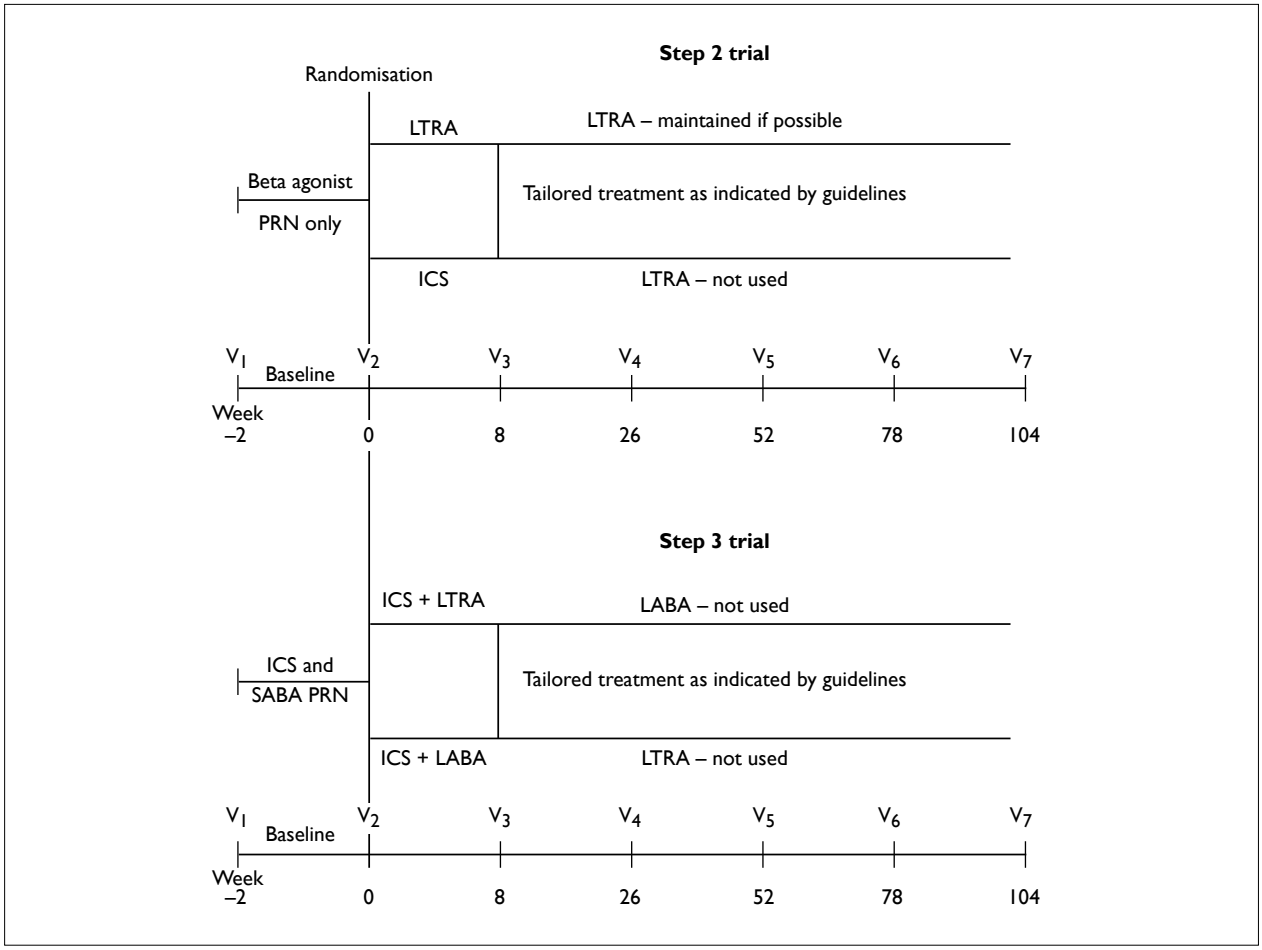

FIGURE 1 *Study flow charts, Patients at step 2 received initial controller therapy with leukotriene antagonist or inhaled steroid, Patients at step 3 received leukotriene antagonist or long-acting β_2-agonist as add-on to inhaled steroid, ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonist; LABA, long-acting β_2-agonist; PRN, 'pro re nata' – as needed; SABA, short-acting β_2-agonist.*

TABLE 1 *Time lines for both step 2 and step 3 trials*

	Baseline		Trial period				
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Study timescale (weeks)	–2	0	8	26	52	78	104
Leeway allowed (days)[a]		±7	±21	±21	±21	±21	±21
GP and/or practice asthma nurse procedures							
Assess inclusion/exclusion criteria	✓						
Informed consent	✓						
Record clinical/asthma history and prior medications		✓					
Review clinical data and asthma therapy (per clinical need)	✓	✓	✓	✓	✓	✓	✓
Check patient has/can adequately use PEF meter	✓						
Treatment arm randomisation by dial-up centre		✓					
Review action plan for worsening asthma	✓	✓	✓	✓	✓	✓	✓
Review any adverse experiences		✓	✓	✓	✓	✓	✓
Record PEF (no inhaled β_2-agonist for 4 hours if possible)	✓	✓	✓	✓	✓	✓	✓
Confirm patient resource utilisation		✓	✓	✓	✓	✓	✓
Blinded research assistant/study office							
Collect completed patient symptom diary card		✓	✓	✓	✓	✓	✓
Collect data on patient costs		✓	✓	✓	✓	✓	✓
Asthma QOL and EQ-5D (quality of life) questionnaries		✓	✓	✓	✓	✓	✓
Rhinitis questionnaires		✓	✓	✓	✓	✓	✓
Dispense patient diary card for subsequent visit	✓	✓	✓	✓	✓	✓	
Collect resource use data from practice records							✓

GP, general practitioner.
a Practices were encouraged, and participants were reminded to have follow-up visits on or near the dates as described, but where for pragmatic reasons participants had follow-up respiratory care visits only between or after the stated dates, information from those dates was utilised.

Recruitment stage 2

At visit 1, participants (and parent or guardian if appropriate) gave written informed consent and were allocated a unique study number. Participants were reviewed for the following additional entry criteria:

- Peak expiratory flow, while withholding β_2-agonist for at least 4 hours, of > 50% predicted.
- Females of child-bearing potential agreed to use adequate contraception throughout the study.

Participants meeting the above criteria completed a 2-week PEF diary,[63] ACQ,[64] and asthma-specific QOL questionnaire (MiniAQLQ)[50] prior to returning for visit 2.

Recruitment stage 3

At visit 2, participants scoring ≥ 1 on the ACQ (range 0–6, with ≤ 0.75 being optimal[65]) and/or ≤ 6 (out of a maximum best score of 7) on the MiniAQLQ were registered and randomised within the step 2 or step 3 study by an automated 'dial-up' centre at the University of East Anglia, Norwich, UK. A computer responded to the telephone calls from practices by recording identification information. It then used input from the practice about the step at which the patient was to enter the study to perform a look-up into predefined tables of randomisation allocations (see Randomisation, below) and then inform the caller of the allocation for that participant.

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Interventions

Using a pragmatic, randomised controlled trial design, leukotriene antagonist prescription was compared with (1) inhaled steroid prescription at step 2 of the guidelines and (2) long-acting β_2-agonist against a background of inhaled steroid at step 3 (*Figure 1*). Patients and health-care providers were aware of treatment allocations, while study data collection and statistical analyses were blinded.

- *Leukotriene receptor antagonist* montelukast 10 mg, once daily (as Singulair®; Merck, Sharp & Dohme Ltd, Hoddesden, UK) or zafirlukast 20 mg, twice daily (as Accolate™, AstraZeneca Ltd, Kings Langley, UK).
- *Inhaled corticosteroid – step 2 study* inhaled beclometasone dipropionate, budesonide or fluticasone propionate.
- *Long-acting β_2-agonist – step 3 study* salmeterol (as Serevent®, GlaxoSmithKline, Uxbridge, UK) or formoterol (as Foradil®, Novartis Pharmaceuticals UK Ltd, Camberley, UK; or Oxis®, AstraZeneca Ltd, Kings Langley, UK); these are also available in fixed dose combinations with inhaled steroid (as Seretide™, GlaxoSmithKline, Uxbridge, UK and Symbicort®, AstraZeneca Ltd, Kings Langley, UK).

All individual drug and device choices within treatment allocations were made according to normal clinical practice by the health professional involved (and bearing in mind BTS guidelines), subject to the restrictions outlined below.

Other asthma medications

- Inhaled short-acting β_2-agonist was permitted throughout the study 'as needed'.
- Theophylline, cromoglycate, nedocromil and ipratropium were permitted if clinically appropriate.
- Inhaled steroids were permitted after randomisation in both arms in the step 2 trial. However, if clinically acceptable, participants within the leukotriene antagonist arm were to be given every chance to manage without inhaled steroid.
- In step 2 and step 3 trials, practices were asked to use leukotriene antagonists only within that treatment arm assigned to them.
- Long-acting β_2-agonists were permitted in both arms of the step 2 trial. Practices were asked not to use them in the leukotriene antagonist step 3 arm.
- If participants required a disallowed asthma medication, this fact was noted, the medication was given and the patient was continued in the study. As the planned analysis was on an intention-to-treat basis, participants were not discontinued for receiving a disallowed medication.

Allowed allergic rhinitis and conjunctivitis medications

- Topical treatment or antihistamines were preferred.

Excluded therapy

- β-Receptor blocking agents (including ocular preparations).
- Non-steroidal anti-inflammatory agents, when a patient had a known or suggestive history of aspirin-sensitive asthma.

Objectives

Primary objective

To compare QOL with leukotriene receptor antagonist against alternative treatments at steps 2 (inhaled corticosteroid) and 3 (long-acting β_2-agonist) of the guidelines, comparing resource use in the short term (over 2 months) and the long term (2 years) to the NHS and society (on an intention-to-treat basis), using cost–utility and cost-effectiveness approaches.

Secondary objectives

To compare two markers of asthma control: (1) the validated ACQ, which evaluates symptoms of asthma and reliever treatment usage, and (2) asthma exacerbations requiring oral steroid therapy or hospitalisation. Other outcomes compared between the two treatment groups at 2 months and throughout the 2-year study period included respiratory tract infections, consultations for respiratory tract infection, short-acting β_2-agonist prescriptions, daily inhaled steroid dose (step 3 study only), per cent predicted PEF (%PPEF) at clinic visits, secondary QOL measures, 2-week domiciliary diary cards of symptoms and PEF, and time off work because of asthma. As the design was pragmatic in nature, and to ensure minimal dropouts, the major focus in terms of data collection were the primary study end points and the markers of asthma control (ACQ and exacerbations).

Outcome measures

- *Primary outcome measure*: The primary outcome was a between-group comparison of disease-specific QOL (described in Health status measures, below) and cost to achieve this to the NHS and patient at 2 months (the primary time point) and 2 years (described in section Resource use assessment, below).
- *Secondary outcome measures*:
  - ACQ score
  - number of asthma exacerbations – defined as requiring at least one course of oral corticosteroids or hospitalisation for asthma; when a patient received more than one course of oral steroid during the course of the study, any two courses of oral steroid prescribed within a 14-day period were considered as a single exacerbation, irrespective of the fact the patient required ≥2 courses of oral steroid.
  - attendance at primary care practice for upper and/or lower respiratory tract infections (number of total respiratory tract infections and number of primary care practice attendances for those respiratory tract infections)
  - short-acting β_2-agonist prescriptions
  - change in inhaled steroid dose (for step 3 participants only)
  - clinic PEF, percentage of predicted normal values calculated using the Roberts equation[66]
  - Mini Rhinitis Quality of Life Questionnaire (mRQLQ) scores[67]
  - Royal College of Physicians – three (RCP3) asthma questions scores[68,69]
  - personal objectives scores
  - changes in treatment after randomisation
  - adherence with prescribed therapy.

Safety was evaluated by the analysis of the overall incidence of adverse experiences.

Health status measures

Participants completed the following self-administered questionnaires at visit 2, and prior to attending visits 3–7. Participants were asked to return completed questionnaires to the study office.

- *Mini Asthma Quality of Life Questionnaire* (age-specific version[50]) The MiniAQLQ is a validated 15-item asthma-specific QOL questionnaire, which is a self-administered shortened version of the 32-item AQLQ,[51,70] used to evaluate the impact of asthma on QOL. Eleven questions assess the presence of asthma-related symptoms rated from 1 (all of the time) to 7 (none of the time); and four questions assess specific activity limitations as a result of asthma, rated from 1 (totally limited) to 7 (not at all limited). The final score is a mean of the responses ranging from 1 (worst) to 7 (best), and the minimum clinically important difference in MiniAQLQ score is 0.5.[51]
- *Asthma Control Questionnaire* The validated ACQ assesses five asthma-related symptoms, judged by international consensus to be the most important in evaluating asthma control.[62] These are night-time awakenings by asthma, severity of asthma symptoms on awakening, daily activity limitations because of asthma, shortness of breath and wheezing; patients score each question on a 7-point scale from 0 (best) to 6 (worst). A sixth question categorises daily number of puffs of short-acting bronchodilator from 0 (none) to 6 (more than 16 puffs most days). The overall score is the mean of the responses from 0 (totally controlled) to 6 (severely uncontrolled). A shortened version of the ACQ, excluding airway calibre, was used in this study.[64] An ACQ score of ≤0.75 is considered to represent well-controlled asthma, whereas a score of ≥1.5 respresents asthma that is not well controlled.[65] The minimum clinically important difference in ACQ score is 0.5.[64]
  - In addition, as mentioned under Participants, above, the ACQ and MiniAQLQ were completed by patients prior to, or at, visit 1 as part of the screening process.
- *European Quality of life-5 Dimensions (EQ-5D) questionnaire* The EQ-5D comprises five questions (dimensions) on aspects of overall health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and a visual analogue scale, recording the respondents' self-rated health status on a vertical graduated (0–100) 'thermometer'.[71] The five questions are converted into a single utility index representing overall health, using equations relevant to the UK population.[72] Alternatively, direct measurements from the visual analogue scale can be used.
- *Mini Rhinoconjunctivitis Quality of Life Questionnaire* The Mini Rhinoconjunctivitis Quality of Life Questionnaire is a shortened 14-item version of the 28-item Rhinoconjunctivitis Quality of Life Questionnaire that assesses how troubled the

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patient has been by rhinoconjunctivitis – from 0 (not troubled) to 6 (extremely troubled) – with regard to five domains: activity limitations, practical problems, nose symptoms, eye symptoms and other symptoms.[73,74]

- *RCP3 questions* The RCP recommends three questions to use to evaluate the impact of disease severity on quality of life in asthma patients (RCP3).[68,69] The questions are (1) Do you have difficulty sleeping because of asthma symptoms *(including cough)*? (2) Have you had usual asthma symptoms (*cough, wheeze, chest tightness, shortness of breath*) during the day? and (3) Has your asthma interfered with your usual activities (*housework, work/school, etc.*)?
- *Personal objectives* At visit 2, participants were asked to identify three activities that occurred regularly (not seasonally) in their life, and which they found difficult to do because of their asthma. These activities were events (e.g. cleaning, walking to work, aerobics), and not things or places avoided (e.g. cats, smoky rooms), as these do not count as activities. At each visit, participants graded their ability to undertake their chosen activities on a visual analogue scale of 0–100.

Resource use assessment

Resource use was divided into four groups: prescribed medications and devices, over-the-counter medications, primary and secondary care activity, and lost productivity. Data were extracted from primary care practice databases using MIQUEST (www.connectingforhealth.nhs.uk/miquest) and APOLLO SQL SUITE (www.apollo-medical.com/products/sql.htm). Where it was not practical to use automated extraction, a researcher transposed the data from the practice record system to the project database manually. Extraction was by the MIQUEST query system at 34 practices and APOLLO SQL SUITE at seven practices; manual retrieval was performed at 17 practices. At four practices, data were collected using both manual and MIQUEST systems during the development of the data extraction and collection tools. Duplicate data were removed. Data were extracted manually for 97 participants, and from MIQUEST or APOLLO data systems for 586. For all participants, 100% of the records were reviewed by a research associate to ensure that the records represented a cost attributable to asthma or asthma-related care as described in the section Prescribed medications, below. Data were also obtained from patient-completed diary cards, as detailed below. The price year for this analysis was 2005, and all costs incurred in the second year post randomisation were discounted by 3.5%.

Prescribed medications

Prescribed medications data were extracted from primary care practice records for the following conditions:

- asthma
- chest infections and/or bronchitis
- other respiratory tract infections
- eczema, hay fever, rhinitis and allergic conjunctivitis
- any adverse events considered to be related to asthma medication, for example oral thrush treatment.

Details recorded were:

- name of medication (brand name if branded medication prescribed) or device
- dosage
- formulation
- amount prescribed
- indication
- date prescribed.

After confirmation of the data in the practice, records were mapped from the various coding systems used by each of the primary care practice software systems (including Read codes), using further information about the product description as given in the MIQUEST 'Rubric' field, to a single table of unit costs indexed using the *British National Formulary*[46] code with unique extensions for each distinct product found [P. Richmond, prescribing data analyst, Broadland Primary Care Trust (PCT): List of unique product descriptions and codes; modified from the ePACT (Electronic Prescribing Analysis and CosT) codes from the Prescription Pricing Authority, 7 July 2005, personal communication]. From this a total quantity and cost were calculated.

Over-the-counter medications

Over-the-counter medication use data were extracted from patient diary cards. Prices were taken as stated by the patient (88%), or, if not stated (12%), from retail pharmacy websites (www.boots.com and www.sainsburys.com). All prices were adjusted to 2005 values using the Retail Prices Index (www.statistics.gov.uk).

NHS activity

All consultations with health-care professionals for conditions listed in Prescribed medications, above, were extracted from primary care records. Consultations initiated for another indication in which these problems were addressed (e.g. a regular consultation for contraception at which

asthma problems were reported) were assigned 50% of the time of the consultation. Consultations were divided into the following categories:

- *Primary care* regular attendance at asthma clinic with nurse or GP.
- *Primary care – patient initiated* GP and nurse clinic/home visits, out-of-hours visits and telephone consultations.
- *Secondary care* outpatient, inpatient, day case, emergency medicine and diagnostic procedures.

Study visits were timed to coincide with routine patient follow-up as per normal clinical practice for the management of asthma. Study visits (e.g. those clinical consultations that occurred for routine patient follow-up and therefore study data collection) were excluded from the analysis, as stated in the study protocol. However, where part of the study visit was used for non-routine patient follow-up, for example treatment of an exacerbation, 50% of the visit time was allocated to acute management of asthma rather than routine care. Unit costs and sources for the consultation scenarios are detailed in Appendix 1 (Unit costs table).

Indirect costs

Data on lost productivity were extracted from patient diaries where participants had noted the number of hours or days taken off work due to hospitalisation, primary care visits or other (asthma exacerbations, etc.). A day was counted as 8 hours.

Secondary outcome measures

At visit 1, and prior to visits 3–7, patients were given a validated diary card containing questions on asthma, to be completed in the 2 weeks immediately prior to the next visit.[63] As the duration between study visits was usually longer than 2 weeks, participants were contacted 2 weeks before study visits by the study office to remind them to complete the diary. The diary captured daytime and overnight symptoms, β_2-agonist use and resource utilisation. Diary cards were explained to study participants at visit 1 and reviewed by their practice nurse at each study visit. Diary cards were inspected by the GP to ensure that (1) the patient demonstrated proper use of the diary card in the baseline period at visit 2 and (2) the participant's symptoms were severe/mild enough to justify a treatment change when the patient reported unstable/stable asthma. Outcome measures collected in the diary were as follows.

Peak expiratory flow

Peak expiratory flow was measured prior to medication in the morning and evening during the 2-week baseline assessment and for 2 weeks before study visits. The best of three blows was recorded. Participants were asked to refrain from using short-acting β_2-agonist during the 4 hours immediately prior to PEF measurement.

Daytime asthma symptoms

Prior to going to bed, participants scored his/her asthma symptoms against a validated four-question daytime symptom score (marked on a 6-point scale of 0–5):

- How often did you experience asthma symptoms today? ('none' to 'all of the time').
- How much did your asthma symptoms bother you today? ('not at all' to 'severely bothered').
- How much activity could you do today? ('more' to 'less than usual').
- How often did your asthma affect your activities today? ('none' to 'all of the time').

Overnight asthma symptom score

Upon arising, and before taking any medications, participants answered the following question:

- Did you wake-up with asthma during the night *or* on arising at normal time? (yes or no)

'As needed' short-acting β_2-agonist use

Participants recorded the total number of 'puffs' of 'as needed' short-acting β_2-agonist used during the day (from waking to time of going to bed) and at night. Salbutamol that was used during study visits to assess airway reversibility was excluded. If nebulised β_2-agonist was used then this was recorded as six puffs.

Change in treatment

Numbers of patients with treatment changes, and reasons for change, were tabulated for all patients who were not lost to follow-up, who did not use a self-management treatment plan, and who had 18-month or 2-year treatment data. In addition, the days to treatment change were recorded.

Perception of therapy and adherence

Comparisons between objective measures of adherence and perceptions of oral therapy post-randomisation provide important complementary data to the cost-effectiveness analysis. Detailed

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patient interviews were conducted at intervals of between 3 and 6 months on 28 participants within the study time period to elucidate information on participants' perceptions of inhaled and oral therapy and adherence to long-term therapy.

Adherence to treatment was further analysed for patients who had at least 6 months of treatment without any change. Actual prescriptions issued versus prescribing instructions for periods in which they were valid were examined.

Safety monitoring and measurements

Action plan for treatment of worsening of asthma (self-management plan)

All participants had a personal asthma action plan provided, which adhered to asthma management guidelines and included information on self-treatment, when to seek help and how urgently to do so.

Evaluating and recording adverse experiences

Adverse experiences were monitored throughout the study and during the 14 days after completion of the study, and were recorded at each examination according to Good Clinical Practice guidelines. Adverse experiences were defined as any unfavourable and unintended change in structure, function or chemistry of the body temporally associated with any study medication, whether or not considered related. Clinically significant worsening of any pre-existing condition is also included. Serious adverse experiences were reported within 24 hours to the sponsor, the Health Technology Assessment (HTA) programme Coordinating Centre and Multi Centre Research Ethics Committee.

Discontinuation

Criteria for patient discontinuation during the study

Participants could discontinue study medication or participation at any time. Participants were discontinued from the study medication or participation if any of the following criteria were met:

- An adverse event occurred that suggested the patient's health could have been in jeopardy from continued study participation or that the patient was unable to complete study procedures successfully.
- The patient became pregnant.

Withdrawal of participants from the study

Participants who were withdrawn post randomisation from the study due to procedural errors (but were not discontinuations) continued to receive normal routine clinical care from their GP following withdrawal from the study.

Sample size and power calculation

This was based on the published literature[50,75] regarding sample sizes for assessing treatment differences in QOL. Treating this as an equivalence study, and assuming no true difference between the treatments in QOL for a two-tailed alpha of 0.05 and an upper limit of 0.3 for the 95% confidence interval (CI) for the difference between arms, a sample size of 142 participants was required. To allow for a 20% dropout rate, we aimed to recruit 178 participants to each study arm, resulting in a total of 356 participants at each of steps 2 and 3 (totalling 712 participants).

Randomisation

Participants were registered for entry into the study after giving written informed consent and returning completed QOL questionnaires. At visit 2, participants eligible for entry into step 2 or step 3 studies were randomised into the study. Randomisation into the study was stratified by practice, with a block size of 6. Practice nurses were informed of the randomised treatment to be given to their patient via an automated telephone centre (see Participants, above).

Blinding

This was a single-blind randomised controlled trial. General practitioners (GPs)/practice asthma nurses and participants were aware of the randomisation, while study research assistants were blinded to the randomisation. The role of the GPs/practice asthma nurses and research assistants in the conduct of the study is described below:

- *General practitioners/practice asthma nurses* GPs/practice asthma nurses had minimal involvement in data collection except baseline prior to randomisation, implementing the randomisation allocation and thereafter in administering the resource data collection sheet with participants. This allowed clinical freedom to change treatment as per normal management. Randomisation allocation was given directly to the GPs/practice asthma nurses by an independent automated telephone answering system.
- *Research assistants* Research assistants were non-clinical personnel who worked with practice staff to ensure proper completion of the diaries and self-completed QOL and disease-related questionnaires. They collected resource use information from participants, data from prescribing records, and clinical resource utilisation data for the participants at the end of the study period. When collecting resource data the research assistants were blind to the randomised allocation of the participants.

Data and statistical analysis

All analyses were performed blind to study arm allocation. This section outlines the statistical analysis procedures that were performed.

Effectiveness analysis

Baseline comparability between treatment groups

Baseline comparability between the treatment groups was evaluated by summarising and comparing the following parameters:

- *Demographics* age, sex, race, education, employment, disease history, weight, height, PEF, %PPEF, and PEF reversibility after salbutamol.
- *Efficacy outcome measures* primary and secondary outcome measures.

For the outcomes recorded on patient diary cards (nocturnal awakenings, symptom score, diurnal variation, etc.), the baseline was defined as the average of all values obtained during the 14 days between visits 1 and 2. For the other continuous efficacy end points, baseline was defined as the last value obtained before the start of randomised therapy. For binary outcomes, the baseline value was the sum of events occurring within the baseline period. For outcome measures obtained from the patient diary card, the baseline period was defined as the 14 days (or, if < 14 days, as many days of data as were available). For data obtained from the electronic patient record, the baseline period was defined as the 12 months prior to randomisation.

Primary outcomes

The primary outcome analysis was an intention-to-treat analysis of the MiniAQLQ score using multiple imputation where data were missing and including all patients with data at baseline and one post-randomisation time point. Analysis of covariance was used, with treatment as a fixed effect, and baseline value as covariate, to analyse MiniAQLQ scores at 2 months (the primary time point) and 2 years. A 95% CI for the difference between treatment mean scores was derived. The treatments were deemed to be equivalent if the 95% CI excluded a mean difference > 0.3 on the MiniAQLQ score (thus, 95% CI between –0.3 and 0.3), a difference chosen using an a priori conservative approach, based on 0.3 being substantially less than the 0.5 minimum clinically important difference for the MiniAQLQ.

This study was designed as two equivalence trials to determine whether leukotriene receptor antagonist is an equal choice to inhaled corticosteroid as monotherapy, and to long-acting β_2-agonist as add-on therapy, for a real-world population of patients with perhaps milder asthma and less likely to adhere to therapy than those enrolled in classical clinical trials.

In addition, a one-sided 95% CI (i.e. the lower bound from a 90% CI) was constructed for the difference in MiniAQLQ score. This was a secondary analysis to examine non-inferiority (rather than equivalence) of leukotriene antagonist versus control.

Secondary outcomes

The ACQ score analysis, like that for MiniAQLQ score, was an intention-to-treat analysis using multiple imputation for missing data, including all patients with data at baseline and one post-randomisation time point. The PEF values as percentage of predicted normal values were calculated using the Roberts equation and were compared between treatment groups at 2 months and 2 years using the Mann–Whitney test. Rates of asthma exacerbations, respiratory tract infections, and consultations for respiratory tract infections were compared using the Wald chi-squared test

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from the Poisson model. For other secondary end points, the last-observation-carried-forward approach was used for patients with missing follow-up data, again including only those with data for at least one post-randomisation time point; and an analysis of covariance was used, including treatment arm and baseline value as covariate.

1. *Frequency of exacerbations requiring hospitalisation, GP attendances and oral steroid courses* The count of exacerbations included all events where data indicated that the participant had a prescription for oral corticosteroids and/or a hospital admission for asthma. Issues of oral steroids related to asthma exacerbations were identified from primary care practice records. Where two or more consecutive courses of oral steroids were issued within 3 days of one course completing and a second being issued, this was regarded as a single exacerbation.
2. *Frequency of consultations for respiratory tract infections* The count of respiratory tract infections included all events where the Read code (or the rubric in the case of manually entered items) was for any diagnosed infection or combination of symptoms that strongly suggested an acute infection of either viral or bacterial aetiology. The combination of symptoms included 'productive cough with green sputum', and 'fever, cough, sore throat'. Events with descriptions such as 'allergic…' or 'chronic…' were excluded. All free text associated with the records was searched for the same phrases. In the case of entries where a single less specific symptom was recorded, such as 'cough', the database was searched for other records that could provide further clarification, for example the acute prescription of an antibiotic on that date. For both exacerbations and respiratory tract infections, when all such records were flagged, multiple records (e.g. clinic visits or courses of oral steroids) for a patient within a period of 14 days were considered to be a single event. Participants were considered to have multiple separate events if the duration between events was > 14 days.
3. *Short-acting β_2-agonist consumption (prescribing records)* Number of inhalers of short-acting β_2-agonist over the 2-year duration of the study was determined by totalling the number of issues requested, adjusting where appropriate for multiple inhalers of short-acting β_2-agonist being prescribed within a single issue.
4. *Daily inhaled corticosteroid dose for step 3 trial only* Daily dose of inhaled steroid was calculated from prescription records for the year prior to randomisation and the following 2 years. Daily dose of inhaled steroid was normalised to the efficacy of beclometasone dipropionate by multiplying daily dose of fluticasone propionate and beclometasone delivered as QVAR® (Ivax Laboratories, Aylesbury, UK) by 2. Budesonide was considered to have equivalent efficacy to beclometasone on a microgram per microgram basis.
5. *Asthma symptoms from diary card (for 2 weeks before each study visit)* Data for the 14 days immediately prior to each visit (or as much as was available if less than 14 days) were averaged or, for binary variables, the percentage of days with a positive response was taken.
6. *Clinic and diary PEF records (for 2 weeks before each study visit).*
7. *Diurnal variation in PEF* Diurnal variability was calculated according to the BTS Guidelines:[4] [(highest PEF–lowest PEF)/highest PEF].
8. *mRQLQ.*
9. *Need for further treatment intervention beyond initial treatment.*

The record of any participant whose medication dosage or device was changed after randomisation was reviewed by research assistants to determine the recorded reason for the change. Reasons for change were categorised as: associated with an asthma exacerbation (a change within 14 days of the use of or written reference to a use of short course of oral steroids or symptoms requiring use of secondary care services); to address poor symptom control (notes of respiratory symptoms); a report or suspicion of a side effect; after an adverse event; patient preference: to decrease the dosage; because of practice-based administrative policies; and/or reason unknown.

To confirm the results of the intention-to-treat analysis, we repeated the analyses after limiting to those participants who completed the study as per protocol and who were on an entirely fixed treatment regime. The population included in these analyses strictly included only participants whose prescribed therapy at randomisation was a fixed dose (not a prescribed range to be adjusted) and who did not have any change in either the initial drug prescribed at randomisation or the prescribed daily dose of that drug, or the addition of any other preventive asthma therapy at any time during the study, including the study final visit.

Planned secondary analysis

Planned subgroup analyses identified in the study protocol and in the minutes of study steering committee meetings are listed in Appendix 2.

Economic analyses

The protocol stated that where equivalence was demonstrated, a cost-minimisation analysis would be performed. As the results suggested 'near-equivalence' and, furthermore, as the study was powered to detect a difference in MiniAQLQ only (and not costs or other outcome measures), we present both comparisons of cost and cost-effectiveness analyses on MiniAQLQ, ACQ and quality-adjusted life-years (QALYs) gained, showing which of the treatments has the highest probability of being cost-effective.

Three cost-effectiveness analyses were performed: (1) comparison of incremental cost with incremental point improvement in MiniAQLQ score; (2) comparison of incremental cost and incremental point improvement in ACQ score; and (3) comparison of incremental cost and incremental QALYs gained (i.e. cost–utility analysis). Each analysis was conducted at 2 months' and 2 years' follow-up, from the NHS and societal perspectives.

Analyses were undertaken, based on complete case analysis, an imputed dataset, and imputed dataset adjusted for baseline MiniAQLQ, ACQ, or utility as appropriate. The imputed data comprised the complete case analysis plus imputed values for missing observations using Rubin's Multiple Imputation approach. This is preferable to single imputation approaches, as it takes account of uncertainty in the missing values themselves, and therefore better characterises the associated uncertainty.[76]

Multiple imputation was carried out on variables at an aggregate level (Appendix 1, *Table 55*) using SOLAS software (Statistical Solutions, Cork, Republic of Ireland). In each case, data were imputed with five iterations using the propensity score method, with all other variables used as potential covariates as well as age, education, employment and gender. The imputed variables were visually reviewed to ensure that predicted values were within logical limits. Summary statistics were generated from the five imputed datasets using Rubin's rule[76] (this is simply the mean of the estimates for each of the imputed data sets). See Appendix 1 (Imputation approach for economic analyses) for a more detailed summary of the imputation technique.

Results are presented as total cost per patient, mean MiniAQLQ, ACQ or total QALYs per patient, increments, and incremental cost-effectiveness ratio (ICER) defined as the difference in cost divided by the difference in outcome:

$$\text{ICER} = \frac{C_2 - C_1}{E_2 - E_1}$$

If this is below a threshold of 'willingness to pay' for a point improvement in outcome score (λ), the intervention is deemed cost-effective in relation to the comparator.

Incremental net benefit (INB) was calculated by rearranging the ICER equation:

$$\text{INB} = \lambda(E_2 - E_1) - (C_2 - C_1)$$

(Note that λ is now on the right-hand side, and thus INB depends on the value of λ being known. We therefore present charts plotting INB for a variety of plausible values of λ.)

A non-parametric bootstrap approach was used to generate CIs around INB and to generate cost-effectiveness acceptability curves (CEACs), showing the probability that leukotriene receptor antagonists are cost-effective compared with inhaled corticosteroid/long-acting β_2-agonist, given varying thresholds of willingness to pay for a point improvement in outcome (MiniAQLQ, ACQ or QALY gained).

Resource use

All items of resource use in the four areas (prescribed medications, over-the-counter medications, NHS activity, and indirect costs) were allocated to one of three time points: 0–2 months post randomisation, > 2 months to 1 year and > 1 year to 2 years. Where primary care record data were truncated, the patient's follow-up was counted as missing for that and subsequent periods (for example, where a patient's record was truncated after 36 weeks of follow-up, period 1 data were counted as present, but periods 2 and 3 were counted as missing).

Unit costs were assigned for each scenario from a variety of relevant sources (Appendix 1, Unit costs table), with prices taken from 2005 sources or adjusted to 2005 values using the Retail Price Index as appropriate. Quantities were multiplied by unit costs to calculate the total and per-patient cost. All costs incurred in the third time period (> 1 year to 2 years) were discounted by 3.5%.

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Indirect costs were valued by multiplying the number of hours off work by a unit cost of £13.13, the national average gross wage in 2005.[77] For many of the indirect cost observations, the date the event took place was not reported. For these events, the date of the activity was taken as the date the patient diary was completed.

Cost-effectiveness analysis

Two cost-effectiveness analyses were performed comparing incremental cost with incremental point improvement in (1) MiniAQLQ score and (2) ACQ score. For both analyses, the primary analyses were based on complete case analysis. Secondary analyses were performed, based on an imputed data set, and the imputed data set adjusted for baseline MiniAQLQ and ACQ, respectively. Results are presented as total cost per patient, mean ACQ/MiniAQLQ score at visits 3 (2 months) and 7 (2 years), increments (95% CIs) and ICER.

Cost–utility analysis

The EQ-5D health profiles were converted into utilities using standard conversion algorithms that were relevant to the UK population.[72] QALYs were calculated from utilities by computing the area under the curve. Where 2-month and 2-year follow-up dates varied from target date, straight-line imputation was used to estimate the utility on the appropriate day. QALYs gained during the second year post randomisation were discounted at 3.5%.

Analyses were based on complete case analysis, the imputed data set and imputed data set adjusted for baseline utility. Observations were included in the complete case analysis for the 2-month follow-up if there was at minimum a valid EQ-5D reading at visit 2 (baseline) and visit 3 (2 months). Missing values for the interim visits (visits 4–6) were estimated using straight-line imputation.

Safety analyses

All randomised participants were included in the safety analyses. The primary variables for the safety analysis were the overall incidence of adverse experiences and incidences of common adverse experiences reported by participants.

Chapter 3
Results

Recruitment

All patients with any evidence of asthma from 53 participating practices were sent a postal asthma symptom questionnaire (adapted from the ACQ), which was used to evaluate initial eligibility. For patients meeting these initial criteria, a review of the their notes was undertaken to confirm eligibility. A further 80 patients from the practices were identified as meeting study entry criteria at the time of clinical visits by general practice staff. Of those patients considered potentially eligible, 449 (step 2) and 482 (step 3) responded positively to an invitation and were booked to attend a screening visit (*Figures 2* and *3*).

Work began on the study in October 2001, with initial piloting in one practice of study procedures completed by May 2002. Further practices were recruited from October 2001 through to September 2004. The first patient was enrolled on 3 May 2002 with the last step 3 patient being enrolled on 18 February 2004. The last step 2 patient was enrolled on 4 February 2005. The last clinical and QOL follow-up data were collected on 8 January 2007. The last resource data collection was in the same week.

Numbers analysed versus screened

For the step 2 trial, of the 449 screened, 123 participants were excluded (99 declined to participate and 24 were identified prior to randomisation as ineligible) and 326 participants were randomised (compared with the target of 356). No significant difference was found in mean age between excluded and analysed populations. There were more females among those excluded than those analysed (*Table 2*). For the step 3 trial, of the 482 screened, 121 participants were excluded (84 declined to participate and 37 were identified prior to randomisation as ineligible) and 361 participants were randomised (compared with the target of 356). No significant difference was found in either the sex distribution or mean age between excluded and analysed populations (*Table 2*).

Duration of follow-up in the study for analysed groups

No significant differences were observed in the duration of follow-up in the study between analysed groups in the step 2 or step 3 studies (*Table 3*).

Numbers analysed

At step 2, 20 patients were excluded post-randomisation (*Figure 2*), and 13 of the remaining 306 patients (4.2%) were lost to follow-up. Post-randomisation data were available for 7 out of the 13 lost to follow-up; thus, 300/306 patients (98%) had post-randomisation data and were included in the primary intention-to-treat analyses. The per-protocol population, who received an entirely fixed treatment regime throughout the study, included 65/145 (45%) patients in the leukotriene antagonist group and 82/155 (53%) patients in the inhaled steroid group.

