Inhaled corticosteroids and long-acting beta$_2$-agonists for the treatment of chronic asthma in children under the age of 12 years: Systematic review and economic analysis

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Southampton Health Technology Assessments Centre (SHTAC), Wessex Institute for Health Research and Development (WIHRD), University of Southampton

AUTHORS:
Ms Caroline Main, Research Fellow, PenTAG
Mr Jonathan Shepherd, Principal Research Fellow, SHTAC
Dr Rob Anderson, Senior Lecturer in Health Economics, PenTAG
Mr Gabriel Rogers, Research Assistant, PenTAG
Dr Jo Thompson Coon, Research Fellow, PenTAG
Ms Zulian Liu, Research Assistant, PenTAG
Dr Debbie Hartwell, Research Fellow, SHTAC
Dr Emma Loveman, Senior Research Fellow, SHTAC
Mr Colin Green, Senior Lecturer in Health Economics, PenTAG (formerly SHTAC)
Dr Martin Pitt, Research Fellow, PenTAG
Dr Ken Stein, Senior Lecturer in Public Health, PenTAG
Ms Petra Harris, Research Fellow, SHTAC
Dr Geoff Frampton, Research Fellow, SHTAC
Dr Matthew Smith, Specialist Registrar in Public Health, SHTAC
Dr Andrea Takeda, Senior Research Fellow, SHTAC
Mrs Alison Price, Information Scientist, SHTAC
Ms Karen Welch, Information Officer, SHTAC
Dr Margaret Somerville, Senior Lecturer and Consultant in Public Health, PenTAG

CORRESPONDENCE TO:

Jonathan Shepherd
Southampton Health Technology Assessments Centre (SHTAC),
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton. SO16 7PX.
jps@soton.ac.uk

Caroline Main
Peninsula Technology Assessment Group (PenTAG),
Noy Scott House,
Barrack Road,
Exeter. EX2 5DW.
Caroline.Main@PenTAG.nhs.uk

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ABOUT SHTAC

The Southampton Health Technology Assessments Centre (SHTAC) was established in 2000. It was formed from the research group that supported the South and West and South East (formerly Wessex) Regional Development and Evaluation Committee from 1991 to 2000. SHTAC is part of the Wessex Institute for Health Research and Development (WIHRD), based in the School of Medicine at the University of Southampton. Collaborative links with the Southampton General Hospital Trust and other health providers nationally provide support for SHTAC's research programme.

SHTAC has a multidisciplinary research team encompassing a wide range of skills developed from a variety of academic and clinical backgrounds. There are currently 17 full and part-time staff, including health economists, economic and statistical modellers, systematic reviewers, and public health consultants. The SHTAC team work closely with experienced information scientists from the WIHRD Information Resource Centre.

ABOUT PENTAG

The Peninsula Technology Assessment Group is part of the Institute of Health and Social Care Research at the Peninsula Medical School. PenTAG was established in 2000 and carries out independent Health Technology Assessments for the UK HTA Programme and other local and national decision-makers. The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Peninsula Medical School is a school within the Universities of Plymouth and Exeter. The Institute of Health and Social Care Research is made up of discrete but methodologically related research groups, among which Health Technology Assessment is a strong and recurring theme.

CONTRIBUTIONS OF AUTHORS

For PenTAG:

Dr Rob Anderson	Economic evaluation and interpretation of results, contributed to model design, identification of inputs for models, analysis and interpretation of results, and report preparation
Mr Colin Green	Economic evaluation and interpretation of results, contributed to model design and report preparation
Ms Zulian Liu	Project support, data extraction and checking, contributed to economic evaluation and report preparation
Ms Caroline Main	Project management, report preparation, data extraction and checking, contributed to model design, identification of inputs for models, interpretation of results
Dr Martin Pitt	Developed and executed the model, analysis and interpretation of results
Mr Gabriel Rogers	Project support, data extraction and checking, contributed to model design, identification of inputs for models, analysis and interpretation of results, report preparation
Dr Margaret Somerville	Project direction, report preparation, contributed to model design, analysis and interpretation of results
Dr Ken Stein	Study design, report preparation, methodological advice
Dr Jo Thompson-Coon	Initial project management, contributed to model design, identification of inputs for model, interpretation of results, report preparation

For SHTAC:

Dr Geoff Frampton	Data extraction and checking, clinical effectiveness synthesis, report preparation
Ms Petra Harris	Data extraction and checking, clinical effectiveness synthesis, report preparation
Dr Debbie Hartwell	Project support, inclusion screening, data extraction and checking, clinical effectiveness synthesis, report preparation
Dr Emma Loveman	Project support, inclusion screening, data extraction and checking, clinical effectiveness synthesis, report preparation
Ms Alison Price	Design and execution of the cost-effectiveness review literature search strategies
Mr Jonathan Shepherd	Project management, protocol development, inclusion screening, data extraction and checking, clinical effectiveness synthesis, report preparation
Dr Matthew Smith	Data extraction and checking, clinical effectiveness synthesis, report preparation
Dr Andrea Takeda	Data extraction and checking, clinical effectiveness synthesis, report preparation
Mrs Karen Welch	Design and execution of the clinical effectiveness review literature search strategies

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NOTES

The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the Department of Health.

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1. Glossary and list of abbreviations

Term/abbreviation	Definition
ACQ-5	Asthma Control Questionnaire
ACTH	Adrenocorticotropic hormone
AE	Adverse Events
AMD	Adjustable maintenance dose
ANCOVA	Analysis of Co-Variance
AQLQ	Asthma Quality of Life Questionnaire
BDP	BDP
b.i.d	Twice daily
BMD	Bone mineral density
BNF	British National Formulary
BTS	British Thoracic Society
BUD	BUD
COPD	Chronic obstructive pulmonary disorder
CFC	Chlorofluorocarbon, a propellant used in pressured metered dose inhalers. Currently being replaced by hydrofluoroalkanes (HFA) propellants.
Cortisol	Cortisol is a corticosteroid hormone that is involved in the response to stress; it increases blood pressure and blood sugar levels and suppresses the immune system.
CI	Confidence interval
CMA	Cost Minimisation Analysis
CRD	Centre for Reviews and Dissemination
DPI	Dry powder inhaler
EMEA	European Agency for the Evaluation of Medicinal Products
Ex-actuator	Used in reference to drug delivery. The content per actuation which is reflected in the labelled strength of the drug. Ex-actuator means metered – the amount of drug that is delivered from the mouthpiece to the patient.
Ex-valve	Used in reference to drug delivery. The content per actuation which is reflected in the labelled strength of the drug. Ex-valve means metered – the amount of drug delivered from the inhaler into the mouthpiece.
ER	Emergency Room
FD	Fixed dose
FP	FP

Term/abbreviation	Definition
FEV_1	Forced expiratory volume. The volume of air exhaled in the second of forced blowing into a spirometer.
$FEF_{25\text{-}75\%}$	Forced expiratory flow
FORM	FF
FVC	Forced vital capacity. The total amount of air that a person can forcibly blow out after full inspiration, measured in litres.
GINA	Global Initiative for Asthma
Hypothalamic-pituitary-adrenal axis (HPA axis)	The hypothalamic-pituitary-adrenal axis (HPA axis) is a major part of the neuroendocrine system that controls reactions to stress and has important functions in regulating various body processes such as digestion, the immune system and energy usage.
HFA	Hydrofluoroalkane, a propellant used in pressured metered dose inhalers. Replacement for chlorofluorocarbon (CFC) propellant.
HRQOL	Health-related quality of life
I^2	A measure used to quantify heterogeneity in a meta-analysis It describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A value greater than 50% may be considered to represent substantial heterogeneity.
ICER	Incremental cost-effectiveness ratio
ICS	Inhaled corticosteroid (e.g. BUD)
IQR	Inter quartile range
ITT	Intention-to-treat
L	Litre
LABA	Long-acting $beta_2$-agonist (e.g. SAL or FF)
LOCF	Last Observation Carried Forward
LS	Least squares
µg	Micrograms
mg	Milligrams
ml	Millilitres
MHRA	Medicines and Health Care Products Regulatory Agency
NICE	National Institute for health and clinical Excellence
NSD / NS	No statistically significant differences
NW	Nocturnal wakenings
OCS	Oral corticosteroids