In the step 3 trial, nine patients were excluded post randomisation (*Figure 3*). Twelve of the remaining 352 patients (3.4%) were lost to follow-up; however, post-randomisation data were available for 10 out of these 12 and thus a total of 350 patients were included in the primary intention-to-treat analysis, including 169 and 181 in leukotriene antagonist and long-acting β_2-agonist groups, respectively. Patients who met the per-protocol definition of a fixed treatment regime and no therapeutic change of any kind and were included in the MiniAQLQ analyses numbered 60/169 (36%) and 80/181 (44%), respectively.

Randomisation data

For the step 2 trial, this process resulted in an almost equal distribution of participants between leukotriene antagonist and inhaled steroid arms (162 and 164 participants, respectively). However, for the step 3 study, 9 fewer participants were randomised to leukotriene antagonist than to long-acting β_2-agonist (176 and 185 participants, respectively). This difference is likely to have arisen for two reasons. Firstly, a small number of practices

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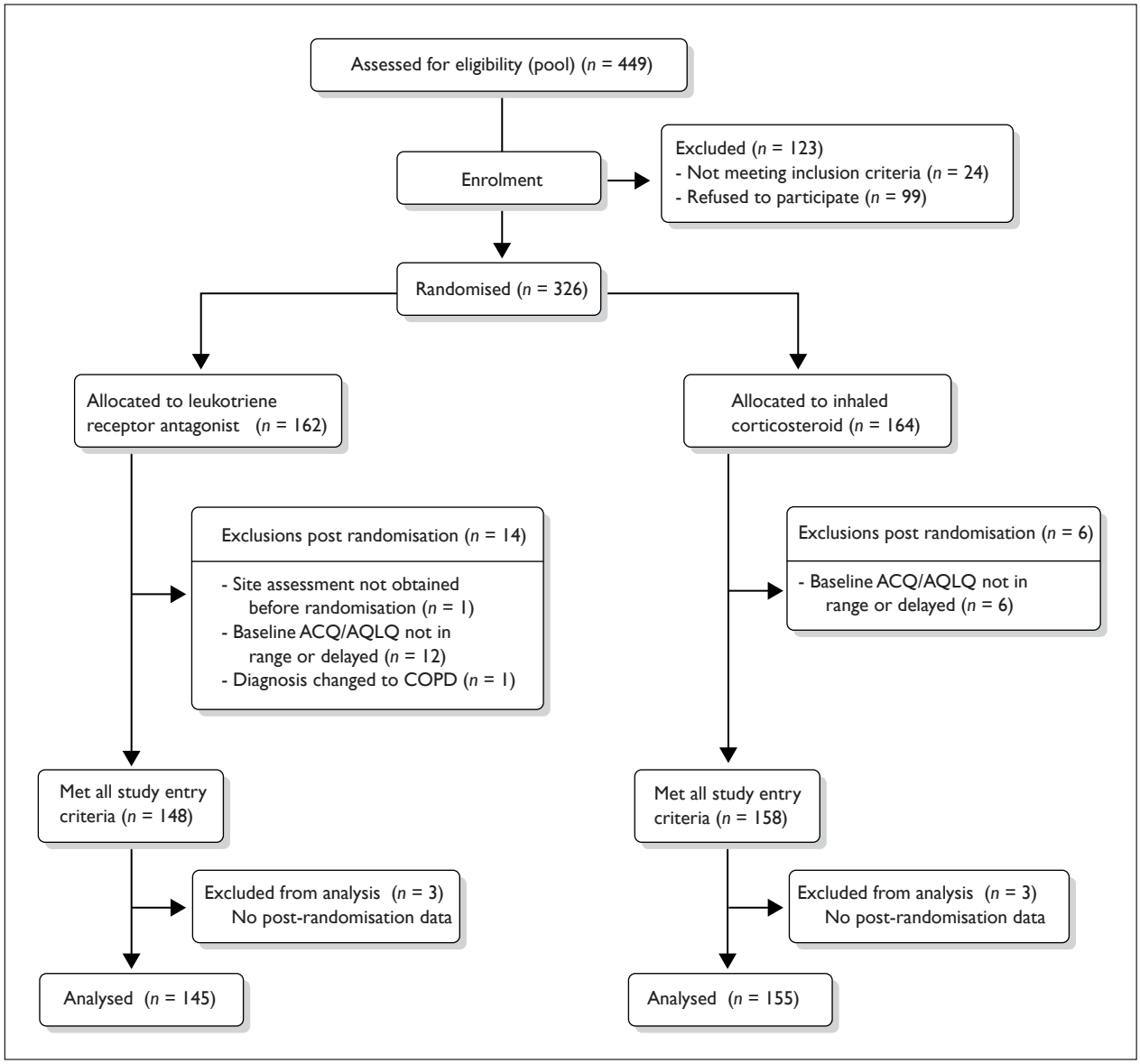

FIGURE 2 *Step 2, the Consolidated Standards of Reporting Trials (CONSORT) e-flowchart for primary end point.*

had one or two more participants randomised to long-acting β_2-agonist than leukotriene antagonist. Secondly, because of an error in the way that the randomisation telephone calls were performed, practice 12 had four more participants randomised to long-acting β_2-agonist than to leukotriene antagonist (13 and 9 participants, respectively). There was never any prior or biasing knowledge of the allocation on the part of the nurse performing the randomisation, but the result was an excess of four participants receiving long-acting β_2-agonist at that practice.

Step 2 trial

Demographics and baseline characteristics

Characteristics of participants screened and found eligible for the step 2 trial are shown in *Tables 4* and *5*.

No substantial differences were identified between the arms. A small female preponderance was noted in the inhaled steroid arm, but not in the leukotriene antagonist arm of the study. Most participants were Caucasian. Mean %PPEF was indicative of airflow obstruction consistent with

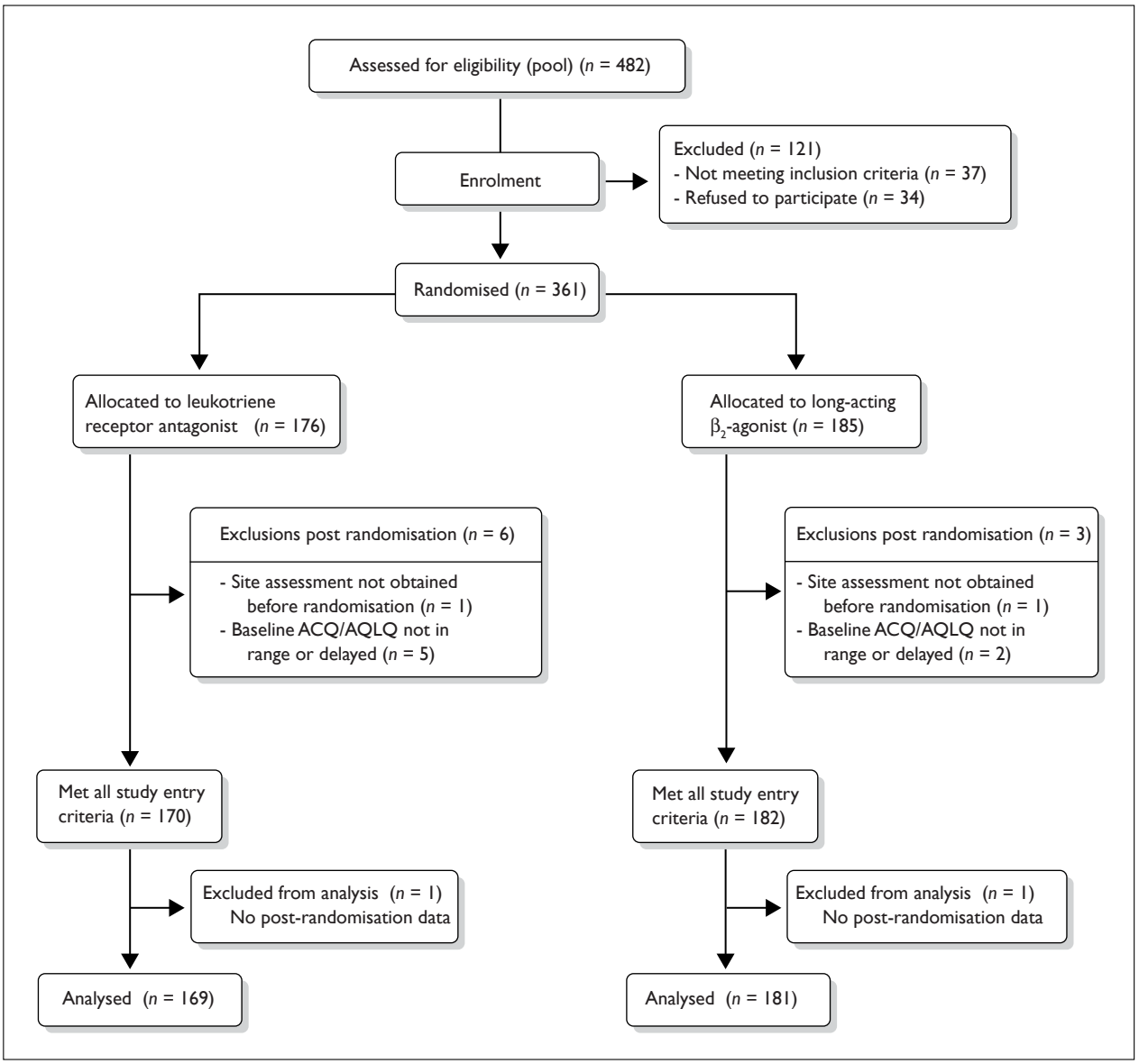

FIGURE 3 *Step 3, the CONSORT e-flowchart for primary end point.*

untreated asthma of mild to moderate severity. Most participants had daytime asthma symptoms, with half having additional night-time symptoms. Half of participants felt that their asthma symptoms interfered with their daily activities. Education and occupation status of participants is shown in *Table 5*.

Most participants were in employment. Only 40% of participants had never smoked. Approximately 20% of participants were active smokers at randomisation into the study, including 26 (9%) who were over the age of 45 (*Table 5*). Baseline diary card data for these participants are shown in *Table 6*.

Primary analyses

Change in QOL

Mini asthma quality of life questionnaire

Mean MiniAQLQ score increased (improved) from baseline in both leukotriene antagonist and inhaled steroid randomised groups (*Table 7* and *Figure 4*).

No statistically significant between-group differences in MiniAQLQ score were found at the 2-month time point, either unadjusted or adjusted for baseline values. At 2 months, the 95% CIs for both the unadjusted and adjusted differences in MiniAQLQ score were within the limits for equivalence: (–0.25 to 0.26) and –0.02 (–0.24 to

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TABLE 2 *Demographics of total excluded patients and analysed participants*

	Total *n* with sex available	Males (%)	Total *n* with age at screening available	Mean (SD), age (years)
Step 2 patients screened = 449				
Excluded	114	40 (35.1)	96	47.30 (17.34)
Analysed	326	162 (49.7)	326	44.74 (16.49)
Total	440	202 (45.9)	422	45.32 (16.70)
Step 3 patients screened = 482				
Excluded	119	52 (43.7)	115	49.74 (17.34)
Analysed	361	136 (37.7)	361	50.02 (15.93)
Total	480	188 (39.2)	476	49.95 (16.84)

SD, standard deviation.
Compared using chi-squared (sex) and Student's unpaired *t*-test (age).

TABLE 3 *Duration (days) of follow-up ('long term') in the study for step 2 and step 3 participants included in analyses*

	Mean days (SD)	Median days	Maximum days	Minimum days
Step 2 trial				
LTRA	746 (75)	743	1260	447
ICS	748 (64)	740	1092	526
Step 3 trial				
LTRA	753 (76)	739	1201	611
LABA	748 (76)	733	1308	573

ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SD, standard deviation.
Compared using unpaired Student's *t*-test.

0.20), respectively, i.e. excluding 0.3. The limit of the one-sided 95% CI for the unadjusted difference was –0.25, and –0.18 for the adjusted difference.

At the 2-year visit, while the difference was again not statistically significant, and the estimated difference between groups was small, the 95% CI did include the equivalence value of 0.3, favouring inhaled steroid [imputed results, unadjusted difference (95% CI) –0.10 (–0.35 to 0.17), adjusted difference (95% CI) –0.11 (–0.35 to 0.13)]. The limit of the one-sided 95% CI for the unadjusted difference was –0.32 and was –0.31 for the adjusted difference, i.e. inferiority could not be excluded.

Asthma Control Questionnaire

Mean ACQ score decreased (improved) substantially from baseline in both leukotriene antagonist and inhaled steroid randomised groups (*Table 8* and *Figure 4*). Again, no significant between-group differences in ACQ score were found at either the 2-month or 2-year time points, whether unadjusted or adjusted for baseline values. At 2 years (imputed results), the adjusted difference (95% CI) was 0.13 (–0.07 to 0.33). The CI is well within the minimum clinically important difference of 0.5.

Quality-adjusted life-years

Leukotriene antagonist participants experienced a mean of 0.122 QALYs over the 2-month period, compared with 0.132 in inhaled steroid participants, a mean (95% CI) difference of approximately 0.01 (–0.019 to 0.001) QALYs, falling to 0.001 (–0.005 to 0.002) QALYs after adjustment for baseline utility (*Table 9*). Over 2 years, leukotriene antagonist participants experienced 0.153 (–0.274 to –0.032) fewer QALYs than inhaled steroid participants. However, after adjusting for baseline utility, the difference falls to 0.050 (–0.126 to 0.026) QALYs, equivalent to 2.5 weeks of perfect health.

TABLE 4 *Step 2 trial: demographics of participants at visit 2*

		Leukotriene antagonist (*N* = 148)	Inhaled steroid (*N* = 158)
Sex	*Female*	73 (49%)	83 (53%)
	Male	75 (51%)	75 (47%)
Age	*Mean (SD)*	47.6 (16.5)	44.1 (16.4)
Race	*Caucasian*	144 (97%)	153 (97%)
	Non-Caucasian	0	1 (1%)
	Not known	4 (3%)	4 (3%)
Height (cm)	*Mean (SD)*	*n* = 138	*n* = 153
		169.6 (9.2)	169.1 (9.6)
PEF (l/min)	*Mean (SD)*	*n* = 147	434 (127)
		438 (139)	
%PPEF (%)	*Median (IQR)*	*n* = 134	*n* = 150
		85.97 (77.43 to 94.16)	85.07 (73.92 to 95.42)
Salbutamol PEF reversibility (%)	*Mean (SD)*	*n* = 128	*n* = 142
		9.20 (10.7)	8.74 (9.17)
SABA puffs/day	*Mean (SD)*	*n* = 140	*n* = 145
		3.0 (3.2)	2.9 (3.1)
Asthma exacerbations in last year	*Mean (SD)*	0.13 (0.036)	0.10 (0.029)
Asthma Control Questionnaire	*Mean (SD)*	1.99 (0.70)	2.06 (0.84)
MiniAQLQ	*Mean (SD)*	4.75 (0.92)	4.72 (0.95)
mRQLQ	*Mean (SD)*	*n* = 113	*n* = 131
		1.58 (1.29)	1.78 (1.35)
EQ-5D utility	*Mean (SD)*	*n* = 118	*n* = 131
		0.795 (0.245)	0.830 (0.195)
Personal objectives (0–100 VAS)	*Mean (SD)*	*n* = 99	*n* = 118
		42.59 (18.03)	38.89 (18.15)
RCP3	*Mean (SD)*	*n* = 133	*n* = 146
		2.07 (0.81)	2.06 (0.79)
Sleep difficulty	*Yes*	79 (58%)	86 (56%)
	No	58 (42%)	67 (44%)
	Missing	11	5
Day symptoms	*Yes*	125 (93%)	142 (94%)
	No	10 (7%)	9 (6%)
	Missing	13	7
Interferes with activities	*Yes*	65 (49%)	74 (49%)
	No	69 (51%)	76 (51%)
	Missing	14	8

IQR, interquartile range; LTRA, leukotriene receptor antagonist; PEF, peak expiratory flow; SABA, short-acting β_2-agonist; SD, standard deviation; VAS, visual analogue scale.
Note: percentages may not add to 100% because of rounding.

Resource use and cost

Point estimate costs and quantities of prescription medicines, over-the-counter medicines, NHS activity and indirect costs are reported in *Tables 10–13*. Total NHS costs are the sum of prescriptions and NHS activity. Total societal costs are NHS costs plus over-the-counter medications and indirect costs.

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TABLE 5 *Step 2 trial: education and lifestyle characteristics of participants at visit 2*

		LTRA (*N* = 148)	ICS (*N* = 158)
Continued education > 16	*Yes*	72 (50%)	81 (53%)
	No	70 (49%)	67 (44%)
	Student	2 (1%)	4 (7%)
	Not known	4	6
Professional qualification	*Yes*	45 (33%)	50 (35%)
	No	88 (64%)	84 (59%)
	Student	4 (3%)	8 (6%)
	Not known	11	16
Employment position	*Employer*	5 (5%)	8 (7%)
	Employee	74 (73%)	90 (84%)
	Self-employed	21 (21%)	9 (8%)
	Disabled	1 (1%)	0
	Not known	47	51
Smoking habit	*Current smoker*	37 (25%)	30 (19%)
	Ex-smoker	54 (37%)	54 (35%)
	Never smoked	56 (38%)	71 (46%)
	Not known	1	3
	Current smoker over age 45	15 (10%)	11 (7%)

ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist.

TABLE 6 *Step 2 trial: baseline diary card symptom scores, PEF and reliever usage*

	LTRA (*N* = 148)	ICS (*N* = 158)
Mean (SD) morning waking with symptoms	0.48 (0.36) *n* = 129	0.48 (0.34) *n* = 147
Mean (SD) puffs of reliever at night	0.78 (0.88) *n* = 125	0.99 (1.37) *n* = 141
Mean (SD) morning PEF	408.9 (99.1) *n* = 127	402.5 (100.2) *n* = 146
Mean (SD) daytime asthma symptom score (0–6)[a]	1.88 (1.18) *n* = 129	1.81 (1.29) *n* = 145
Mean (SD) score for daytime 'bother from asthma symptoms' (0–6)[a]	1.63 (1.18) *n* = 128	1.48 (1.23) *n* = 145
Mean (SD) daily activity score (0–6)[b]	2.68 (1.12) *n* = 126	2.38 (1.27) *n* = 145
Mean (SD) score for interference on activities from asthma (0–6)[a]	1.38 (1.24) *n* = 128	1.28 (1.33) *n* = 147
Mean (SD) puffs of reliever during the day	2.26 (1.67) *n* = 126	2.18 (1.99) *n* = 145
Mean (SD) evening PEF	420.6 (101.1) *n* = 127	413.9 (103.0) *n* = 147
Mean (SD) diurnal variation in PEF (%)	7.1 (4.8) *n* = 127	7.7 (5.4) *n* = 147

ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; PEF, peak expiratory flow; SD, standard deviation.
a 0 = 'none' to 6 = 'all of the time or severely bothered'.
b 0 = 'more exercise than normal' to 6 = 'less than usual'.

TABLE 7 *Step 2 trial: mean (SD) and differences (95% CI) between means for MiniAQLQ scores at 2 months and 2 years*

Treatment duration	Outcome measure	LTRA	ICS	Difference (95% CI) LTRA–ICS	Adjusted difference[a] (95% CI)
2 months (visit 3)	*n*	122	132	0.0 (–0.25 to 0.26)	–0.02 (–0.24 to 0.20)
	Mean	5.25	5.28		
	SD	1.03	1.10		
2 years[b]	*n*	145	155	–0.10 (–0.35 to 0.17)	–0.11 (–0.35 to 0.13)
	Mean	5.52	5.63		
	SD	1.07	1.16		

CI, confidence interval; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Adjusted for baseline values.
b Multiple imputation was used to impute missing data.

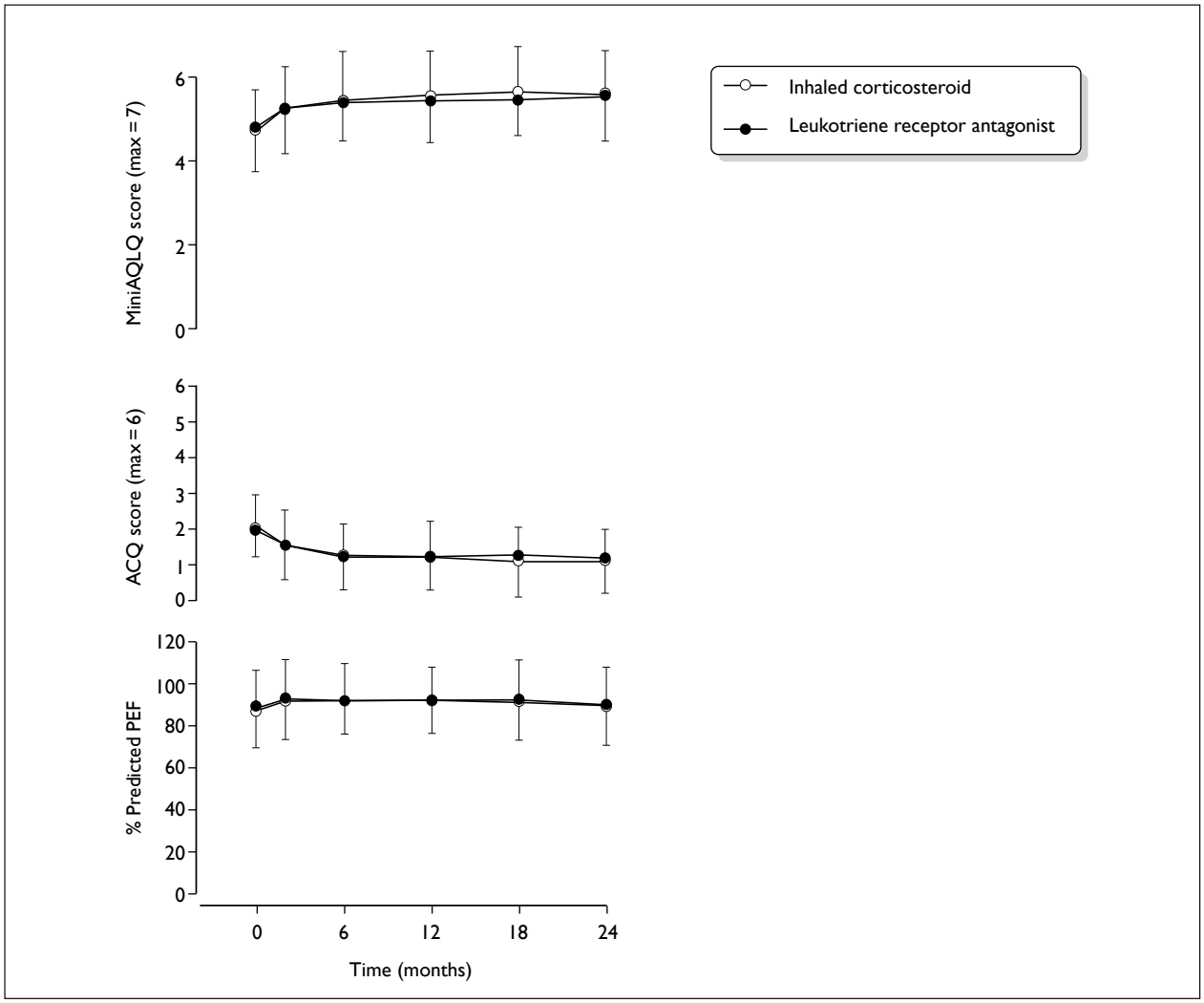

FIGURE 4 *Step 2: ACQ, MiniAQLQ and %PPEF over 2 years of treatment. Mean (standard deviation) ACQ (from 0 'best' to 6 'worst') and MiniAQLQ (from 1 'worst' to 7 'best') scores and median (interquartile range) %PPEF at baseline and over 2 years of treatment with leukotriene antagonist or inhaled steroid.*

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TABLE 8 *Step 2 trial: mean (SD) and differences (95% CI) between means for ACQ scores at 2 months and 2 years*

Treatment duration		LTRA	ICS	Difference (95% CI) LTRA–ICS	Adjusted difference[a] (95% CI)
2 months (visit 3)	*n*	123	132	–0.02 (–0.24 to 0.21)	0.01 (–0.20 to 0.22)
	Mean	1.54	1.53		
	SD	0.93	1.00		
2 years[b]	*n*	145	155	0.10 (–0.11 to 0.32)	0.13 (–0.07 to 0.33)
	Mean	1.23	1.15		
	SD	0.95	0.92		

CI, confidence interval; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Adjusted for baseline values.
b Multiple imputation was used to impute missing data.

TABLE 9 *Step 2 trial: mean (SD) EQ-5D and differences between means for QALYs at 2 months and 2 years*

	LTRA		ICS		Difference (95% CI) LTRA–ICS	Adjusted difference[a] (95% CI)
	n	Mean (SD)	*n*	Mean (SD)		
EQ-5D utility						
Baseline	118	0.795 (0.245)	131	0.830 (0.195)	–	–
2 months	118	0.819 (0.261)	124	0.856 (0.212)	–	–
2 years	132	0.826 (0.261)	143	0.881 (0.218)	–	–
QALYs gained						
2 months	95	0.122 (0.036)	106	0.132 (0.025)	–0.010 (–0.019 to 0.001)	–0.001 (–0.005 to 0.002)
2 years (discounted)	81	1.569 (0.458)	94	1.722 (0.327)	–0.153 (–0.274 to –0.032)	–0.050 (–0.126 to 0.026)

CI, confidence interval; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Adjusted for baseline utility.

Over 2 months and 2 years, patients who were prescribed leukotriene antagonists were significantly more expensive than patients who were prescribed inhaled steroid participants in terms of both NHS (NHS activity plus prescription medicines) and societal costs (all costs – *Table 14*). At 2 months, leukotriene antagonist participants cost on average £70 more, or 2.5 times the cost, of inhaled steroid participants (95% CI £29 to £111), and at 2 years, £294 more, or 1.8 times the cost of inhaled steroid participants (95% CI £107 to £481). This may be driven principally by higher prescription costs and possibly compliance (including leukotriene antagonists themselves) and/or higher NHS activity in the leukotriene antagonist group.

Cost-effectiveness analyses

Mini Asthma Quality of Life Questionnaire

At both 2 months (*Table 15*) and 2 years (*Table 16*), inhaled steroid is, on average, a dominant strategy over leukotriene antagonist. Mean INB is negative, irrespective of willingness to pay for a point improvement in MiniAQLQ.

Incremental net benefit details (± 95% CI) are shown in *Figure 5a–d*. Note, however, that there is a great deal of uncertainty around these estimates (95% CI in *Figure 5*).

Even with a very high willingness to pay for a point improvement in MiniAQLQ, there is, at most, only a 25% probability of leukotriene antagonist being cost-effective compared with inhaled steroid in step 2 patients (*Figure 6*).

TABLE 10 *Step 2 trial: cost of prescription medicines at 2 months and 2 years*[a]

	LTRA					ICS				
Treatment duration	***n***	**Total items**	**Mean (SD) items**	**Total cost (£)**	**Mean (SD) cost (£)**	***n***	**Total items**	**Mean items (SD)**	**Total cost (£)**	**Mean (SD) cost (£)**
2 months	159	463	2.88 (1.87)	10,055.61	62.46 (31.30)	164	330	2.01 (1.38)	2969.78	18.11 (14.92)
2 years (discounted)	154	3489	22.7 (16.1)	60,509.00	393 (299)	157	2797	17.8 (15.2)	28,882.00	184 (237)

ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Total and mean (SD) costs of asthma-related prescription medicines prescribed during the step 2 trial.

TABLE 11 *Step 2 trial: cost of over-the-counter medicines at 2 months and 2 years*[a]

	LTRA					ICS				
Treatment duration	***n***	**Total items**	**Mean (SD) items**	**Total cost (£)**	**Mean (SD) cost (£)**	***n***	**Total items**	**Mean items (SD)**	**Total cost (£)**	**Mean (SD) cost (£)**
2 months	109	49	0.45 (0.73)	211.26	1.94 (6.96)	108	79	0.73 (1.16)	1041.07	9.64 (46.97)
2 years (discounted)	109	225	2.06 (1.52)	756.39	6.94 (11.83)	108	268	2.48 (2.33)	1637.09	15.16 (49.66)

ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Total and mean (SD) costs of asthma-related over-the-counter medicines prescribed during the step 2 trial.

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TABLE 12 *Step 2 trial: cost of NHS activity at 2 months and 2 years*[a]

	LTRA					ICS				
Treatment	***n***	**Total contacts**	**Mean (SD) contacts**	**Total cost (£)**	**Mean (SD) cost (£)**	***n***	**Total contacts**	**Mean (SD) contacts**	**Total cost (£)**	**Mean (SD) cost (£)**
2 months										
Total routine care	156	41	0.26 (0.63)	331.67	2.13 (5.52)	158	25	0.16 (0.56)	255.00	1.61 (5.98)
Total patient initiated	156	50	0.32 (0.75)	1153.05	7.39 (22.79)	158	22	0.14 (0.46)	371.00	2.35 (8.08)
Total secondary care	156	4	0.03 (0.25)	635.95	4.08 (41.93)	158	3	0.02 (0.18)	381.00	2.41 (22.53)
Total NHS activity	**156**	**95**	**0.61 (1.09)**	**2120.67**	**13.59 (61.00)**	**158**	**50**	**0.32 (0.71)**	**1007.00**	**6.37 (24.16)**
2 years (discounted)										
Total routine care	151	474	3.14 (2.53)	4055.67	26.86 (24.92)	151	420	2.78 (2.32)	3827.35	25.35 (22.92)
Total patient initiated	151	397	2.63 (3.19)	8761.64	58.02 (78.46)	151	416	2.75 (3.46)	9181.14	60.80 (81.95)
Total secondary care	151	40	0.26 (0.87)	12,045.23	79.77 (601.74)	151	55	0.36 (1.06)	8446.08	55.93 (268.62)
Total NHS activity	**151**	**911**	**6.03 (4.89)**	**24,862.54**	**164.65 (633.99)**	**151**	**891**	**5.90 (5.25)**	**21,454.57**	**142.08 (310.13)**

ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Total and mean (SD) costs of asthma NHS health care-related activity during the step 2 trial.

TABLE 13 *Step 2 trial: indirect costs at 2 months and 2 years*[a]

	LTRA					ICS				
Treatment duration	***n***	**Total hours**	**Mean (SD) hours**	**Total cost (£)**	**Mean (SD) cost (£)**	***n***	**Total hours**	**Mean hours (SD)**	**Total cost (£)**	**Mean (SD) cost (£)**
2 months	80	335	4.19 (18.54)	4398.55	54.98 (243.43)	71	142	2.00 (10.37)	1864.46	26.26 (136.16)
2 years (discounted)	80	1309.5	16.37 (62.61)	14,938.39	186.73 (740.80)	71	1075	15.14 (86.24)	14,114.75	198.80 (1132.29)

ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Total and mean (SD) indirect costs during the step 2 trial.

TABLE 14 *Step 2 trial: total NHS and societal costs at 2 months and 2 years*[a]

	LTRA			ICS			
Treatment duration	***n***	**Total cost (£)**	**Mean (SD) cost (£)**	***n***	**Total cost (£)**	**Mean (SD) cost (£)**	**Cost (£) difference (95% CI)**
Total NHS costs (prescription medicines and NHS activity combined)							
2 months	156	12,029.60	77.11 (66.38)	158	3839.82	24.30 (30.56)	52.81 (41.29 to 64.33)
2 years (discounted)	147	84,309.00	573.00 (764)	148	49,090.00	332.00 (435)	242.00 (100 to 384)
Societal costs (prescription and over-the-counter medicines – NHS activity and indirect costs combined)							
2 months	74	8704.96	117.63 (152.94)	65	3097.17	47.65 (81.52)	69. 99 (29.47 to 110.50)
2 years (discounted)	70	46,628.00	666.00 (664)	60	22,341.00	372.00 (374)	294.00 (107 to 481)

CI, confidence interval; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Total and mean (SD) NHS and societal costs during the step 2 trial.

Asthma Control Questionnaire

At both 2 months (*Table 17*) and 2 years (*Table 18*), inhaled steroid is on average, a dominant strategy over leukotriene antagonist. Mean INB is negative, irrespective of willingness to pay for a point improvement in ACQ. However, there is great deal of uncertainty around this estimate (95% CIs in *Figure 7*).

Incremental net benefit (± 95% CI) is shown in *Figure 7a–d*. A higher ACQ score indicates worsening of asthma control, and negative incremental ACQ indicates that leukotriene antagonist is less effective than inhaled steroid.

Even with a very high willingness to pay for a point improvement in ACQ, there is only at most a 22% probability of leukotriene antagonist being cost-effective compared with inhaled steroid in step 2 patients (*Figure 8*).

Quality-adjusted life-years (cost–utility analysis)

At both 2 months (*Table 19*) and 2 years (*Table 20*) inhaled steroid is, on average, a dominant strategy over leukotriene antagonist. Mean INB is negative, irrespective of willingness to pay for QALY (*Figure 9*).

At a typical willingness to pay of £30,000 per QALY gained, mean (95% CI) INB at 2 months is –£155 (–£305 to £0) or –£145 (–£305 to £8) from the NHS and societal perspectives, respectively, deteriorating to –£2255 (–£4450 to £211) and –£2241 (–£4542 to £118) at 2 years. At the £30,000 threshold, there is a very low probability (2.8% to 3.5%) of leukotriene antagonist being cost-effective compared with inhaled steroid in patients at step 2 of the national asthma guidelines (*Tables 19 and 20*, and *Figure 10*).

Figure 10 indicates that in all cases the probability of leukotriene antagonist being cost-effective compared with inhaled steroid is below 50%, irrespective of the willingness to pay for a QALY.

Summary of cost-effectiveness analyses

The results of the cost-effectiveness analyses suggest that leukotriene antagonists are both more expensive and less, although not statistically significantly, effective than inhaled steroids, with a very low probability of cost-effectiveness compared with inhaled steroids for patients initiating controller therapy at step 2 of the national asthma guidelines.

Whether an intervention is deemed cost-effective is dependent upon the willingness-to-pay threshold for a unit of outcome. For QALYs, a 'reasonable' willingness to pay is thought to be in the order of £30,000. The threshold for a point improvement in MiniAQLQ or ACQ is less well established. However, even given an infinite willingness to pay for a point improvement in MiniAQLQ or ACQ, there is at best a 22–25% probability that leukotriene antagonists are a cost-effective alternative to inhaled steroids in patients at step 2 of the national asthma guidelines (depending on time horizon and perspective).

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TABLE 15 *Step 2: incremental cost-effectiveness ratio at 2 months*[a]

	n		Cost (£)		MiniAQLQ		Source data only			Including imputed data			Including imputed data (adjusted for baseline MiniAQLQ)		
	LTRA	ICS	LTRA	ICS	LTRA	ICS	Inc. cost (£)	Inc. AQLQ	ICER (£)	Inc. cost (£)	Inc. AQLQ	ICER (£)	Inc. cost (£)	Inc. AQLQ	ICER (£)
NHS	120	127	80	25	5.242	5.278	55	–0.036	(ICS dominant)	52	–0.019	(ICS dominant)	53	–0.081	(ICS dominant)
Societal	63	57	117	52	5.257	5.410	65	–0.153	(ICS dominant)	37	–0.019	(ICS dominant)	38	–0.081	(ICS dominant)

ICS, inhaled corticosteroid; inc., incremental; LTRA, leukotriene receptor antagonist.
a Inc. cost, inc. MiniAQLQ and ICERs are reported for patient groups with complete societal and NHS cost and MiniAQLQ data, following imputation for missing data and adjustment for baseline MiniAQLQ.

TABLE 16 *Step 2: incremental cost-effectiveness ratio at 2 years*[a]

	n		Cost (£)		MiniAQLQ		Source data only			Including imputed data			Including imputed data (adjusted for baseline MiniAQLQ)		
	LTRA	ICS	LTRA	ICS	LTRA	ICS	Inc. cost (£)	Inc. AQLQ	ICER (£)	Inc. cost (£)	Inc. AQLQ	ICER (£)	Inc. cost (£)	Inc. AQLQ	ICER (£)
NHS	*133*	*140*	587	327	5.529	5.633	260	–0.104	(ICS dominant)	233	–0.086	(ICS dominant)	242	–0.151	(ICS dominant)
Societal	*64*	*60*	666	372	5.549	5.681	294	–0.132	(ICS dominant)	209	–0.086	(ICS dominant)	217	–0.151	(ICS dominant)

ICS, inhaled corticosteroid; inc., incremental; LTRA, leukotriene receptor antagonist.
a Inc. cost, inc. MiniAQLQ and ICERs are reported for patient groups with complete societal and NHS cost and MiniAQLQ data, following imputation for missing data and adjustment for baseline MiniAQLQ.

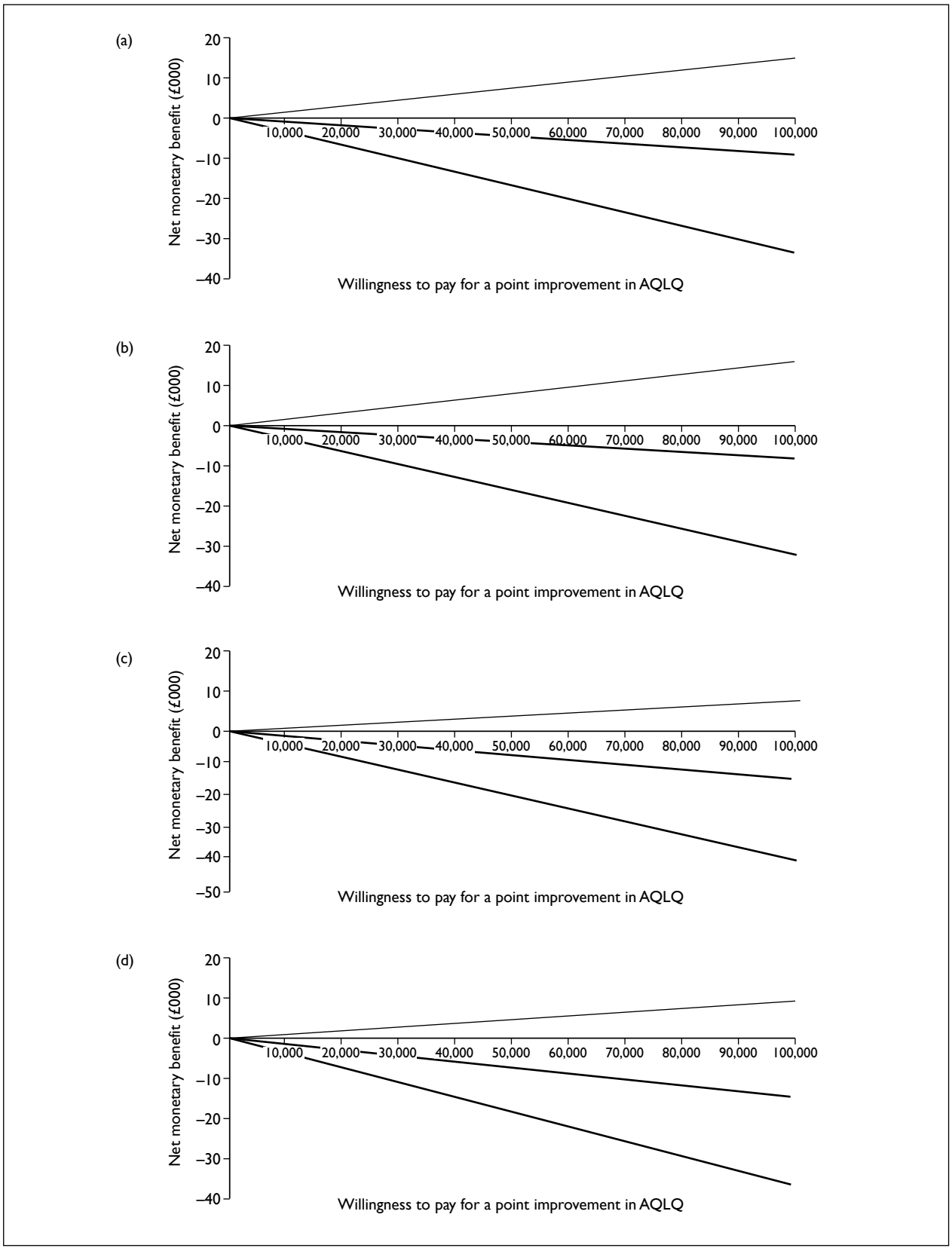

FIGURE 5 *Step 2: INB, MiniAQLQ, INB and 95% CI are shown for (a) 2-month NHS; (b) 2-month societal; (c) 2-year NHS; and (d), results based on imputed data adjusted for baseline MiniAQLQ.*

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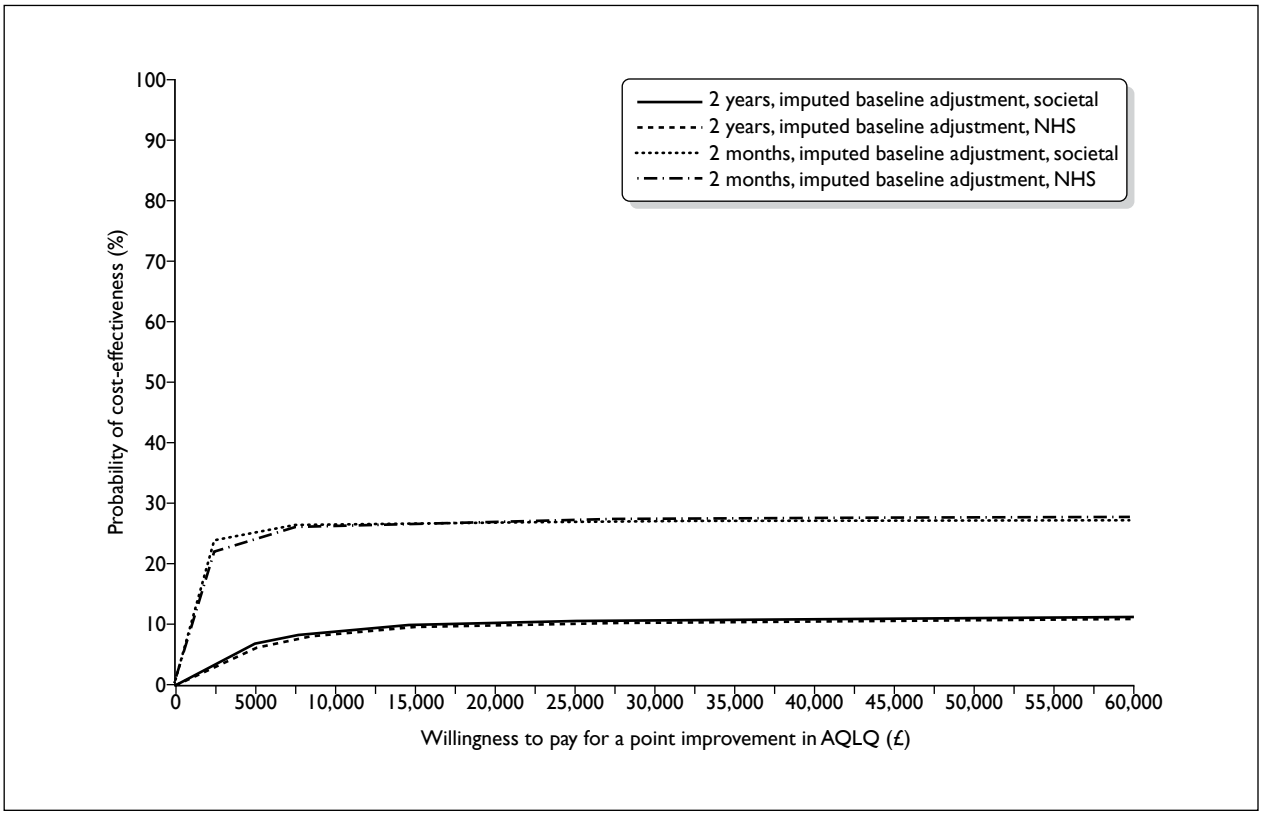

FIGURE 6 *Step 2: MiniAQLQ CEACs. Based on imputed, adjusted results of MiniAQLQ, societal/NHS indicates that results were from a societal or NHS cost perspective, respectively, and these outcomes took place at 2 months or 2 years. This figure indicates that in all cases the probability of leukotriene antagonist being cost-effective compared with inhaled steroid is < 50%, irrespective of the willingness to pay for a point improvement in MiniAQLQ.*

Secondary analyses

Asthma exacerbations, hospitalisations and respiratory tract infections

No significant differences were found in the number of exacerbations or respiratory tract infections experienced by participants receiving leukotriene antagonist or inhaled steroid (*Table 21*). (Number of exacerbations included hospitalisations as well as courses of oral steroids.) Similarly, no significant difference was found in the number of consultations associated with respiratory tract infections.

There were no hospital admissions during the first 2 months of the study. Subsequently, over the remainder of the 2 years, there were four hospital admissions for seven nights in total in the leukotriene antagonist group and two hospital admissions for six nights in total in the inhaled steroid group.

Prescribed short-acting β_2-agonist

No significant difference was found in the use of short-acting β_2-agonist (*Table 21*). On average, participants randomised to leukotriene antagonist received 1.28 short-acting β_2-agonist inhalers every 3 months, whereas those randomised to inhaled steroid received 1.19 short-acting β_2-agonist inhalers every 3 months. Over the 2-year study period, on average 10.22 compared with 9.49 short-acting β_2-agonist inhalers were issued to participants who were randomised to leukotriene antagonist and inhaled steroid, respectively.

Clinic %PPEF and domiciliary data

For clinic %PPEF, minor improvement was observed in both leukotriene antagonist and inhaled steroid treated groups, and no significant differences were found between the groups at either the 2-month or 2-year time points (*Table 22* and *Figure 4*).

Diary cards were completed by approximately one-half of participants at 2 months and one-third at 2 years. No significant differences were observed in the diary card data at either 2 months (*Table 23*) or 2 years (*Table 24*).

TABLE 17 *Step 2: ICER at 2 months*[a]

	n		Cost (£)		ACQ		Source data only			Including imputed data			Including imputed data (adjusted for baseline ACQ)		
	LTRA	ICS	LTRA	ICS	LTRA	ICS	Inc. cost (£)	Inc. ACQ	ICER (£)	Inc. cost (£)	Inc. ACQ	ICER (£)	Inc. cost (£)	Inc. ACQ	ICER (£)
NHS	121	127	80	25	1.550	1.541	55	–0.009	(ICS dominant)	52	–0.015	(ICS dominant)	53	–0.083	(ICS dominant)
Societal	64	57	116	52	1.544	1.489	64	–0.055	(ICS dominant)	37	–0.015	(ICS dominant)	38	–0.083	(ICS dominant)

ICS, inhaled corticosteroid; inc., incremental; LTRA, leukotriene receptor antagonist.
a Inc. cost, inc. ACQ and ICERs are reported for patient groups with complete societal and NHS cost and ACQ data, following imputation for missing data and adjustment for baseline ACQ.

TABLE 18 *Step 2: ICER at 2 years*[a]

	n		Cost (£)		ACQ		Source data only			Including imputed data			Including imputed data (adjusted for baseline ACQ)		
	LTRA	ICS	LTRA	ICS	LTRA	ICS	Inc. cost (£)	Inc. ACQ	ICER (£)	Inc. cost (£)	Inc. ACQ	ICER (£)	Inc. cost (£)	Inc. ACQ	ICER (£)
NHS	133	140	587	327	1.223	1.142	260	–0.081	(ICS dominant)	233	–0.062	(ICS dominant)	249	–0.116	(ICS dominant)
Societal	64	60	666	372	1.086	1.094	294	0.009	34546	209	–0.062	(ICS dominant)	220	–0.116	(ICS dominant)

ICS, inhaled corticosteroid; inc., incremental; LTRA, leukotriene receptor antagonist.
a Inc. cost, inc. ACQ (95% CI) and ICERs are reported for patient groups with complete societal and NHS cost and ACQ data and following imputation for missing data.

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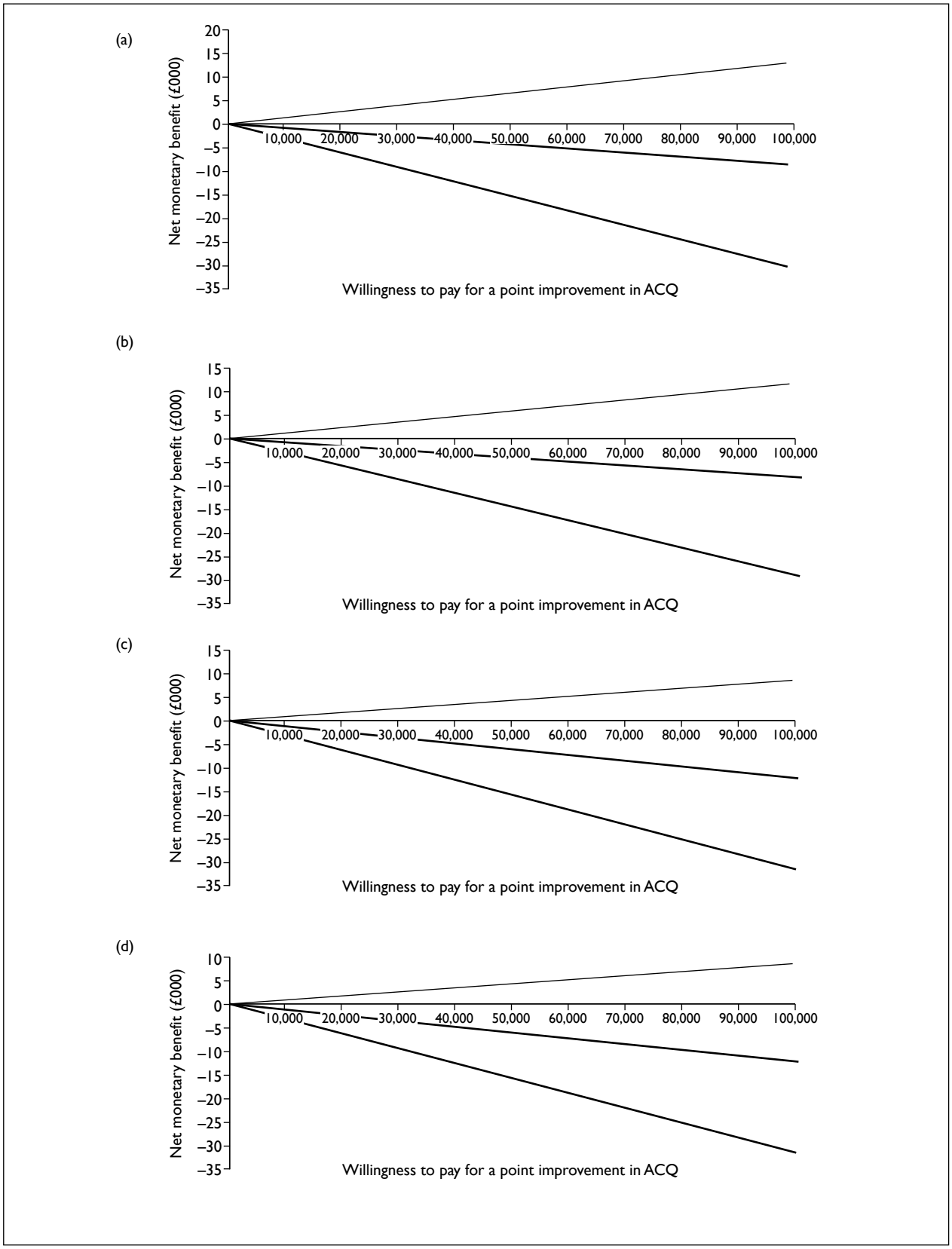

FIGURE 7 *Step 2: INB, ACQ, INB and 95% CI are shown for (a) 2-month NHS; (b) 2-month societal; (c) 2-year NHS; and (d) 2-year societal perspectives. Results based on imputed data adjusted for baseline ACQ.*

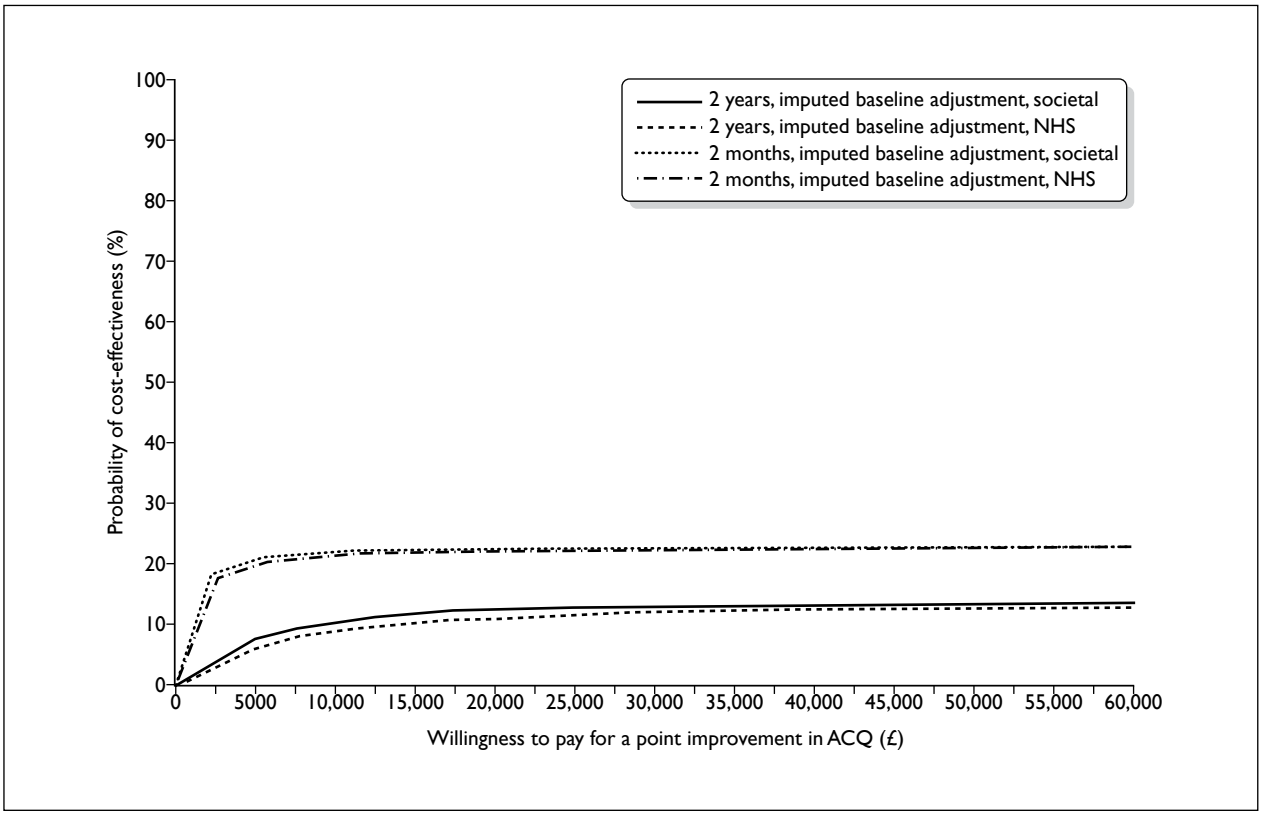

FIGURE 8 *Step 2: ACQ CEACs. Based on imputed, adjusted results of ACQ, societal/NHS indicates that results were from a societal or NHS cost perspective, respectively, and these outcomes took place at 2 months or 2 years. This figure indicates that in all cases the probability of leukotriene antagonist being cost-effective compared with inhaled steroid is < 50%, irrespective of the willingness to pay for a point improvement in ACQ.*

Secondary QOL scores and rhinitis scores

No significant differences were observed in the mRQLQ, RCP3 questions or personal objectives scores after 2 months or 2 years (*Table 25*). However, at both time points all measures showed a substantial improvement from baseline.

Changes in treatment after randomisation

At 2 months, eight patients (6%) and five patients (3%) in the leukotriene antagonist and inhaled steroid groups, respectively, had a change in treatment from initial randomised therapy class. By the end of the study 45 (31%) and 32 (21%), respectively, patients had a change in treatment. The changes in treatment by 2 months and 2 years are tabulated in *Table 26*.

Per-protocol population (fixed treatment regime and no changes within or from randomised therapy class) analyses

Our per-protocol population was defined as those patients who were prescribed a fixed treatment regime at randomisation (i.e. no self-management plan) and who had no change in that fixed regime at any time including the final study visit, i.e. no change in device, dose or therapeutic class. After restricting the groups to only those who had completed the entire study intervention period as per this definition of per-protocol and who had analysable data, 65 leukotriene antagonist and 82 inhaled steroid participants were identified. There was a preponderance of male participants in both treatment groups (56–57% – Appendix 5, *Table 59*). Randomised therapy was changed or varied during the study for the remaining 83 and 76 participants in leukotriene antagonist and inhaled steroid groups, respectively.

Results for these per-protocol participants are reported in Appendix 5, *Tables 59–66*. There was no significant difference (unadjusted or adjusted) between treatment groups in either MiniAQLQ or ACQ score at any time point. For MiniAQLQ scores, the adjusted differences between treatment groups at 2 months and 2 years favoured leukotriene antagonist, with 95% CI outside the limits of equivalence at both time points [adjusted difference for imputed results at 2 years, 0.05 (–0.28 to 0.37)]. Similarly, all ACQ differences favoured leukotriene antagonist.

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TABLE 19 *Step 2: ICER at 2 months*

	n		Cost (£)		QALYs		Source data only				
	LTRA	ICS	LTRA	ICS	LTRA	ICS	Inc. cost (£)	Inc. QALYs	ICER (£)	P£30k (%)	INB/£30k (95% CI)
NHS	94	102	85	27	0.122	0.133	58	–0.011	(ICS dominant)	0.10	–277 (–454 to 97)
Societal	52	45	115	59	0.118	0.135	56	–0.017	(ICS dominant)	0.20	–406 (–677 to 159)

CI, confidence interval; ICS, inhaled corticosteroid; inc., incremental; LTRA, leukotriene receptor antagonist.
a Inc. cost, inc. QALY (95% CI), ICERs and probability that the intervention is cost-effective given a willingness to pay of £30,000 for QALY (P£30k, see *Figure 6*) are reported for patient groups with complete societal and NHS cost and QALY data and following imputation for missing data.

TABLE 20 *Step 2: ICER at 2 years*[a]

	n		Cost (£)		QALYs		Source data only				
	LTRA	ICS	LTRA	ICS	LTRA	ICS	Inc. cost (£)	Inc. QALYs	ICER (£)	P£30k (%)	INB/£30k (95% CI)
NHS	78	89	616	369	1.571	1.736	247	–0.165	(ICS dominant)	0.00	–3551(–5986 to 1270)
Societal	43	39	711	433	1.524	1.731	278	–0.207	(ICS dominant)	1.00	–4349(–8157 to 762)

CI, confidence interval; ICS, inhaled corticosteroid; inc., incremental; LTRA, leukotriene receptor antagonist.
a Inc. cost, inc. QALY (95% CI), ICERs and probability that the intervention is cost-effective given a willingness to pay of £30,000 for QALY (PE30k, see *Figure 6*) are reported for patient groups with complete societal and NHS cost and QALY data and following imputation for missing data.

Results for the secondary analyses were similar to those for the intention-to-treat analyses. There were no significant differences between treatment groups other than a marginally better result for clinic %PPEF in the leukotriene antagonist group at 2 years ($p = 0.058$).

Adherence to therapy

Adherence data were analysable for 217 participants overall. In the leukotriene antagonist group ($n = 121$, or 82%), median adherence (interquartile range) to leukotriene antagonist therapy was 61.4% (17.5–92.1%). In the inhaled steroid group ($n = 96$, or 61%), median adherence to inhaled steroid therapy was 41.1% (13.7–65.4%).

Step 3 trial

Demographics and baseline characteristics

Characteristics of participants screened and found eligible for the step 3 trial are shown in *Tables 27* and *28*. No substantial differences were identified between the arms. A female preponderance was noted in both arms of the trial. Most participants were Caucasian. Mean %PPEF was indicative of airflow obstruction consistent with asthma of mild to moderate severity (with ongoing treatment with inhaled steroid).

Most participants had daytime asthma symptoms, with half having additional night-time symptoms. Half of participants felt that their asthma symptoms interfered with their daily activities. Education and occupation status of participants are shown in *Table 28*. Most participants were in employment. Only 40% of patients had never smoked; 17% of participants were active smokers, including 26 (9%) who were over the age of 45 (*Table 28*). Baseline diary card data for these participants are shown in *Table 29*.

Including imputed data					Including imputed data (adjusted for baseline utility)				
Inc. cost (£)	**Inc. QALYs**	**ICER (£)**	**P£30k (%)**	**INB/£30k (95% CI)**	**Inc. cost (£)**	**Inc. QALYs**	**ICER (£)**	**P£30k (%)**	**INB/£30k (95% CI)**
52	–0.006	(ICS dominant)	1.24	–177(–151 to 112)	52	–0.004	(ICS dominant)	2.82	–155 (–305 to 0)
37	–0.006	(ICS dominant)	2.12	–128 (–212 to 142)	36	–0.004	(ICS dominant)	3.50	–145 (–305 to 8)

Including imputed data					Including imputed data (adjusted for baseline utility)				
Inc. cost (£)	**Inc. QALYs**	**ICER (£)**	**P£30k (%)**	**INB|£30k (95% CI)**	**Inc. cost (£)**	**Inc. QALYs**	**ICER (£)**	**P£30k (%)**	**INB/£30k (95% CI)**
233	–0.091	(ICS dominant)	0.98	–698	228	–0.073	(ICS dominant)	3.30	–2255 (–4550 to 211)
209	–0.091	(ICS dominant)	1.26	–87	204	–0.073	(ICS dominant)	3.14	–2241 (–4542 to 118)

Primary analyses

Change in QOL

Mini Asthma Quality of Life Questionnaire

Mean MiniAQLQ score increased from baseline in both leukotriene antagonist and long-acting β_2-agonist randomised groups (*Table 30* and *Figure 11*). No statistically significant between-group differences in MiniAQLQ score were found at the 2-month time point either unadjusted or adjusted for baseline values. In each case, the point estimate of the mean difference between groups was small. The 95% CIs for the unadjusted difference in MiniAQLQ score was just at the limits for equivalence: (–0.18 to 0.30). However, the 95% CI for the adjusted difference was within the value of 0.3, i.e. (–0.29 to 0.10). The limit of the one-sided 95% CI for the unadjusted difference was –0.16 and was –0.28 for the adjusted difference.

At the 2-year visit, the estimated between-group mean difference was again small and not statistically significant. The 95% CI for the unadjusted difference did not include 0.3 (–0.22 to 0.25). The 95% CI for the adjusted difference did, although marginally, include 0.3 in favour of long-acting β_2-agonist (–0.32 to 0.11). The limit of the one-sided 95% CI for the unadjusted difference was –0.30 and was –0.28 for the adjusted difference, i.e. inferiority of leukotriene antagonist could be excluded.

Asthma Control Questionnaire

Mean ACQ score decreased (improved) from baseline in both leukotriene antagonist and long-acting β_2-agonist randomised groups (*Table 31* and *Figure 11*). No significant differences in ACQ score were found at either the 2-month or 2-year time points. At 2 years, the adjusted difference (95% CI) was 0.04 (–0.15 to 0.22). The CI is well within the minimum clinically important difference of 0.5.

Quality-adjusted life-years

Leukotriene antagonist patients experienced a mean 0.122 QALYs over the 2-month period, compared with 0.120 in long-acting β_2-agonist

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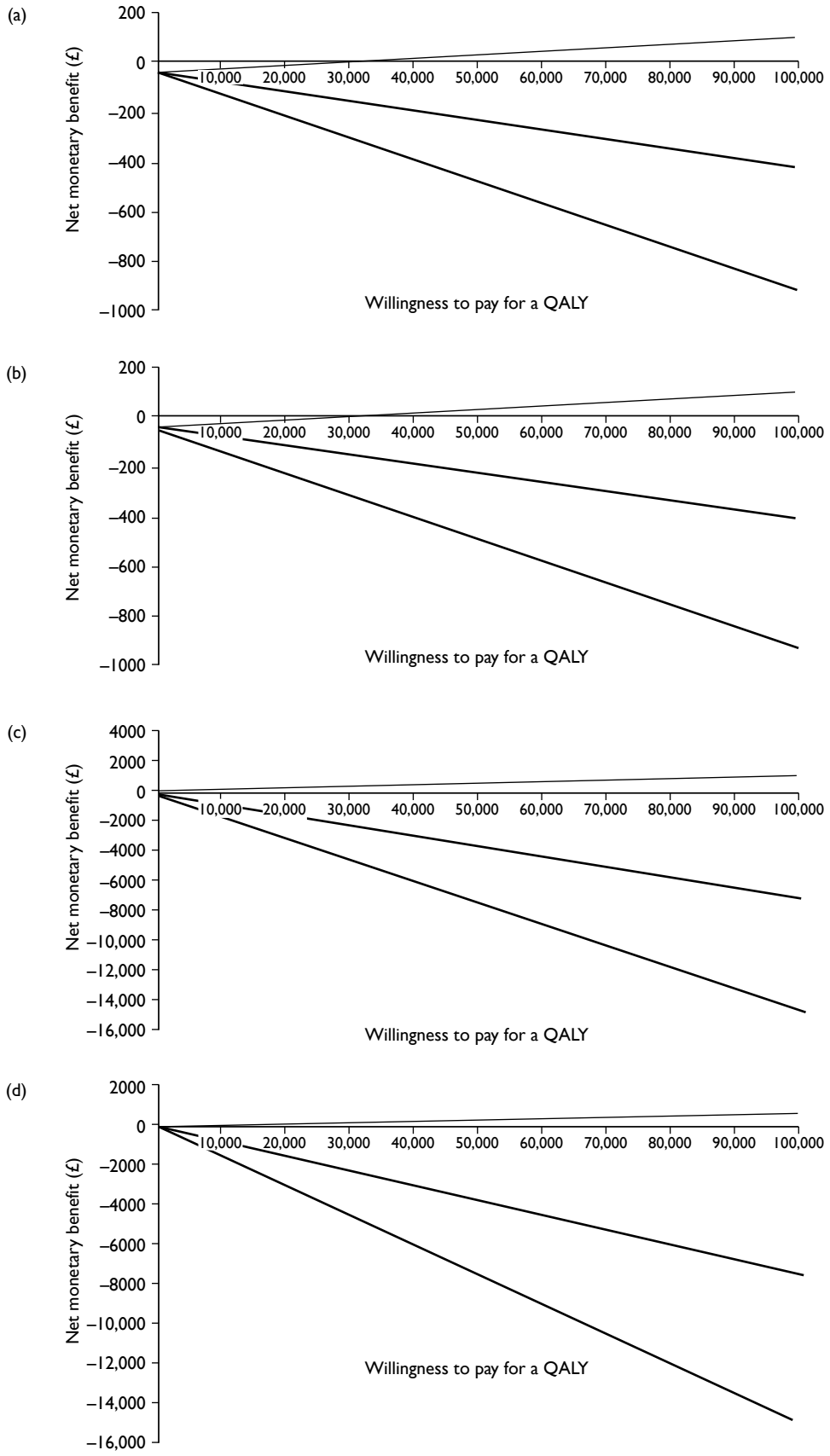

FIGURE 9 *Step 2: INB, QALYs, INB and 95% CI are shown for (a) 2-month NHS; (b) 2-month societal; (c) 2-year NHS; and (d) 2-year societal perspectives. Results based on imputed data adjusted for baseline utility.*

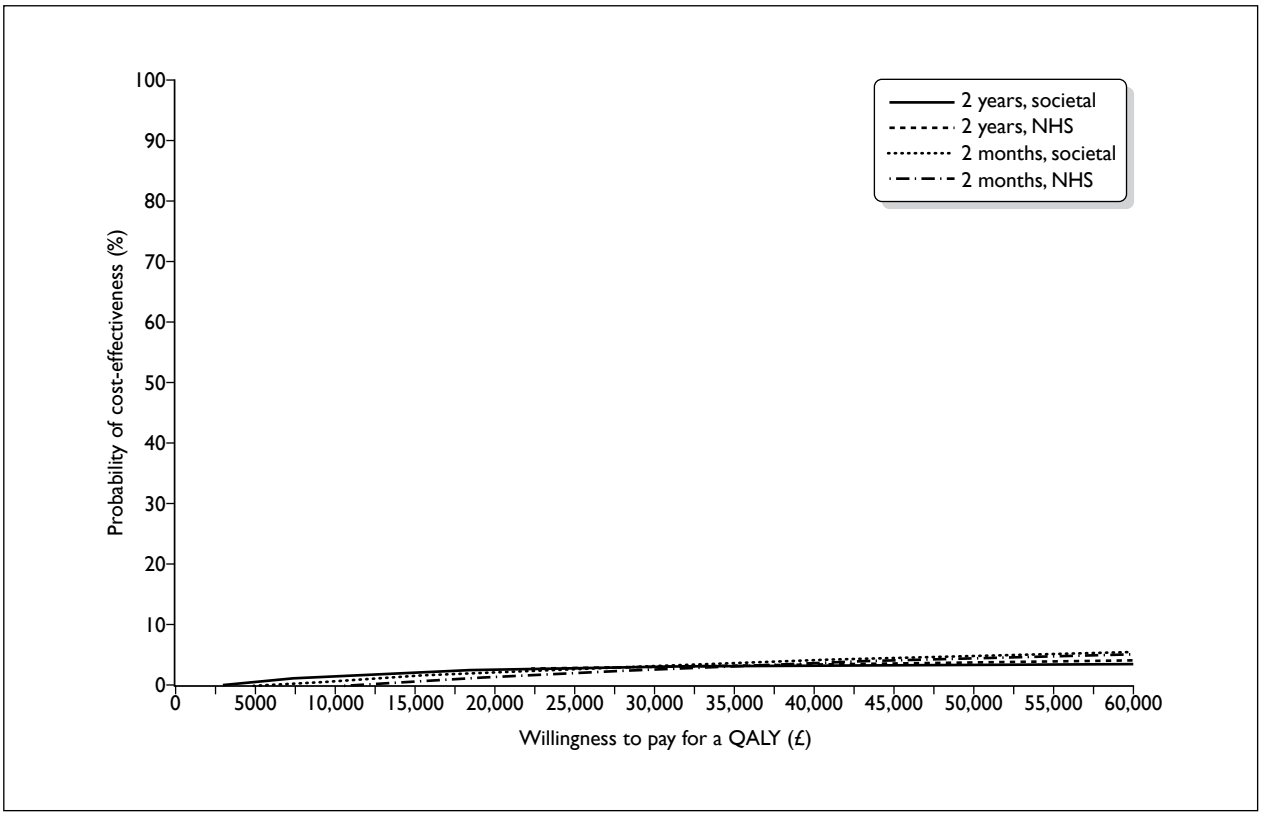

FIGURE 10 *Step 2: Cost–utility analysis – CEACs. Based on imputed, adjusted results of cost–utility analysis, societal/NHS indicates that results were from a societal or NHS cost perspective, respectively, and these outcomes took place at 2 months or 2 years. This figure indicates that the probability of leukotriene antagonist being cost-effective compared with inhaled corticosteroid is approximately 2.8–3.5%, given a typical willingness to pay of £30,000 per QALY gained.*

TABLE 21 *Step 2: exacerbations, respiratory tract infections, and short-acting β_2-agonist prescriptions*

	LTRA (*n* = 148)	**ICS (*n* = 158)**	**Rate ratio (95% CI)**
Mean (SD) exacerbations over 2 years	0.44 (0.94)	0.35 (0.95)	1.27 (0.83 to 1.92), $p = 0.230$
Mean (SD) respiratory tract infections over 2 years	1.01 (1.68)	1.06 (1.57)	0.95 (0.70 to 1.30), $p = 0.764$
Mean (SD) consultations for respiratory tract infections over 2 years	1.23 (2.12)	1.20 (1.82)	1.02 (0.74 to 1.41), $p = 0.891$
			Adjusted difference[a] (95% CI) LTRA–ICS
Mean (SD) SABA inhalers prescribed over 2 years (inhalers/day)	*n* = 138 0.014 (0.015)	*n* = 140 0.013 (0.014)	0.001 (–0.001 to 0.004), $p = 0.260$

CI, confidence interval; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; SABA, short-acting β_2-agonist; SD, standard deviation.
a Adjusted for baseline values.

patients, a mean (95% CI) difference of +0.002 (–0.007 to 0.010) QALYs, falling to –0.001 (–0.004 to 0.002) QALYs after adjustment for baseline utility (*Table 32*). Over 2 years, leukotriene antagonist patients gained 0.041 (–0.072 to 0.156) more QALYs than long-acting β_2-agonist patients. However, after adjusting for baseline utility, the difference drops to 0.012 (–0.064 to 0.088) QALYs, equivalent to 4.4 days of perfect health gained.

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TABLE 22 *Step 2: median (interquartile range) clinic %PPEF*

Measure	LTRA	ICS	*p*-value
Baseline	*n* = 134 85.97 (77.43 to 94.16)	*n* = 150 85.07 (73.92 to 95.42)	
2 months	*n* = 98 88.15 (80.09 to 97.90)	*n* = 106 86.56 (75.38 to 97.18)	*p* = 0.228
2 years	*n* = 100 88.84 (81.93 to 99.96)	*n* = 112 87.62 (76.13 to 99.56)	*p* = 0.197

ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist.

TABLE 23 *Step 2: symptom diary cards at 2 months*

	LTRA (*N* = 148)	ICS (*N* = 158)	Difference (95% CI) LTRA–ICS, *p*-value	Adjusted difference[a] (95% CI)
Mean (SD) morning waking with symptoms	*n* = 76 0.29 (0.33)	*n* = 81 0.29 (0.32)	–0.01 (–0.11 to 0.09) *p* = 0.873	0.01 (–0.08 to 0.10) *p* = 0.866
Mean (SD) puffs of reliever at night – original scale	*n* = 69 0.67 (0.90)	*n* = 73 0.77 (1.19)	–0.11	
Mean (SD) puffs of reliever at night – logged scale	*n* = 69 0.39 (0.47)	*n* = 73 0.42 (0.51)	–0.03 (–0.19 to 0.14) *p* = 0.729	–0.01 (–0.16 to 0.13) *p* = 0.857
Mean (SD) morning PEF	*n* = 74 417.0 (99.1)	*n* = 81 419.4 (111.2)	–2.4 (–35.9 to 31.2) *p* = 0.889	–3.4 (–14.8 to 8.0) *p* = 0.558
Mean (SD) daytime asthma symptom score	*n* = 75 1.26 (1.12)	*n* = 80 1.34 (1.14)	–0.08 (–0.44 to 0.28) *p* = 0.663	–0.08 (–0.40 to 0.25) *p* = 0.632
Mean (SD) score for daytime 'bother from asthma symptoms'	*n* = 75 1.10 (1.08)	*n* = 80 1.14 (1.08)	–0.04 (–0.39 to 0.30) *p* = 0.801	–0.09 (–0.39 to 0.21) *p* = 0.556
Mean (SD) daily activity score	*n* = 74 2.38 (1.21)	*n* = 79 2.26 (1.32)	0.12 (–0.28 to 0.53) *p* = 0.555	0.02 (–0.35 to 0.38) *p* = 0.930
Mean (SD) score for interference on activities from asthma	*n* = 75 0.96 (1.11)	*n* = 80 1.08 (1.13)	–0.13 (–0.48 to 0.23) *p* = 0.482	–0.20 (–0.52 to 0.11) *p* = 0.203
Mean (SD) puffs of reliever during the day – original scale	*n* = 70 1.57 (1.67)	*n* = 78 1.42 (1.49)	0.15	
Mean (SD) puffs of reliever during the day – logged scale	*n* = 70 0.76 (0.60)	*n* = 78 0.72 (0.56)	0.04 (–0.15 to 0.23) *p* = 0.669	0.03 (–0.14 to 0.20) *p* = 0.703
Mean (SD) evening PEF	*n* = 74 426.9 (100.3)	*n* = 81 423.7 (112.0)	3.3 (–30.6 to 37.1) *p* = 0.848	–2.4 (–13.0 to 8.2) *p* = 0.654
Mean (SD) PEF diurnal variability (%)	*n* = 74 5.8 (4.3)	*n* = 81 6.2 (4.4)	–0.4 (–1.8 to 0.9) *p* = 0.529	–0.3 (–1.7 to 1.0) *p* = 0.621

CI, confidence interval; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Adjusted for baseline values.