Term/abbreviation	Definition
OR	Odds ratio
PEFR	Peak expiratory flow rate. The maximum rate at which air is expired from the lungs when blowing into a peak flow meter or spirometer.
PC	Plasma cortisol
PC20	The provocative concentration of methacholine to induce a 20% decline in FEV1
PD20	A value obtained in methacholine challenge testing to indicate severity of asthma
pMDI	Pressured metered dose inhaler
PP	Per protocol
QALY	Quality Adjusted Life Year
QCT	Quantitative computed tomography
q.d.	Once daily
q.i.d.	Four times daily
RCT	Randomised Controlled Trial
SAL	SAL
SD	Standard Deviation
SE / SEM	Standard Error of the Mean
SFD	Symptom-free Days
SFN	Symptom-free Nights
SIGN	Scottish Intercollegiate Guidelines Network (SIGN)
SMD	Standardised Mean Difference
Spacer	Device attached to an inhaler to maximise the delivery of the drug to the lungs. A spacer consists of a container, usually in two halves that fit together. One end fits to a mouth- piece or a face- mask (e.g. for young children). The other end fits to the inhaler.
Spirometry	A pulmonary function test, measuring lung function
tx	Treatment
wk	Week
WMD	Weighted Mean Difference
μg	Microgram

2. Executive summary

2.1 Background to asthma

Asthma is a chronic inflammatory disorder of the airways leading to airway narrowing from both inflammatory processes and constriction of the smooth muscle in airway walls. Symptoms include recurring episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in the early morning. Common risk factors include viral respiratory infections, allergens such as pollens, moulds, animal fur and house dust mite, cold and exercise. It is estimated that there are around 5.2 million people in the UK with asthma. It is the most common chronic disease in children with a prevalence varying between 17 and 23%.

The aims of asthma management are the control of symptoms, including nocturnal symptoms and exercise-induced asthma, prevention of exacerbations and the achievement of the best possible lung function, with minimal side effects. A variety of strategies are used in the prevention and management of the condition. Pharmacological management includes, amongst other drugs, inhaled corticosteroids (ICS), and short- and long-acting beta$_2$-agonists (SABAs / LABAs).

Three ICS are available as licensed preparations for children aged under 12 years: beclometasone dipropionate (BDP), budesonide (BUD) and fluticasone propionate (FP). Two of the ICS are available as licensed preparations in combination with LABA: FP used in combination with salmeterol (SAL), and BUD used in combination with formoterol fumarate (FF).

2.2 Objectives

The aim of this health technology assessment is to assess the clinical and cost-effectiveness ICS alone and ICS used in combination with a LABA, in the treatment of chronic asthma in children aged under 12 years.

The objectives are:

- To identify, appraise and synthesise, where appropriate, the current evidence base which addresses the specific research questions on clinical effectiveness listed below.
- To identify the costs associated with the different treatments.
- To identify, appraise and synthesise, where appropriate, the current evidence base which addresses the specific research questions on cost-effectiveness listed below.
- To provide estimates of cost-effectiveness, where possible, of the different treatment options.

An accompanying health technology assessment has been conducted in adults and children over 12 years.

2.3 Methods

The assessment comprises a systematic review of clinical and cost-effectiveness studies and economic analyses to answer the stated research questions.

The assessment was conducted within the context of the British Thoracic Society (BTS) / Scottish Intercollegiate Guidelines Network (SIGN) guidelines on the management of asthma. Using the treatment steps in the guidelines, the following review questions were identified:

1. Which is the most clinically and cost-effective of the three ICS when used in low doses (200 – 400µg BDP per day or equivalent) at Step 2 of the guidelines?
2. Which is the most clinically and cost-effective of the three ICS when used in high doses (400-800µg BDP per day or equivalent), at Step 4 of the guidelines?
3. Which is the more clinically and cost-effective approach to introducing a LABA into a treatment regimen at steps 2-3 of the guidelines:

   a. To increase the dose of ICS alone or to add a LABA to treatment with ICS?

   b. To continue with an ICS alone or to add a LABA to treatment with a similar dose of ICS using a combination inhaler?

4. Which is the more clinically and cost-effective treatment:

   FP and SAL in a combination inhaler or given in separate inhalers?

   BUD and FF in a combination inhaler or given in separate inhalers?

5. Which is the more clinically and cost-effective treatment: FP/SAL in a combination inhaler or BUD/FF in a combination inhaler, when used at Step 3 of the guidelines?

For the assessment of clinical effectiveness a literature search was conducted on a number of electronic databases, up to February/March 2006 (and updated again in October 2006). Systematic reviews and Randomised Controlled Trials (RCTs) were included. Trials testing different drugs by different inhalers or propellants, and trials testing the same drug by different inhalers were not included. The following outcomes were relevant: objective measures of lung function (e.g. FEV_1, PEFR); symptoms (e.g. symptom-free days and nights); incidence of mild and severe acute exacerbations; use of rescue medication; adverse effects of treatment; health-related quality of life; adverse effects; mortality. Titles and abstracts of studies identified by the searches were screened according to inclusion criteria. Full papers for studies that appeared relevant were retrieved and screened in detail. All trials, except those included in relevant Cochrane reviews, were fully data extracted and quality assessed. Results of the included trials were synthesised narratively. Quantitative meta-analysis was not possible due to differences in dose; limited available data and variations in outcomes.

Methods of economic analysis

ICS versus ICS

Cost comparisons were undertaken to compare the three ICS with each other on the basis of there being no consistent significant differences in effects between them at low or high dose.

ICS/LABA versus ICS alone

No trials were identified that assessed the effects in children of the addition of a LABA to ICS versus a higher dose of ICS alone. Since equivalence in outcomes between the two strategies could not be assumed, an exploratory cost-offset analysis based on medication and exacerbation treatment costs only is presented.

ICS/LABA versus ICS/LABA

A cost comparison was undertaken to compare the combination inhalers with the same drugs delivered in separate inhalers on the basis of there being no significant differences in effects between the two modes of drug delivery. No trials were identified in children that compared the combination inhalers with each other. Therefore only the costs associated with each of the combination inhalers is presented.

2.4 Results

2.4.1 Clinical effectiveness review

Of 5175 records identified through systematic literature searching, 34 records describing 25 studies were included. Of these,

- 16 were fully published RCTs
- 6 were systematic reviews
- 3 were post-2004 conference abstracts

Noticeably absent from the evidence base are studies in children and infants aged under four years.

The most frequently reported relevant outcomes in the 16 RCTs were PEFR (13 trials), FEV_1 (13 trials), symptoms (13 trials), adverse events or exacerbations (13 trials), use of rescue medication (12 trials), markers of adrenal function (e.g. blood or urine cortisol concentrations) (13 trials), height and/or growth rate (7 trials), and markers of bone metabolism (2 trials). The detail of reporting outcomes varied considerably among the studies.

Five RCTs were identified that compared the three ICS with each other at low doses according to Step 2 of the guidelines and seven comparing them at high doses according to Step 4 of the guidelines. No consistent differences or patterns among the outcomes were evident when single ICS were compared with each other at either low or high doses at the accepted clinically equivalent doses. Where differences were statistically significant at high doses, such as for lung function and growth, they favoured FP, but this was generally in studies which did not compare the ICS at the accepted clinically equivalent doses. Differences between the drugs in impact on adrenal suppression were only significant in two studies. Occurrence of adverse events appeared similar.

Only one trial was identified that compared ICS at a higher dose with ICS and LABA in combination. It included a relatively small proportion (~12%) of children and reported only growth rate and adrenal function for the child cohort. Growth rate significantly favoured the combination inhaler (FP/SAL) whereas no significant difference in adrenal function between ICS monotherapy (FP) and the combination inhaler was observed.

The overall trial results (including adults) significantly favoured combination therapy in prolonging the time to first severe and mild exacerbation compared to ICS alone. Furthermore, combination treatment was significantly associated with reduced reliever medication use, improvements in measures of lung function, and the number of night-time awakenings relative to monotherapy.

Two large, multi-centre trials were identified that compared ICS at the same dose with ICS and LABA in combination. In both trials most outcomes numerically favoured the combination inhaler (either FP/SAL compared against FP, or BUD/FF compared against BUD). However, in one of the studies (FP/SAL) it is unclear whether any of the differences were statistically significant, whilst in the other study (BUD/FF) only lung function outcomes differed significantly.