Resource use and cost

Point estimate costs and quantities of prescription medicines, over-the-counter medicines, NHS activity and indirect costs are reported in *Tables 33–36*.

Total NHS costs are the sum of prescriptions and NHS activity. Total societal costs are NHS costs plus over-the-counter medications and indirect costs. At 2 months, costs were similar between the two groups, although point estimate was higher in leukotriene antagonist patients [+£2 (95% CI –£7 to +£11 from NHS perspective), +£15 (95% CI –£35 to +£65 from societal perspective – *Table 37*)]. At 2 years, leukotriene antagonist patients cost £115 (–£46 to £276) or £263 (–£3 to £529) more than long-acting β_2-agonist patients from the NHS or societal perspectives, respectively.

TABLE 24 *Step 2: symptom diary cards at 2 years*

	LTRA (*N* = 148)	ICS (*N* = 158)	Difference (95% CI) LTRA–ICS, *p*-value	Adjusted difference[a] (95% CI), *p*-value
Mean (SD) morning waking with symptoms	*n* = 47 0.31 (0.34)	*n* = 57 0.21 (0.29)	0.10 (–0.02 to 0.23) *p* = 0.105	0.11 (–0.01 to 0.23) *p* = 0.063
Mean (SD) puffs of reliever at night – original scale	*n* = 45 0.52 (0.79)	*n* = 52 0.48 (0.96)	0.05	
Mean (SD) puffs of reliever at night – logged scale	*n* = 45 0.33 (0.41)	*n* = 52 0.28 (0.42)	0.05 (–0.12 to 0.22) *p* = 0.546	0.03 (–0.14 to 0.21) *p* = 0.717
Mean (SD) morning PEF	*n* = 47 412.4 (102.6)	*n* = 54 419.2 (137.8)	–6.77 (–55.3 to 41.8) *p* = 0.783	–21.5 (–50.5 to 7.6) *p* = 0.146
Mean (SD) daytime asthma symptom score	*n* = 47 1.43 (1.15)	*n* = 55 1.16 (1.21)	0.27 (–0.20 to 0.73) *p* = 0.259	0.12 (–0.31 to 0.55) *p* = 0.577
Mean (SD) score for daytime 'bother from asthma symptoms'	*n* = 47 1.24 (1.15)	*n* = 56 1.14 (1.39)	0.11 (–0.37 to 0.61) *p* = 0.673	–0.01(–0.43 to 0.41) *p* = 0.957
Mean (SD) daily activity score	*n* = 47 2.22 (1.37)	*n* = 56 2.07 (1.44)	0.15 (–0.40 to 0.71) *p* = 0.581	0.02 (–0.57 to 0.62) *p* = 0.934
Mean (SD) score for interference on activities from asthma	*n* = 47 1.08 (1.16)	*n* = 55 0.88 (1.26)	0.19 (–0.29 to 0.67) *p* = 0.427	0.01 (–0.41 to 0.43) *p* = 0.959
Mean (SD) puffs of reliever during the day – original scale	*n* = 45 1.67 (1.70)	*n* = 56 1.24 (1.42)	0.43	
Mean (SD) puffs of reliever during the day – logged scale	*n* = 45 0.80 (0.60)	*n* = 56 0.64 (0.57)	0.16 (–0.07 to 0.39) *p* = 0.172	0.16 (–0.07 to 0.38) *p* = 0.170
Mean (SD) evening PEF	*n* = 46 419.6 (104.7)	*n* = 57 408.8 (129.8)	10.8 (–36.1 to 57.7) *p* = 0.649	–12.5 (–37.6 to 12.5) *p* = 0.322
Mean (SD) PEF diurnal variability (%)	*n* = 37 4.4 (3.4)	*n* = 44 4.6 (3.0)	–0.1 (–1.6 to 1.3) *p* = 0.852	–0.2 (–1.7 to 1.2) *p* = 0.742

CI, confidence interval; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Adjusted for baseline values.

TABLE 25 *Step 2: secondary QOL measures*

Measure	LTRA	ICS	Difference (95% CI) LTRA–ICS, *p*-value	Adjusted difference[a] (95% CI), *p*-value
2-month outcomes				
mRQLQ	*n* = 114 1.48 (1.15)	*n* = 124 1.55 (1.20)	–0.07 (–0.37 to 0.23), *p* = 0.638	0.07 (–0.35 to 0.21), *p* = 0.639
RCP3	*n* = 123 1.21 (0.96)	*n* = 139 1.37 (1.06)	–0.16 (–0.40 to 0.09), *p* = 0.216	–0.13 (–0.38 to 0.12), *p* = 0.322
Personal objectives (0–100 VAS)	*n* = 82 54.7 (22.4)	*n* = 90 50.3 (22.6)	4.44 (–11.21 to 2.33), *p* = 0.197	2.40(–4.53 to 9.32), *p* = 0.495
2-year outcomes				
mRQLQ	*n* = 145 1.26 (1.23)	*n* = 152 1.26 (1.28)	0.00 (–0.29 to 0.28), *p* = 0.355	0.02 (–0.27 to 0.31), *p* = 0.900
RCP3	*n* = 147 1.23 (0.99)	*n* = 155 1.14 (0.98)	0.10 (–0.13 to 0.31), *p* = 0.432	0.11 (–0.12 to 0.34), *p* = 0.360
Personal objectives (0–100 VAS)	*n* = 97 66.5 (20.9)	*n* = 107 69.1 (18.9)	–2.58 (–8.07 to 2.91), *p* = 0.355	–4.62 (–10.75 to 1.51), *p* = 0.139

CI, confidence interval; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; VAS, visual analogue scale.
a Adjusted for baseline value.

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TABLE 26 *Step 2: changes in treatment by 2 months and 2 years*

Treatment change by 2 months,* n *(%)	
Participants in ICS arm	*N = 155*
Add LABA	3 (2)
Change to LTRA	2 (1)
Total	5 (3)
Participants in LTRA arm	*N = 145*
Change to ICS	6 (4)
Change to ICS and LABA	1 (1)
Multiple changes	1 (1)
Total	8 (6)
Treatment change by 2 years,* n *(%)	
Participants in ICS arm	*N = 155*
Add LABA	28 (18)
Change to LTRA	4 (3)
Total	32 (21)
Participants in LTRA arm	*N = 145*
Add ICS	4 (3)
Add ICS and LABA	2 (1)
Change to ICS	27 (19)
Change to ICS and LABA	8 (6)
Change to ICS and then add LABA	3 (2)
Multiple changes	1 (1)
Total	45 (31)

ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist.

TABLE 27 *Step 3 trial: demographics of participants at visit 2*

		LTRA (*N* = 170)	**LABA (*N* = 182)**
Sex	*Female*	109 (64%)	111 (61%)
	Male	61 (36%)	71 (39%)
Age	*Mean (SD)*	*n* = 169 51.0 (16.0)	49.7 (16.1)
Race	*Caucasian*	168	178
	Non-Caucasian	0	2
	Not known	2	2
Height (cm)	*Mean (SD)*	*n* = 156 167.0 (10.0)	*n* = 171 167.0 (9.3)
PEF (l/min)	*Mean (SD)*	*n* = 166 416 (125)	*n* = 178 419 (125)
%PPEF	*Median (IQR)*	*n* = 152 90.46 (80.24 to 99.67)	*n* = 167 88.64 (76.67 to 99.89)
Salbutamol PEF reversibility (%)	*Mean (SD)*	*n* = 163 9.01 (10.1)	*n* = 170 8.26 (9.63)
ICS dose (μg/day)[a]	*Mean (SD)*	425 (351)	451 (390)
SABA puffs/day, prior year	*Mean (SD)*	*n* = 162 4.3 (4.0)	*n* = 175 4.4 (3.5)
Asthma exacerbations in last year	*Mean (SD)*	0.18 (0.44)	0.24 (0.56)

TABLE 27 *Step 3 trial: demographics of participants at visit 2 (continued)*

		LTRA (*N* = 170)	LABA (*N* = 182)
ACQ	*Mean (SD)*	2.01 (0.85)	2.19 (0.87)
MiniAQLQ	*Mean (SD)*	4.63 (1.03)	4.41 (1.04)
mRQLQ	*Mean (SD)*	*n* = 139 1.95 (1.27)	*n* = 159 2.02 (1.31)
EQ-5D utility	*Mean (SD)*	*n* = 148 0.780 (0.237)	*n* = 159 0.772 (0.234)
Personal Objectives (0–100 VAS)	*Mean (SD)*	*n* = 130 38.12 (19.24)	*n* = 142 36.35 (19.05)
RCP3	*Mean (SD)*	*n* = 159 1.98 (0.86)	*n* = 177 2.03 (0.81)
Sleep difficulty	*Yes*	91 (54%)	85 (49%)
	No	76 (46%)	89 (51%)
	Missing	3	8
Day symptoms	*Yes*	155 (94%)	162 (94%)
	No	11 (6%)	12 (6%)
	Missing	4	8
Interferes with activities	*Yes*	82 (50%)	79 (46%)
	No	83 (50%)	92 (54%)
	Missing	5	11

ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β_2-agonist; VAS, visual analogue scale.
a Beclometasone dipropionate equivalent dose.
Note: percentages may not add to 100% because of rounding.

TABLE 28 *Step 3 trial: education and lifestyle characteristics of participants at visit 2*

		LTRA (*N* = 170)	LABA (*N* = 182)
Continued education > 16 years	Yes	78 (47%)	87 (48%)
	No	89 (53%)	93 (52%)
	Not known	3	2
Professional qualification	Yes	39 (23%)	46 (26%)
	No	127 (77%)	133 (74%)
	Not known	4	3
Employment position	Employer	9 (8%)	4 (3%)
	Employee	91 (78%)	95 (77%)
	Self-employed	17 (15%)	25 (20%)
	Not known	53	58
Smoking habit	Current smoker	29 (17%)	31 (17%)
	Ex-smoker	63 (38%)	75 (42%)
	Never smoked	76 (45%)	74 (41%)
	Not known	2	2
	Current smoker and over age 45	16 (10%)	16 (9%)

LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist.

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TABLE 29 *Step 3 Trial: baseline diary card symptom scores, PEF and reliever usage*

	LTRA (*N* = 170)	LABA (*N* = 182)
Mean (SD) morning waking with symptoms	0.47 (0.35) *n* = 159	0.46 (0.36) *n* = 176
Mean (SD) puffs of reliever at night	0.95 (1.42) *n* = 153	0.91 (1.01) *n* = 168
Mean (SD) morning PEF	391.1 (101.5) *n* = 158	393.7 (104.7) *n* = 175
Mean (SD) daytime asthma symptom score[a]	1.91 (1.23) *n* = 159	1.91 (1.13) *n* = 176
Mean (SD) score for daytime 'bother from asthma symptoms'[a]	1.65 (1.24) *n* = 159	1.68 (1.10) *n* = 174
Mean (SD) daily activity score[b]	2.58 (1.21) *n* = 156	2.45 (1.10) *n* = 173
Mean (SD) score for interference on activities from asthma[a]	1.38 (1.32) *n* = 157	1.52 (1.18) *n* = 174
Mean (SD) puffs of reliever during the day	2.73 (2.59) *n* = 154	2.74 (2.01) *n* = 175
Mean (SD) evening PEF	397.3 (100.0) *n* = 156	405.4 (101.5) *n* = 173
Mean (SD) diurnal variation in PEF (%)	6.5 (4.4) *n* = 158	6.5 (4.4) *n* = 175

LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a 0 = 'none' to 6 = 'all of the time or severely bothered'.
b 0 = 'more exercise than normal' to 6 = 'less than usual'.

TABLE 30 *Step 3 trial: MiniAQLQ scores*[a]

Treatment duration	Outcome measure	LTRA	LABA	Difference (95% CI) LTRA–LABA	Adjusted difference[b] (95% CI)
2 months (visit 3)	*n*	153	156	0.06 (–0.18 to 0.30)	–0.10 (–0.29 to 0.10)
	Mean (SD)	5.09 (1.15)	5.04 (1.11)		
2 years[c] (visit 7)	*n*	169	181	0.01 (–0.22 to 0.25)	–0.11 (–0.32 to 0.11)
	Mean (SD)	5.43 (1.14)	5.42 (1.08)		

CI, confidence interval; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Mean (SD) and differences (95% CI) between means for MiniAQLQ scores at 2 months and 2 years.
b Adjusted for baseline values.
c Multiple imputation was used to impute missing data.

TABLE 31 *Step 3 trial: ACQ scores. Mean (SD) and differences (95% CI) between means for ACQ scores at 2 months and 2 years*

Treatment duration		LTRA	LABA	Difference (95% CI) LTRA–LABA	Adjusted difference[a] (95% CI)
2 months (visit 3)	*n*	153	156	0.01 (–0.20 to 0.22)	0.12 (–0.06 to 0.30)
	Mean (SD)	1.62 (1.00)	1.60 (0.98)		
2 years[b] (visit 7)	*n*	169	181	–0.04 (–0.24 to 0.16)	0.04 (–0.15 to 0.22)
	Mean (SD)	1.31 (0.96)	1.34 (0.92)		

CI, confidence interval; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Adjusted for baseline values.
b Multiple imputation was used to impute missing data.

Cost-effectiveness analyses

MiniAQLQ

The incremental cost per point improvement in MiniAQLQ is £48 and £115, respectively, from the NHS and societal perspectives at 2 months (*Table 38*). At 2 years this has deteriorated to £3366 and £6267 (*Table 39*). Mean INB is positive so long as the willingness to pay for a point improvement in MiniAQLQ is greater than these mean estimates.

TABLE 32 *Step 3 trial: mean (SD) EQ-5D and differences between means for QALYs at 2 months and 2 years*

	LTRA		LABA		Difference (95% CI) LTRA–LABA	Adjusted difference[a] (95% CI)
	n	Mean (SD)	*n*	Mean (SD)		
EQ-5D utility						
Baseline	148	0.780 (0.237)	159	0.772 (0.234)	–	–
2 months	127	0.796 (0.267)	130	0.794 (0.225)	–	–
2 years	160	0.807 (0.255)	170	0.798 (0.268)	–	–
QALYs gained						
2 months	120	0.122 (0.35)	120	0.120 (0.032)	0.002 (–0.007 to 0.010)	–0.001 (–0.004 to 0.002)
2 years (discounted)	112	1.597 (0.418)	115	1.556 (0.451)	0.041 (–0.072 to 0.156)	0.012 (–0.064 to 0.088)

CI, confidence interval; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Adjusted for baseline utility.

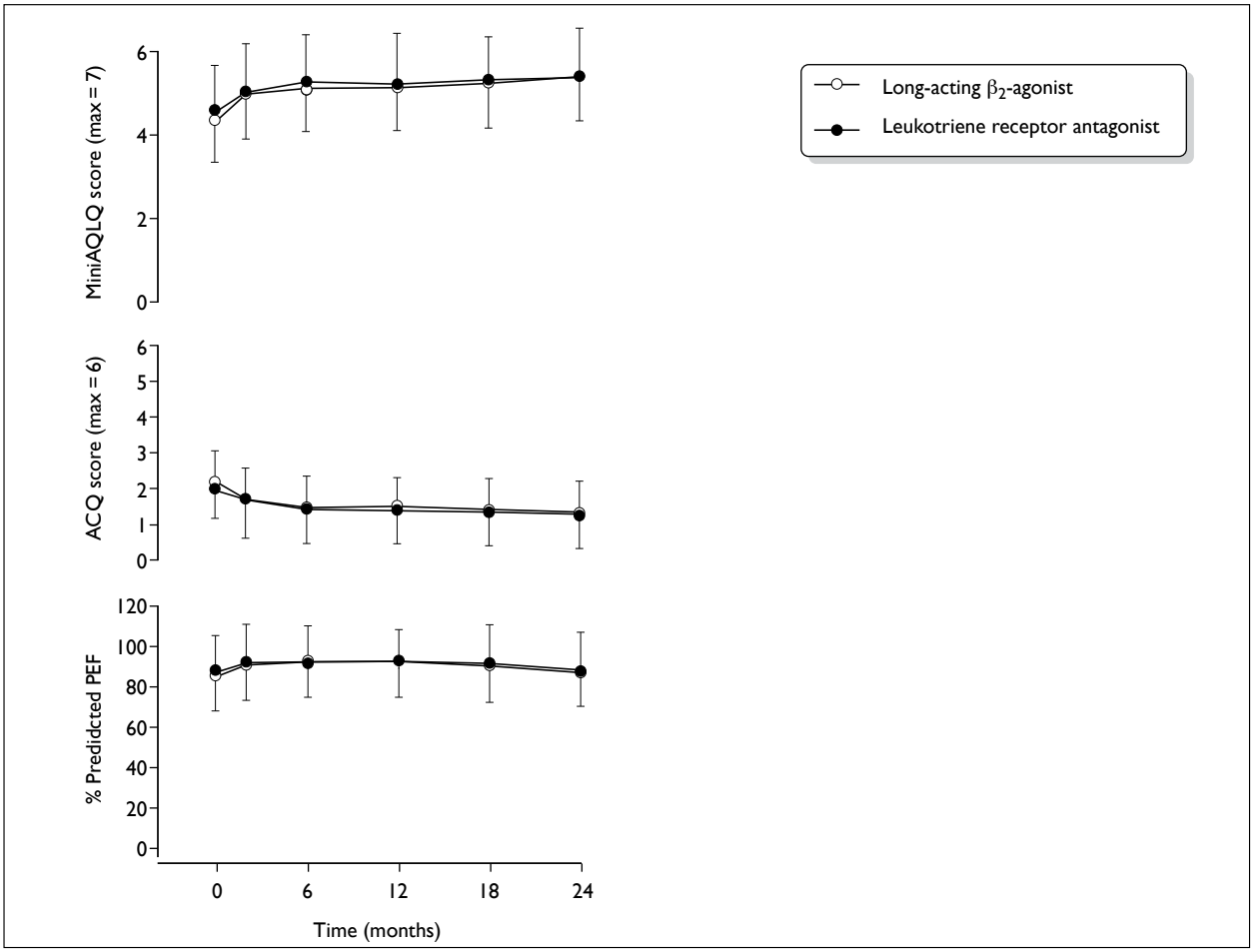

FIGURE 11 *Step 3: ACQ, MiniAQLQ and %PPEF over 2 years of treatment. Mean (standard deviation) ACQ (from 0 'best' to 6 'worst') and MiniAQLQ (from 1 'worst' to 7 'best') scores and median (interquartile range) %PPEF at baseline and over 2 years of treatment with leukotriene receptor antagonist or long-acting β_2-agonist as add-on to ICS.*

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TABLE 33 *Step 3 trial: cost of prescription medicines at 2 months and 2 years*[a]

	LTRA					LABA				
Treatment duration	***n***	**Total items**	**Mean (SD) items**	**Total cost (£)**	**Mean (SD) cost (£)**	***n***	**Total items**	**Mean items (SD)**	**Total cost (£)**	**Mean (SD) cost (£)**
2 months	175	707	4.02 (2.30)	12,984	73.77 (33.22)	184	682	3.69 (2.61)	13,403	73 (38)
2 years (discounted)	169	7129	42.2 (27.3)	116,477	689 (404)	177	6262	35.4 (31.1)	103,599	585 (437)

LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Total and mean (SD) costs of asthma-related prescription medicines prescribed during the step 3 trial.

TABLE 34 *Step 3 trial: cost of over-the-counter medicines at 2 months and 2 years*[a]

	LTRA					LABA					
Treatment duration	***n***	**Total items**	**Mean (SD) items**	**Total cost (£)**	**Mean (SD) cost (£)**	***n***	**Total items**	**Mean items (SD)**	**Total cost (£)**	**Mean (SD) cost (£)**	**Cost (£) difference**
2 months	131	130	0.99 (0.96)	453.34	3.46 (11.32)	142	133	0.94 (0.88)	362.80	2.55 (7.02)	0.91
2 years (discounted)	131	293	2.24 (2.11)	1024.69	7.82 (18.82)	142	311	2.19 (1.46)	850.38	5.99 (10.54)	1.83

LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Total and mean (SD) costs of asthma-related over-the-counter medicines prescribed during the step 3 trial.

TABLE 35 *Step 3 trial: cost of NHS activity at 2 months and 2 years*[a]

	LTRA					LABA				
Treatment	***n***	**Total items**	**Mean (SD) items**	**Total cost (£)**	**Mean (SD) cost (£)**	***n***	**Total items**	**Mean items (SD)**	**Total cost (£)**	**Mean (SD) cost (£)**
2 months										
Total routine care	175	38	0.22 (0.59)	403.34	2.30 (6.32)	182	47	0.26 (0.73)	398.34	2.19 (6.61)
Total patient initiated	175	59	0.34 (0.79)	1154	6.59 (17.17)	182	56	0.31 (0.75)	1129	6.20 (15.54)
Total secondary care	175	1	0.01 (0.08)	191	1.09 (17.44)	182	4	0.02 (0.18)	76	0.42 (3.43)
Total NHS activity	175	98	0.56 (0.99)	1748.34	9.99 (25.00)	182	107	0.59 (1.05)	1603.34	8.81 (17.64)
2 years (discounted)										
Total routine care	169	646	3.82 (2.63)	5710.33	33.79 (26.53)	176	699	3.97 (2.56)	5934.30	33.72 (24.49)
Total patient initiated	169	654	3.87 (4.20)	13,333.99	78.90 (89.75)	176	561	3.19 (2.94)	12,187.43	69.25 (71.42)
Total secondary care	169	74	0.44 (1.16)	12,873.62	76.18 (370.05)	176	47	0.27 (0.91)	13,091.82	74.39 (511.48)
Total NHS activity	169	1374	8.13 (5.94)	31,917.94	188.86 (398.89)	176	1307	7.43 (4.19)	31,213.56	177.35 (541.93)

LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Total and mean (SD) costs of asthma NHS health care-related activity during the step 3 trial.

TABLE 36 *Step 3 Trial: indirect costs at 2 months and 2 years*[a]

	LTRA					LABA				
Treatment duration	***n***	**Total hours**	**Mean (SD) hours**	**Total cost (£)**	**Mean (SD) cost (£)**	***n***	**Total hours**	**Mean hours (SD)**	**Total cost (£)**	**Mean (SD) cost (£)**
2 months	110	292	2.65 (13.94)	3833.96	34.85 (183.08)	115	295	2.57 (13.57)	3873.35	33.68 (178.14)
2 years (discounted)	110	1468	13.35 (51.96)	19,274.84	175.23 (682.17)	115	1077	9.37 (53.84)	13,368.11	116.24 (702.80)

LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Total and mean (SD) indirect costs during the step 3 trial.

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TABLE 37 *Step 3 trial: total NHS and societal costs at 2 months and 2 years*[a]

	LTRA			LABA			
Treatment	***n***	**Total cost (£)**	**Mean (SD) cost (£)**	***n***	**Total cost (£)**	**Mean (SD) cost (£)**	**Cost (£) difference (95% CI)**
Total NHS costs (prescription medicines and NHS activity combined)							
2 months	175	14,732.57	84.19 (41.71)	262.83 (–3 to 529)	14,911.91	81.93 (45.84)	2.25 (–6.88 to 11.39)
2 years (discounted)	166	147,299.54	887.35 (617.05)		132,052.97	772.24 (862.96)	115.11 (–46 to 276)
Societal costs (prescription and over-the-counter medicines – NHS activity and indirect costs combined)							
2 months	101	12,818.31	126.91 (202.11)		11,655.96	112.08 (158.73)	14.84 (–35.13 to 64.80)
2 years (discounted)	97	111,196.77	1146.36 (965.55)		87,469.45	883.53 (923.89)	262.83 (–3 to 529)

CI, confidence interval; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Total and mean (SD) NHS and societal costs during the step 3 trial.

TABLE 38 *Step 3: ICER at 2 months*[a]

	n		Cost (£)		MiniAQLQ		Source data only			Including imputed data			Including imputed data (adjusted for baseline MiniAQLQ)		
	LTRA	LABA	LTRA	LABA	LTRA	LABA	Inc. cost (£)	Inc. AQLQ	ICER (£)	Inc. cost (£)	Inc. AQLQ	ICER (£)	Inc. cost (£)	Inc. AQLQ	ICER (£)
NHS	153	155	84	82	5.092	5.038	3	0.055	47	3	0.040	67	3	0.058	48
Societal	95	90	129	115	5.110	4.978	14	0.132	109	6	0.040	162	7	0.058	115

Inc., incremental; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist.

a Inc. cost, inc. MiniAQLQ (95% CI) and ICERs are reported for patient groups with complete societal and NHS cost and MiniAQLQ data and following imputation for missing data (*).

TABLE 39 *Step 3: ICER at 2 years*[a]

	n		Cost (£)		MiniAQLQ		Source data only			Including imputed data			Including imputed data (adjusted for baseline MiniAQLQ)		
	LTRA	LABA	LTRA	LABA	LTRA	LABA	Inc. cost (£)	Inc. AQLQ	ICER (£)	Inc. cost (£)	Inc. AQLQ	ICER (£)	Inc. cost (£)	Inc. AQLQ	ICER (£)
NHS	155	164	891	791	5.452	5.416	100	0.037	2734	111	0.016	6886	114	0.034	3366
Societal	94	96	1152	893	5.352	5.438	259	–0.086	(LABA dominant)	213	0.016	13,235	215	0.034	6367

Inc., incremental; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist.

a Inc. cost, inc. MiniAQLQ (95% CI) and ICERs are reported for patient groups with complete societal and NHS cost and MiniAQLQ data and following imputation for missing data(*).

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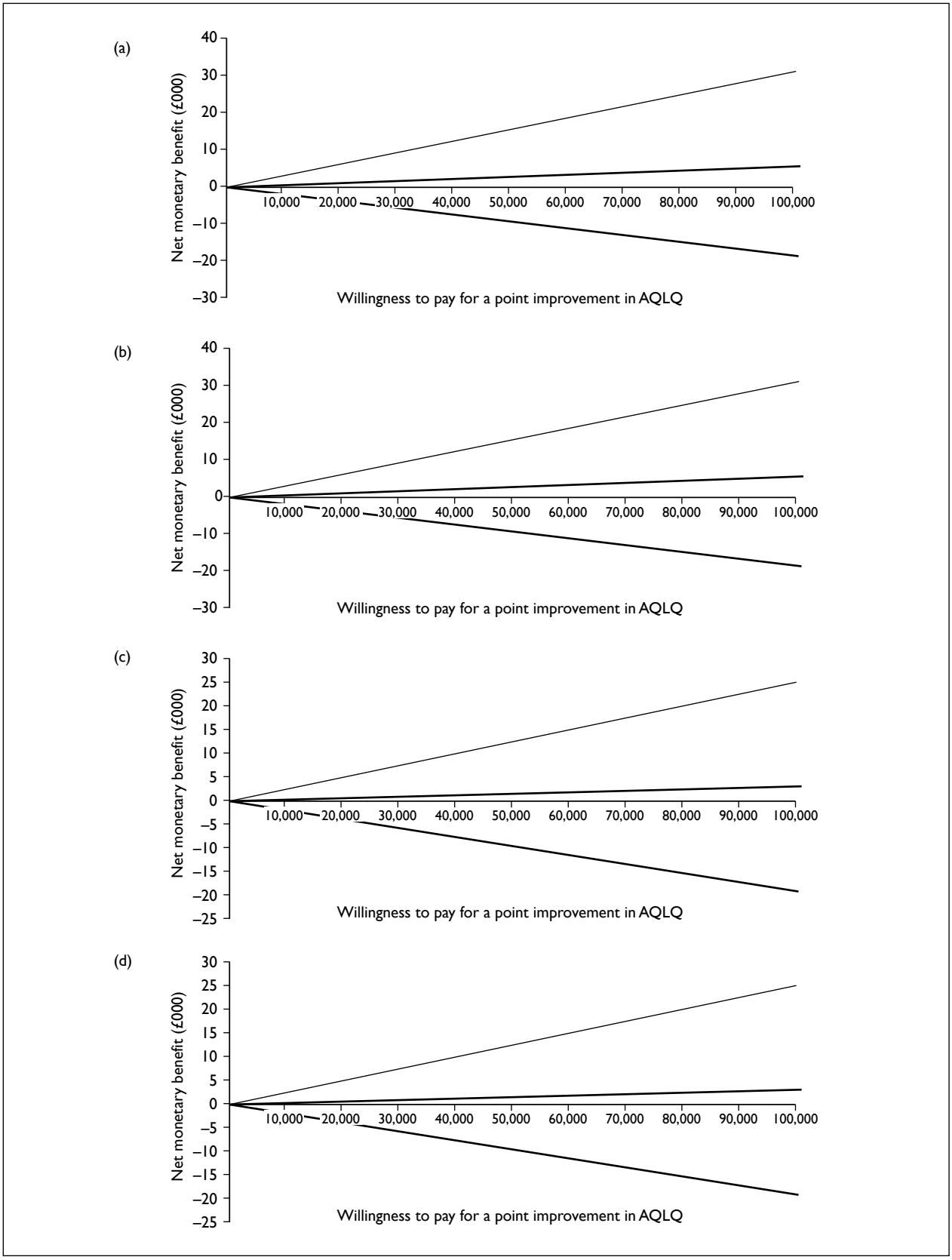

FIGURE 12 *Step 3: INB, MiniAQLQ, INB and 95% CI for (a) 2-month NHS; (b) 2-month societal; (c) 2-year NHS; and (d) 2-year societal perspectives. Results based on imputed data adjusted for baseline MiniAQLQ.*

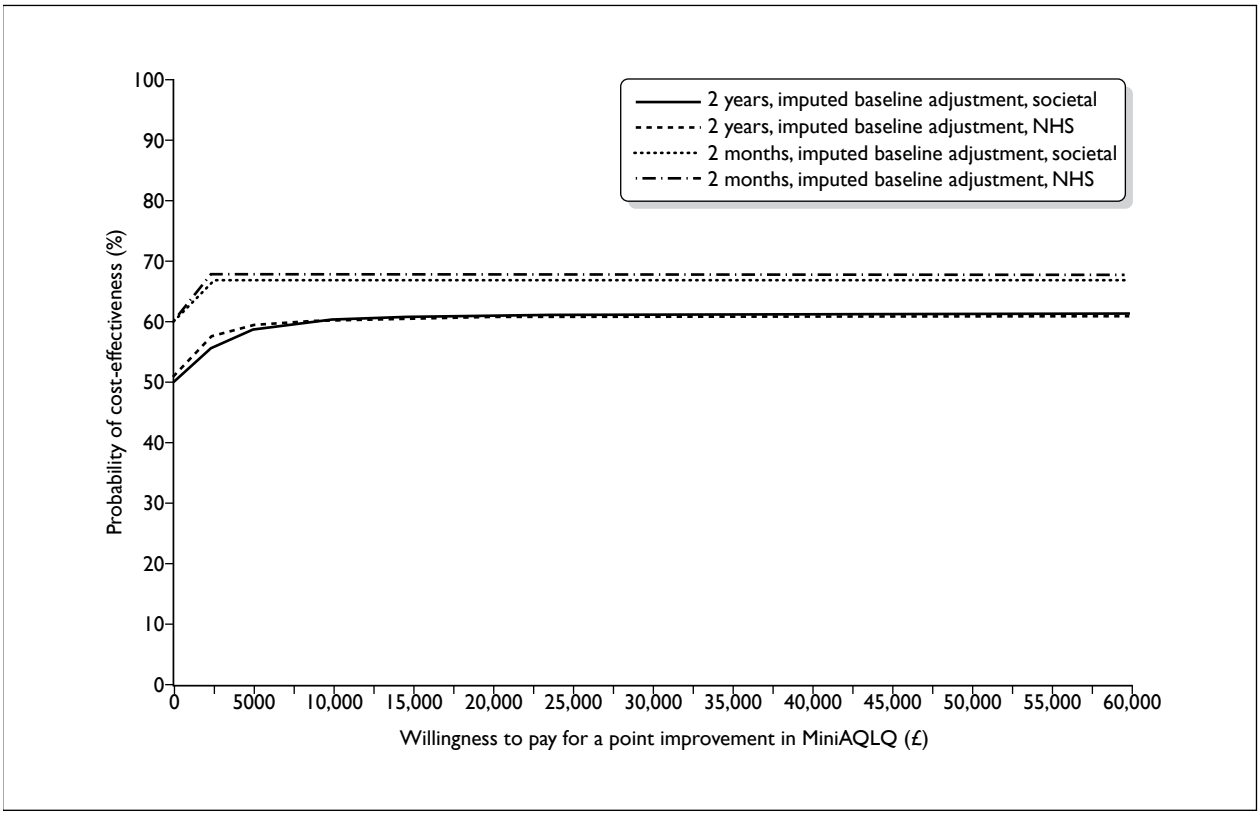

FIGURE 13 *Step 3: MiniAQLQ CEACs. Based on imputed, adjusted results of MiniAQLQ, societal/NHS indicates that results were from a societal or NHS cost perspective, respectively, and that these outcomes took place at 2 months or 2 years. The figure indicates that in all cases the probability of leukotriene antagonist being cost-effective compared with long-acting β_2-agonist is above 50%, irrespective of the willingness to pay for a point improvement in MiniAQLQ. The exception is the 2-year analysis from a societal perspective, where the probability is above 50% as long as the willingness to pay for a point improvement in MiniAQLQ is > £432.*

However, we did not detect a statistically significant result at any threshold (*Figure 12*).

At higher thresholds, there is between a 61% and 68% probability of leukotriene antagonist being cost-effective compared with long-acting β_2-agonist in step 3 patients (*Figure 13*). However, from a societal perspective over 2 years, there is a 50% or greater probability of leukotriene antagonists being cost-effective only when the threshold is above £385 per point improvement in MiniAQLQ.

Asthma Control Questionnaire

Over 2 months (*Table 40*) and 2 years (*Table 41*), long-acting β_2-agonist is, on average, a dominant strategy over leukotriene antagonist. Mean INB is negative, irrespective of willingness to pay for a point improvement in ACQ. However, there is great deal of uncertainty around this estimate (*Figure 14*).

Even with a very high willingness to pay for a point improvement in ACQ, there is up to a 49% probability of leukotriene antagonist being cost-effective compared with long-acting β_2-agonist in step 3 patients (depending on perspective and time horizon – *Figure 15*).

Quality-adjusted life-years (cost–utility analysis)

The incremental cost per QALY gained is between £5521 and £22,589, dependent upon perspective and time horizon (*Tables 42* and *43*).

At a typical willingness to pay of £30,000 per QALY gained, mean (95% CI) INB at 2 months is £14 (–£161 to £194) or £9 (–£155 to £191) from the NHS and societal perspectives, and £154 (–£2443 to £2893) and £142 (–£2567 to £2825) at 2 years (*Tables 42* and *43*, and *Figure 16*).

At the £30,000 threshold, there is between a 51.6% and 54.6% probability of leukotriene antagonist being cost-effective compared with long-acting β_2-agonist in patients at step 3 of the national asthma guidelines (dependent on time horizon and perspective – *Tables 42* and *43*, and *Figure 17*).

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TABLE 40 *Step 3: ICER at 2 months*[a]

	n		Cost (£)		ACQ		Source data only			Including imputed data			Including imputed data (adjusted for baseline ACQ)		
	LTRA	LABA	LTRA	LABA	LTRA	LABA	Inc. cost (£)	Inc.ACQ	ICER (£)	Inc. cost (£)	Inc.ACQ	ICER (£)	Inc. cost (£)	Inc. ACQ	ICER (£)
NHS	153	155	84	82	1.616	1.606	3	0.010	(LABA dominant)	3	0.020	(LABA dominant)	4	0.106	(LABA dominant)
Societal	95	90	129	115	1.642	1.619	14	0.024	(LABA dominant)	6	0.020	(LABA dominant)	7	0.106	(LABA dominant)

Inc., incremental; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist.
a Inc. cost, inc. ACQ (95% CI) and ICERs are reported for patient groups with complete societal and NHS cost and ACQ data and following imputation for missing data.

TABLE 41 *Step 3: ICER at 2 years*[a]

	n		Cost (£)		ACQ		Source data only			Including imputed data			Including imputed data (adjusted for baseline ACQ)		
	LTRA	LABA	LTRA	LABA	LTRA	LABA	Inc. cost (£)	Inc. ACQ	ICER (£)	Inc. cost (£)	Inc. ACQ	ICER (£)	Inc. cost (£)	Inc. ACQ	ICER (£)
NHS	154	164	886	791	1.272	1.350	96	–0.077	1241	111	–0.063	1768	133	0.002	(LABA dominant)
Societal	94	96	1152	893	1.349	1.306	259	0.044	(LABA dominant)	213	–0.063	3398	226	0.002	(LABA dominant)

Inc., incremental; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist.
a Inc. cost, inc. ACQ (95% CI) and ICERs are reported for patient groups with complete societal and NHS cost and ACQ data and following imputation for missing data.

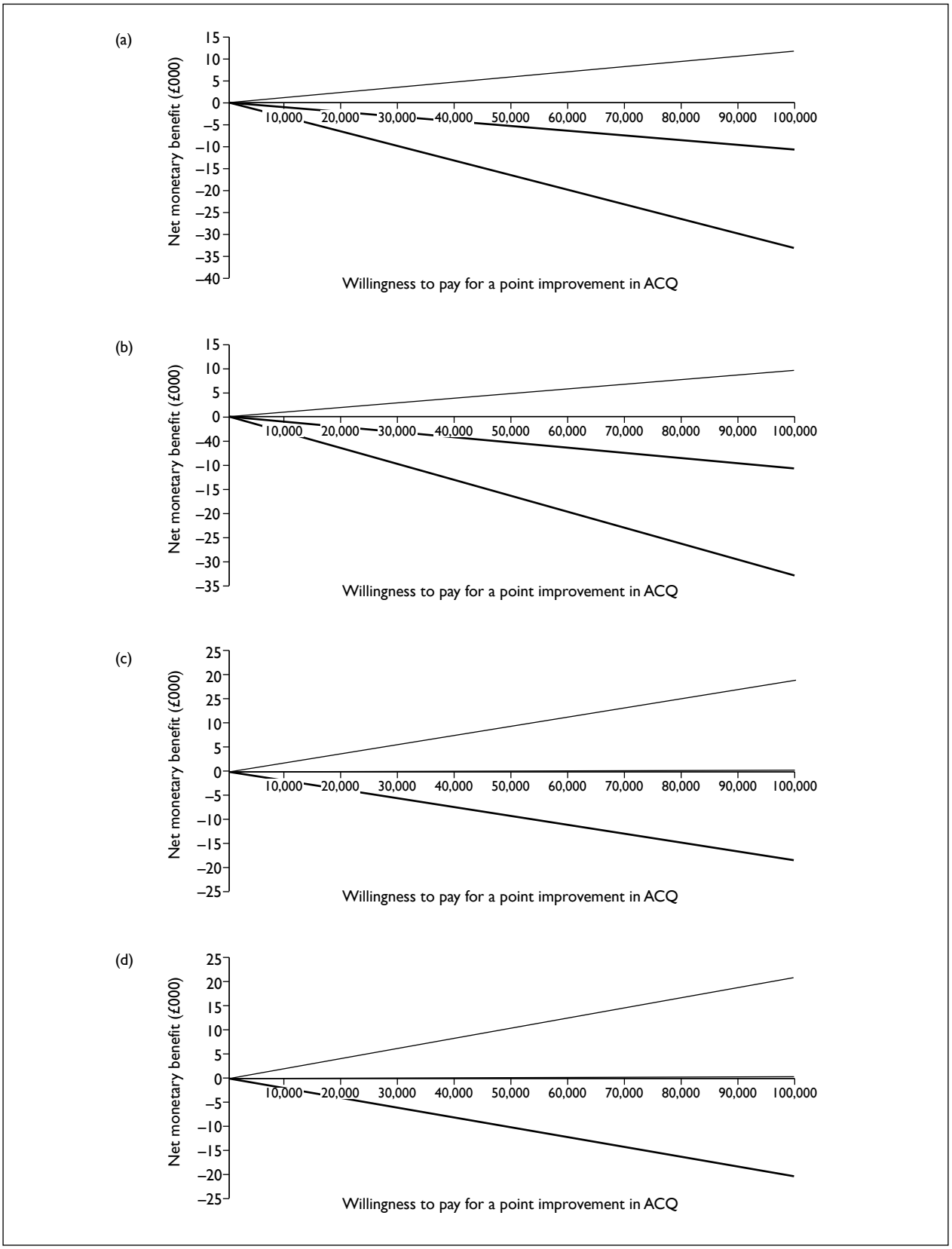

FIGURE 14 *Step 3: INB, ACQ, INB and 95% CI are shown for (a) 2-month NHS; (b) 2-month societal; (c) 2-year NHS; and (d) 2-year societal perspectives. Results based on imputed data adjusted for baseline ACQ.*

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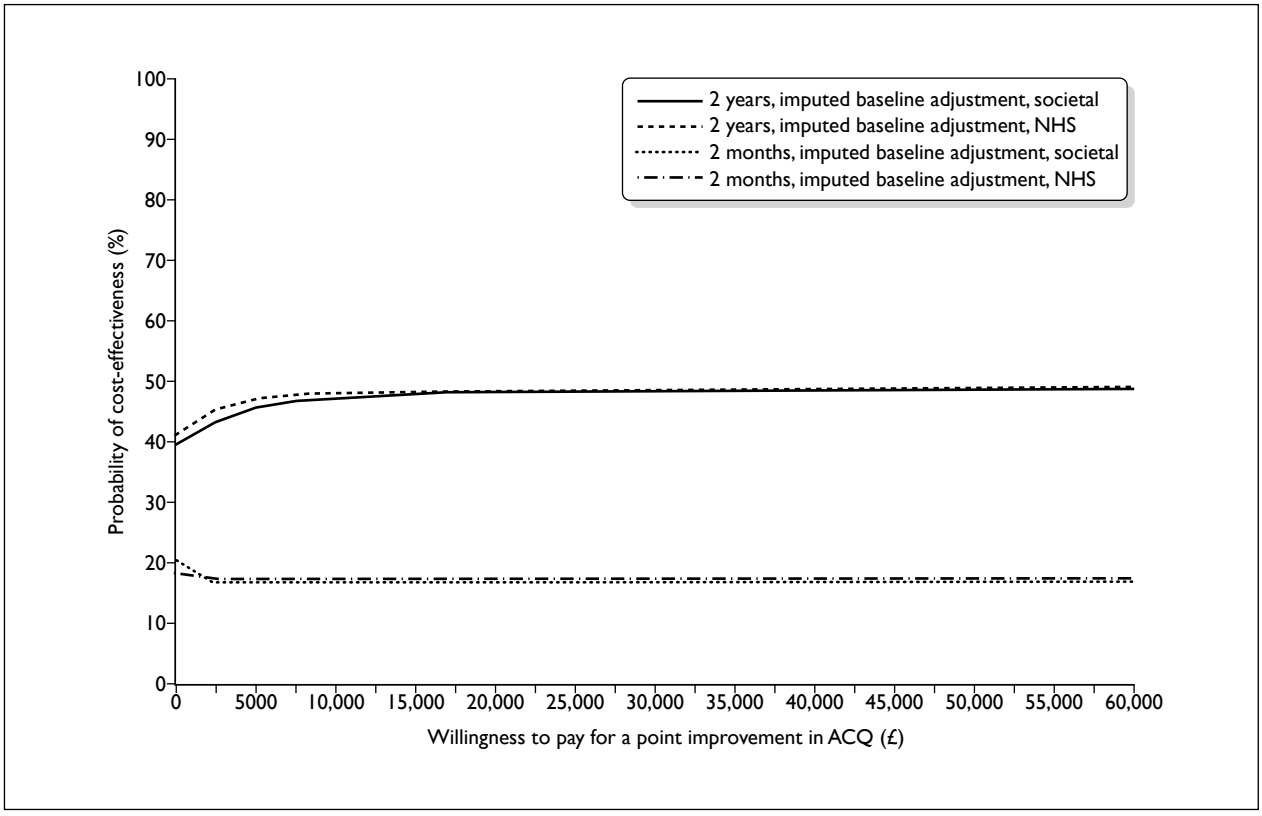

FIGURE 15 *Step 3: ACQ CEACs. Based on imputed, adjusted results of ACQ, societal/NHS indicates that results were from a societal or NHS cost perspective, respectively, and that these outcomes took place at 2 months or 2 years. This figure indicates that over a 2-year time horizon the probability of leukotriene antagonist being cost-effective compared with long-acting β_2-agonist approaches 50% as the willingness to pay for a point improvement in ACQ rises.*

Summary of cost-effectiveness analyses

The results of the cost-effectiveness analyses are somewhat equivocal: mean INB is positive when considering MiniAQLQ, as long as the willingness to pay for a point improvement in MiniAQLQ is > £6267 (2-year time horizon, societal analysis). However, when considering ACQ as the outcome measure, mean INB is always negative, yet the point estimate of the ICER is £22,589 (which would yield a positive mean INB at a 'typical' £30,000 threshold). The results are therefore contradictory, depending on the outcome measure.

There is at least a 50% probability of leukotriene antagonist being cost-effective, so long as the willingness to pay for a point improvement in MiniAQLQ is, at worst, £6200, and, at best, £47 (depending upon perspective and time horizon), and for a QALY, at least £6180–£23,600.

Whether an intervention is deemed cost-effective is dependent upon this willingness-to-pay threshold. A 'reasonable' threshold for QALYs is thought to be in the order of £30,000. The threshold for a point improvement in MiniAQLQ or ACQ is less well established. However, the results of the cost–utility analysis suggest a 51.6–54.6% probability of cost-effectiveness at a willingness to pay of £30,000 per QALY gained.

Secondary analyses

Asthma exacerbations, hospitalisations and respiratory tract infections

No significant differences were found in the number of exacerbations or respiratory tract infections experienced by participants receiving leukotriene antagonist or long-acting β_2-agonist (*Table 44*). Similarly, no significant difference was found in the number of consultations associated with respiratory tract infections.

There were no hospital admissions during the first 2 months of the study. Subsequently, over the remainder of the 2 years there were three hospital admissions for four nights total in the leukotriene antagonist group, and five hospital admissions for six nights in total in the long-acting β_2-agonist group.

Prescribed short-acting β_2-agonist and inhaled corticosteroid

Participants receiving leukotriene antagonist were prescribed significantly more short-acting β_2-agonist inhalers than participants receiving long-acting β_2-agonist (*Table 44*). On average, participants randomised to leukotriene antagonist received 2.01 short-acting β_2-agonist inhalers every 3 months compared with 1.55 short-acting β_2-agonist inhalers every 3 months for those receiving long-acting β_2-agonist. Over the 2-year study period an average of 16.06 versus 12.41 short-acting β_2-agonist inhalers were issued to participants randomised to leukotriene antagonist and long-acting β_2-agonist, respectively.

No significant change in inhaled steroid dose/day was observed from baseline to 12 or 24 months following randomisation for leukotriene antagonist or long-acting β_2-agonist {leukotriene antagonist: difference at 12 months and 24 months = –15.0 [standard deviation (SD) 243] and –36.2 (SD 324) µg/day; long-acting β_2-agonist: difference at 12 months and 24 months = –17.4 (SD 306) and 10.4 (SD 331) µg/day}. Similarly, no significant difference was found between the groups receiving leukotriene antagonist or long-acting β_2-agonist at either time point (*Table 44*).

Clinic per cent predicted peak expiratory flow and domiciliary data

For clinic %PPEF, slight improvement was observed in both leukotriene antagonist and long-acting β_2-agonist-treated groups at 2 months, followed by a slight decrease at 2 years. However, no significant differences between the groups were found at either the 2-month or 2-year time points (*Table 45* and *Figure 11*).

Diary cards were completed by approximately two-thirds of participants at 2 months and half at 2 years. As recorded on the diary cards at 2 months, participants receiving long-acting β_2-agonist had significantly higher morning and evening domiciliary PEF than participants receiving leukotriene antagonist (*Table 46*).

By 2 years, morning PEF was still significantly higher in participants receiving long-acting β_2-agonist, although the mean difference was unlikely to be clinically significant (396 versus 420 l/minute in leukotriene antagonist and long-acting β_2-agonist groups, respectively); no significant difference was found in the evening PEF (*Table 47*). At 2 months, participants receiving leukotriene antagonist had higher diurnal variability than participants receiving long-acting β_2-agonist, although this difference did not reach significance ($p = 0.064$). No significant difference was found after 2 years. At 2 months, participants receiving long-acting β_2-agonist required significantly fewer daytime and night-time puffs of short-acting β_2-agonist than participants receiving leukotriene antagonist, although by 2 years this difference was no longer apparent. No significant differences in symptom scores were found.

Secondary QOL scores and rhinitis scores

No significant differences were observed in RCP3 questions or personal objectives scores after 2 months or 2 years (*Table 48*). However, at both time points, these two measures showed a substantial improvement from baseline. A trend towards significance was observed in the personal objectives, with participants receiving long-acting β_2-agonist achieving a higher score at 2 months. However, this benefit was lost after 2 years. The mRQLQ score was significantly better ($p = 0.01$) in the leukotriene antagonist than the long-acting β_2-agonist group at 2 months, but was comparable in the two groups at 2 years.

Changes in treatment after randomisation

Overall, by 2 months, seven patients (4%) in the leukotriene antagonist group and none (0%) in the long-acting β_2-agonist group had a change in treatment from initial randomised therapy class. Over the course of the study, 43 patients (27%) in the leukotriene antagonist group and none (0%) in the long-acting β_2-agonist group had a change in treatment. The changes in treatment by 2 months and 2 years are tabulated in *Table 49*.

Per-protocol population (fixed treatment regime and no changes within or from randomised therapy class) analyses

Our per-protocol population was defined as those patients who were prescribed a fixed treatment regime at randomisation (i.e. no self-management plan) and who had no change in that fixed regime at any time including the final study visit, i.e. no change in device, dose or therapeutic class. After restricting the participant groups to only those meeting that definition and who had analysable data, 60 leukotriene antagonist and 80 long-acting β_2-agonist participants were identified (Appendix 5). Conversely, 110 and 102 patients, respectively, received a different treatment or variable course of treatment during the 2 years. Results for the per-protocol participant groups are summarised in Appendix 5, *Tables 67–74*.

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TABLE 42 *Step 3: ICER at 2 months*[a]

	n		Cost (£)		QALYs		Source data only				
	LTRA	LABA	LTRA	LABA	LTRA	LABA	Inc. cost (£)	Inc. QALYs	ICER (£)	P£30k (%)	INB/£30k (95% CI)
NHS	119	119	87	87	0.122	0.120	0	0.001	(LTRA dominant)	60.00	24 (–143 to 204)
Societal	77	74	117	126	0.122	0.119	–9	0.002	(LTRA dominant)	67.80	54 (–181 to 276)

CI, confidence interval; inc., incremental; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist.
a Inc. cost, inc. QALY (95% CI), ICERs and probability that the intervention is cost-effective given a willingness to pay of £30,000 for QALY (P£30k – see *Figure 8*) are reported for patient groups with complete societal and NHS cost and QALY data and following imputation for missing data (*).

TABLE 43 *Step 3: ICER at 2 years*[a]

	n		Cost (£)		QALYs		Source data only				
	LTRA	LABA	LTRA	LABA	LTRA	LABA	Inc. cost (£)	Inc. QALYs	ICER (£)	P£30k (%)	INB/£30k (95% CI)
NHS	108	109	956	869	1.601	1.548	88	0.053	1643	81.60	983 (–1429 to 3449)
Societal	72	70	1157	952	1.610	1.566	205	0.044	4668	68.60	680 (–2308 to 3547)

CI, confidence interval; inc., incremental; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist.
a Inc. cost, inc. QALY (95% CI), ICERs and probability that the intervention is cost-effective given a willingness to pay of £30,000 for QALY (P£30k – see *Figure 8*) are reported for patient groups with complete societal and NHS cost and QALY data and following imputation for missing data (*).

There were no significant differences between treatment groups in MiniAQLQ or ACQ scores for these participants (Appendix 5, *Tables 69* and *70*). Adjusted differences at 2 months and 2 years favoured long-acting β_2-agonist with 95% CI outside the limits of equivalence [MiniAQLQ adjusted difference (95% CI) at 2 years = –0.05 (–0.36 to 0.26)].

In contrast to the intention-to-treat results, these results did not show significant differences between groups for short-acting β_2-agonist prescriptions, equivalent to 12.4 versus 11 inhalers over 2 years in leukotriene antagonist and long-acting β_2-agonist groups, respectively (Appendix 5, *Table 72*). Consistent with the intention-to-treat analyses, at 2 months the leukotriene antagonist group had significantly lower (i.e. better) mRQLQ scores than the long-acting β_2-agonist group (Appendix 5, *Table 74*). Although the mRQLQ score was still lower at 2 years for the leukotriene antagonist than the long-acting β_2-agonist group, this difference was no longer significant (Appendix 5, *Table 74*).

Adherence to treatment

Adherence data were analysable for 220 patients, overall, who had at least 6 months of unchanged therapy. In the leukotriene antagonist group (n = 99, or 60%), median adherence (interquartile range) to inhaled steroid was 82.1% (34.2–116.3%) and to leukotriene antagonist 90.1% (23.2–99.6%). In the long-acting β_2-agonist group (n = 121, or 69%), median adherence to inhaled steroid was 64.9% (36.7–93.6%) and to long-acting β_2-agonist 49.3% (20–73.9%).

Adverse events

Adverse reactions to study medications

Twenty-six adverse reactions to study medication were reported by practices participating in the study. Fifteen patients (four at step 2 and 11 at step 3) had a total of 19 adverse reactions to the leukotriene antagonist montelukast, of which one

Including imputed data					Including imputed data (adjusted for BL utility)				
Inc. cost (£)	**Inc. QALYs**	**ICER (£)**	**P£30k (%)**	**INB/£30k (95% CI)**	**Inc. cost (£)**	**Inc. QALYs**	**ICER (£)**	**P£30k (%)**	**INB/£30k (95% CI)**
3	0.001	2470	60.00	57 (–15 to –44)	3	0.001	5521	54.64	14 (–161 to 194)
6	0.001	6018	58.56	36 (7 to –36)	6	0.001	12,290	54.10	9 (–155 to 191)

Including imputed data					Including imputed data (adjusted for BL utility)				
Inc. cost (£)	**Inc. QALYs**	**ICER (£)**	**P£30k (%)**	**INB/£30k (95% CI)**	**Inc. cost (£)**	**Inc. QALYs**	**ICER (£)**	**P£30k (%)**	**INB/£30k (95% CI)**
111	0.015	7164	57.76	–378 (1673 to 1896)	113	0.009	11919	53.16	154 (–2443 to 2893)
213	0.015	13,769	54.34	168 (327 to 1369)	214	0.009	22,589	51.56	142 (–2567 to 2825)

was considered by the site nurse practitioner or GP to be a 'serious adverse reaction' (*Table 50*).

Two patients (both at step 2) reported a total of three adverse reactions (non-serious) to the inhaled steroid beclometasone dipropionate and a further two patients (both at step 3) reported a total of four adverse reactions (non-serious) to the long-acting β_2-agonist salmeterol (*Table 51*). All other adverse reactions reported were consistent with the manufacturer's product information. All patients recovered from the adverse reactions.

Adverse events unrelated to study medication

One patient reported an adverse reaction to Tylex (*Table 52*). The medication was stopped and the patient recovered. No change was made to the study medication as a result of this adverse event.

Serious adverse events unrelated to study medication

One patient, randomised to inhaled steroid in the step 2 study, died as a result of a bronchogenic carcinoma (*Table 53*). This was considered to be unrelated to the medication.

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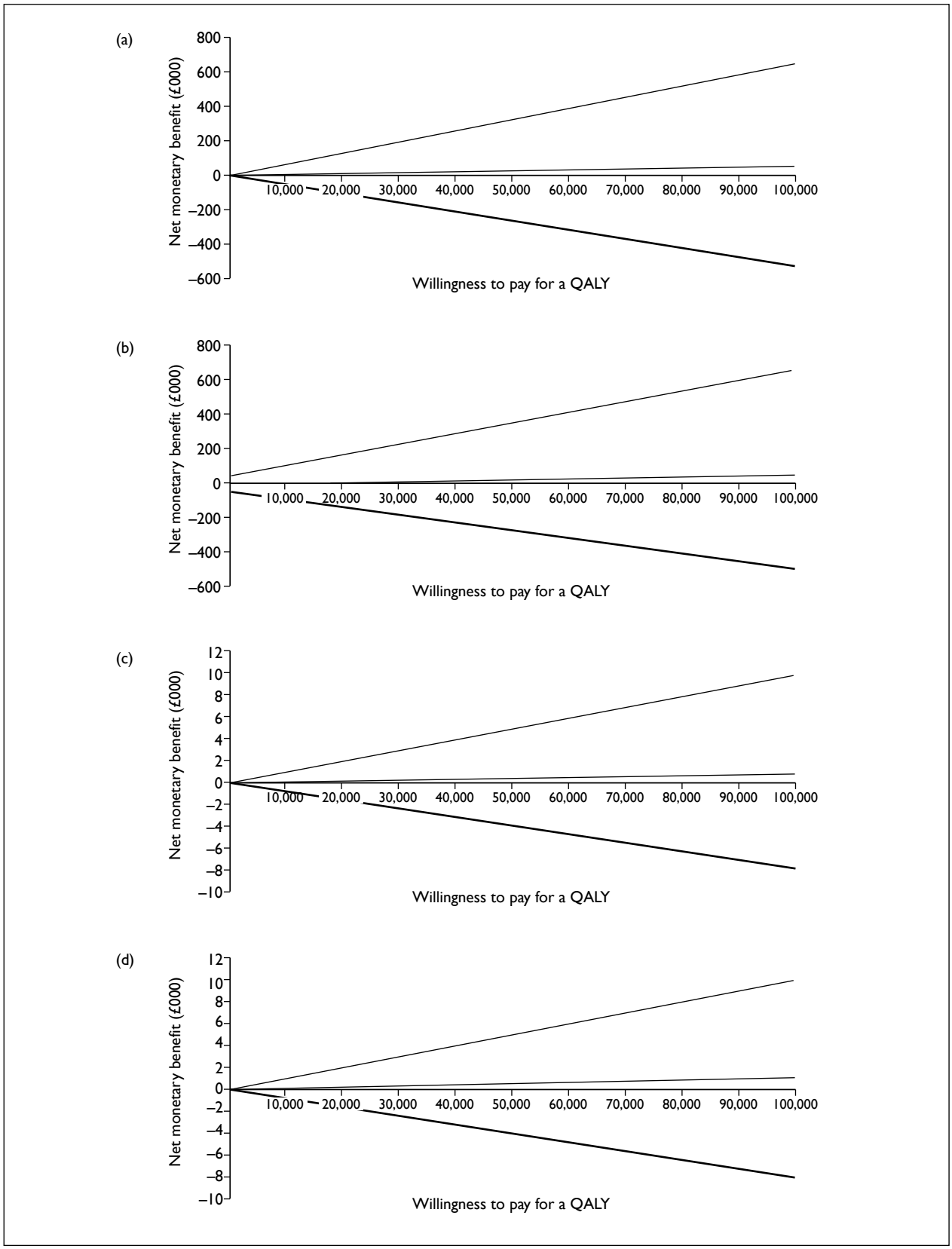

FIGURE 16 *Step 3: INB, QALYs. INB and 95% CI are shown for (a) 2-month NHS; (b) 2-month societal; (c) 2-year NHS; and (d) 2-year societal perspectives. Results based on imputed data adjusted for baseline utility.*

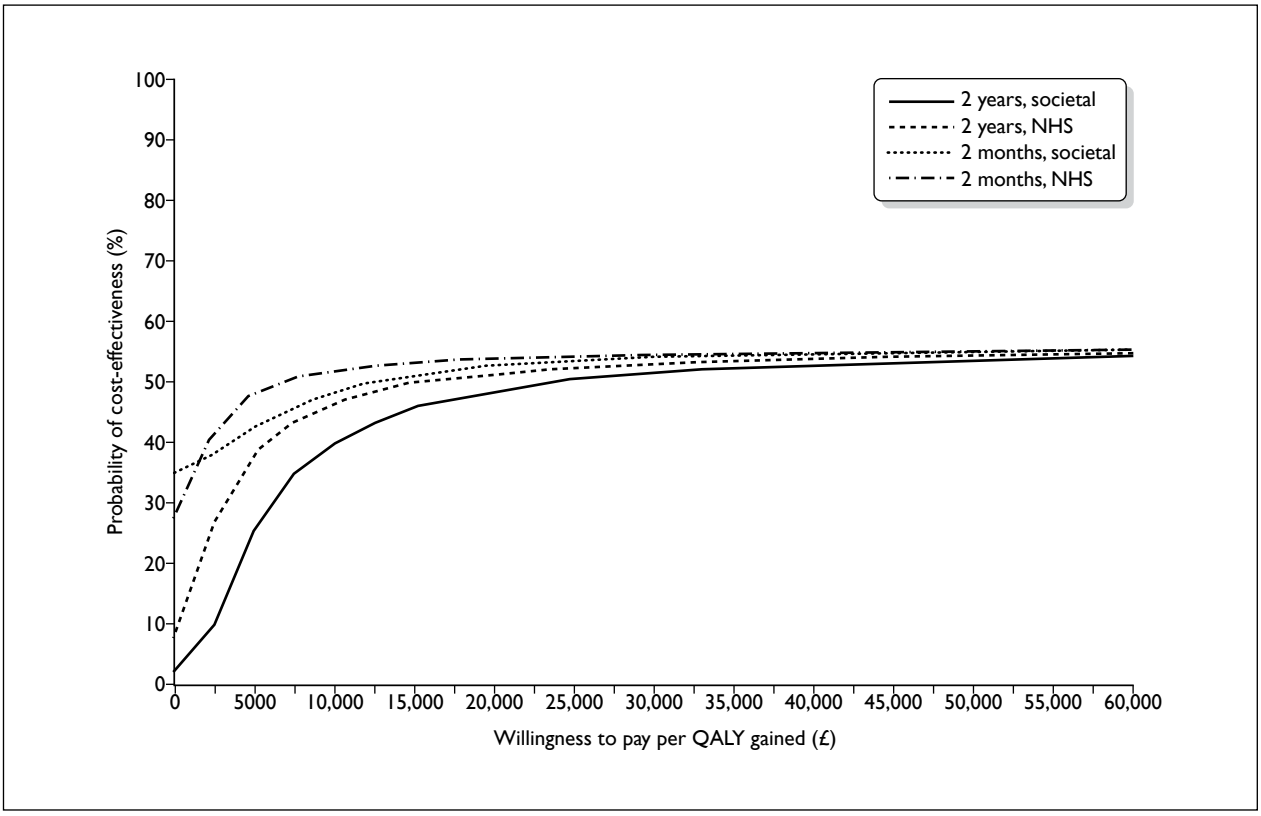

FIGURE 17 *Step 3: cost–utility analysis: CEACs. Based on imputed, adjusted results of cost–utility analysis, societal/NHS indicates that results were from a societal or NHS cost perspective, respectively, and these outcomes took place at 2 months or 2 years. This figure indicates that in all cases the probability of leukotriene antagonist being cost-effective compared with long-acting β_2-agonist is marginally above 50%, given a typical willingness to pay of £30,000 per QALY gained. At a willingness to pay of £20,000, the probability is between 48.5% and 54.0%, depending upon time horizon and perspective.*

TABLE 44 *Step 3: exacerbations, respiratory tract infections, short-acting β_2-agonist prescriptions and inhaled corticosteroid dose*

	LTRA (*n* = 170)	**LABA (*n* = 182)**	**Rate ratio (95% CI)**
Mean (SD) exacerbations over 2 years	0.62 (1.13)	0.61 (1.03)	1.02 (0.74 to 1.41), $p = 0.895$
Mean (SD) respiratory tract infections over 2 years	1.23 (2.01)	1.33 (1.72)	0.93 (0.70 to 1.22), $p = 0.581$
Mean (SD) consultations for respiratory tract infections over 2 years	1.49 (2.62)	1.52 (2.07)	0.98 (0.74 to 1.30), $p = 0.897$
			Adjusted difference[a] (95% CI) LTRA–LABA
Mean (SD) SABA inhalers prescribed over 2 years (inhalers/day)	0.022 (0.020)	0.017 (0.017)	0.004 (0.002 to 0.006), $p = 0.001$
Mean (SD) ICS dose (μg/day) for year 1	445 (20.4)	467 (19.7)	–7.87 (–63.4 to 47.6), $p = 0.780$
Mean (SD) ICS dose (μg/day) for year 2	466 (24.8)	438 (23.9)	42.8 (–24.0 to 109.6), $p = 0.208$

CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β_2-agonist; SD, standard deviation.
a Adjusted for baseline values.

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TABLE 45 *Step 3: median (interquartile range) clinic %PPEF*

Measure	LTRA	LABA	*p*-value
Baseline	*n* = 152	*n* = 167	
	90.46 (80.24 to 99.67)	88.64 (76.67 to 99.89)	
2 months	*n* = 131	*n* = 142	*p* = 0.451
	93.22 (84.02 to 105.04)	92.78 (80.19 to 102.87)	
2 years	*n* = 120	*n* = 136	*p* = 0.563
	91.43 (80.94 to 99.36)	89.68 (77.31 to 100.41)	

LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist.

TABLE 46 *Step 3: symptom diary cards at 2 months*

	LTRA (*n* = 170)	LABA (*n* = 182)	Difference (95% CI) LTRA–LABA, *p*-value	Adjusted difference[a] (95% CI), *p*-value
Mean (SD) morning waking with symptoms	*n* = 113 0.31 (0.34)	*n* = 123 0.25 (0.32)	0.06 (–0.02 to 0.15), *p* = 0.144	0.03 (–0.04 to 0.10), *p* = 0.402
Mean (SD) puffs of reliever at night – original scale	*n* = 101 0.91 (1.38)	*n* = 110 0.60 (0.99)	0.30	
Mean (SD) puffs of reliever at night – logged scale	*n* = 101 0.48 (0.53)	*n* = 110 0.35 (0.47)	0.14 (0.00 to 0.27), *p* = 0.050	0.12 (0.01 to 0.24), *p* = 0.036
Mean (SD) morning PEF	*n* = 112 399.0 (108.3)	*n* = 121 419.1 (102.3)	–20.2 (–47.4 to 7.0), *p* = 0.145	–17.9 (–26.8 to –8.9), *p* < 0.001
Mean (SD) daytime asthma symptom score	*n* = 113 1.63 (1.37)	*n* = 122 1.53 (1.37)	0.10 (–0.25 to 0.46), *p* = 0.562	0.04 (–0.25 to 0.34), *p* = 0.778
Mean (SD) score for daytime 'bother from asthma symptoms'	*n* = 112 1.46 (1.39)	*n* = 122 1.39 (1.41)	0.07 (–0.29 to 0.43), *p* = 0.709	0.05 (–0.26 to 0.36), *p* = 0.751
Mean (SD) daily activity score	*n* = 110 2.42 (1.28)	*n* = 122 2.27 (1.37)	0.15 (–0.19 to 0.50), *p* = 0.390	0.08 (–0.23 to 0.39), *p* = 0.622
Mean (SD) score for interference on activities from asthma	*n* = 111 1.41 (1.42)	*n* = 121 1.32 (1.37)	0.09 (–0.27 to 0.46), *p* = 0.607	0.12 (–0.19 to 0.43), *p* = 0.439
Mean (SD) puffs of reliever during the day – original scale	*n* = 108 2.45 (2.75)	*n* = 118 1.67 (1.96)	0.78	
Mean (SD) puffs of reliever during the day – logged scale	*n* = 108 0.98 (0.70)	*n* = 118 0.77 (0.63)	0.21 (0.04 to 0.39), *p* = 0.018	0.19 (–0.04 to 0.33), *p* = 0.011
Mean (SD) evening PEF	*n* = 112 402.0 (107.5)	*n* = 122 425.2 (99.4)	–23.2 (–49.9 to 3.5), *p* = 0.089	–10.8 (–19.4 to –2.2), *p* = 0.014
Mean (SD) PEF diurnal variability (%)	*n* = 112 5.8 (4.4)	*n* = 122 4.9 (3.6)	–0.9 (–0.1 to 1.9), *p* = 0.085	0.8 (–0.05 to 1.7), *p* = 0.064

CI, confidence interval; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Adjusted for baseline values.

TABLE 47 *Step 3: symptom diary cards at 2 years*

	LTRA ($n=170$)	LABA ($n=182$)	Difference (95% CI) LTRA–LABA, p-value	Adjusted difference[a] (95% CI), p-value
Mean (SD) morning waking with symptoms	$n=85$ 0.29 (0.35)	$n=98$ 0.24 (0.33)	0.05 (–0.05 to 0.15), $p=0.288$	0.01 (–0.07 to 0.10), $p=0.723$
Mean (SD) puffs of reliever at night – original scale	$n=75$ 0.69 (1.04)	$n=87$ 0.63 (0.87)	0.07	
Mean (SD) puffs of reliever at night – logged scale	$n=75$ 0.38 (0.50)	$n=87$ 0.37 (0.45)	0.01 (–0.14 to 0.15), $p=0.897$	0.00 (–0.14 to 0.14), $p=0.950$
Mean (SD) morning PEF	$n=83$ 395.6 (105.9)	$n=98$ 419.8 (97.0)	–24.2 (–54.0 to 5.6), $p=0.111$	–13.7 (–25.6 to –1.8), $p=0.024$
Mean (SD) daytime asthma symptom score	$n=85$ 1.40 (1.28)	$n=97$ 1.44 (1.24)	–0.04 (–0.41 to 0.33), $p=0.849$	–0.08 (–0.40 to 0.23), $p=0.606$
Mean (SD) score for daytime 'bother from asthma symptoms'	$n=85$ 1.12 (1.19)	$n=97$ 1.26 (1.27)	–0.14 (–0.50 to 0.23), $p=0.454$	–0.06 (–0.37 to 0.26), $p=0.721$
Mean (SD) daily activity score	$n=83$ 2.23 (1.22)	$n=97$ 2.32 (1.39)	–0.09 (–0.47 to 0.30), $p=0.666$	–0.06 (–0.41 to 0.27), $p=0.697$
Mean (SD) score for interference on activities from asthma	$n=85$ 1.13 (1.25)	$n=97$ 1.25 (1.39)	–0.12 (–0.51 to 0.27), $p=0.551$	0.01 (–0.31 to 0.34), $p=0.920$
Mean (SD) puffs of reliever during the day – original scale	$n=84$ 1.89 (2.31)	$n=95$ 1.49 (1.65)	0.40	
Mean (SD) puffs of reliever during the day – logged scale	$n=84$ 0.80 (0.70)	$n=95$ 0.73 (0.60)	0.07 (–0.18 to 0.27), $p=0.447$	0.08 (–0.09 to 0.25), $p=0.336$
Mean (SD) evening PEF	$n=83$ 401.7 (106.0)	$n=98$ 425.8 (96.8)	–24.1 (–53.8 to 5.7), $p=0.112$	–5.7 (–17.8 to 6.3), $p=0.349$
Mean (SD) PEF diurnal variability (%)	5.7 (4.7)	5.2 (4.3)	0.6 (–0.9 to 2.0), $p=0.443$	0.2 (–1.1 to 1.5), $p=0.718$

CI, confidence interval; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Adjusted for baseline values.

TABLE 48 *Step 3: secondary QOL measures*

Measure	LTRA	LABA	Difference (95% CI) LTRA–LABA, p-value	Adjusted difference[a] (95% CI), p-value
2-month outcomes				
mRQLQ	$n=125$ 1.50 (1.06)	$n=131$ 1.89 (1.28)	–0.39 (–0.68 to –0.10), $p=0.01$	–0.26 (–0.50 to –0.03), $p=0.029$
RCP3	$n=150$ 1.40 (1.00)	$n=154$ 1.25 (0.96)	0.15 (–0.07 to 0.37), $p=0.194$	0.15 (–0.07 to 0.37), $p=0.181$
Personal objectives	$n=106$ 52.4 (23.6)	$n=115$ 55.4 (24.5)	–2.96 (–9.34 to 3.43), $p=0.362$	–4.64 (–10.3 to 1.04), $p=0.109$
2-year outcomes				
mRQLQ	$n=162$ 1.32 (1.22)	$n=178$ 1.55 (1.29)	–0.23 (–0.50 to 0.04), $p=0.10$	–0.13 (–0.38 to 0.11), $p=0.273$
RCP3	$n=167$ 1.01 (0.94)	$n=181$ 1.14 (0.93)	–1.01 (–1.16 to 0.87), $p=0.190$	–0.11 (–0.31 to 0.08), $p=0.255$
Personal objectives	$n=120$ 65.9 (22.6)	$n=146$ 67.4 (20.3)	–1.51 (–6.70 to 3.68), $p=0.568$	–3.68 (–8.98 to 1.62), $p=0.173$

CI, confidence interval; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist.
a Adjusted for baseline value.

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TABLE 49 *Step 3: changes in treatment by 2 months and 2 years*

Treatment change by 2 months, n (%)	
Participants in LABA arm	*N = 181*
	0 (0)
Participants in LTRA arm	*N = 161*
Add LABA	1 (1)
Change to LABA	6 (4)
Total	7 (4)
Treatment change by 2 years, n (%)	
Participants in ICS arm	*N* = 181
	0 (0)
Participants in LTRA arm	*N = 161*
Add LABA	18 (11)
Change to LABA	25 (16)
Total	43 (27)

ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist.

TABLE 50 *Step 2: serious adverse reactions related to study medications*

Randomised treatment	Study medication	SAR	Discontinued medication	Continued medication	Total	Recovered
LTRA	Montelukast	Increase in epileptic fits	1	–	1	1

LTRA, leukotriene receptor antagonist; SAR, serious adverse reaction.

TABLE 51a *Step 2: adverse reactions related to study medications*

Randomised treatment	Study medication	Adverse reactions	Discontinued medication	Continued medication	Total	Recovered
LTRA	Montelukast	Headache	1	–	1	1
		Disturbed sleep	–	1	1	1
		Not known	–	1	1	1
		Increase in epileptic fits	1	–	1	1
ICS	Beclometasone dipropionate	Cough	–	1	1	1
		Breathlessness	–	1	1	1
		Symptoms of oesophagitis	1	–	1	1

ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist.

TABLE 51b *Step 3: adverse reactions related to study medications*

Randomised treatment	Study medication	Adverse reaction	Discontinued medication	Continued medication	Total	Recovered
LTRA	Montelukast	Headache	2[a]	–	2	2
		Disturbed sleep	1	2	3	3
		Lethargy	2	–	2	2
		Bloating	1	–	1	1
		Swollen fingers	1	–	1	1
		Dry cough	1	–	1	1
		Altered (mild) mental status	1	–	1	1
		Not known	2	–	2	2
LABA	Salmeterol	Palpitations	–	1 (half dose)	1	1
		Tingling in arms	–	1 (half dose)	1	1
		Not known	2	–	2	2

LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist.
a Of two cases with headaches, one case was reported initially by the practice nurse as 'serious', but, on follow-up assessment by the investigators, the reaction was found not to meet any of the standard criteria for serious adverse reactions.

TABLE 52 *Adverse events*[a]

Adverse event	Drug involved	Action	Outcome	Randomised treatment
Allergic reaction	Tylex	Discontinued Tylex	Recovered	Step 2, LTRA (montelukast)

LTRA, leukotriene receptor antagonist.
a Adverse events, reported during the study, which were considered to be unrelated to the study medication.

TABLE 53 *Serious adverse events*[a]

Adverse event	Cause	Randomised treatment
Death	Bronchogenic carcinoma	Step 2, ICS (beclometasone)

ICS, inhaled corticosteroid.
a Serious adverse events, reported during the study, considered to be unrelated to study medications.