Only one trial was identified that compared combination inhalers with the same drugs delivered in separate inhalers. There were no statistically significant differences in measures of lung function between the two treatment regimens. The mean difference in the morning PEFR was within a defined range for clinical equivalence.

No trials have so far been conducted in children to compare the clinical effectiveness of two combination inhalers.

2.4.2 Economic analysis

Results

ICS versus ICS

At daily doses of 200μg (BDP-CFC equivalent) per day CFC-propelled BDP is the current cheapest ICS product. If CFC-propelled products are excluded from the available products, BDP is still usually the cheapest but at a higher annual cost. At doses of 400μg per day, BDP remains the cheapest ICS product available both with the inclusion and exclusion of CFC-propelled products, although the differences between products are smaller when CFC-propelled products are excluded.

On average, at daily doses of 800μg (BDP-CFC equivalent) per day, although BDP is the current cheapest ICS product both with the inclusion and exclusion of CFC-propelled products, it is only slightly cheapter than BUD or FP. However, whilst the use of weighted averages provides a useful way to compare the mean annual cost between the different ICS, at all dose levels it disguises the often large cost differences between the different preparations of each ICS.

ICS versus ICS/LABA

For both combination inhalers, FP used in combination with SAL, and BUD used in combination with FF, are slightly cheaper than FP or BUD on their own at double the dose of the ICS in combination except CFC-BDP 400μg/day (including CFC-propelled products). Compared with the lowest cost preparation for each ICS drug, the combination inhalers are more expensive than the ICS products at increased dose.

ICS/LABA versus ICS/LABA

Taking either FP in combination with SAL or BUD in combination with FF is cheaper than taking the relevant ingredient drugs in separate inhalers.

Based on a comparison of the costs only, BUD in combination with FF is more expensive that both the FP/SAL combination drugs currently available.

2.5 Discussion

This review identified a very limited evidence base of trials including children under the age of 12 years and none including children under the age of five years. Methodological quality of the included RCTs varied, and there was variability in the way outcomes were measured and reported. In general there were few statistically significant differences between the three ICS when evaluated in pair-wise comparisons. The ICS could therefore be considered generally equivalent in clinical terms, although few studies explicitly aimed to assess clinical equivalence / non-inferiority. At all doses of ICS licensed for use in children, BDP, both including and excluding CFC-propelled products, is the cheapest ICS currently available. When non-CFC propelled products only are considered the mean annual cost of ICS therapy increases for all three ICS, but the overall cost differences between the drugs diminishes.

There is very limited evidence available for the efficacy and safety of ICS and LABAs in children. Where significant differences between ICS compared to ICS and LABA have been identified they have favoured the latter. Based on costs only, the extra annual cost of combination therapy versus an increased dose of ICS alone varies enormously depending on the exact ICS preparation used. The more expensive ICS products used at higher dose are more expensive than combination inhaler products, whilst the use of cheaper ICS preparations compared to combination therapy will be cost saving. Use of a combination inhaler is always cheaper than taking the same ingredient drugs in separate inhalers. At the present time the combination inhaler containing BUD/FF is more expensive than the combinations containing FP/SAL. However, these combination products have not been compared in direct head-to-head trials, and therefore differences in clinical effects cannot be ruled out.

2.6 Conclusions

The limited evidence available indicates there are no consistent significant differences in effectiveness between the three ICS licensed for use in children at either low or high dose. BDP CFC-propelled products are often currently the cheapest ICS available at both low and high dose, and may remain so even when CFC-propelled products are excluded. Exclusion of CFC-propelled products increases the mean annual cost of all BUD and BDP, while the overall cost differences between the comparators diminishes.

There is very limited evidence available for the efficacy and safety of ICS and LABAs in children. From this limited evidence there appears to be no significant clinical differences in effects between the use of a combination inhaler versus the same drugs in separate inhalers. There is a lack of evidence comparing ICS at a higher dose with ICS and LABA in combination and comparing the combination products with each other.

In the absence of any evidence concerning the effectiveness of ICS at higher dose with ICS and LABA, a cost consequence analysis gives mixed results.

There are potential cost savings to the NHS with the use of combination inhalers compared to separate inhalers. At present prices, the combination of BUD/FF is cheaper than those containing FP/SAL, but it is not known whether there are clinically significant differences between them.

3. Background

SECTION CONTENTS

3.1 Natural history of asthma

3.1.1 Definition

Asthma is a chronic inflammatory disorder of the airways leading to airway narrowing from both inflammatory processes and constriction of the smooth muscle in airway walls (bronchoconstriction). Another characteristic of the pathology of the disease is a process known as remodelling. This consists of mucus gland and smooth muscle hypertrophy and increased collagen deposition in airway walls. Asthma is characterised by widespread, variable airflow obstruction and increased responsiveness of the airways to various stimuli. Resulting symptoms include recurring episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in the early morning. Common risk factors include respiratory (viral) infections, allergens such as pollens, moulds, animal fur and house dust mite, cold and exercise.[1;2]

3.1.2 Diagnosis

There is no confirmatory diagnostic test or investigation for asthma. It is usually diagnosed on the basis of symptoms (wheeze, shortness of breath, chest tightness and cough) together with objective tests of lung function such as peak expiratory flow rate (PEFR) and forced expiratory volume in one second (FEV_1). Typical asthma symptoms tend to be variable, intermittent, worse at night and provoked by triggers (e.g. allergens or exercise). Variability of PEFR and FEV_1, either spontaneously over time or in response to therapy is a characteristic feature of asthma which is also often used in diagnosis.[1]

Diagnosis of asthma in young children is difficult. Objective measurements of lung function are often difficult to obtain and may be unreliable, particularly in very young children. The Global Initiative for Asthma Pocket Guide for Asthma Management in Children suggests that lung function measurement using either FEV_1 or PEFR can greatly enhance diagnostic confidence in those over five years of age.[3] The BTS/SIGN Guidelines[1] recommends that the diagnosis of asthma in young children is based on the presence of key features and careful consideration of alternative diagnoses (e.g. cystic fibrosis, developmental anomaly, reflux, recurrent milk aspiration and tuberculosis), the assessment of potential co-morbidities, and the response to trials of treatment.

3.1.3 Asthma severity

Assessing asthma severity is difficult and depends on the level of treatment. The Global Initiative for Asthma Guideline (GINA) classifies asthma severity as intermittent or persistently mild, moderate or severe based on combined assessments of symptoms and lung function (*Table 1*) for children over five years of age. Severity varies amongst individuals, does not necessarily correlate with the frequency or persistence of symptoms, and can change in one individual over time. When an individual is already on treatment, the classification of severity is based on the clinical features present and the daily medication regimen that the individual is currently on. Under this classification, the presence of one of the features of severity is sufficient to place an individual in that category. Individuals at any level of severity can have severe exacerbations.[3]

TABLE 1 *GINA classification of asthma severity in children over five years of age*

	Symptoms/day	**Symptoms/night**	**PEFR or FEV1** PEFR variability
STEP 1 **Intermittent**	< once a week Asymptomatic and normal PEFR between exacerbations	≤ 2 times a month	≥ 80% < 20%
STEP 2 **Mild persistent**	> once a week but < once a day Exacerbations may affect activity	> 2 times a month	≥ 80% 20-30%
STEP 3 **Moderate persistent**	Daily Exacerbations affect activity	> once a week	60-80% > 30%
STEP 4 **Severe persistent**	Continuous Limited physical activity	Frequent	≤ 60% > 30%
Source: Pocket Guide for Asthma Management and Prevention in Children[3]			

A cross-sectional study of 12,203 patients from 393 general practices in the UK, performed by Neville and colleagues in 1994/5 reported that the majority of individuals with asthma in the UK are treated at steps one and two of the BTS/SIGN Guidelines.[4] This appears particularly true for children, in whom only around 10% were treated at Steps 4 and 5 of the guidelines, indicating more severe disease.