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Chapter 4
Discussion

Interpretation

The results of this study provide no evidence of superiority of inhaled steroid or long-acting β_2-agonist over leukotriene antagonist, nor vice versa, in patients at either step 2 or step 3, in terms of the primary end point of asthma-specific QOL (MiniAQLQ score). For initial controller therapy at step 2, the results were equivalent at 2 months. After adjusting for baseline characteristics at 2 years, the 95% CIs did include the threshold for equivalence of 0.3 in favour of inhaled steroid. This was true of the one-sided 95% CI, i.e. inferiority of leukotriene antagonist could not be excluded. Conversely, the per-protocol population (fixed treatment regime and no changes within randomised therapy class at any stage) results also included the threshold for equivalence of 0.3, but this time in favour of leukotriene antagonist. Therefore, the results were inconsistent between the intention to treat and per-protocol analyses and equivalence could not be excluded. However, any possible advantage of one over the other looks clinically insignificant.

For add-on therapy at step 3, at 2 months results were equivalent, and at 2 years the intention-to-treat analysis resulted in near equivalence of leukotriene antagonist and long-acting β_2-agonist (the lower bounds marginally missing the equivalence value) with the possibility of a minor advantage for long-acting β_2-agonist. The per-protocol results were consistent with this, but, again, any advantage of long-acting β_2-agonist appears clinically insignificant.

We chose a conservative approach in selecting 0.3 as the threshold for equivalence or non-inferiority, because the minimum clinically important difference for MiniAQLQ is 0.5.[51] Therefore, although a difference from 0.3 to 0.5 does not meet our study definition of equivalence, the outer bounds of the CIs for the differences are less than the minimum that is clinically important difference for this parameter.

There were no significant differences between treatment groups in results for most of the secondary end points, including, most importantly, the two markers of asthma control, ACQ score and exacerbation rate. The 95% CIs for differences in ACQ score were well within the 0.5 minimum clinically important difference for both step 2 and 3 trials at both time points and in both intention-to-treat and per-protocol analyses. In addition, there were no significant differences in secondary health-related QOL measures, asthma symptoms as measured by diary card, the RCP3 questions and respiratory tract infections. Hospitalisations were infrequent in both step 2 and 3 trials.

At step 2, no significant differences were found in short-acting β_2-agonist prescriptions between arms. At step 3, short-acting β_2-agonist prescriptions over 2 years were significantly greater in the leukotriene antagonist arm than the long-acting β_2-agonist arm of the intention-to-treat population but not the per-protocol population. Calculations of short-acting β_2-agonist prescriptions in this study were based on the numbers of inhalers prescribed and do not reliably represent actual short-acting β_2-agonist use, because prescribed inhalers may not have been dispensed or used. Instead, ACQ scores, which incorporate a question on actual short-acting β_2-agonist use (puffs/day) during the prior 7 days, were not significantly different between leukotriene antagonist and long-acting β_2-agonist groups. Composite measures, such as the ACQ, are recommended for evaluating asthma control by the current European Respiratory Society (ERS)/American Thoracic Society (ATS) task force, which notes the challenges in measuring and comparing short-acting β_2-agonist use in clinical trials, suggesting that this outcome be derived from a diary or visit-based questionnaire.[78] Statistically significant differences in diary-recorded lung function between treatment groups in the step 3 trial were small and unlikely to be of clinical significance.

The number of participants included in the per-protocol analysis for both study arms was small [in the step 2 study 65/145 (45%) and 82/155 (53%) of the LTRA and ICS arms respectively, and 60/169 (36%) and 80/181 (44%) of the LTRA and LABA arms respectively in the step 3 study] because of substantial use of self-management plans with prescription instructions permitting

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adjustments to dosage, prescriptions which were technically changes (often within randomised class) but which were the result of a change of practice prescription policy, or prescriptions from an encounter with a non-study aware provider who made a change as allowed as per normal asthma management, often only for a single prescription issue, and which thus did not truly represent a substantial change in therapy. Nonetheless, these changes resulted in participants being excluded from the per-protocol group.While large and clinically as well as statistically comparable improvements from baseline were seen in all treatment groups investigated in this study, final mean outcomes are still not optimal and suggest that further intervention is required for many of the patients studied.

From a health economic perspective, mean results indicate that in a primary care setting, at step 2, inhaled steroids are more cost-effective than leukotriene antagonists due, principally, to the greater acquisition costs of leukotriene antagonists than inhaled steroids. At step 3 of the guidelines, results are somewhat inconsistent. Whilst leukotriene antagonists were slightly more expensive than long-acting β_2-agonists, patients receiving leukotriene antagonists had marginally better overall health-related QOL (as measured in QALYs), and hence we estimate a mean incremental cost per QALY gained of £22,589 (societal perspective, 2-year time horizon), with a probability of between 51.6% and 54.6% of leukotriene antagonists being cost-effective compared with long-acting β_2-agonist at a willingness to pay of £30,000 per QALY gained. There was no statistically significant difference in INB at any threshold willingness to pay for a point improvement in MiniAQLQ or ACQ, or at a threshold of £30,000 per QALY gained (the exception being at low thresholds for QALYs in step 2 patients, for which the upper bound for the 95% CI for INB is negative – see *Figures 6, 8, 10, 13, 15* and *17*). Mean results based on ACQ also suggested that long-acting β_2-agonist dominated leukotriene antagonist.

In the step 2 trial, we observed that, by 2 months, patients receiving leukotriene antagonist had received approximately twice as many NHS contacts as their inhaled steroid counterparts, and that the majority of the contacts were in primary care. Whether this was related to the issuing of prescriptions for leukotriene antagonist and a greater perceived need to follow the patient, given that leukotriene antagonists are rarely used in the UK as first-line anti-inflammatory therapy, is unknown. However, given that leukotriene antagonists are available only in 28-day packs, compared with a 200-dose inhaler that could sustain a patient for up to 3 months, the likelihood of greater follow-up in the leukotriene antagonist group to reissue prescriptions is to be expected due to repeat prescriptions being used as a trigger for review in many practices. This explanation is further supported by the lack of difference in ACQ score and exacerbations. If lack of familiarity with this class of therapy contributed to consultations this would be likely to be a smaller factor in the future and reduce the cost of treatment to the NHS of using a leukotriene antagonist.

Indirect costs are costs attributable to lost productivity and/or time off work due to ill health. Our results indicate that over the longer time horizon mean indirect costs are lower for leukotriene antagonist versus inhaled steroid patients at step 2 but higher for leukotriene antagonist versus long-acting β_2-agonist at step 3. Although we cannot exclude chance in explaining these findings (and response rate to time off work questions was poor), it should be noted that in step 2 patients at 2 years the hours of work lost per patient randomised to inhaled steroid were lower than those lost per patient randomised to leukotriene antagonist, yet the cost is slightly higher. This apparent contradiction is due to the differential timing of costs and the effect of discounting: a greater proportion of the time off work was reported for the inhaled steroid group in the first year.

A key driver of the cost-effectiveness of one drug compared with another is usually the acquisition cost. At current prices, we estimate a mean ICER of £22,589 in step 3 patients. If the price of leukotriene antagonists falls following patent expiry, the ICER will also fall and the probability of their being cost-effective compared with long-acting β_2-agonists in these patients (step 3) will rise.

Study strengths and limitations

Conducting a pragmatic randomised control trial in a primary care setting has advantages and disadvantages over conducting a randomised controlled trial as a clinical and explanatory clinical trial.

TABLE 54 *Comparison of baseline characteristics of patients in the current study with those in the GOAL study*[83]

	Current study, step 2 (*n* = 306)	GOAL, stratum 1 (*n* = 1098)	Current study, step 3 (*n* = 352)	GOAL, stratum 2 (*n* = 1163)
Sex (% female)	51	57	63	59
Age, mean (SD)	45.8 (16.4)	36.3 (15.6)	50.4 (16.0)	40.4 (16.5)
MiniAQLQ/AQLQ score	4.7 (0.9)	4.4 (1.0)	4.5 (1.0)	4.6 (1.1)
Lung function, %PPEF	86	77	90	78
Per cent reversibility	8.9 (9.8)	Median = 22[a]	8.7 (9.8)	Median = 22[a]
Current smoking (%)	22	9[b]	17	6[b]
Dropout rate (%)	4.2	15.4	3.4	15.4

FEV_1, forced expiratory volume in 1 second; GOAL, Gaining Optimal Asthma controL study.
a FEV_1 reversibility of > 15% was required for study eligibility.
b Smoking history of < 10 pack-years required.

Generalisability

Conducting this study in a 'real-life' setting has enabled this project to collect valuable information about outcomes and the costs associated with the management of asthma. To ensure that we maintained scientific validity while minimising the impact of the study on the day-to-day management of asthma, we used a concealed randomised allocation of participants to the two treatment arms, using a telephone automated dial-up centre, standardised procedures for the recording and collection of outcomes data (by non-clinicians blinded to the randomisation) and blinded data analysis.

There is a substantial body of evidence that suggests that outcomes in a clinical trial setting may not be matched in real life, in particular because patients in clinical trials are highly selected and < 10% of outpatients with asthma meet trial selection criteria.[79,80] Indeed, as depicted in *Table 54*, the baseline characteristics of patients in this study differed in several respects from those of patients in the Gaining Optimal Asthma controL (GOAL),[81] one of the largest, long-term asthma studies undertaken in adults in the last few years. Patients in the present study had similar health-related QOL impairment, but less lung function impairment and were more likely to be smokers.

We are confident that the generalisability (external validity) of this multipractice trial is high. The conduct of this study in a patient's own primary care practice by their normal GP and practice nurse retained the 'real-life' setting, thereby enabling the generalisability of our results to primary care. Conversely, the fact that therapy was administered in open-label fashion, and provision of asthma care was not dictated by study design, could reduce the internal validity of the study, as the risk of error or bias increases.

Our choice of primary outcome measure was made because the asthma-specific QOL is a patient-centred outcome, which is increasingly recognised as reflecting the impact of asthma. Our secondary outcomes focused on asthma control as measured by the ACQ and exacerbations of asthma, this being in line with the latest ERS/ATS task force on outcome measures for studies of asthma.[78]

The broad inclusion criteria for this study meant that active smokers, who are typically excluded from clinical trials, were included in our study population in proportions similar to reported asthma population norms for the UK. This exclusion criterion is usually included in clinical trials, as increasing evidence suggests that active smokers may not respond to asthma treatments to the same extent or in the same way as non-smokers.[82–84] Also, we did not use as an entry criterion a minimum of a 15% increase in FEV_1 above baseline following 400 µg salbutamol, which is one that is conventionally used in clinical trials designed to evaluate asthma therapies. Due to time constraints in general practice, the minimum of 20 minutes required to perform this test often prohibits its use in 'real life'. The omission of this criterion means that a small proportion of participants included in our study population may have had a mix of asthma and chronic obstructive pulmonary disease. Again, this reflects real life more closely and therefore increases the external validity of this study.

To reflect real-life management, active monitoring (e.g. dose or pill counting) was not included in the design of this study. Instead, the rate at which

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prescriptions are refilled for asthma therapy is used in primary care to monitor disease stability and adherence to treatment. This indirect measure of adherence was included in the design of the study resulting in our results being highly generalisable to real-life primary care management of asthma. In an explanatory clinical trial, adherence to treatment is often much higher than in primary care, typically because of intensive monitoring. This often generates disparities between the apparent outcomes of a clinical trial and the benefits afforded by the same treatment in real life.

A limitation of this study was that by 2 years many patients were switched from initial randomised therapy to alternative therapy due to a range of factors including practice protocols for inhalers and chlorofluorocarbon transition (6 out of 126 at step 2; 31 out of 132 at step 3). However, few patients had changed therapy before 2 months and thus results at 2 months can be considered to represent the efficacy of assigned therapy.

Some patients randomised to leukotriene antagonist, on being reviewed by a GP at their practice who was unfamiliar with the study, were changed to inhaled steroid or long-acting β_2-agonist, as per normal clinical protocol depending on their study arm. In addition, because of shorter durations of drug supplies in those provided with a leukotriene antagonist, greater review resulted, providing greater opportunities to change therapy. Whilst no difference in exacerbations or objective markers of asthma control was found, clinical records suggested that many patients had a change in therapy due to current symptoms. It is difficult to interpret whether this is due simply to the variable nature of asthma or ongoing poor asthma control.

Poor adherence to the completion of PEF diary cards was found in both studies, but was most pronounced in the step 2 trial in which only one-third of patients completed the diary cards throughout the study. Whether poor adherence to the completion of symptom diary cards is a reflection of poor adherence in general, is unknown. While symptom diary cards for predicting subsequent episodes of poor asthma control[85] and asthma control questionnaires for predicting health-care utilisation[86] have been suggested as useful tools, they are useful only when patients are willing to complete them. Further work is required to improve the uptake of symptom diary cards as a means of monitoring disease severity in patients with mild to moderate asthma.

Ideally, we would have determined expenditure on prescription medications other than the randomised treatments. However, the wide use during the study of combination devices that codeliver an inhaled steroid and long-acting β_2-agonist (for example Seretide contains fluticasone and salmeterol, and Symbicort contains budesonide and formoterol) prevented the isolation of the cost of a long-acting β_2-agonist from the cost of inhaled steroid. Indeed the pragmatic nature of the study design placed no restriction on the antiasthma medications that could be prescribed. However, it is reasonable to conclude that for the step 2 trial, the significantly higher cost of prescribed medications received by the leukotriene antagonist randomised group compared with the inhaled steroid control group could at least, in part, be due to the higher relative cost of a leukotriene antagonist (~£25 per 28-day course) compared with low-dose inhaled steroid (typically £8 per 28-day course). For the step 3 trial, the combination of fluticasone or budesonide (at 800 µg beclometasone dipropionate equivalent dose) with a leukotriene antagonist amounts to ~£47 for a 28-day course, compared with ~£38 for an equivalent 28-day course of either Seretide or Symbicort. This difference may at least, in part, be responsible for the significantly higher cost of prescription medications for the leukotriene antagonist group than the long-acting β_2-agonist group.

Smoking and response to asthma therapies

Active smoking has been shown to reduce the anti-inflammatory efficacy of inhaled steroids.[82,83] As the anti-inflammatory action of long-acting β_2-agonist reported *in vitro* has not been confirmed *in vivo*, leukotriene antagonists may provide an alternative anti-inflammatory treatment for asthma in smokers. Indeed Lazarus and colleagues[84] recently reported that mild asthmatics who were also active smokers had a significantly lower response to inhaled steroid than non-smoking mild asthmatics. However, the active smokers had a significantly greater response to the leukotriene antagonist montelukast than the non-smoking patients, suggesting that in contrast with inhaled steroid, smoking does not significantly affect the action of the leukotriene antagonist montelukast. Whether this difference reflects changes in the mediation of airway inflammation in smokers or not, is not known. Furthermore, as Lazarus and colleagues[84] conducted their study under clinical trial conditions, whether comparable results would

be found under 'real-life' primary care conditions is unknown.

Comparison with prior studies

To our knowledge, there have been no other published pragmatic, head-to-head studies comparing leukotriene antagonist and inhaled steroid at step 2 or leukotriene antagonist and long-acting β_2-agonist as add-on to inhaled steroid at step 3 for patients with asthma in primary care. Specifically, prior studies have enrolled selective patient populations, requiring evidence of airway reversibility, substantially impaired lung function and/or excluding patients with concomitant conditions or who smoke. They have also suffered from relatively high dropout rates, which may influence intention-to-treat approaches to analysis. Nonetheless, results of longer-term studies could be of relevance in comparison with the present study.

At step 2, open-label treatment for 36 weeks with fluticasone or montelukast gave comparable results for some patients with mild asthma, whereas fluticasone improved asthma control more than montelukast for patients who had decreased lung function and greater albuterol use at baseline.[87] In another study, the effectiveness of montelukast and inhaled beclometasone was similar over 2+ years of open-label treatment, and the authors speculated that the initially greater mean effect of beclometasone on lung function was offset over time by better adherence to orally administered montelukast.[48] We found that adherence to treatment with leukotriene antagonist was substantially better than that to inhaled therapy by patients in this study who had at least 6 months of unchanged therapy. At step 2, median adherence was 61% and 41% to leukotriene antagonist and inhaled steroid, respectively. At step 3, median adherence was substantially higher in the leukotriene antagonist arm than in the long-acting β_2-agonist arm, both to inhaled steroid (82% versus 65%) and to add-on therapy (90% with montelukast versus 49% with long-acting β_2-agonist).

With regard to step 3, a recent systematic review looking only at studies of ≥ 12 weeks' duration comparing montelukast with salmeterol as add-on to inhaled steroid found that while salmeterol may be more effective with regard to most clinical outcomes in the medium term, over 48 weeks, the proportions of patients with ≥ 1 exacerbation were similar, as were hospitalisation and emergency treatment rates.[36] The rate of serious adverse events over 48 weeks was significantly higher with add-on salmeterol; thus, montelukast may have a better long-term safety profile.

Prior reviews of health economic studies in asthma have pointed out the need for longer-term studies using a pragmatic trial design and outcome measures that reflect asthma control and are clinically meaningful and relevant to patients.[88,89] We believe that the design of this study addresses that need and provides results meaningful for decision-makers.

Statistical issues

Missing data are a limitation in any clinical trial. This is a particular issue in economic evaluations, where, typically, not only are multidimensional QOL and other outcome measures collected, but complex resource use questionnaires may also be required. Indeed, in this study, we collected data on the costs associated with prescription and over-the-counter medications, NHS resources and time off work. The number of observations for which both outcome and cost data were available is therefore less than the number of observations for either outcomes or cost data alone.

We used Rubin's multiple imputation technique[76] to handle missing data. Imputation of missing values is feasible in this study and desirable as while there were a large number of observations with incomplete data, the actual number of data elements missing from each individual observation was small [218/683 patients (32%) had complete data, yet 514/683 (75%) had only four or fewer of the 13 data items missing]. The complete case analysis therefore excludes a lot of valid data. The particular strength of Rubin's multiple imputation approach is that it acknowledges that missing values are uncertain, and therefore estimates several possible values for each (five imputations are usually considered sufficient[76]). It therefore provides a better characterisation of uncertainty than single-imputation techniques.

Nevertheless, the use of multiple imputation rests on a number of assumptions. Firstly, that the data are at least missing at random (that is, the probability that an observation is missing can depend on the observed variables, but not on the missing variable itself), and, secondly, that the data follow a multivariate normal distribution.

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If data are not missing at random then, in principle, the missingness process could be modelled. However, this adds to the (already substantial) complexity of the model and studies have shown that even when 'missing at random' is violated, multiple imputation may still be superior to other approaches.[90] Furthermore, multiple imputation may provide a sufficient approximation of missing data with appropriately transformed variables, and it is suggested that even binary variables may be approximated by estimating under a normal assumption and rounding the continuous values.[91]

We presented results of the economic evaluation in terms of the ICER. Whether or not an intervention is deemed cost-effective depends on whether or not the ICER is below some threshold of willingness to pay for that unit of outcome. Where the unit of outcome is QALYs gained, a threshold of approximately £30,000 is considered a de facto standard. However, such a threshold for point improvement in MiniAQLQ and ACQ is currently undefined. This has implications for representing uncertainty in the estimate of cost-effectiveness because a standard 95% CI is not necessarily defined for the ICER due to its ratio properties. We therefore calculated CEACs as well as the INB and its associated CI. However, to estimate a meaningful value of the INB requires knowledge of the threshold, which for MiniAQLQ and ACQ is unknown. Therefore we presented INB based on MiniAQLQ and ACQ plotted for an arbitrarily wide range of values (see *Figures 6, 8, 13* and *15*), rather than stating a point estimate (with CI) in *Tables 14–17* and *37–40*.

Further study

There are several validated assessment tools that are currently used for different aspects of asthma compliance and control. In addition to the Juniper ACQ,[62,64] MiniAQLQ,[50] EQ-5D[71] and RCP3 questions[68,69] that we used here, additional measures that have been used to evaluate asthma compliance and control include the Beliefs about Medicines Questionnaire,[92] the Illness Perception Questionnaire,[93] the Medication Adherence Report Scale (R. Horne, University of London, 2004, personal communication), and the Satisfaction with Information about Medicines Scale.[94] However, a limitation of these tools is that no one single measure allows the evaluation of patient perceptions about their illness and therapy, and current symptoms, adherence, side effects and control. In addition, the RCP3 questions is a set of questions that has not been validated. The development of a unified and yet easily performed test that would aid in the assessment of all of these areas would provide a valuable tool for both research use as well as clinical management of patients. A Minimal Asthma Assessment Tool was developed alongside these trials, partially utilising data collected from the patient-reported outcome measures.[95]

Twenty-eight in-depth interviews have also been conducted and are currently being analysed to understand patients' perceptions of preventative therapies. This substudy has been described in a PhD thesis[96] and is being analysed for potential further publication.

Chapter 5
Conclusions

Results of this pragmatic trial in UK primary care were equivalent with regard to asthma-specific QOL (MiniAQLQ) at 2 months after commencing controller therapy with leukotriene antagonist or inhaled steroid (step 2 of the BTS guidelines). Our equivalence criterion for MiniAQLQ was not met at 2 years; however, there were no statistically significant differences between treatment groups at this time. There were no differences in asthma control measures (ACQ score and exacerbations) at 2 months or 2 years; thus, any possible advantage of one over the other appears to be clinically unimportant. All treatments were associated with substantial mean improvements which may at least in part have been due to regression to the mean or treatment effects. At 2005 UK prices of leukotriene antagonist and inhaled steroid, leukotriene antagonist was not a cost-effective alternative to inhaled steroid at step 2.

Results of add-on therapy with leukotriene antagonist or long-acting β_2-agonist for patients with uncontrolled asthma already receiving inhaled steroid (step 3) were equivalent at 2 months (step 3 of the BTS guidelines), and at 2 years almost met our equivalence criterion. There were no significant differences between treatment groups in ACQ score or exacerbations. Leukotriene antagonist was of borderline cost-effectiveness compared with long-acting β_2-agonist.

Implications for health care

The evidence suggests that while any advantage of one treatment over the other appears to be clinically unimportant, leukotriene receptor antagonists are unlikely to be a cost-effective alternative to inhaled corticosteroids, at 2005 prices, as initial asthma controller therapy at step 2. In addition, the evidence suggests that leukotriene antagonists may be clinically equivalent to long-acting β_2-agonists as add-on to inhaled steroids in terms of QOL as well as secondary measures, and, furthermore, suggests that leukotriene antagonists could be repositioned as an equal alternative to long-acting β_2-agonists at step 3 of the BTS guidelines. When generic leukotriene antagonist formulations become available in the next few years their cost-effectiveness as an alternative to ICS may justify further evaluation, particularly in the subgroup of patients with limited impairment of lung function, those newly diagnosed with asthma to minimise inhaler education and those with fears about inhalers or inhaled steroids.

Recommendations for research

- Establish in primary care, whether leukotriene antagonists will be more or less beneficial than inhaled steroids alone or as an add-on to inhaled steroids in treating patients with asthma who are also active smokers.
- Determine why the ACQ correlates more poorly with economic outcomes of asthma than the MiniAQLQ and EQ-5D.
- Understand further the reasons why patients were switched from study medication when there was no real clinical indication to do so, and examine ways to minimise this happening in future pragmatic primary care-based clinical trials.

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Participating practices

Thorpewood Surgery, Norwich; Bacon Road Medical Centre, Norwich; Drayton and St Faith Medical Practice, Drayton; Botesdale Health Centre, Botesdale; Fakenham Medical Practice, Fakenham; Beccles Medical Centre, Beccles; Siam Surgery, Sudbury; Beach Road Surgery, Lowestoft; Grimston Medical Centre, Grimston; Cutlers Hill Surgery, Halesworth; Mattishall Surgery, Mattishall; Aldborough Surgery, Norwich; Needham Market Country Practice, Needham Market; Costessey Medical Centre, Old Costessey, Norwich; Attleborough Surgeries, Attleborough; Coltishall Surgery, Coltishall; Bungay Medical Practice, Bungay; South Quay Surgery, Great Yarmouth; Millwood Surgery, Bradwell, Great Yarmouth; Lattice Barn Surgery, Ipswich; Leiston Surgery, Leiston; Harleston Medical Centre, Harleston; East Thurrock Medical Centre, Grays; Stowmarket Health Centre, Stowmarket; Orchard Medical Centre, Ipswich; Church Plain Surgery, Loddon; Holt Medical Practice, Holt; Mersea Road Surgery, Colchester; Birchwood Surgery, North Walsham; Leighton Road Surgery, Linslade; Kingswood Medical Centre, Basildon; Parish Fields Practice, Diss; Barrow Hill Surgery, Bury St Edmunds; Little Waltham Surgery, Chelmsford; John Tasker House, Great Dunmow; Yaxley Group Practice, Yaxley, Peterborough; James Fisher Medical Centre, Bournemouth; Neera Medical Centre, Stanford-le-Hope; Hethersett Surgery, Hethersett; The White House Surgery, Weston, Southampton; West Pottergate Health Centre, Norwich; Grays Surgery, Grays; Laindon Health Centre, Basildon; Rigg-Milner Medical Centre, East Tilbury; Sheringham Health Centre, Sheringham; The Barn Surgery, Gillingham; Lynwood Health Centre, Romford; The Burnhams Surgery, King's Lynn; Angel Hill Surgery, Bury St Edmunds; Framfield House, Woodbridge; Hoveton & Wroxham Medical Centre, Hoveton; The Woottons Surgery, King's Lynn; Rookery Medical Partnership, Newmarket; Wells Health Centre, Wells Next The Sea; Wood Lane Surgery, Hornchurch; Capital Road Surgery, Higher Openshaw, Manchester; The Witham Health Centre, Witham.

Contribution of authors

David Price (Professor, Primary Care Medicine) was involved in original design and grant submission,

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management and steering committee activity, data validation, analysis plan production, interpretation of data, study report and final publication. Stanley Musgrave (Research Associate, Norwich Medical School) was involved in study implementation, management and steering committee activity, data validation, analysis plan production, interpretation of data, study report and final publication. Ed Wilson (Lecturer, Health Economics), was involved in data validation, analysis plan production, interpretation of data, study report and final publication. Erika Sims (Research Fellow, Health Economics) was involved in management and steering committee activity, data validation, analysis plan production, interpretation of data, study report and final publication. Lee Shepstone (Professor, Medical Statistics) was involved in original design and grant submission, management and steering committee activity, data validation, analysis plan production, interpretation of data, study report and final publication. Annie Blyth (Research Associate, Norwich Medical School) was involved in study implementation, management and steering committee activity, data validation, study report and final publication. Jamie Murdoch (Research Associate, School of Nursing and Midwifery) was involved in study implementation, management and steering committee activity, data validation, analysis plan production, interpretation of data, study report and final publication. Miranda Mugford (Professor, Health Economics) was involved in original design and grant submission, management and steering committee activity, analysis plan production, interpretation of data, study report and final publication. Elizabeth Juniper (Professor Emeritus, Clinical Epidemiology and Biostatistics) was involved in original design and grant submission, management and steering committee activity, analysis plan production, interpretation of data, study report and final publication. Jon Ayres (Professor, Environmental and Respiratory Medicine) was involved in original design and grant submission, management and steering committee activity, analysis plan production, interpretation of data, study report and final publication. Stephanie Wolfe (Respiratory and Research Nurse) was involved in original design and grant submission, management and steering committee activity, analysis plan production, interpretation of data, study report and final publication. Daryl Freeman (General Practitioner) was involved in study management and steering committee activity, analysis plan production, interpretation of data, study report and final publication. Alistair Lipp (Director, Public Health) was involved in study management and steering committee activity, analysis plan production, interpretation of data, study report and final publication. Richard Gilbert (General Practitioner) was involved in study management and steering committee activity, analysis plan production, interpretation of data, study report and final publication. Ian Harvey (Professor and Dean, Faculty of Health) was involved in original design and grant submission, management and steering committee activity, data validation, analysis plan production, interpretation of data, study report and final publication.

Conflicts of interest

David Price has consultant arrangements with Astra Zeneca, GlaxoSmithKline, Merck, Sharpe and Dohme, Schering Ploughm and Teva; has grants/research support from AstraZeneca, GlaxoSmithKline, Merck, Sharpe and Dohme, Mundipharma, Novartis, Schering Plough and Teva; and is a member of the speakers' bureau fgor GlaxoSmithKline, Merck, Sharpe and Dohme, Mundipharma, Novartis, Schering Plough and Teva.

Stanley Musgrave owned stock in Merck Sharpe and Dohme (MSD) within 3 years of beginning this work. He disposed of that stock prior to beginning this work and has had no further financial interest in MSD. During the time that he owned MSD stock he had no role in the preparation of this study. He has grants/research support from MSD and AstraZeneca, and Altana Pharma.

Ed Wilson has received a consultancy fee from a manufacturer of a budesonide inhaler (Meda Pharmaceuticals, 2006).

Erika Sims has received funding from MSD and AstraZeneca to attend international conferences. She has previously undertaken research studies sponsored by MSD, although the funding for these trials did not support her salary.

Elizabeth Juniper has consultant arrangements with GlaxoSmithKline and Astra Zeneca. She also has stock/other equity ownership in GlaxoSmithKline and Pfizer; and is a copyright holder of the MiniAQLQ, ACQ and MiniRQLQ. During the last 5 years she has had financial support from Johnson & Johnson, Schering Plough, Medpointe Pharma, CMP Therapeutics,

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Stephanie Wolfe is on the advisory boards of Teva, Novartis, Astra Zeneca and GSK. She also attends speaker meetings for: Pfizer, Boehringer, Astra Zeneca, Altana Pharma (a Nycomed company), GSK and MSD.

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Appendix 1

Background information for economic analysis

Read codes for asthma-related medications

The following Read codes were used to search for relevant asthma-related prescriptions in the MIQUEST searches. In cases where the GP practice software system used other codes, the analogous codes were used.

Clinical use	Read code(s)	BNF codes	Description related to Read codes
Respiratory	c..	3[a]	All respiratory medications
	p4..	3.1.5	Respiratory devices – spacers, peak flow meters
Oral steroids	fe6..	6.3.2	Prednisolone
Antibiotic and antifungal	ey..	5.4.8	Pneumocystitis drugs
	eh..	5.2	Antifungal drugs
	lc..	12.3.2	Oropharyngeal anti-infective drugs
	ec-ed	5.1.8–5.1.9	Sulphonamides, trimethoprim, antituberculosis drugs
	e1-ea	5.1.1–5.1.6	Penicillinase-sensitive penicillins, penicillinase-resistant penicillins, broad-spectrum penicillins, antipseudomonal penicillins, other penicillins, cephalosporins and cephalomycins, tetracyclines systemic, aminoglycosides, macrolides, clindamycin and lincomycin
	eb2..	5.1.7	Chloramphenicol (systemic)
	eb7..		Vancomycin
Conjunctivitis	k6..	11.4.2	Corticosteroids and anti-inflammatory preps – eye
	k3..	11.3	Topical preparations eye
Skin	m1-m5	13.1 – 13.5	Vehicles and diluents, emollients and barrier preparations, local anaesthetic and antipruritic preparations, topical corticosteroids, psoriasis and eczema preparations
	mb..	13.9	Scalp preparations
	mc-me mh-mi mn..	13.10.1 13.10.2 13.11	Antibacterial, antifungal topical preparations, disinfecting cleansing agents, wound ulcer preparations
Rhinitis	l8..	12.2.1	Nasal allergy drugs
	l9..	12.2.2	Topical nasal decongestants

BNF, *British National Formulary*.
a Read codes and BNF chapters for respiratory medications are detailed in the table below.

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Details of respiratory prescriptions

Read codes	BNF subchapter	Medication
c1..	3. 1. 1. 1	Selective β_2-agonists
	3. 1. 1. 1	Formoterol
	3. 1. 1. 1	Salbutamol inhaler
	3. 1. 1. 1	Salbutamol – other forms
	3. 1. 1. 1	Salmeterol
	3. 1. 1. 1	Terbutaline
c3.. and c5..	3.1.2 and 3.1.4	Antimuscarinic
c4..	3. 1. 3	Xanthine
c1D.. and c67	3. 2	Compound ICS/LABA
c6..	3. 2	Inhaled corticosteroids
c7..	3. 3. 1	Cromolyn
cA..	3. 3. 2	LTRA
c8..	3. 4. 1	Antihistamines
bp1..	3. 4. 3	Allergic emergencies
cd..-ce..	3. 7	Mucolytics
cf..	3. 8	Aromatics
cg.. – ch..	3. 9	Cough preparations
ci..	3. 10	Systemic nasal decongestants

ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist.

Unit costs

Description of scenarios	Cost (£)	Source
Acute condition appointment (therefore 10 min), non-study visit, seen by nurse, respiratory-related reason is primary reason for consultation, seen in surgery	10.00	Nurse consultation including qualification costs (PSSRU 2005, p. 130)[a]
Routine clinic appointment (therefore 30 min), non study visit, seen by nurse, primary reason for consultation, seen in surgery	15.00	Nurse consultation per hour in clinic including qualification costs/2 (PSSRU 2005, p. 130)[a]
Acute condition appointment, non-study visit, seen by nurse, secondary reason for consultation (therefore 5? min), seen in surgery	5.00	Nurse consultation including qualification costs/2 (PSSRU 2005, p. 130)[a]
Routine clinic appointment, non study visit, seen by nurse, secondary reason for consultation (therefore 5? min), seen in surgery	5.00	Nurse consultation including qualification costs/2 (PSSRU 2005, p. 130)[a]
Routine appointment, study visit, seen by nurse, primary reason for consultation, seen in surgery	15.00	Nurse consultation per hour in clinic including qualification costs/2 (PSSRU 2005, p. 130)[a]
Acute condition, study visit, seen by nurse, primary reason for consultation, seen in surgery	15.00	Nurse consultation per hour in clinic including qualification costs/2 (PSSRU 2005, p. 130)[a]
Acute condition, study visit, seen by nurse, secondary reason for consultation, seen in surgery	5.00	Nurse consultation including qualification costs/2 (PSSRU 2005, p. 130)[a]
Routine appointment, study visit, seen by nurse, secondary reason for consultation, seen in surgery	5.00	Nurse consultation including qualification costs/2 (PSSRU 2005, p. 130)[a]
Acute condition, non-study visit, GP consultation, primary reason for consultation (therefore 10 min), seen in surgery	24.00	GP surgery consultation of 10 minutes including qualification costs and direct care staff costs (PSSRU 2005, p. 133)[a]

Description of scenarios	Cost (£)	Source
Acute condition, non-study visit, GP consultation-secondary reason for consultation (therefore 5? min), seen in surgery	12.00	GP surgery consultation of 10 minutes including qualification costs and direct care staff costs/2 (PSSRU 2005, p. 133)[a]
GP home visit	69.00	GP home visit of 13.2 minutes, including 12 minutes' travel time, direct care staff and qualification costs (PSSRU 2005, p. 133)[a]
Paramedic home visit	311.00	Average cost per patient journey, paramedic unit (PSSRU 2005, p. 108)[a]
Ambulance run	311.00	Note: Unit cost data cannot distinguish between these – data should indicate one or the other, not both or else this is double counting
Nurse telephone consultation	10.00	No data available. Assumed same cost as 10-minute nurse appointment
GP telephone consultation	25.00	GP telephone consultation lasting 10.8 minutes, including direct care staff costs and qualification costs (PSSRU 2005, p. 133)[a]
Out-of-hours GP consultation, not at night	49.61	Scott *et al.* (2003)[b]
Out-of-hours GP consultation, at night	49.61	Scott *et al.* (2003)[b]
Out-of-hours GP telephone consultation	51.68	OOH GP visit costs 2.067 as much as a routine GP visit. Therefore, assume OOHT costs 2.067 × daytime GP telephone consultation
'Walk-in-clinic' visit	26.06	NHS Reference Costs 2005. PCT and trust combined data, TA&EMIS, weighted average of walk-in centre unit costs (HRGs V100WIFA and V100WIFU). URL: www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4133221&chk=TxHkqo
Call to NHS Direct	15.00	Approximation of average cost per call across three sites in 2001. Is crude average so spurious precision to adjust to 2005 price. URL: www.shef.ac.uk/content/1/c6/02/40/50/nhsd3.pdf
Saw a consultant – first visit	191.00	NHS Reference Costs 2005. PCT and trust combined data, outpatient, first attendance, adult (TOPS FAA), Thoracic medicine (specialty code 340). URL: www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4133221&chk=TxHkqo
Saw a consultant – repeat visit	127.00	NHS Reference Costs 2005. PCT and trust combined data, outpatient, follow-up attendance, adult (TOPS FUA), thoracic medicine (specialty code 340). URL: www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4133221&chk=TxHkqo
Saw private consultant	127.00	Some patients saw private consultant. For external validity purposes, these cost the same as NHS and accrued to NHS

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Description of scenarios	Cost (£)	Source
Hospital service/appointment	127.00	NHS Reference Costs 2005. PCT and trust combined data, outpatient, follow-up attendance, adult (TOPS FUA), thoracic medicine (specialty code 340). URL: www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4133221&chk=TxHkqo
Chest X-ray	19.00	NHS Reference Costs 2005. PCT and trust combined data, (TRADIO), Band A – (no further details provided) (code RBA1). URL: www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4133221&chk=TxHkqo
CT scan – chest	69.00	NHS Reference Costs 2005. PCT and trust combined data, (TRADIO), Band C5 – CT other (code RBC5). URL: www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4133221&chk=TxHkqo
Labs – RAST tests	7.15	NHS Reference Costs 2005. PCT and trust combined data, (TPATH), immunology. URL: www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4133221&chk=TxHkqo
Labs – skin prick allergen sensitivity test	127.00	Assumed is same as consultant repeat visit
Microbiology diagnostics	6.31	NHS Reference Costs 2005. PCT and trust combined data, (TPATH), microbiology/immunology cost URL: www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4133221&chk=TxHkqo
Day-case admission	394.73	NHS Reference Costs 2005. PCT and trust combined data, (TDC), weighted average asthma admission with and without complications (HRG D21 and D22) URL: www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4133221&chk=TxHkqo
General ward – further nights		
Inpatient admission for asthma	1979.88	NHS Reference Costs 2005. PCT and trust combined data, (TELIP), weighted average asthma admission with or without complications (HRG D21 and D22) URL: www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4133221&chk=TxHkqo
Admission to specialist thoracic care ward	1979.88	Assumed equal to inpatient admission for asthma
Admission to intensive care unit		Note: reference costs should include ICU costs – danger of double counting
A&E attendance	70.95	NHS Reference Costs 2005. PCT and trust combined data, (TA&E, weighted average HRGs V07 and V08). No investigation died/admitted and referred/discharged. URL: www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4133221&chk=TxHkqo

Description of scenarios	Cost (£)	Source
Influenza vaccine	5.00	£5 for 'flu vaccine alone (price range £3.98–6.59, BNF 49, March 2005). Note: excludes nurse visit
Pneumococcal vaccine	21.67	£21.67 (means price of pneumococcal vaccine, BNF 49, March 2005). Note: excludes nurse visit
Nebulisation (with short-acting beta/salbutamol) in surgery, for acute symptoms	30.00	Nurse hour in clinic including qualification costs (PSSRU 2005, p. 130)
MRI scan	312.00	NHS Reference Costs 2005. PCT and trust combined data, (TRADIO RBF1, Band F1 – MRI) URL: www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4133221&chk=TxHkqo

BNF, *British National Formulary*; HRG, health-care resource group; OOH, out of hours; OOHT, out-of-hours telephone; PSSRU, Personal Social Services Research Unit; RAST, radioallergosorbent test.

a Curtis L, Netten A. *Unit Costs of Health and Social Care*. 2005. URL: www.pssru.ac.uk/pdf/uc/uc2005/uc2005.pdf (accessed 11 March 2010).

b Scott A, Simoens S, Heaney D, O'Donnell CA, Thomson H, Moffat KJ, *et al*. What does GP out of hours care cost? An analysis of different models of out of hours care in Scotland. *Scot Med J* 2004;**49**:61–6.

Imputation approach for economic analyses

TABLE 55 *Variables subject to multiple imputation*

Variable	Description
AQLQV2	Baseline miniAQLQ score
ACQV2	Baseline ACQ score
V2Utility	Baseline EQ-5D utility score
QALY8wk	QALYs gained at 8 weeks
NHS8wk	NHS costs at 8 weeks
Societal8wk	Societal costs at 8 weeks
AQLQv3	MiniAQLQ score at visit 3 (8 weeks)
ACQv3	ACQ score at visit 3 (8 weeks)
AQLQv7	MiniAQLQ score at visit 7 (2 years)
ACQv7	ACQ score at visit 7 (2 years)
QALY104wkDisc	QALYs gained at 2 years (discounted at 3.5%)
NHS104wkDisc	NHS costs at 2 years (discounted at 3.5%)
Societal104wkDisc	Societal costs at 2 years (discounted at 3.5%)

Summary of missing data

In total, 687 patients were enrolled in the study (steps 2 and 3). Four patients were excluded from the analysis due to their ineligibility (one due to incorrect diagnosis, three due to site not approved).

Overall, across all patients enrolled in the study (both steps 2 and 3), 7065 out of 8879 data points (80%) were present. Societal costs and QALY scores were variables with the highest proportion of missing data. These are the most complex compound variables, therefore, in any analysis, are most likely to have missing values (*Table 56*). Analysed by observation, 218 out of 683 patients (32%) had compete data at all time points; however, 75% of patients had at most four of the 13 variables missing (*Table 57* and *Figure 18*).

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TABLE 56 *Summary of missingness by variable*

Variable	Present	Missing	Missing (%)	Sum
AQLQV2	614	69	10	683
ACQV2	617	66	10	683
V2Utility	554	129	19	683
QALY8wk	439	244	36	683
NHS8wk	671	12	2	683
Societal8wk	344	339	50	683
AQLQv3	582	101	15	683
ACQv3	583	100	15	683
AQLQv7	653	30	4	683
ACQv7	650	33	5	683
QALY104wkDisc	400	283	41	683
NHS104wkDisc	632	51	7	683
Societal104wkDisc	326	357	52	683

TABLE 57 *Summary of missingness by observation*

Complete data	218 (32%)
≤1 missing item	234 (34%)
≤2 missing items	416 (61%)
≤3 missing items	463 (68%)
≤4 missing items	514 (75%)
≤5 missing items	575 (84%)
≤10 missing items	676 (99%)
≤13 missing items	683 (100%)

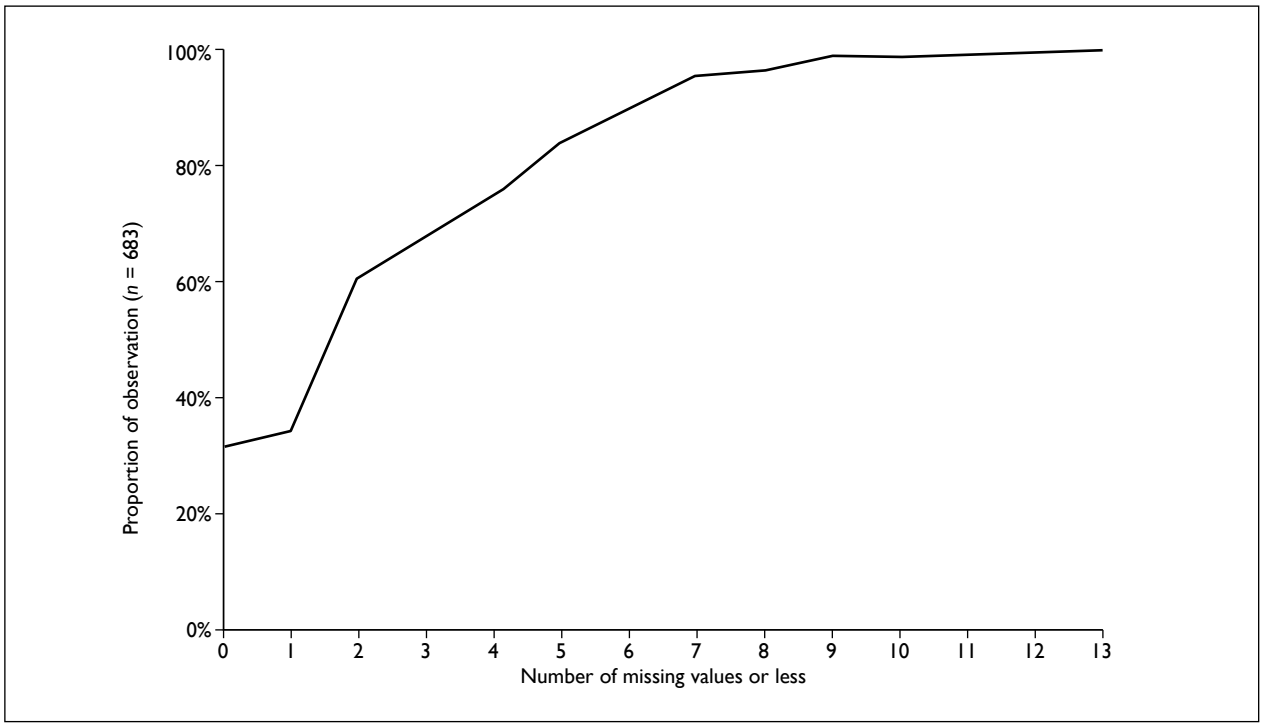

FIGURE 18 *Summary of missingness by observation.*

Interpretation 75% of observations had four or less missing values out of 13 variables.

Missing data were imputed as follows. Firstly, distributions of data were visualised to check for normality. Skewed data were transformed to improve their approximation to a normal distribution. *Table 58* summarises transformations performed.

TABLE 58 *Summary of data transformations*

Variable	Skewed	Transformation	Transformed variable name
AQLQV2	Left	Square	sqAQLQv2
ACQV2	Symmetric	–	–
V2Utility	Left	Square	sqV2Utility
QALY8wk	Left	Square	sqQALY8wk
NHS8wk	Right	Natural Log	lnNHS8Wk
Societal8wk	Right	Natural Log	lnSocietal8Wk
AQLQv3	Left	Square	sqAQLQv3
ACQv3	Right	Natural Log	lnACQv3
AQLQv7	Left	Square	sqAQLQv7
ACQv7	Right	Natural Log	lnACQv7
QALY104wkDisc	Left	Square	sqQALY8wkDisc
NHS104wkDisc	Right	Natural Log	lnNHS104WkDisc
Societal104wkDisc	Right	Natural Log	lnSocietal104WkDisc

The variables ACQv2, AQLQv2, QALY8Wk and QALY104WkDisc exhibited bimodal distributions, with a number of observations recorded at full health. Therefore additional binary variables were defined: 'ACQ_V2_zero', 'AQLQ_v2_zero', 'Healthy0', 'Healthy8' and 'Healthy104' with a value of 1 where the patient reported full health at each of these time points. Resulting QALYs were then estimated using a two-part model.

Due to computational constraints, it was not possible to impute missing values for all variables simultaneously. Therefore. they were split into groups (*Table 59*). In each case, data were imputed with five iterations using the propensity score method, with all other variables employed as potential covariates as well as age, education, employment and gender. The imputed variables were re-transformed to natural units and visually reviewed to ensure predicted values were within logical limits.

TABLE 59 *Imputation groups*

1. Costs	lnNHS8wklnSocietal8WklnNHS104WkDisclnSocietal104WkDisc
2. Baseline utility/QALYs	Healthy0SqV2Utility
3. EQ-5D utility < 1 at 8 or 104 weeks	Healthy8Healthy104
4. 8-week QALY scores	sqQALY8wk
5. 2-year QALY scores	sqQALY104wkDisc
6. Baseline ACQ and MiniAQLQ scores	ACQv2sqAQLQv2ACQ_V2_zeroAQLQ_V2_zero
7. MiniAQLQ and ACQ scores	AQLQv3ACQv3AQLQv7ACQv7

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Appendix 2

Planned secondary analysis

The following items have been collated from several sources, including the study protocol and the study steering committee meeting minutes.

- A per-protocol analysis will also be performed for the primary and the key secondary end points. It will be used to corroborate the conclusions drawn from the intention-to-treat analyses. The per-protocol analysis population will exclude patients and/or data points with clinically important protocol deviations based on a set of prespecified criteria.
- A per-treatment maintained analysis will be performed to look at the impact of clinical decisions about discontinuing perceived ineffective treatments.
- A repeated measures analysis of variance will be used to examine changes in life quality over time using scores from each visit. A comparison of profiles over time will be made between treatment groups.
- Treatment differences for secondary end points will be examined using appropriate statistical tests and expressed together with 95% CIs.
- The time course of the treatment effect will be studied using the morning PEF measurements obtained from the patient-recorded diary cards. The daily morning PEF measurements will be expressed as changes from baseline and analysed using a repeated measures analysis of variance.
- A sensitivity analysis will be undertaken, including those patients with either missing or out of range baseline MiniAQLQ or ACQ scores as their clinician had determined that they should have an increase in asthma therapy.
- The analysis should be repeated in the following subgroups:
  - by age stratification
  - those with the presence or absence of any evidence for a mixture of chronic and reactive obstructive pulmonary disease
  - the sub group who would meet European Medicines Evaluation Agency inclusion criteria (compare with observational data publications comparing with randomised controlled trials)
  - the subgroups of those with rhinitis versus those without rhinitis – and, subdividing those with rhinitis by how the information was obtained: clinical history of rhinitis (from GP practice data), versus use of rhinitis medications, versus response on questionnaire (RQLQ)
  - those with reversibility versus non reversibility
  - those staying with assigned randomised therapy versus those going off that therapy/those going to other therapy
  - smokers/non-smokers
  - analysis of population defined with higher ACQ cut points (1.25 suggested by LJ)
  - duration since diagnosis versus response
  - diagnostic and prescribing standards versus outcomes (by practice)
  - comparative analysis of QOL measures (e.g. ACQ/AQLQ, RCP3 and 21, patient-defined targets, symptom diary card, etc).

Validation of tools: RCP3 & 21 questions, EQ-5D, oral steroid use (as an independent measure of asthma control).

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Appendix 3
Details of NHS activity costs

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Step 2 study: NHS activity costs at 2 months

Quantities and costs of asthma-related NHS resources during the first 2 months of treatment.

	LTRA							ICS							
Treatment	***n***	**Total quantity**	**Mean quantity**	**SD**	**Total cost (£)**	**Mean cost (£)**	**SD (£)**	***n***	**Total quantity**	**Mean quantity**	**SD**	**Total cost (£)**	**Mean cost (£)**	**SD (£)**	***p*-value**
Routine nurse visits	156	25	0.16	0.40	235	1.51	4.66	158	19	0.12	0.41	225	1.42	5.47	
Vaccinations	156	16	0.10	0.30	97	0.62	2.25	158	6	0.04	0.19	30	0.19	0.96	
Total routine care	**156**	**41**	**0.26**	**0.63**	**332**	**2.13**	**5.52**	**158**	**25**	**0.16**	**0.56**	**255**	**1.61**	**5.98**	
GP in clinic	156	31	0.20	0.54	720	4.62	12.75	158	14	0.09	0.38	276	1.75	7.40	
GP home visit	156	0	0.00	0.00	0	0.00	0.00	158	0	0.00	0.00	0	0.00	0.00	
GP out of hours at night	156	5	0.03	0.33	248	1.59	16.35	158	0	0.00	0.00	0	0.00	0.00	
GP telephone consultation[a]	156	3	0.02	0.14	75	0.48	3.44	158	1	0.01	0.08	25	0.16	1.99	
Nurse in clinic	156	5	0.03	0.18	50	0.32	1.77	158	5	0.03	0.18	50	0.32	1.76	
Nurse telephone consultation	156	6	0.04	0.19	60	0.38	1.93	158	2	0.01	0.11	20	0.13	1.12	
Other	156	0	0.00	0.00	0	0.00	0.00	158	0	0.00	0.00	0	0.00	0.00	
Total patient initiated	**156**	**50**	**0.32**	**0.75**	**1153**	**7.39**	**22.79**	**158**	**22**	**0.14**	**0.46**	**371**	**2.35**	**8.08**	
Outpatient	156	2	0.01	0.11	254	1.63	14.33	158	3	0.02	0.18	381	2.41	22.53	
Inpatient admission	156	0	0.00	0.00	0	0.00	0.00	158	0	0.00	0.00	0	0.00	0.00	
Day-case admission	156	0	0.00	0.00	0	0.00	0.00	158	0	0.00	0.00	0	0.00	0.00	
Accident and emergency	156	2	0.01	0.16	382	2.45	30.58	158	0	0.00	0.00	0	0.00	0.00	
Diagnostics	156	0	0.00	0.00	0	0.00	0.00	158	0	0.00	0.00	0	0.00	0.00	
Total secondary care	**156**	**4**	**0.03**	**0.25**	**636**	**4.08**	**41.93**	**158**	**3**	**0.02**	**0.18**	**381**	**2.41**	**22.53**	
Total NHS resources used	**156**	**95**	**0.61**	**1.09**	**2121**	**13.59**	**61.00**	**158**	**50**	**0.32**	**0.71**	**1007**	**6.37**	**24.16**	**0.008**

ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Day-time and out-of-hours figures combined.

Step 3 study: NHS activity costs at 2 months

Quantities and costs of asthma related NHS resources during the first 2 months of treatment.

	LTRA							LABA							
Treatment	***n***	**Total quantity**	**Mean quantity**	**SD**	**Total cost (£)**	**Mean cost (£)**	**SD (£)**	***n***	**Total quantity**	**Mean quantity**	**SD**	**Total cost (£)**	**Mean cost (£)**	**SD (£)**	***p*-value**
Routine nurse visits	175	26	0.15	0.39	310	1.77	4.97	182	31	0.17	0.47	285	1.57	4.80	
Vaccinations	175	12	0.07	0.30	93	0.53	3.01	182	16	0.09	0.30	113	0.62	2.82	
Total routine care	**175**	**38**	**0.22**	**0.59**	**403**	**2.30**	**6.32**	**182**	**47**	**0.26**	**0.73**	**398**	**2.19**	**6.61**	
GP in clinic	175	32	0.18	0.55	756	4.32	13.07	182	42	0.23	0.61	984	5.41	14.52	
GP home visit	175	2	0.01	0.11	138	0.79	7.36	182	0	0.00	0.00	0	0.00	0.00	
GP out of hours at night	175	0	0.00	0.00	0	0.00	0.00	182	0	0.00	0.00	0	0.00	0.00	
GP telephone consultation[a]	175	1	0.01	0.08	25	0.14	1.89	182	1	0.01	0.07	25	0.14	1.85	
Nurse in clinic	175	16	0.09	0.38	155	0.89	3.70	182	8	0.04	0.23	70	0.38	2.13	
Nurse telephone consultation	175	8	0.05	0.24	80	0.46	2.35	182	5	0.03	0.16	50	0.27	1.64	
Other	175	0	0.00	0.00	0	0.00	0.00	182	0	0.00	0.00	0	0.00	0.00	
Total patient initiated	**175**	**59**	**0.34**	**0.79**	**1154**	**6.59**	**17.17**	**182**	**56**	**0.31**	**0.75**	**1129**	**6.20**	**15.54**	
Outpatient	175	1	0.01	0.08	191	1.09	14.44	182	0	0.00	0.00	0	0.00	0.00	
Inpatient admission	175	0	0.00	0.00	0	0.00	0.00	182	0	0.00	0.00	0	0.00	0.00	
Day-case admission	175	0	0.00	0.00	0	0.00	0.00	182	0	0.00	0.00	0	0.00	0.00	
Accident and emergency	175	0	0.00	0.00	0	0.00	0.00	182	0	0.00	0.00	0	0.00	0.00	
Diagnostics	175	0	0.00	0.00	0	0.00	0.00	182	4	0.02	0.18	76	0.42	3.43	
Total secondary care	**175**	**1**	**0.01**	**0.08**	**191**	**1.09**	**14.44**	**182**	**4**	**0.02**	**0.18**	**76**	**0.42**	**3.43**	
Total NHS resources used	**175**	**98**	**0.56**	**0.99**	**1748**	**9.99**	**25.00**	**182**	**107**	**0.59**	**1.05**	**1603**	**8.81**	**17.64**	**0.900**

LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Day-time and out-of-hours figures combined.

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Step 2 study: NHS activity costs at 104 weeks

Quantities and costs of asthma related NHS resources during 104 weeks of treatment.

	LTRA							ICS							
Treatment	***n***	**Total quantity**	**Mean quantity**	**SD**	**Total cost (£)**	**Mean cost (£)**	**SD (£)**	***n***	**Total quantity**	**Mean quantity**	**SD**	**Total cost (£)**	**Mean cost (£)**	**SD (£)**	***p*-value**
Routine nurse visits	151	300	1.99	1.70	2858	18.93	20.15	151	272	1.80	1.54	2807	18.59	18.19	
Vaccinations	151	174	1.15	1.08	1198	7.93	9.88	151	148	0.98	0.98	1020	6.75	8.95	
Total routine care	**151**	**474**	**3.14**	**2.53**	**4056**	**26.86**	**24.92**	**151**	**420**	**2.78**	**2.32**	**3827**	**25.35**	**22.92**	
GP in clinic	151	301	1.99	2.77	6787	44.95	64.89	151	308	2.04	2.50	6947	46.01	57.20	
GP home visit	151	5	0.03	0.21	336	2.22	14.37	151	5	0.03	0.34	333	2.21	22.33	
GP out of hours at night	151	11	0.07	0.40	544	3.60	19.90	151	15	0.10	0.41	731	4.84	20.13	
GP telephone consultation[a]	151	17	0.11	0.41	495	3.28	14.55	151	21	0.14	0.69	515	3.41	16.92	
Nurse in clinic	151	46	0.30	0.84	432	2.86	7.97	151	44	0.29	0.84	413	2.73	8.09	
Nurse telephone consultation	151	17	0.11	0.42	168	1.11	4.19	151	21	0.14	0.37	207	1.37	3.60	
Other	151	0	0.00	0.00	0	0.00	0.00	151	2	0.01	0.11	35	0.23	2.41	
Total patient initiated	**151**	**397**	**2.63**	**3.19**	**8762**	**58.02**	**78.46**	**151**	**416**	**2.75**	**3.46**	**9181**	**60.80**	**81.95**	
Outpatient	151	14	0.09	0.41	1752	11.60	50.66	151	30	0.20	0.71	3795	25.13	90.33	
Inpatient admission	151	4	0.03	0.26	7853	52.00	503.32	151	2	0.01	0.11	3826	25.34	219.42	
Day-case admission	151	1	0.01	0.08	395	2.61	32.12	151	0	0.00	0.00	0	0.00	0.00	
Accident and emergency	151	9	0.06	0.33	1823	12.08	85.60	151	8	0.05	0.30	548	3.63	20.62	
Diagnostics	151	12	0.08	0.32	222	1.47	5.88	151	15	0.10	0.36	277	1.84	6.65	
Total secondary care	**151**	**40**	**0.26**	**0.87**	**12,045**	**79.77**	**601.74**	**151**	**55**	**0.36**	**1.06**	**8446**	**55.93**	**268.62**	
Total NHS resources used	**151**	**911**	**6.03**	**4.89**	**24,863**	**164.65**	**633.99**	**151**	**891**	**5.90**	**5.25**	**21,455**	**142.08**	**310.13**	**0.635**

ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Day-time and out-of-hours figures combined.

Step 3 study: NHS activity costs at 104 weeks

Quantities and costs of asthma-related NHS resources during 104 weeks of treatment.

	LTRA							LABA							
Treatment	***n***	**Total quantity**	**Mean quantity**	**SD**	**Total cost (£)**	**Mean cost (£)**	**SD (£)**	***n***	**Total quantity**	**Mean quantity**	**SD**	**Total cost (£)**	**Mean cost (£)**	**SD (£)**	***p*-value**
Routine nurse visits	169	414	2.45	1.82	4129	24.43	21.54	176	437	2.48	1.69	4106	23.33	18.86	
Vaccinations	169	232	1.37	1.02	1581	9.36	9.69	176	262	1.49	1.08	1828	10.39	10.57	
Total routine care	**169**	**646**	**3.82**	**2.63**	**5710**	**33.79**	**26.53**	**176**	**699**	**3.97**	**2.56**	**5934**	**33.72**	**24.49**	
GP in clinic	169	452	2.67	3.17	10,152	60.07	72.71	176	417	2.37	2.29	9253	52.57	51.22	
GP home visit	169	9	0.05	0.23	612	3.62	15.31	176	13	0.07	0.40	874	4.96	26.91	
GP out of hours at night	169	4	0.02	0.15	195	1.15	7.44	176	8	0.05	0.21	390	2.22	10.19	
GP telephone consultation[a]	169	32	0.19	0.66	814	4.82	16.63	176	24	0.14	0.48	641	3.64	12.62	
Nurse in clinic	169	118	0.70	1.17	1123	6.65	11.26	176	68	0.39	0.87	628	3.57	8.39	
Nurse telephone consultation	169	34	0.20	0.52	336	1.99	5.13	176	26	0.15	0.52	257	1.46	5.16	
Other	169	5	0.03	0.17	101	0.60	3.97	176	5	0.03	0.20	146	0.83	5.77	
Total patient initiated	**169**	**654**	**3.87**	**4.20**	**13,334**	**78.90**	**89.75**	**176**	**561**	**3.19**	**2.94**	**12,187**	**69.25**	**71.42**	
Outpatient	169	40	0.24	0.83	5668	33.54	120.42	176	19	0.11	0.54	2500	14.21	72.09	
Inpatient admission	169	3	0.02	0.17	5806	34.35	330.56	176	5	0.03	0.25	9766	55.49	484.06	
Day-case admission	169	1	0.01	0.08	395	2.34	30.36	176	0	0.00	0.00	0	0.00	0.00	
Accident and emergency	169	3	0.02	0.23	453	2.68	34.84	176	0	0.00	0.00	0	0.00	0.00	
Diagnostics	169	27	0.16	0.49	552	3.27	11.29	176	23	0.13	0.40	826	4.69	27.02	
Total secondary care	**169**	**74**	**0.44**	**1.16**	**12,874**	**76.18**	**370.05**	**176**	**47**	**0.27**	**0.91**	**13,092**	**74.39**	**511.48**	
Total NHS resources used	**169**	**1374**	**8.13**	**5.94**	**31,918**	**188.86**	**398.89**	**176**	**1307**	**7.43**	**4.19**	**31,214**	**177.35**	**541.93**	**0.920**

LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Day-time and out of hours combined.

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Appendix 4

Study data collection instruments

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Study visit form

The form presented here is the version of the form used at study visit 2. A slight variant of this form was used at visits 3 to 7 which had fewer instructions on the first page, since the text of the Personal Objectives were only specified by the participants at V2, thereafter they were pre-filled by study staff. Therefore, the response was only marking a score, and the instructions were modified accordingly.

The **ELEVATE** Study

Effectiveness of Leukotriene receptor antagonists in the Evaluation of Asthma Therapies and for health Economics

UEA NORWICH

Study ID Number: ☐☐☐☐☐☐

Practice no: ☐☐ **Patient Initials:** ☐☐☐ **Date:** ☐☐ ☐☐ ☐☐

Laminated sheet of example targets used? *Yes* ☐ *No* ☐

Thank you for taking part in the ELEVATE study.

If you have any questions you need answering about this study please ring and speak to:

At your GP practice: ☐

At UEA: ***01603 591106***

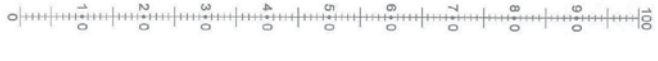
THANK YOU AGAIN……..PLEASE NOW GO ON TO COMPLETE THE QUESTIONNAIRE BELOW AND ON THE NEXT FEW PAGES

PERSONAL OBJECTIVES FOR YOUR ASTHMA (THERMOMETER SCALES)

Please think about three things you would like to be better about your asthma. This may be things or activities that asthma causes you difficulty doing or particular problems asthma causes for you.

It really does not matter what you choose as long as they are three things which are IMPORTANT to YOU.

When you have written in your targets below, please draw a line on the thermometer like scales below where you feel you are at present. As the study goes on you will be asked again to do this, and we will remind you next time of the three targets you have chosen.

Your targets:	Thermometer scales (0 not met at all – 100% fully met)
1	
2	
3	

Office Use Only 1 ☐☐☐ 2 ☐☐☐ 3 ☐☐☐

Clinical record form

The form presented here is the version of the form used for step 3 participants in the study. The form for step 2 participants differed solely in the page headers, which labelled it as step 2; the text regarding identification of eligible patients based on medication taken before enrolment; and the instructions for the medication at randomisation.

Effectiveness of Leukotriene receptor antagonists in the EValuation of Asthma Therapies and for health Economics
Tel: 01603 - 591106 or – 593309

UEA NORWICH

THIS CRF IS FOR PATIENTS ON INHALED CORTICOSTEROIDS ONLY PRIOR TO STUDY
This patient will start on STEP 3 in ELEVATE

Study identification no.:__ __ __ __ __ __ Patient initials___ ___ ___ Date:___/___/___		
Please confirm:		
Patient meets all inclusion criteria (as listed on audit sheet)	Yes ☐	If criteria failed, stop, but call study office if you think patient should be in study
Patient does not have any exclusion criteria (as listed on audit sheet)	Yes ☐	
Patient information sheets reviewed and informed consent obtained?	Yes ☐	
DEMOGRAPHY – *complete with patient*		
Sex : Male ☐ Female ☐	**Postcode:**	**Date of birth: _____/_____/_____**
Race: White ☐ Mixed ☐ Asian ☐ Black ☐ Chinese ☐ Other ☐		
Did education continue after minimum school leaving age?	☐ Yes ☐ No	
Does patient have a degree or equivalent professional qualification?	☐ Yes ☐ No	
Which of following best describes patient's main activity?	(tick one)	
• employment or self-employment. *Specify job description below.*	☐	
• retired *Specify last main job description below.*	☐	
• housework	☐	
• student	☐	
• seeking work	☐	
• other, *specify here*	☐	
Job Description *If answer "employed or self employed" or "retired" above:* 1. Tick appropriate box for: employer, self-employed (without employees) or employee. 2. In space below, specify:	employer ☐ self-employed (without employees) ☐ employee ☐	

(…. Visit 1 continues on next page….)

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Patient ID #_____ Initials_____ date____/____/_____ time:_____

PEF (no inhaled ß-agonist for 4 hours if possible)

Tick if last β-agonist was **more** than 4 hours ago: ☐			
Tick if last β-agonist **less** than 4 hours (& state time of dose) ☐	**Time: _____:_____**		
PEF	1st reading	2nd reading	3rd reading
	____L/m	**____L/m**	**____L/m**
Symptoms during the last four weeks:	**If yes, how often?**		
difficulty sleeping because of asthma symptoms (*including cough*)?	☐ **Yes** ☐ **No (days per week 0-7)** _____		
had usual asthma symptoms (*cough, wheeze, chest tightness, sob*) during day?	☐ **Yes** ☐ **No (days per week 0-7)** _____		
has asthma interfered with usual activities (*e.g. housework, work/school etc*)?	☐ **Yes** ☐ **No (days per week 0-7)** _____		
Physical exam	☐ normal	☐ abnormal	☐ not done
Specify any abnormalities:			
Height:	**_____cms**		

Other steps to be completed at this stage of this visit:

a) All medications prescribed in previous 3 months recorded on the medications sheet *(see red tab at back of CRF).*	☐
b) Give Symptom Diary forms to patient and instruct patient in their use. *(see opposite)*	☐
c) Remind patient that they should not, if possible, use a reliever for 4 hours before next visit. (But of course they may use the reliever if they really need it.)	☐
d) Ask patient to fill contact information sheet. Return it to ELEVATE office in freepost envelope along with top copy of this page	☐

Next study appointment date - 2 weeks. Note: If patient clinically has to have their therapy increased* now, *you may go to visit 2 immediately – see instructions*.	____/____/____

We recommend that patients should follow national guidelines on asthma management.

Patient should consult their GP/nurse, as normal, at any time during the study

Name of practitioner seeing patient and completing this form. _____

Remove top copies of this page and previous page and return to UEA, with contact info sheet, using Freepost envelopes ☐

Patient ID #_____ Initials_____ date____/____/_____ time:_____

PEF (no inhaled ß-agonist for 4 hours if possible)

Tick if last β-agonist was **more** than 4 hours ago:	☐		
Tick if last β-agonist **less** than 4 hours (& state time of dose)	☐	**Time** _____	
PEF	1st reading	2nd reading	3rd reading
	____L/m	**____L/m**	**____L/m**
Reversibility testing administer β-agonist now, and complete following 3 pages while waiting.	Time drug given	____:____	
	Drug & dosage		

MEDICAL HISTORY

CATEGORY	MEDICAL HISTORY TERM	YEAR OF DIAGNOSIS	ACTIVE?
Active Medical Conditions & Significant Past Medical History (not minor illnesses)	Asthma		No ☐ Yes ☐
			No ☐ Yes ☐
			No ☐ Yes ☐
			No ☐ Yes ☐
			No ☐ Yes ☐
			No ☐ Yes ☐
			No ☐ Yes ☐
			No ☐ Yes ☐
Drug Allergies:			
Respiratory and other investigations or procedures: **e.g. Lab tests** *if clinically significant or abnormal.* **e.g. Surgery, or procedures,** *if relevant*		**YEAR** *(Or "NA" if never done)*	**RESULT OR OUTCOME**
	Allergy skin prick test		
	IgE / RAST		
	chest x-ray(s) (any abnormal or latest)		

Comments:

(….Visit 2 continues on next page….)

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Patient ID #_____ Initials_____ date____/____/_____ time:_____

Baseline Asthma Profile - FROM CLINICAL RECORD (may confirm with patient if required)			
1.	Is diagnosis of asthma recorded in clinical record?	☐ Yes	☐ No
Basis for diagnosis is:		(tick ☑ any or all of A to E that apply)	
A)	Reversibility after inhaled β-agonist	☐ PEF or	☐ FEV1
	date		
	value pre medication		
	value post medication		
	% change		
	other, *specify*		
B)	PEF variability	☐	
	date		
	highest PEF		
	lowest PEF		
	% change		
	other, *specify*		
C)	Response to other treatment (eg ICS trial), *specify:*	☐	
D)	Physician diagnosis, based on history and examination, *specify:*	☐	
E)	Other, *specify:*	☐	
2.	Does patient have asthma symptoms brought on by:		
	exercise or physical activity	☐ Yes	☐ No
	viral infections	☐ Yes	☐ No
	cold air	☐ Yes	☐ No
	animals, specify	☐ Yes	☐ No
	occupation, specify	☐ Yes	☐ No
	aspirin or other NSAID	☐ Yes	☐ No
	others, specify	☐ Yes	☐ No
3.	Smoking -- has the patient ever smoked?	☐ yes, (smoked)	☐ no, (never)
	-- what age did patient start smoking?	age:____	
	-- average number of cigarettes daily?		
	-- other, e.g. pipe, roll-ups, cigars. Specify:		
	Still smoking? ☐ no, (stopped)	☐ yes, (still smokes) ⇩ *next question*	⇩ *next question*
	What age did patient stop smoking? age:____		

(….Visit 2 continues on next page….)

Patient ID #_____ Initials_____ date____/____/_____ time:_____

a) Ask patient for Symptom Diary Card, check if this was understood and completed. Post it to UEA.	☐
b) Record all medications changes, since Visit 1, on medications sheet *(see red tab at back of CRF).*	☐
c) Give visit 2 Questionnaires (enter Patient ID and Practice numbers) and Freepost envelopes to patient to be completed and returned to UEA *(see opposite).* *Explain Patient oriented targets*	☐
d) Complete Resource Data Collection Sheet with patient *(also use clinical records).* Give fridge magnet and Resource Diary to use until next visit, and explain.	☐

Report reversibility test (at least 15 minutes after β-agonist given).

PEF	1st reading	2nd reading	3rd reading
	____L/m	**____L/m**	**____L/m**
Symptoms during the last four weeks: ○ difficulty sleeping because of asthma symptoms (*including cough*)? ○ had usual asthma symptoms (*cough, wheeze, chest tightness, sob*) during day? ○ has asthma interfered with usual activities (*e.g. housework, work/school etc*)?	**If yes, how often?** ☐ Yes ☐ No (days per week 0-7) _____ ☐ Yes ☐ No (days per week 0-7) _____ ☐ Yes ☐ No (days per week 0-7) _____		

Randomisation to treatment arm *(see opposite)*	
Arm A – Inhaled Steroid plus LAB	☐
Arm B – Inhaled Steroid plus LTRA	☐

Other steps to be completed on this visit:

e) Study medication prescription given by GP and recorded	☐
f) Patient pocket information card given to patient	☐
g) Put treatment arm sticker put on medical record *(if appropriate)*	☐

Date of next study appointment - 2 months (+/- 3 weeks; may be provisional) *Make appointment now, or make provision for this to be done through normal practice appointing procedures.*	____/____/_____
We recommend that patients should follow national guidelines on asthma management. Patient should consult their GP/nurse, as normal, at any time during the study	
Name of practitioner seeing patient and completing this form. _____	

Remove top copies of this page and previous pages and return to UEA, using Freepost envelopes	☐

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Patient ID #_____ Initials_____ date____/____/_____ time:_____

face to face☐ telephone☐

PEF (no inhaled ß-agonist for 4 hours if possible)

Tick if last β-agonist was **more** than 4 hours ago:	☐		
Tick if last β-agonist **less** than 4 hours (& state time of dose)	☐	**Time:** _____:_____	
PEF	1st reading	2nd reading	3rd reading
	____L/m	**____L/m**	**____L/m**
Symptoms during the last four weeks:	**If yes, how often?**		
○ difficulty sleeping because of asthma symptoms (*including cough*)?	☐ **Yes** ☐ **No (days per week 0-7)** _____		
○ had usual asthma symptoms (*cough, wheeze, chest tightness, sob*) during day?	☐ **Yes** ☐ **No (days per week 0-7)** _____		
○ has asthma interfered with usual activities (*e.g. housework, work/school etc*)?	☐ **Yes** ☐ **No (days per week 0-7)** _____		

Other steps to be completed this visit:

Record all medication changes, since last study visit, on medications sheet *(see red tab at back of CRF).*	☐
Confirm patient received questionnaire and returned to UEA. (*If not, call study office to inform).*	☐
Complete Resource Data Collection form with patient, using clinical records and Patient Resource Diary Card. (*DO NOT alter diary by updating it with any information that arises during this visit).*	☐
If patient's status changes (discontinuation or change of medication, becomes pregnant, discontinues contraception, or withdraws from some or all follow up) fill status form (*see green tab at end of CRF)* and send copy to the UEA	☐
If patient has any adverse event, fill in Adverse event form (*see yellow tab at the end of the CRF)* and send copy to UEA	☐

Date of next study appointment - 4 months (+/- 3 weeks; may be provisional) *Make appointment now, or make provision for this to be done through normal practice appointing procedures.*	_____/_____/____

We recommend that patients should follow national guidelines on asthma management.

Patient should consult their GP/nurse, as normal, at any time during the study

Name of practitioner seeing patient and completing this form. _____

Remove top copies & return to UEA, using Freepost envelopes ☐

Patient ID #_____ Initials_____ date____/____/_____ time:_____

face to face☐ telephone☐

PEF (no inhaled ß-agonist for 4 hours if possible)

Tick if last β-agonist was **more** than 4 hours ago:	☐		
Tick if last β-agonist **less** than 4 hours (& state time of dose)	☐	**Time: _____:_____**	
PEF	1st reading	2nd reading	3rd reading
	____L/m	**____L/m**	**____L/m**
Symptoms during the last four weeks:	**If yes, how often?**		
○ difficulty sleeping because of asthma symptoms (*including cough*)?	☐ **Yes** ☐ **No (days per week 0-7)** _____		
○ had usual asthma symptoms (*cough, wheeze, chest tightness, sob*) during day?	☐ **Yes** ☐ **No (days per week 0-7)** _____		
○ has asthma interfered with usual activities (*e.g. housework, work/school etc*)?	☐ **Yes** ☐ **No (days per week 0-7)** _____		

Other steps to be completed this visit:

Record all medication changes, since last study visit, on medications sheet *(see red tab at back of CRF).*	☐
Confirm patient received questionnaire and returned to UEA. (*If not, call study office to inform).*	☐
Complete Resource Data Collection form with patient, using clinical records and Patient Resource Diary Card. (*DO NOT alter diary by updating it with any information that arises during this visit).*	☐
If patient's status changes (discontinuation or change of medication, becomes pregnant, discontinues contraception, or withdraws from some or all follow up) fill status form (*see green tab at end of CRF)* and send copy to the UEA	☐
If patient has any adverse event, fill in Adverse event form (*see yellow tab at the end of the CRF)* and send copy to UEA	☐

Date of next study appointment - 6 months (+/- 3 weeks; may be provisional) *Make appointment now, or make provision for this to be done through normal practice appointing procedures.*	**_____/_____/____**

We recommend that patients should follow national guidelines on asthma management.