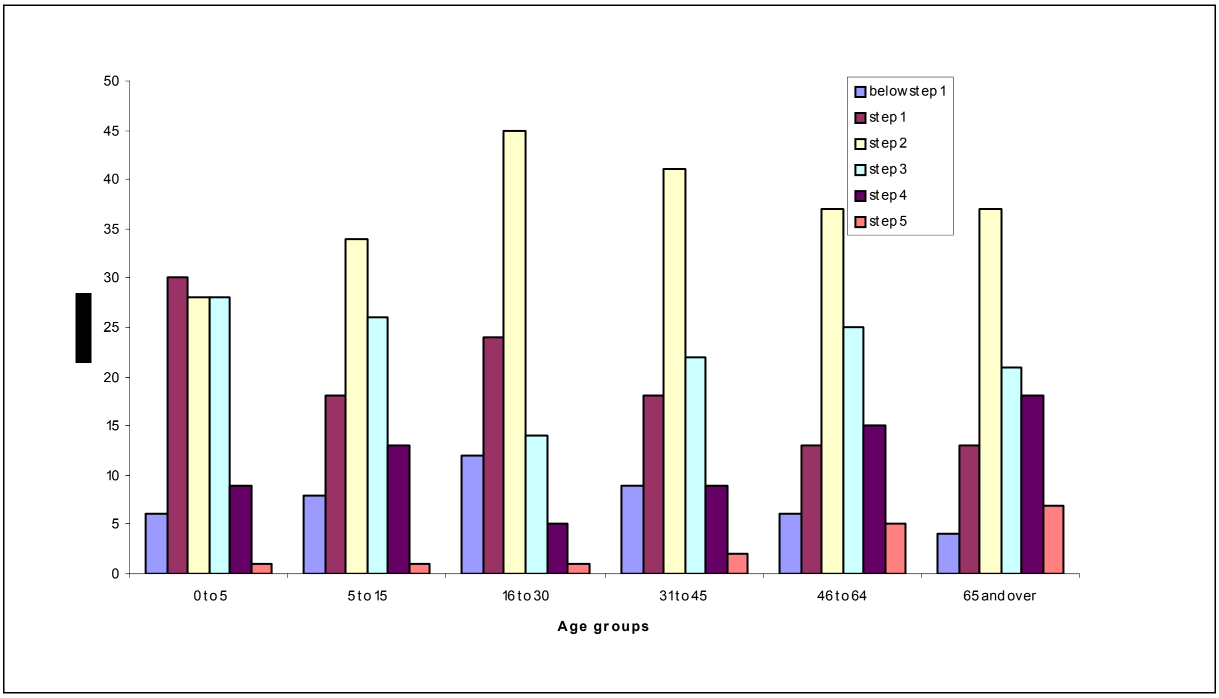


FIGURE 1 *Percentage of individuals at each step of the BTS/SIGN Guidelines by age from a cross-sectional study performed by Neville and colleagues in 1994/95*

Source: Neville and colleagues[4]

3.1.4 Asthma exacerbations

Asthma exacerbations are acute episodes of a progressive increase in shortness of breath, cough, wheezing or chest tightness or a combination of these symptoms, usually triggered be an external stimulus, most commonly a viral respiratory infection. Severe exacerbations can be life threatening. Most exacerbations can be treated with high doses of inhaled short-acting beta$_2$-agonists (SABAs), although sometimes a short course of oral corticosteroids is also needed.[1]

3.1.5 Asthma control

The aims of asthma management are the control of symptoms, including nocturnal symptoms and exercise-induced asthma, prevention of exacerbations and the achievement of the best possible lung function, with minimal side effects.[1] A fixed level of lung function or symptom control is not normally defined as individuals may have different goals for treatment and may wish to balance these against potential side effects.

3.1.6 Prognosis

The natural history of wheezing in children is well documented. Longitudinal population studies that have followed children into adulthood suggest that in some young children diagnosed with asthma, wheezing resolves spontaneously whilst in others, symptoms persist into adulthood.[5-11] Various factors including a family history of atopy (particularly a maternal history of atopy), co-existence of atopic disease, gender, bronchiolitis in infancy, parental smoking, birthweight and prematurity, age at first presentation, severity and frequency of episodes and lung function measurements have been demonstrated to influence the persistence of asthma into adulthood.[5-9;12]

Epidemiologists have suggested that there are several asthma phenotypes reflecting a heterogeneous collection of conditions that follow a common pathway (recurrent reversible airways obstruction) and that these conditions may have different prognostic outcomes.[10;13-15] Identified phenotypes include *transient early wheezing* (up to age three), *non-atopic wheezing in pre-school and school-aged children* and *IgE-mediated wheezing/asthma*. *Transient early wheezing* is associated with reduced lung function, prematurity and exposure to other siblings/children at day-care centres and is usually not associated with a family history of atopy. *Non-atopic wheezing in pre-school and school-aged children* appears to be associated with viral infection, most commonly following respiratory syncytial virus (RSV) bronchiolitis. Studies suggest that RSV infection is a risk for subsequent wheezing during childhood, but that this type of wheezing generally resolves by the age of 13. *IgE-mediated wheezing/asthma* is associated with atopy and a genetic predisposition for sensitisation to allergens and is more likely to persist into adulthood. Early allergic sensitisation seems to play an important role in persistent asthma.[13-16]

Epidemiological studies of the natural history of lifetime lung function in healthy subjects show that FEV_1 increases during normal growth in childhood, followed by a stable phase in adolescence and early adulthood and a slow decline in FEV_1 after the age of 32 years. The maximum level of FEV_1 achieved and the rate of decline determine the severity of lung function impairment later in life in symptomatic adults. Risk factors associated with smaller increases in lung function and lower maximally attained levels of lung function in children and adolescents include lower respiratory tract infections and passive and active smoking.[17-19] The rate of decline is generally greater in people who smoke and in those with asthma than in the general population,[20] possibly as a result of deterioration in potentially reversible disease or the development of persistent obstruction following airway remodelling.[21] The natural variability in maximally achievable FEV_1 is reflected in reference values used to calculate lung function as a percentage of that predicted for a person of similar height, sex, age and race (weight is also sometimes considered) without a diagnosis of asthma (e.g. FEV_1 % predicted).

3.2 Epidemiology of asthma

3.2.1 Prevalence in the UK

Asthma UK estimate that there are 5.2 million people with asthma in the UK; this includes 700,000 people over the age of 65 years and 590,000 teenagers, approximately 2.9 million women and girls and 2.3 million men and boys.[22] The Health Survey for England commissioned by the Department of Health in 1997 included data on self reported asthma symptoms and diagnosis and measurements of lung function obtained from approximately 7,000 children.[23] The prevalence of doctor-diagnosed asthma was 23% in boys and 18% in girls aged between two and 15 years (*Figure 2*). Approximately 19% of boys and 17% of girls reported wheezing within the preceding 12 months.[23]

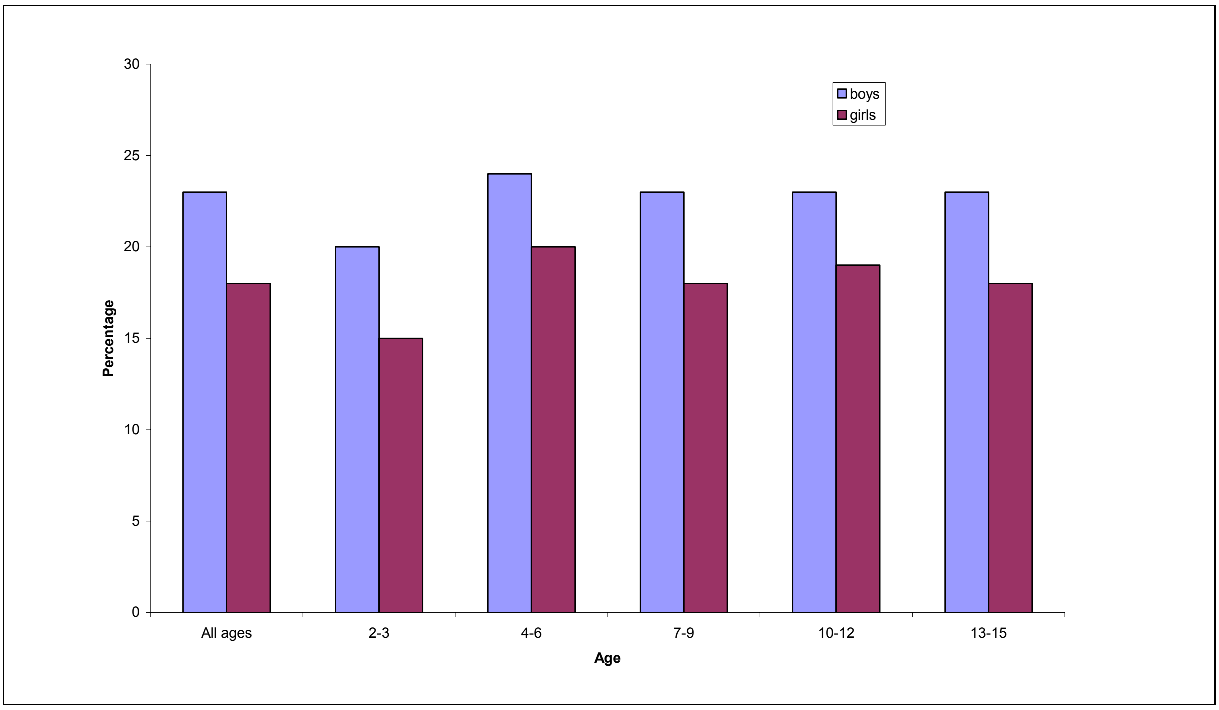


FIGURE 2 *Percentage of boys and girls (aged 2-15) with a doctor-diagnosis of asthma in the Health Survey of England 1997*

Source: Health Survey for England 1997[23]

The 1998 figures from the General Practice Research Database with a sampling frame of 211 General Practices in England and Wales indicated that the prevalence of treated asthma per 1000 patients was 97.0 (95% CI: 93.8; 100.2) and 132.1 (95% CI: 129.9; 134.3) for boys aged between 0-4 years and 5-15 years respectively. For girls the corresponding figures were 62.5 (95% CI: 59.8; 65.2) and 104.1 (95% CI: 102.0; 106.1) for each age group.[24]

3.2.2 Mortality

Asthma deaths are rare; there were 1266 reported deaths due to asthma in 2004 (*Figure 3*) Most of these (70%) were in people over the age of 65; asthma deaths were more common in women than in men (64% vs. 36%). There was one reported death due to asthma in 2004 amongst children younger than four years old and 37 in those between the ages of 5 and 14. Slightly more deaths occurred in boys than in girls (23 versus 15). Several audits and case-control studies of asthma deaths in the UK have been conducted and suggest that risk factors fall into four categories i) disease severity, ii) medical care factors both prior to and during the fatal episode, iii) health behaviour such as reduced concordance with prescribed medication, poor inhaler technique and reduced contact with primary care services and iv) adverse psychosocial factors. Therefore a proportion of deaths due to asthma are preventable, especially in those under the age of 65 years.[25-29]

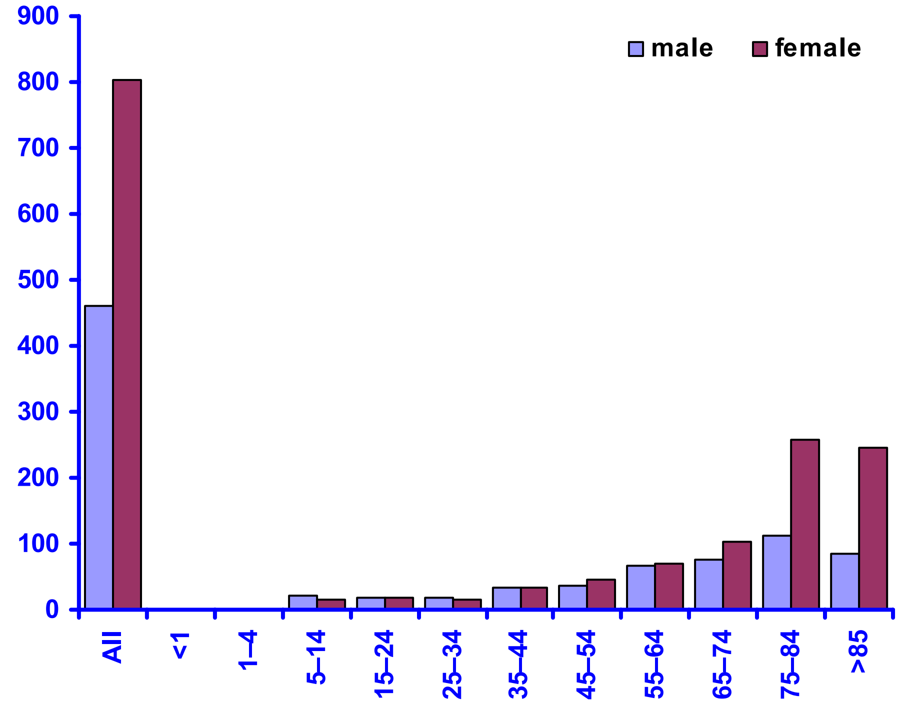


FIGURE 3 *Asthma deaths by age and sex, registrations in 2004*
Source: Office of National Statistics[30]

3.2.3 Impact of asthma on health related quality of life (HRQL) in children

Health related quality-of-life (HRQL) refers to the impact of disease and treatment on daily life. In contrast to the physiological outcome measures used to define control, the aim of HRQL measurement is to assess the impact asthma has on a persons daily functioning and emotional well-being.[31] Studies suggest that individuals with asthma have impaired HRQL, and that morbidity as expressed by HRQL in individuals with asthma is substantial.[32]

When considering the impact of asthma it is important to acknowledge the differences that may exist between control of disease, as defined by clinical measures, and its impact on HRQL. It should not be assumed that meeting clinical treatment goals will necessarily be meaningful to individuals with asthma, in terms of improvements in HRQL.[33]

In the Living with Asthma Study performed in Australia, one in five children with asthma did not ride a bike, play at school or play with animals, and one in three did not participate in organised sports.[34] The study also reported that parents of children with asthma were more anxious than parents of children who did not have asthma. In a UK study of children with asthma aged between five and 17 years, children reported that asthma restricted their participation in everyday activities and caused frequent school absences and night disturbances.[35]

The assessment of HRQL in children is challenging.[36;37] HRQL measures may not be appropriate for use in paediatric populations, due to either lack of content validity or differences in the measurement process itself.

Adult instruments have been used in studies of HRQL in children, and additionally several instruments have been devised for use within paediatric populations, including the Childhood Asthma Questionnaire (CHQ),[38] the Paediatric Asthma Quality of Life Questionnaire (PAQLQ),[39] the Asthma Symptoms and Disability Questionnaire (ASDQ),[40] the Life Activities Questionnaire for Childhood Asthma (LAQCA),[41] the Paediatric Asthma Health Outcome Measure (PAHOM),[42] the Paediatric Asthma Impact Survey (PAIS-6), the DYNHA Paediatric Asthma Impact Survey,[43] the About My Asthma (AMA) questionnaire[44] and the Adolescent Asthma Quality of Life Questionnaire (AAQOL).[31] Chiou and colleagues have also proposed that the PAHOM, a multi-attribute measure of health in asthma, may be used to estimate a single index measure of health status (a QALY value).[42] There are potential methodological issues with many of these instruments which may be specific to particular age-ranges within the paediatric study population.

3.3 Current Service Provision

3.3.1 Asthma management in the UK

As stated previously, the management of asthma in the UK is largely based on the BTS/SIGN Guideline.[1] The Guideline is evidence-based and was developed in collaboration with Asthma UK, the Royal College of Physicians of London, the Royal College of Paediatrics and Child Health, the General Practice Airways Group, and the British Association of Accident & Emergency Medicine using SIGN methodology adapted for UK-wide utilisation. The Guideline recommends strategies for both non-pharmacological and pharmacological management of chronic and acute asthma. Only the pharmacological management of chronic asthma is relevant to this appraisal and is described in more detail below.

The Guideline advocates a stepwise approach to pharmacological management, which aims to achieve early control and to maintain control by stepping up treatment when control is poor and stepping down treatment when control is good. Recommendations differ slightly depending on the age of the child (*Figure 4* and *Figure 5*). At all levels, there is an emphasis on checking inhaler technique and concordance with existing therapy and the identification and avoidance of trigger factors before the level of therapy is increased. Regular review of treatment level and asthma control is also recommended at all levels, so that individuals are maintained at the lowest possible step of the Guideline.