Patient should consult their GP/nurse, as normal, at any time during the study

Name of practitioner seeing patient and completing this form. _____

Remove top copies & return to UEA, using Freepost envelopes ☐

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Patient ID #_____ Initials_____ date____/____/_____ time:_____

face to face☐ telephone☐

Annual Review - Demographic update:

Has patient's employment changed in the past year? Yes ☐ No ☐

If yes, complete the questions on the demographic update page at the end of the CRF

Smoking update:

Has patient stopped or started smoking in the past year? Yes ☐ No ☐

If yes, tick box for stopped or started stopped ☐

started ☐

and specify date date : _____/_____/_____

PEF (no inhaled ß-agonist for 4 hours if possible)

Tick if last β-agonist was **more** than 4 hours ago:	☐		
Tick if last β-agonist **less** than 4 hours (& state time of dose)	☐	**Time:** _____:_____	
PEF	1st reading	2nd reading	3rd reading
	____L/m	**____L/m**	**____L/m**
Symptoms during the last four weeks:	**If yes, how often?**		
○ difficulty sleeping because of asthma symptoms (*including cough*)?	☐ **Yes** ☐ **No (days per week 0-7)** _____		
○ had usual asthma symptoms (*cough, wheeze, chest tightness, sob*) during day?	☐ **Yes** ☐ **No (days per week 0-7)** _____		
○ has asthma interfered with usual activities (*e.g. housework, work/school etc*)?	☐ **Yes** ☐ **No (days per week 0-7)** _____		

Other steps to be completed this visit:

Record all medication changes, since last study visit, on medications sheet *(see red tab at back of CRF).*	☐
Confirm patient received questionnaire and returned to UEA. (*If not, call study office to inform).*	☐
Complete Resource Data Collection form with patient, using clinical records and Patient Resource Diary Card. (*DO NOT alter diary by updating it with any information that arises during this visit).*	☐
If patient's status changes (discontinuation or change of medication, becomes pregnant, discontinues contraception, or withdraws from some or all follow up) fill status form (*see green tab at end of CRF)* and send copy to the UEA	☐
If patient has any adverse event, fill in Adverse event form (*see yellow tab at the end of the CRF)* and send copy to UEA	☐
Date of next study appointment - 6 months (+/- 3 weeks; may be provisional) *Make appointment now, or make provision for this to be done through normal practice appointing procedures.*	____/____/_____

We recommend that patients should follow national guidelines on asthma management.

Patient should consult their GP/nurse, as normal, at any time during the study

Name of practitioner seeing patient and completing this form.

_____

Remove top copies & return to UEA, using Freepost envelopes ☐

Patient ID #_____ Initials_____ date____/____/_____ time:_____

face to face☐ telephone☐

PEF (no inhaled ß-agonist for 4 hours if possible)

Tick if last β-agonist was **more** than 4 hours ago:	☐		
Tick if last β-agonist **less** than 4 hours (& state time of dose)	☐	**Time:** _____:_____	
PEF	1st reading	2nd reading	3rd reading
	____L/m	**____L/m**	**____L/m**
Symptoms during the last four weeks: ○ difficulty sleeping because of asthma symptoms (*including cough*)? ○ had usual asthma symptoms (*cough, wheeze, chest tightness, sob*) during day? ○ has asthma interfered with usual activities (*e.g. housework, work/school etc*)?	**If yes, how often?** ☐ **Yes** ☐ **No (days per week 0-7)** _____ ☐ **Yes** ☐ **No (days per week 0-7)** _____ ☐ **Yes** ☐ **No (days per week 0-7)** _____		

Other steps to be completed this visit:

Record all medication changes, since last study visit, on medications sheet *(see red tab at back of CRF).*	☐
Confirm patient received questionnaire and returned to UEA. (*If not, call study office to inform).*	☐
Complete Resource Data Collection form with patient, using clinical records and Patient Resource Diary Card. (*DO NOT alter diary by updating it with any information that arises during this visit).*	☐
If patient's status changes (discontinuation or change of medication, becomes pregnant, discontinues contraception, or withdraws from some or all follow up) fill status form (*see green tab at end of CRF)* and send copy to the UEA	☐
If patient has any adverse event, fill in Adverse event form (*see yellow tab at the end of the CRF)* and send copy to UEA	☐

Date of next study appointment - 6 months (+/- 3 weeks may be provisional) *Make appointment now, or make provision for this to be done through normal practice appointing procedures.*	**_____/_____/_____**

We recommend that patients should follow national guidelines on asthma management.

Patient should consult their GP/nurse, as normal, at any time during the study

Name of practitioner seeing patient and completing this form. _____

Remove top copies & return to UEA, using Freepost envelopes ☐

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Patient ID #_____ Initials_____ date____/____/_____ time:_____

face to face☐ telephone☐

1. DEMOGRAPHIC update

Has the patient's employment changed in the past year? Yes ☐ No ☐

If yes, complete the questions on the demographic update page at the end of the CRF

Smoking update:

Has patient stopped or started smoking in the past year? Yes ☐ No ☐

If yes, tick box for stopped or started stopped ☐

started ☐

and specify date date : _____/_____/_____

PEF (no inhaled ß-agonist for 4 hours if possible)

Tick if last β-agonist was **more** than 4 hours ago: ☐			
Tick if last β-agonist **less** than 4 hours (& state time of dose) ☐	**Time:** _____:_____		
PEF	1st reading	2nd reading	3rd reading
	____L/m	**____L/m**	**____L/m**
Symptoms during the last four weeks:	**If yes, how often?**		
difficulty sleeping because of asthma symptoms (*including cough*)?	☐ **Yes** ☐ **No (days per week 0-7)** _____		
had usual asthma symptoms (*cough, wheeze, chest tightness, sob*) during day?	☐ **Yes** ☐ **No (days per week 0-7)** _____		
has asthma interfered with usual activities (*e.g. housework, work/school etc*)?	☐ **Yes** ☐ **No (days per week 0-7)** _____		
Physical exam	☐normal	☐abnormal	☐not done
Specify any abnormalities:			

Other steps to be completed this visit:

Record all medication changes, since last study visit, on medications sheet *(see red tab at back of CRF).*	☐
Confirm patient received questionnaire and returned to UEA. (*If not, call study office to inform).*	☐
Complete Resource Data Collection form with patient, using clinical records and Patient Resource Diary Card. *DO NOT alter diary by updating it with any information that arises during this visit.*	☐
If patient's status changes (discontinuation or change of medication, becomes pregnant, discontinues contraception, or withdraws from some or all follow up) fill status form (*see green tab at end of CRF)* and send copy to the UEA	☐
If patient has any adverse event, fill in Adverse event form (*see yellow tab at the end of the CRF)* and send copy to UEA	☐

We recommend that patients should follow national guidelines on asthma management.

Patient should consult their GP/nurse, as normal, at any time during the study

Name of practitioner seeing patient and completing this form. _____

Remove top copies & return to UEA, using Freepost envelopes ☐

Medications for Asthma:

& other respiratory problems or respiratory tract infections.

(For other – general - medications please use next page)

Post top copy to UEA after visit 3, post remaining copy after visit 7

DRUG NAME	ROUTE	TOTAL DAILY DOSAGE Dose	Units	START DATE (DD Mon-YYYY)	STOP DATE (DD Mon-YYYY)	WHY? If new: name of medical condition being treated – If dosage change: reason	Adverse Event?	Visit 7 only – continuing?
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐

**If any AE "YES" box is checked, complete the ADVERSE EXPERIENCE form (see yellow tab at end of CRF).*

Drug Name: use generic name except: use trade name for fixed combinations only, and use trade name for medications with multiple active ingredients. **Route**: PO (oral), IV (intravenous infusion), IM (intramuscular), INH (inhalant), Other.

Name of practitioner seeing patient and completing this form. ______________________________

FINAL DRAFT

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Other CONCOMITANT Medications:

for general, non-asthma, non- respiratory conditions.

Post top copy to UEA after visit 3, post remaining copy after visit 7

DRUG NAME	ROUTE	TOTAL DAILY DOSAGE Dose	TOTAL DAILY DOSAGE Units	START DATE (DD Mon-YYYY)	STOP DATE (DD Mon-YYYY)	**WHY?** If new: name of medical condition being treated – If dosage change: reason	Adverse Event?	Visit 7 only **continuing?**
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐
				___/___/___	___/___/___		If Yes ☐	☐

**If any AE “YES” box is checked, complete the ADVERSE EXPERIENCE form (see yellow tab at end of CRF).*

Drug Name: use generic name except: use trade name for fixed combinations only, and use trade name for medications with multiple active ingredients. **Route**: PO (oral), IV (intravenous infusion), IM (intramuscular), INH (inhalant), Other.

Name of practitioner seeing patient and completing this form. ______________________________

Date:____/____/_____ Visit: _____

Complete this page if there are changes in Employment Details

DEMOGRAPHY UPDATE	
Which of following best describes patient's main activity?	(tick one)
• employment or self-employment. *Specify job description below.*	☐
• retired *Specify last main job description below.*	☐
• housework	☐
• student	☐
• seeking work	☐
• other, *specify here*	☐
Job Description *If answer "employed or self employed" or "retired" above:* 1. Tick appropriate box for: employer, self-employed (without employees) or employee. 2. In space below, specify:	employer ☐ self-employed (without employees) ☐ employee ☐
What date did employment change?	___/___/___

Name of practitioner seeing patient and completing this form. _____

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Patient status - Changes from the study protocol
•1 **Discontinuation of study medication** •2 **Optional change from study medication** •3 **Withdrawal from study data collection**

Changes to therapy and follow up may occur in several ways and should be documented as below. Complete form below within 2 weeks of any change in medication, or follow up plan, and post to UEA.

1. Distinguish which of the following categories apply (more than one may apply), and treat as indicated:

Category - Description	Study medication	Follow up data collection	Tick here
1. Need to discontinue study medication due to potentially jeopardising **adverse event or pregnancy**	Cease or change study medication as AE or pregnancy requires.	Continue as much as possible	☐
2. Change from study medication **by choice**	Patient or clinician chooses to change from study medication	Continue as much as possible	☐
3. Partial withdrawal from some follow up or data collection.	Continues as randomised, modified if indicated by national guidelines	Continue as much as can be agreed	☐
3.a. Patient moves away from study but agrees to continue to fill forms.	Continue as much as can be agreed, need to get new address and GP name. *(Write in plan, below)*		☐
4. Complete withdrawal (withdraws consent)	Out of study, so therapy as indicated by national guidelines	None (after completing and sending this form.)	☐

2. Specific reason for change/discontinuation/withdrawal (include as much of symptoms, physical exam, history and any labs as possible/appropriate):

3. If patient agrees to a follow up plan (e.g. all or any part of the planned study visits and data collection forms), describe plan:

If patient has moved/will move, please give their new address & Tel, and GP name/address:

Date: ____/____/_____

Name of practitioner seeing patient and completing this form. _____

Please remove the copy of this form and post it to the ELEVATE office, in Freepost envelope.

Please call UEA if there are any questions

Symptom diary card

The form presented here is the version of the form used for all participants at the baseline visit. At study visits 3 to 7, the form for each of the four study arms was modified appropriately for that arm, differing slightly in the labelling on the instruction side of the form (printed on the reverse of the form), but are other wise identical.

ELEVATE study

Patient symptom diary card – baseline visit

INSTRUCTIONS TO THE PATIENT

Please complete the asthma diary in the following manner:

Each day fill in the date and then:

OVERNIGHT ASTHMA SYMPTOMS

Complete in the morning upon arising and before taking any medication.

- Overnight asthma symptoms.
- Total number of puffs of reliever (blue inhaler) taken since you went to bed.
- Peak Flow Measurement.

DAYTIME ASTHMA SYMPTOMS

Complete in the evening before going to bed just before taking your asthma treatment:

- Peak Flow Measurement.
- Daytime asthma symptoms. Asthma symptoms may include: chest discomfort (tightness), cough, wheezing and shortness of breath (breathlessness). Choose a number from 0 to 6 which best describes your answer to each of the first four questions.
- Total number of puffs of reliever (blue inhaler) taken since arising. Do *NOT* count any puffs taken at the clinic.

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START DATE: | | | | | | | VISIT: | | PATIENT INITIALS: | | | | PATIENT STUDY NO | | | | | | |

ON WAKING							IN THE EVENING									ANYTIME during the DAY
Date	Did you wake up with asthma symptoms? Yes	No	Puffs relief inhaler used since going to bed?	Best of 3 peak flow readings in the morning L/m	Did you take relief treatment in 4 hrs before the PEF reading? Yes	No	How often did you experience asthma symptoms today? Scale 0-6 (0 = none of the time, 6 = all the time	How much did your asthma symptoms bother you today? Scale 0-6 (0=not at all, 6 = severely bothered	How much activity could you do today? Scale 0-6 (0 = more than usual, 6 = less than usual	How often did your asthma affect your activities Scale 0-6 (0 = none of the time, 6 = all the time	Puffs relief inhaler used since rising this morning *See note* *	Best of 3 peak flow readings in the evening L/m	Did you take relief treatment in 4 hrs before the PEF reading? Yes	No		

* do not count any puffs taken at the clinic

Resource data collection sheet

The form presented here is the version of the form used at study visits 3–7. A variant of this form was used at visit 2, which had a slight difference in the wording of the prompting phrase about the time period that applied to the questions. On the visit 2 version, the phrase 'In the last year' is used instead of 'Since your last visit for this study (*state that date*)*:*__/__/__ …'

Did patient bring their resource diary? Yes ☐ No ☐ *(If not, please give them a freepost envelope & ask them to post it to study office) Please* ***do not alter or update the diary*** *based on this information.*

Since your last visit for this study** *(state that date)* **:__/__/__ due to asthma, breathing difficulties, chest infections or allergic reactions of nose and/or eyes:**

1. Have you been to hospital? (Admission, A&E or Outpatient) *(if you need more space for any response please add extra sheet(s) of paper)*

Date	What was (were) the reason(s)?	A&E	Out-patient	Admitted? yes	Admitted? No. nights	For this visit (& recovery period), did you take time off work? (days/hours)	Anyone take time off work to transport or care for you How much?	Anyone take time off work to transport or care for you Their job?	How go to hospital? By bus, taxi, Ambulance, paid carer, friend, your car?
		☐	☐	☐		days hours	days hours		
		☐	☐	☐		days hours	days hours		
		☐	☐	☐		days hours	days hours		
		☐	☐	☐		days hours	days hours		

2. Have you been to see, or called, any GP, nurse, on call service, or other health professional or alternative practitioner?

For example: physiotherapist, homeopath, psychologist, acupuncturist, emergency cover GP

Date	What was (were) the reason(s)?	Who did you see or talk to?	How seen? in person	How seen? phone	Where? (home, surgery, clinic, A&E or other)	When? surgery hrs,	When? 6-10PM,	When? 10PM-8AM	For you: time off work?		Anyone take time off work to transport or care for you time off work?		Anyone take time off work to transport or care for you Their job?
			☐	☐		☐	☐	☐	days	hours	days	hours	
			☐	☐		☐	☐	☐	days	hours	days	hours	
			☐	☐		☐	☐	☐	days	hours	days	hours	
			☐	☐		☐	☐	☐	days	hours	days	hours	
			☐	☐		☐	☐	☐	days	hours	days	hours	
			☐	☐		☐	☐	☐	days	hours	days	hours	
			☐	☐		☐	☐	☐	days	hours	days	hours	

** "last visit" refers to the previous scheduled visit to your GP for the ELEVATE Study. The 7 scheduled study visits are at 0, 2, 10, 26, 52, 78 & 104 weeks.

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Since your last visit, due to asthma, breathing difficulties, chest infections or allergic reactions of nose and/or eyes:

3. Have you bought anything from pharmacy, or some other source, to help you with your health?

For example: antihistamines, analgesics, nicotine patches, peak flow meter, cleaning devices, special bedding, air conditioner, humidifier, nebuliser, ioniser

Date	What did you purchase?	Cost	Why purchase

***4.** Have there been **any other occasions** when your asthma has been worse –eg. when you had to take time off work?*

Date	Did you treat yourself?	What did you do, or use, in self-treating?	Did you take time off work?	Number hrs or days off (specify days or hrs)		Anyone take time off for you?			Any other costs? comments?
						time off work?		Their job?	
				days	hours	days	hours		
				days	hours	days	hours		
				days	hours	days	hours		
				days	hours	days	hours		
				days	hours	days	hours		
				days	hours	days	hours		

Please collect the resource diary from the patient and post it to the study office along with this and the other forms.

FINAL DRAFT

ELEVATE STUDY - ASTHMA RESOURCE DIARY

Instructions

It would be very helpful if you could complete this if any of the following occur while you are participating in the ELEVATE study:

Any time there is a problem from your asthma symptoms

1. **Any time you increase your preventer (inhaled steroid, LTRA or LABA) treatment**
2. **Any time you have to start oral steroids or other medications for your asthma**
3. **Any time you take off work or school due to asthma or your chest**
4. **Any time you see or talk to a doctor or nurse, visit A&E, outpatient or hospital about your asthma or chest.**

At any time (whether you are ill, or are well and just getting routine supplies)

5. **Any time you buy anything from a pharmacist or any other shop for your asthma, chest (e.g. cough mixtures), hay fever or for a nose problem.**

Please bring this form with you to the surgery at the time of your next study visit.

Thank for your co-operation and participation in this study

In an emergency, or If you have any medical questions about your Asthma and its management, please contact your GP.
If you have any questions about this form or other aspects of the study, please contact the study office on 01603-591106,
or if you move from your current residence or leave the care of the practice where you have been seen, so that we may continue to contact you about the study.

PATIENT INITIALS: ____ ____ ____ PATIENT STUDY NUMBER: ____ ____ ____ ____ ____ ____

Please complete a line for each time any of the following occur

Date *1st day if more than 1 d/mm/yy*	Because asthma worsened? *yes*	*no*	Time off work due to asthma? *state hours or days*	See or talk to any nurse, doctor or alternative practitioner? * *If yes, state who & where*	Did you go to A&E? *Tick if yes*	Were you admitted to hospital? *yes*	*number of nights*	Anybody take time off work to transport or care for you? *How much?*	*Their job?*	How did you get to hospital or practice? *eg: Ambulance, taxi, paid carer, personal car, bus or other*	Have you bought, or has anyone bought for you, anything from chemist's, or other source, to help with your health? *Please state what*	Cost £. p.	Comments
1	☐	☐	Days / hours		☐	☐		Days / hours					
2	☐	☐	Days / hours		☐	☐		Days / hours					
3	☐	☐	Days / hours		☐	☐		Days / hours					
4	☐	☐	Days / hours		☐	☐		Days / hours					
6	☐	☐	Days / hours		☐	☐		Days / hours					
7	☐	☐	Days / hours		☐	☐		Days / hours					
8	☐	☐	Days / hours		☐	☐		Days / hours					
9	☐	☐	Days / hours		☐	☐		Days / hours					

* include calls to NHS direct and other alternative sources: homeopaths, etc.
If this episode lasts for more than one day, record the first day

Please continue on additional sheet if necessary

FINAL DRAFT

Appendix 5

Details of findings for per-protocol (fixed treatment regime and no changes within or from randomised therapy class) participants

TABLE 59 *Step 2 study: demographics of per-protocol participants at visit 2*

		LTRA (*n* = 65)	ICS (*n* = 82)
Sex	*Female*	28 (43%)	36 (44%)
	Male	37 (57%)	46 (56%)
Age, years	*Mean (SD)*	45.7 (17.1)	41.8 (16.0)
Height, cm	*Mean (SD)*	*n* = 60	*n* = 80
		170.9 (8.4)	170.1 (9.7)
%PPEF	*Median (IQR)*	*n* = 58	*n* = 78
		82.99 (74.97 to 90.54)	83.61 (73.06 to 92.12)
SABA in last year, puffs/day	*Mean (SD)*	*n* = 58	*n* = 74
		3.24 (3.52)	2.57 (2.71)
MiniAQLQ	*Mean (SD)*	4.78 (0.86)	4.65 (0.97)
ACQ	*Mean (SD)*	1.92 (0.68)	2.07 (0.85)
mRQLQ	*Mean (SD)*	*n* = 51	*n* = 62
		1.71 (1.14)	1.92 (0.165)
Personal objectives (0–100 VAS)	*Mean (SD)*	*n* = 28	*n* = 57
		41.6 (19.1)	38.04 (2.19)
EQ-5D utility	*Mean (SD)*	*n* = 53	*n* = 62
		0.821 (0.22)	0.843 (0.17)
RCP3 questions	*Mean (SD)*	*n* = 59	*n* = 76
		1.83 (0.83)	2.11 (0.79)
Sleep difficulty	*Yes*	31 (53%)	55 (67%)
	No	28 (47%)	27 (33%)
	Missing	6	0
Day symptoms	*Yes*	54 (92%)	75 (94%)
	No	5 (9%)	5 (6%)
	Missing	6	2
Interferes with activities	*Yes*	31 (53%)	36 (45%)
	No	28 (47%)	44 (55%)
	Missing	6	2

ICS, inhaled corticosteroid; IQR; interquartile range; LTRA, leukotriene receptor antagonist; PEF, peak expiratory flow; SABA, short-acting β_2-agonist; SD, standard deviation; VAS, visual analogue scale
Note: Percentages may not add to 100% because of rounding.

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TABLE 60 *Step 2 study: education and lifestyle characteristics of per-protocol participants at visit 2*

		LTRA (*n* = 65)	ICS (*n* = 82)
Continued education > 16	*Yes*	32 (52%)	43 (56%)
	No	30 (48%)	34 (44%)
	Not known	3	5
Professional qualification	*Yes*	21 (36%)	27 (37%)
	No	37 (64%)	46 (63%)
	Not known	7	9
Employment position	*Employer*	4 (9%)	5 (9%)
	Manager	0	0
	Employee	31 (67%)	44 (80%)
	Self-employed	11 (24%)	6 (11%)
	Not known	19	27
Smoking habit	*Current smoker*	17 (26%)	17 (21%)
	Ex-smoker	20 (31%)	21 (26%)
	Non-smoker	28 (43%)	43 (53%)
	Not known	–	1

ICS, inhaled corticosteroid; LTRA, long-acting β_2-agonist.

TABLE 61 *Step 2 study: MiniAQLQ Scores for per-protocol participants*[a]

Treatment duration	Outcome measure	LTRA (*n* = 65)	ICS (*n* = 82)	Difference (95% CI) LTRA–ICS	Adjusted difference[b] (95% CI)
2 months (visit 3)	*n*	*n* = 57	*n* = 66	0.12 (–0.24 to 0.48)	0.14 (–0.15 to 0.44)
	Mean (SD)	5.47 (0.98)	5.35 (1.03)		
2 years[c]	*n*	*n* = 64	*n* = 79	0.10 (–0.27 to 0.47)	0.05 (–0.28 to 0.37)
	Mean (SD)	5.80 (1.04)	5.70 (1.18)		

CI, confidence interval; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Mean (SD) and differences (95% CI) between means for MiniAQLQ scores at 2 months and 2 years.
b Adjusted for baseline values.
c Last observation carried forward when 2-year data were missing.

TABLE 62 *Step 2 study: ACQ scores for per-protocol participants*[a]

Treatment duration	Outcome measure	LTRA (*n* = 65)	ICS (*n* = 82)	Difference (95% CI) LTRA–ICS	Adjusted difference[a] (95% CI)
2 months (visit 3)	*n*	*n* = 57	*n* = 66	–0.12 (–0.45 to 0.21)	–0.10 (–0.38 to 0.19)
	Mean (SD)	1.34 (0.85)	1.45 (0.99)		
2 years[b]	*n*	*n* = 64	*n* = 79	–0.15 (–0.45 to 0.15)	–0.08 (–0.35 to 0.19)
	Mean (SD)	0.97 (0.85)	1.12 (0.93)		

CI, confidence interval; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Mean (SD) and differences (95% CI) between means for MiniAQLQ scores at 2 months and 2 years.
b Adjusted for baseline values.
c Last observation carried forward when 2-year data were missing.

TABLE 63 *Step 2 study: QALYs gained for per-protocol participants*[a]

Treatment duration	Outcome measure	LTRA (*n* = 65)	ICS (*n* = 82)	Difference (*p*-value) LTRA–ICS	Adjusted difference[b] (*p*-value)
2 months (visit 3)	*n*	*n* = 41	*n* = 46	–0.02 (*p* = 0.06)	–0.003 (*p* = 0.117)
	Mean (SD)	0.12 (0.04)	0.14 (0.02)		
2 years (visit 7)	*n*	*n* = 35	*n* = 43	–0.18 (*p* = 0.03)	–0.077 (*p* = 0.151)
	Mean (SD)	1.61 (0.43)	1.79 (0.21)		

CI, confidence interval; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Mean (SD) and differences (95% CI) between mean QALYs gained at 2 months and 2 years.
b Adjusted for baseline values.

TABLE 64 *Step 2 study: exacerbations, respiratory tract infections and short-acting β_2-agonist prescriptions for per-protocol participants*

	LTRA (*n* = 65)	ICS (*n* = 82)	Rate ratio (95% CI)
Mean (SD) exacerbations over 2 years	0.20 (0.47)	0.15 (0.45)	1.37 (0.71 to 2.63), *p* = 0.352
Mean (SD) respiratory tract infections over 2 years	0.91 (1.66)	0.91 (1.22)	0.99 (0.62 to 1.56), *p* = 0.975
Mean (SD) consultations for respiratory tract infections over 2 years	1.18 (2.28)	1.05 (1.53)	1.12 (0.69 to 1.82), *p* = 0.621
			Adjusted difference[a] (95% CI) LTRA–ICS
Mean (SD) SABA inhalers prescribed over 2 years (inhalers/day)	*n* = 57 0.011 (0.012)	*n* = 71 0.011 (0.012)	–0.001 (–0.004 to 0.002) *p* = 0.356

CI, confidence interval; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; SABA, short-acting β_2-agonist; SD, standard deviation.
a Adjusted for baseline values.

TABLE 65 *Step 2 study: median (interquartile range) clinic %PPEF for per-protocol participants*

Measure	LTRA	ICS	*p*-value
Baseline	*n* = 58	*n* = 78	
	82.99 (74.97 to 90.54)	83.61 (73.06 to 92.12)	
2 months	*n* = 46	*n* = 51	*p* = 0.942
	88.25 (77.81 to 95.69)	87.58 (80.19 to 97.58)	
2 years (imputed)	*n* = 42	*n* = 55	*p* = 0.058
	91.28 (83.37 to 100.40)	85.79 (77.53 to 96.93)	

ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist.

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TABLE 66 *Step 2 study: secondary QOL measures for per-protocol participants*

Measure	LTRA	ICS	Difference (95% CI)[a] LTRA–ICS	Adjusted difference[a] (95% CI) LTRA–ICS
8-week outcomes				
mRQLQ	*n* = 50 1.31 (1.03)	*n* = 60 1.53 (1.14)	–0.222 (–0.636 to 0.191), *p* = 0.284	–0.194 (–0.562 to 0.173), *p* = 0.297
RCP3	*n* = 62 1.02 (0.95)	*n* = 67 1.22 (0.92)	–0.207 (–0.533 to 0.118), *p* = 0.209	–0.183 (–0.564 to 0.199), *p* = 0.345
Personal objectives (0–100 VAS)	*n* = 45 61.42 (21.46)	*n* = 30 53.65 (22.04)	7.77 (–2.47 to –18.01), *p* = 0.134	6.31 (–5.25 to 17.87), *p* = 0.279
2-year outcomes				
mRQLQ	*n* = 64 1.09 (1.15)	*n* = 76 1.22 (1.26)	–0.130 (–0.538 to 0.277), *p* = 0.528	0.00 (–0.446 to 0.441), *p* = 0.991
RCP3	*n* = 64 0.42 (0.69)	*n* = 78 0.42 (0.71)	–0.112 (–0.421 to 0.197), *p* = 0.763	–0.139 (–0.456 to 0.177), *p* = 0.386
Personal objectives (0–100 VAS)	*n* = 36 74.74 (16.35)	*n* = 56 71.79 (18.15)	2.95 (–4.47 to 10.36), *p* = 0.421	2.75 (–6.48 to 11.98), *p* = 0.395

CI, confidence interval; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; VAS, visual analogue scale.
a Adjusted for baseline values.

TABLE 67 *Step 3 study: demographics of per-protocol participants at visit 2*

		LTRA (*N* = 60)	LABA (*N* = 80)
Sex	*Female*	35 (58%)	42 (53%)
	Male	25 (42%)	38 (47%)
Age, years	*Mean (SD)*	50.7 (15.5)	48.2 (16.9)
Height, cm	*Mean (SD)*	168.6 (12.1)	167.9 (9.9)
	Missing	4	5
%PPEF	*Median (IQR)*	*n* = 56 92.31 (82.10 to 101.94)	*n* = 74 88.65 (76.67 to 99.89)
SABA in last year, puffs/day	*Mean (SD)*	*n* = 57 4.23 (3.35)	*n* = 77 4.04 (2.91)
MiniAQLQ	*Mean (SD)*	4.78 (1.01)	4.30 (1.06)
ACQ	*Mean (SD)*	1.91 (0.84)	2.25 (0.92)
mRQLQ	*Mean (SD)*	*n* = 53 1.73 (1.24)	*n* = 73 2.09 (1.23)
Personal objectives (0–100 VAS)	*Mean (SD)*	*n* = 44 39.86 (18.55)	*n* = 61 35.80 (16.43)
EQ-5D utility	*Mean (SD)*	*n* = 56 0.80 (0.25)	*n* = 73 0.78 (0.24)
RCP3 questions	*Mean (SD)*	*n* = 59 1.81 (0.88)	*n* = 80 2.13 (0.82)
Sleep difficulty	*Yes*	25 (43%)	41 (54%)
	No	33 (57%)	35 (46%)
	Missing	2	4

TABLE 67 *Step 3 study: demographics of per-protocol participants at visit 2 (continued)*

Day symptoms	*Yes*	55 (95%)	72 (95%)
	No	3 (5%)	4 (5%)
	Missing	2	4
Interferes with activities	*Yes*	23 (40%)	35 (47%)
	No	34 (60%)	40 (53%)
	Missing	3	5

LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; PEF, peak expiratory flow; VAS, visual analogue scale.
Note: Percentages may not add to 100% because of rounding.

TABLE 68 *Step 3 study: education and lifestyle characteristics of per-protocol participants at visit 2*

		LTRA (*n* = 60)	**LABA (*n* = 80)**
Continued education > 16	*Yes*	29 (49%)	40 (51%)
	No	30 (51%)	39 (49%)
	Not known	1	1
Professional qualification	*Yes*	14 (24%)	21 (27%)
	No	44 (76%)	58 (73%)
	Not known	2	1
Employment position	*Employer*	5 (12%)	3 (5%)
	Employee	26 (63%)	41 (71%)
	Self-employed	10 (24%)	14 (24%)
	Not known	19	22
Smoking habit	*Current smoker*	7 (12%)	15 (19%)
	Ex-smoker	27 (45%)	32 (41%)
	Non-smoker	26 (43%)	32 (41%)
	Not known	–	1

LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist.

TABLE 69 *Step 3 study: MiniAQLQ Scores for per-protocol participants*[a]

Treatment duration	**Outcome measure**	**LTRA (*n* = 60)**	**LABA (*n* = 80)**	**Difference (95% CI) LTRA–LABA**	**Adjusted difference**[b] **(95% CI)**
2 months (visit 3)	*n*	*n* = 56	*n* = 67	0.32 (–0.10 to 0.74)	–0.02 (–0.36 to 0.31)
	Mean (SD)	5.38 (1.10)	5.06 (1.22)		
2 years[c]	*n*	*n* = 60	*n* = 80	0.16 (–0.36 to 0.50)	–0.05 (–0.36 to 0.26)
	Mean (SD)	5.65 (0.92)	5.49 (1.08)		

a Mean (SD) and differences (95% CI) between means for MiniAQLQ scores at 2 months and 2 years.
b Adjusted for baseline values.
c Last observation carried forward when 2-year data were missing.

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TABLE 70 *Step 3 study: ACQ scores for per-protocol participants*[a]

Treatment duration	Outcome measure	LTRA (*n* = 60)	LABA (*n* = 80)	Difference (95% CI) (LTRA–LABA)	Adjusted difference[b] (95% CI)
2 months (visit 3)	*n*	*n* = 56	*n* = 67	–0.09 (–0.45 to 0.27)	0.11 (–0.22 to 0.44)
	Mean (SD)	1.37 (0.98)	1.47 (1.01)		
2 years[c]	*n*	*n* = 60	*n* = 80	–0.13 (–0.40 to 0.13)	–0.01 (–0.27 to 0.24)
	Mean (SD)	1.07 (0.73)	1.20 (0.85)		

CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Mean (SD) and differences (95% CI) between means for ACQ scores at 2 months and 2 years.
b Adjusted for baseline values.
c Last observation carried forward when 2-year data were missing.

TABLE 71 *Step 3 study: QALYs gained for per-protocol participants*[a]

Treatment duration	Outcome measure	LTRA (*n* = 60)	LABA (*n* = 80)	Difference (*p*-value) LTRA–LABA	Adjusted difference[b] (*p*-value)
2 months (visit 3)	*n*	*n* = 47	*n* = 50	0.01 (*p* = 0.329)	0.000 (*p* = 0.938)
	Mean (SD)	0.13 (0.03)	0.12 (0.04)		
2 years (visit 7)	*n*	*n* = 41	*n* = 48	0.12 (*p* = 0.221)	0.038 (*p* = 0.519)
	Mean (SD)	1.66 (0.42)	1.54 (0.51)		

CI, confidence interval; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SD, standard deviation.
a Mean (SD) and differences (95% CI) between mean QALYs gained at 2 months and 2 years.
b Adjusted for baseline values.

TABLE 72 *Step 3 study: exacerbations, respiratory tract infections and short-acting β_2-agonist prescriptions for per-protocol participants,*

	LTRA (*n* = 60)	LABA (*n* = 80)	Rate ratio (95% CI)
Mean (SD) exacerbations over 2 years	0.33 (0.84)	0.43 (0.91)	0.79 (0.42 to 1.45), *p* = 0.441
Mean (SD) respiratory tract infections over 2 years	1.07 (2.11)	1.25 (1.87)	0.85 (0.52 to 1.41), *p* = 0.534
Mean (SD) consultations for respiratory tract infections over 2 years	1.43 (3.00)	1.40 (2.14)	1.02 (0.62 to 1.69), *p* = 0.927
			Adjusted difference[a] (95% CI) LTRA–LABA
Mean (SD) SABA inhalers prescribed over 2 years (inhalers/day)	*n* = 60 0.017 (0.017)	*n* = 73 0.015 (0.013)	0.002 (–0.002 to 0.006), *p* = 0.307

CI, confidence interval; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β_2-agonist; SD, standard deviation.
a Adjusted for baseline values.

TABLE 73 *Step 3 study: median (interquartile range) clinic %PPEF for per-protocol participants*

Measure	LTRA	LABA	*p*-value
Baseline	*n* = 56 92.31 (82.10 to 101.94)	*n* = 74 88.65 (76.67 to 99.89)	
2 months	*n* = 50 96.04 (86.58 to 106.09)	*n* = 61 92.37 (80.01 to 101.63)	*p* = 0.243
2 years (imputed)	*n* = 44 90.21 (79.56 to 100.44)	*n* = 55 89.84 (79.46 to 102.87)	*p* = 0.949

LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist.

TABLE 74 *Step 3 study: secondary QOL measures for per-protocol participants*

Measure	LTRA	LABA	Difference (95% CI) LTRA–LABA	Adjusted difference[a] (95% CI) LTRA–LABA
8-week outcomes				
mRQLQ	*n* = 47 1.26 (1.00)	*n* = 55 1.79 (1.15)	–0.530 (–0.957 to –0.103), *p* = 0.016	–0.404 (–0.772 to –0.036), *p* = 0.032
RCP3 questions	*n* = 55 1.16 (0.92)	*n* = 69 1.19 (0.96)	–0.025 (–0.362 to 0.312), *p* = 0.884	0.036 (–0.310 to 0.381), *p* = 0.839
Personal objectives (0–100 VAS)	*n* = 38 58.22 (21.23)	*n* = 54 55.89 (22.97)	2.33 (–11.70 to 7.04), *p* = 0.618	0.95 (–7.43 to 9.32), *p* = 0.823
2-year outcomes				
mRQLQ	*n* = 59 1.10 (1.11)	*n* = 78 1.24 (1.11)	–0.141 (–0.520 to 0.238), *p* = 0.463	0.079 (–0.275 to 0.433), *p* = 0.659
RCP3 questions	*n* = 59 0.83 (0.77)	*n* = 80 1.18 (0.92)	–0.345 (–0.637 to –0.052), *p* = 0.021	–0.276 (–0.571 to 0.019), *p* = 0.066
Personal objectives (0–100 VAS)	*n* = 46 64.57 (24.56)	*n* = 69 66.03 (19.39)	–1.46 (–9.61 to 6.68), *p* = 0.735	–5.02 (–13.09 to 3.05), *p* = 0.220

CI, confidence interval; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; VAS, visual analogue scale.
a Adjusted for baseline value.

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Dr Simon Wright,
GP Partner, Walkden Medical Centre, Manchester

Observers

Dr Kay Pattison,
Senior NIHR Programme Manager, Department of Health

Dr Morven Roberts,
Clinical Trials Manager, Health Services and Public Health Services Board, Medical Research Council

Professor Tom Walley, CBE,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

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We look forward to hearing from you.

NETSCC, Health Technology Assessment
Alpha House
University of Southampton Science Park
Southampton SO16 7NS, UK
Email: hta@hta.ac.uk
www.hta.ac.uk

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