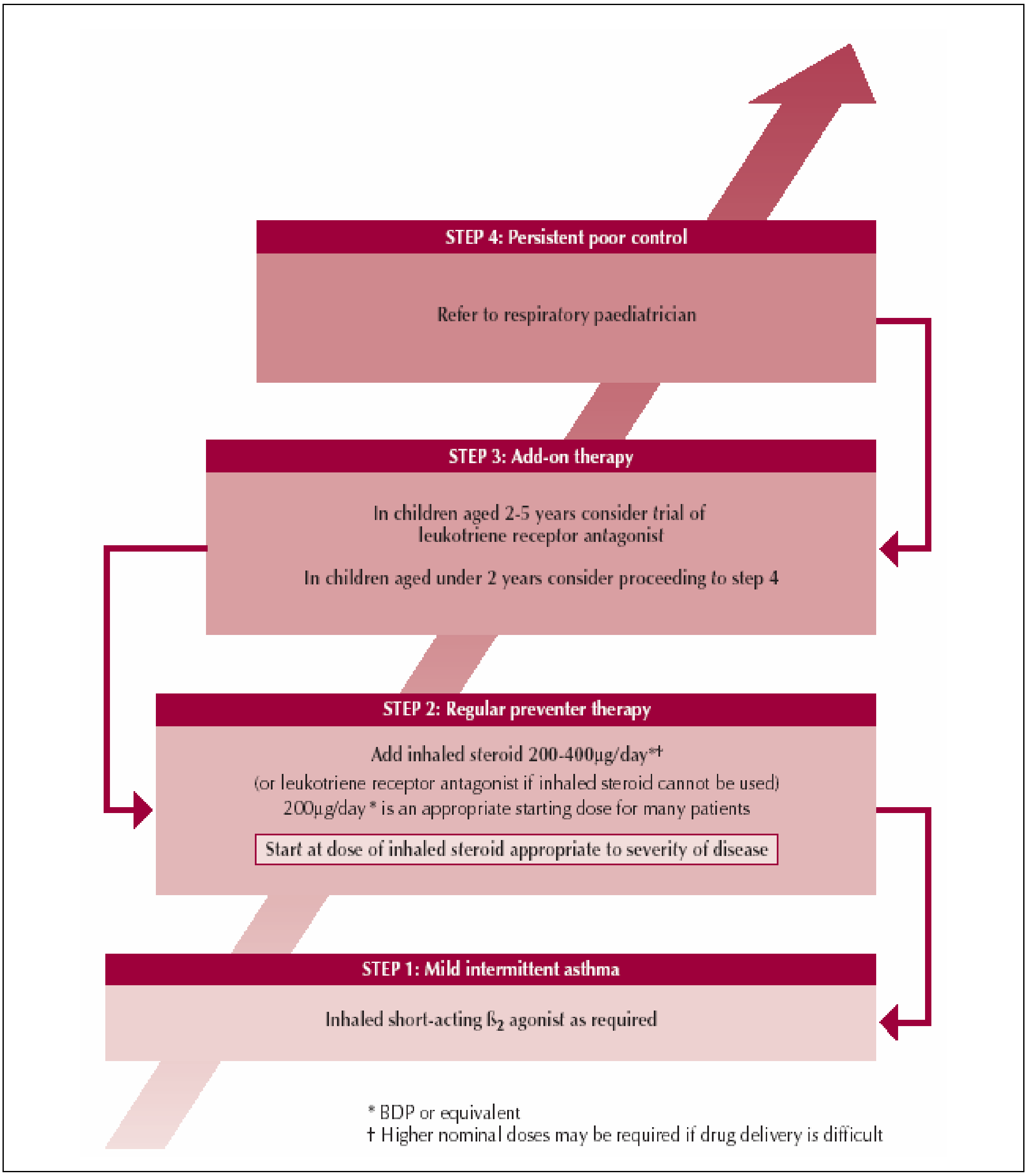


FIGURE 4 *Summary of stepwise management in children aged 0 to 5 years*

Source: BTS/SIGN Guidelines[1]

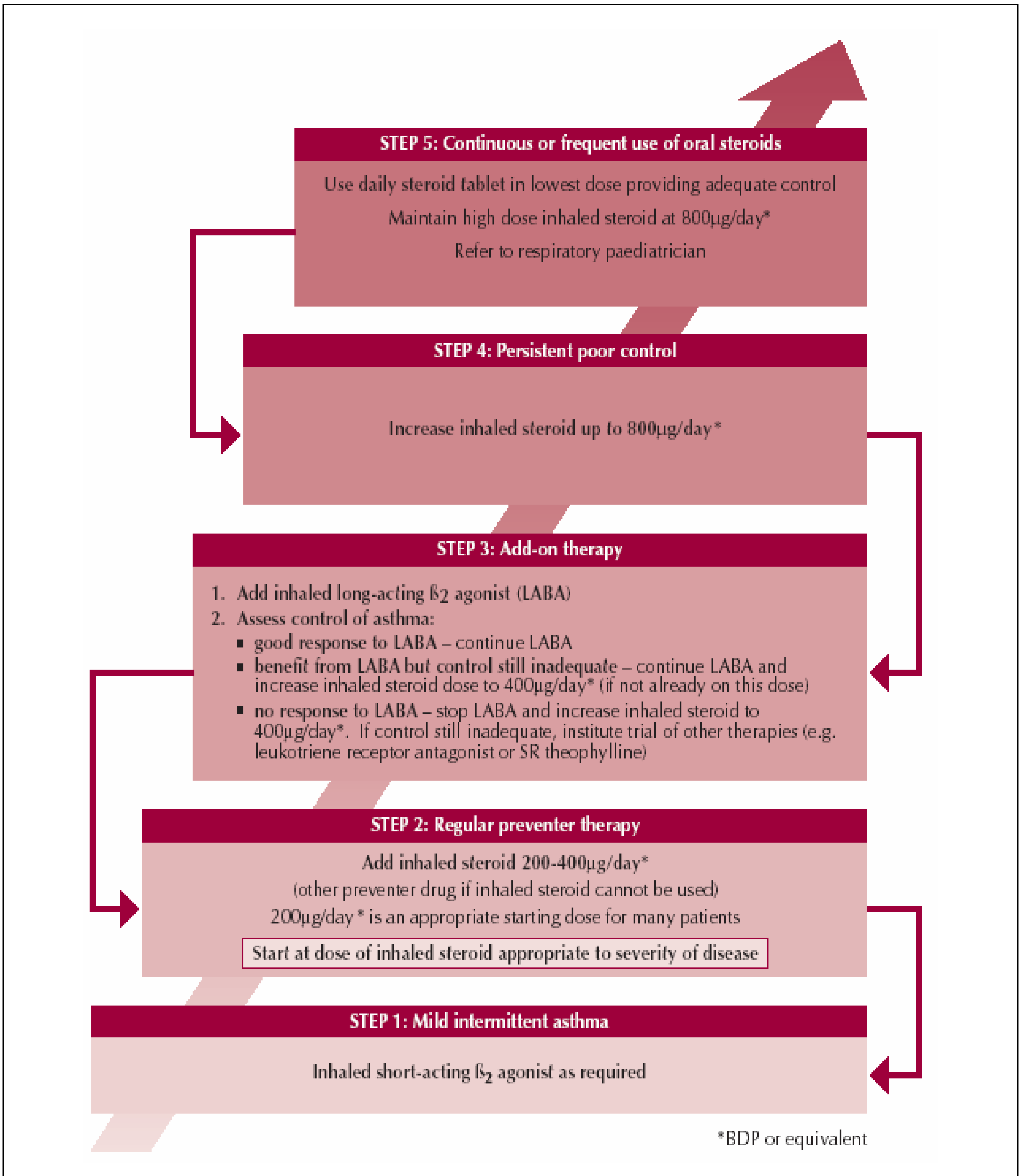


FIGURE 5 *Summary of stepwise management in children aged 5 to 12 years*
Source: BTS/SIGN Guidelines[1]

At *Step one* (mild intermittent asthma), inhaled SABAs are recommended as the agent of choice, to be prescribed as needed. A review of asthma management with possible movement to *Step two* (introduction of regular preventer therapy) is indicated if an individual has had exacerbations of asthma in the last two years, is using inhaled SABAs three times a week or more or is symptomatic three times a week or more, or waking on one occasion a week. The exact threshold at which movement to step two should be considered has not been firmly established and varies between individuals. The recommended preventer therapy at step two is an inhaled corticosteroid (*ICS*) at a starting dose of 200µg per day (BDP [*BDP*] equivalent; given as 100µg twice daily). The highest recommended dose at this level is 400µg per day (BDP equivalent), although higher doses may be required in children less than five years of age if drug delivery is difficult. The dose should be titrated to the lowest dose at which effective control of asthma is maintained. If ICS cannot be used, a leukotriene receptor antagonist is the next therapy of choice. If asthma control is not adequate at this level of treatment, movement to *Step three* may be necessary. In children less than two years of age, referral to a respiratory paediatrician is the recommended course of action. A trial of a leukotriene receptor antagonist may be considered in those between the ages of two and five years of age. For children between the ages of five and 12, the first choice of add-on therapy is a LABA, although other agents can be used such as leukotriene receptor antagonists, theophyllines and slow-release beta$_2$-agonist tablets. However, anecdotal reports suggest that leukotriene receptor antagonists are becoming more popular than LABAs as a first choice of add-on therapy. If asthma control remains sub-optimal after the addition of a LABA, the dose of ICS may be increased to 400µg day (BDP equivalent) with or without the LABA. If asthma control is still sub-optimal, despite treatment with 400µg per day of ICS, other agents should be trialled before moving to *Step four*. *Step four* in the under fives involves referral to a respiratory paediatrician. In older children (between five and 12 years old), the dose of ICS may be increased to 800µg per day. *Step five* involves referral to a respiratory paediatrician and the addition of a daily oral corticosteroid tablet at the lowest dose possible to provide adequate control. There is no step five in children under the age of five. Administration of ICS above 400µg per day (BDP equivalent) may be associated with systemic side effects (see section 3.4.1.5) and therefore the monitoring of growth and adrenal function is recommended. Once control of asthma is achieved, it is recommended that treatment be stepped down to the lowest possible level.[1]

A large proportion of individuals with asthma are managed within primary care, often within nurse-led asthma clinics. As part of the new General Medical Services contract and Quality Outcomes Framework in England, general practitioners are encouraged to perform annual reviews on all registered individuals with asthma within their practice.[45] Figures for England for 2004-2005 suggest that most practices are achieving the targets for asthma set out within the framework.[46]

3.3.2 Asthma management plans (action plans)

The use of written plans to aid individuals in the self-management of their asthma symptoms has been shown to lead to reduced utilisation of health care resources, days off work or school and improvements in nocturnal asthma symptoms,[47] and to protect against death from asthma.[48] The use of action plans is advocated in the BTS/SIGN Guidelines.[1] The aim of such plans is to provide individuals with information that allows them to respond to changes in their asthma control either by changing their level of treatment or by seeking advice from a health professional at the first signs of an asthma exacerbation. The evidence for their efficacy in adults with moderate to severe asthma, treated primarily within the secondary care setting, is particularly strong.[49-51] Plans based on both symptom scores and measurements of PEFR have both been found to be effective in adults.[52] There have been fewer studies conducted on the effectiveness of action plans in children and these are further complicated by the fact that either the parent/carer or the child themselves may be responsible for monitoring asthma control and responding appropriately to the guidance provided in the action plan. However, there is evidence that children with a written asthma management plan are at risk of fewer exacerbations requiring the need for acute intervention than those without.[53] Anecdotal reports suggest that most children in the UK have a written asthma management plan that may be used by either the parent/carer or the child themselves. Most of these are based on symptoms rather than measurements of PEFR. Despite this evidence of effectiveness, there is some indication in the literature that asthma management plans are not very popular with health professionals or with individuals.[54] Action plans that incorporate an individuals' personal experience of their disease are likely to be more successful.[55]

3.3.3 Concordance

Improving concordance with ICS therapy is recognised as an important aim for education and management. Since the effects of ICS can take several weeks both to manifest themselves following initiation of therapy and to decline following cessation of therapy, there may appear to be little incentive for individuals to take these medications, as prescribed, for long periods of time. Anxiety surrounding the risk of adverse events with ICS may also affect concordance, especially amongst parents of young children.[56] A systematic review conducted in 2000 by Cochrane and colleagues identified ten studies that reported concordance with ICS measured using electronic devices contained within the inhaler device.[57] All but one of these studies was conducted in adults. Overall, subjects took the recommended doses of medication on 20% to 73% of days. Average concordance, measured as the ratio of doses taken to doses prescribed ranged from 63 to 92%.[57] The study conducted in children was based on only 14 children, and reported 55% of days when children used less than 50% of the prescribed dose.[58] A further study conducted amongst children in the United States also using an electronic device within the inhaler, reported an average of 50% concordance with perfect dosing (100% of prescribed daily dose taken); when the timing of doses was also considered the concordance was even lower. Non-concordance was highest amongst older children and adolescents, non-white children and those with poorer functioning families.[59] Non-concordance was associated with a higher probability of relapse with a need for treatment with oral corticosteroids. Concordance measured in these studies may be better than that seen in the community since individuals were aware that their concordance with prescribed treatment regimens was under scrutiny.

An alternative method of measuring concordance with prescribed medication is to study the uptake of repeat prescriptions. A study that used records from the General Practice Research Database in the UK and included 284,733 individuals prescribed ICS over a ten-year study period found that only 42% of individuals obtained a repeat prescription for ICS within the expected timeframe of the preceding prescription.[60] A further UK study, conducted in a general practice in Nottinghamshire reported that 39% of individuals with asthma on regular corticosteroids had requested less than 80% of the expected dose. The authors comment that this may be due to non-concordance or due to individuals adjusting their ICS dose as a result of improvements in asthma control.[61]

Poor concordance is associated with poor asthma control[62] and increased exacerbation frequency[63] in children. Concordance is likely to be enhanced if both the parent/carer and the child are involved and if using inhalers is part of the household routine.[62] There was also an indication from this study that some parents are apprehensive about long-term prophylactic treatment and would rather treat their children's asthma as a series of acute events (often requiring courses of oral corticosteroids).[62] Education programmes have been shown to improve concordance in adults and may also play a role in improving concordance within families.[64]

3.4 Description of technology under assessment

3.4.1 Inhaled corticosteroids

Products available

There are currently three ICS licensed for use in children in England and Wales.

- *Beclometasone dipropionate* (*BDP*) was the first ICS available in the UK, introduced in 1972. It is available in metered dose inhalers with CFC-propellants in both proprietary (Becloforte and Becotide [Allen and Hanburys] and non-proprietary formulations (AeroBec [3M], Beclazone Easi-Breathe [IVAX], Filair [3M], Filair Forte [3M], Pulvinal BDP [Trinity]), dry powder inhalers (Asmabec Clickhaler [Celltech], Becodisks [Allen & Hanburys], Easyhaler [Ranbaxy]) and hard capsule powder inhalers (BDP Cyclocaps [APS]).
- *Budesonide* (*BUD*) is available in metered dose inhalers with CFC-propellants in both proprietary (Pulmicort [AstraZeneca]) and non-proprietary formulations (Novolizer [Viatris]), dry powder inhalers (Pulmicort Turbohaler [AstraZeneca]) and hard capsule powder inhalers (BUD Cyclocaps [APS]).
- *Fluticasone propionate* (*FP*) is available in metered dose inhalers with non-CFC propellants (Flixotide Evohaler [Allen & Hanburys]) and in dry powder inhalers (Flixotide Accuhaler, Flixotide Diskhaler [Allen & Hanburys]).

3.4.1.1 Devices

Several types of inhaler device have been developed in order to deliver drugs directly to the airways, rather than rely on absorption of oral preparations.

Metered dose inhalers (MDIs) may be breath activated or pressurised (pMDI). They contain the drug either as a suspension in a carrier liquid or as a solution which is delivered through a chlorofluorocarbon (CFC) or hydrofluoroalkane (HFA) propellant. HFA propellants were phased in to replace CFC propellants when it was realised that the latter may have ozone depleting properties. Studies show that HFA propellants deliver a greater proportion of fine particles than CFC propellants in the same device, resulting in a greater proportion of the drug being deposited in the small airways.[65] Use of a spacer device in conjunction with a MDI can also alter patterns of lung deposition by delivering a greater proportion of fine particles.[65] Many devices used in younger children (especially those below the age of five) incorporate a MDI and a valved holding chamber or spacer. Using one of these devices involves inhalation of the drug by breathing normally through the spacer, rather than requiring breath-activation or other physical coordination.

Dry powder inhalers (DPIs) require less co-ordination by an individual in order to achieve correct inhaler technique. However, lung deposition is flow-dependent requiring a forceful, deep inhalation to correctly trigger the device. The higher the flow rate, the smaller the particle size and the better the lung deposition.[66] DPIs are often not appropriate for children below the ages of five or six.

There are a wide variety of available delivery systems based on these three types of inhaler device. Inhaler technique, individual preference and cost are all factors that may guide health care professionals in their choice of inhaler device. Although potentially important in the decision as to which ICS might be best suited to an individual, the comparison of inhaler devices is beyond the scope of this appraisal.

3.4.1.2 Inhaler technique

The ability to use an inhaler correctly is essential if the anticipated dose of an agent is to be delivered successfully to the correct area within the lungs. A systematic review of the assessment of correct inhaler technique identified 15 studies in adults that evaluated inhaler technique using a variety of inhaler devices (including metered dose and DPIs).[57] Physicians assessed inhaler technique as ‘good’ in between 5% and 86% of subjects. Co-ordination of MDI activation with onset of inspiration was cited as a task which individuals found particularly difficult (17% to 68% of individuals were unable to do this in this set of studies).[57] In several studies, education improved technique, but the amount of improvement was variable (from 6% to 46% in one study[67]). Studies in children suggest that this facet of effective asthma therapy is even more problematic and that repeated comprehensive education is necessary to ensure adequate inhaler technique.[68;69]

3.4.1.3 Mechanism of action

ICS suppress inflammation in the lungs and are the mainstay in the prophylactic treatment of chronic asthma. Regular treatment with corticosteroids reduces inflammation, swelling and mucus production in the lungs resulting in better airflow in and out of the airways, fewer exacerbations, better control of symptoms and lung function and ultimately a reduction in hospital admissions and deaths from asthma.[70-72] The anti-inflammatory effects may take between one to three weeks to become apparent and it may take up to 12 weeks of regular daily treatment before maximum benefit is seen. However, the length of time taken to achieve maximal treatment benefit is dependent upon both asthma severity at baseline and the outcome measure used to assess treatment effect.[73;74] Those with severe asthma when ICS treatment is started may take longer to achieve maximal treatment effect compared to those with mild asthma.[73] ICS are often referred to by individuals with asthma as ‘preventers’.

3.4.1.4 Pharmacology

The mechanism of action of corticosteroids in asthma has not been fully elucidated. However, corticosteroids are known to exert their effects by binding to a glucocorticoid receptor located in the cytoplasm of target cells. Once activated the drug-receptor complex moves into the nucleus of the cell and binds to the deoxyribonucleic acid (DNA) and directly or indirectly regulates the transcription of target genes. Control of inflammation is believed to be a result of an increase in the transcription of anti-inflammatory genes and a decrease in the transcription of inflammatory genes.[75] Potency of a given corticosteroid is governed by the affinity of the drug to bind to the glucocorticoid receptor. Receptor affinity is usually measured relative to dexamethasone. Of the corticosteroids currently licensed for use in children, FP has the highest relative receptor affinity, followed by the active metabolites of BDP (BDP 17-monopropionate). (*Table 2*).

One of the currently available corticosteroids (BDP) is also a prodrug i.e. a pharmacologically inactive compound which is activated by esterases found only in the lungs.[75] This mechanism should serve to decrease the occurrence of local side effects with this agent.

Due to the ubiquitous nature of the glucocorticoid receptor, corticosteroids act on a wide range of cell types and are therefore capable of producing unwanted systemic effects in addition to their anti-inflammatory actions (see section 3.4.1.5). In theory, by administering corticosteroids directly to the airways via inhaler devices, smaller doses of the drug are required, drug concentrations at the site of action are higher and the likelihood of systemic side effects is reduced. However the pharmacokinetics of each individual product will substantially modify these effects.

The bioavailability of ICS determines the extent of systemic side effects and is a measure of the rate and extent at which the drug reaches the target site and the systemic circulation. After inhalation, a large proportion of the dose is swallowed. Oral bioavailability depends on absorption characteristics from the gastrointestinal tract and the extent of first pass metabolism and ranges from 1% (FP) to 26% (active metabolite of BDP) for currently available compounds (*Table 2*). Pulmonary bioavailability depends on the amount deposited in the lungs, will differ for different delivery devices and ranges from 17% for FP delivered via a DPI to 55-60% for BDP delivered via a MDI with HFA propellant. (*Table 2*).[76-80]

Once it reaches the circulation, most of the absorbed drug binds to plasma proteins and only the unbound fraction is pharmacologically active.[76-82] All currently available ICS are cleared by the liver.

TABLE 2 *Pharmacodynamic and pharmacokinetic characteristics of currently available ICS*

	RRA	**Oral bioavailability (%)**	**Pulmonary bioavailability (device) [%]**	**Comments**	**Refs**
BDP	53	15-20	55-60 (HFA-MDI)		76
17-BMP	1,345	26	36 (CFC-MDI)	Active metabolite of BDP	76
BUD	935	11	18 (CFC-MDI)		77;78
FP	1,800	<1	17 (DPI) 26 (CFC-MDI) 29 (HFA-MDI)		79;80

3.4.1.5 Adverse events

Adverse events associated with ICS use can be categorised into local or systemic events. There appears to be a wide spectrum of level of concern amongst clinicians about the occurrence of adverse events as a result of therapy with ICS. Anecdotally, some clinicians appear to be very aware of the risk of systemic adverse events, whilst others are reassured by the low frequency at which they are encountered in practice.

Local adverse events are the most commonly observed and whilst they do not cause significant morbidity, they may lead to diminished concordance. The most frequently occurring local adverse events are dysphonia, oropharyngeal candidiasis, cough, throat irritation and reflex bronchoconstriction.

- *Dysphonia* is reasonably common in individuals using ICS.[83] Although the exact mechanism of dysphonia is unknown, it is thought to be related to vocal cord inflammation.[84] Measures that reduce deposition of the drug around the larynx help to alleviate symptoms. These can include the use of a spacer device or alternative inhaler device, slowing the speed of inhalation, holding post-inspiratory breath for a longer period of time, and decreasing the dose and frequency, although in some cases temporary withdrawal of medication may be necessary.

- *Oral candidiasis* occurs less commonly than dysphonia, being reported in approximately 4% to 13% of adult ICS users, and 1% of children.[85;86] Its prevalence is positively correlated with total daily dose and with dosing frequency.[87;88] Other risk factors include concomitant antibiotic therapy, concomitant nasal or systemic corticosteroids, and immunosuppression. Candida overgrowth is usually the direct result of local corticosteroid inhibition of the normal host defence functions of neutrophils, macrophages, and T lymphocytes at the oral mucosal surface. Therefore overgrowth can be reduced by use of a spacer device, decreasing the dosing frequency and rinsing the mouth after drug administration.

- The adverse events of *cough, throat irritation and bronchoconstriction* are thought to be caused primarily by upper airway irritation by the propellants or surfactants present in the aerosol. This reaction, which may be most marked after upper respiratory tract infections, can prevent adequate deposition of the inhaled steroid in the lungs, and thereby cause a worsening of asthma symptoms. These post inhalation symptoms can be reduced by pre-treatment with a bronchodilator, use of a spacer device, use of a slow inhalation technique or a change to a dry powder formulation.[83]

Systemic adverse events occur as a result of the amount of drug that reaches systemic circulation by absorption through the lungs or the gastro-intestinal system. As previously outlined, this is influenced by the pharmacokinetics of the ICS, the site of deposition, as well as inter-individual characteristics that may influence the risk of systemic adverse events.

Accurate assessment of systemic adverse events associated with ICS use is often confounded by the concomitant use of other steroid preparations, such as oral or nasal inhaled steroids.[87;89;90] The most commonly occurring systemic adverse events potentially associated with long term ICS use are adrenal suppression, growth retardation in infants, children and adolescents, osteoporosis, skin thinning and easy bruising, cataract formation and glaucoma.

The effects of ICS on *suppression of hypothalamic-pituitary-adrenal (HPA) function* have been well documented.[90-92] In general, studies have indicated that HPA axis suppression is associated with the use of doses exceeding the equivalent of 1,500µg per day of BDP or BUD in adults (the equivalent of 400µg of BDP or BUD per day in children). The effect appears to be more marked with BDP than with BUD.[93-97] Dose-ranging studies in adults and children indicate that single doses of FP exhibit threefold greater adrenal suppression than BUD, on a microgram equivalent basis.[98] One randomised controlled trial compared the effects of FP 1,500µg per day and BUD 1,600µg per day with placebo in both healthy participants and participants with moderately severe asthma over a seven day duration.[99] The trial used the outcomes of urinary levels of total cortisol metabolites (TCM), morning serum cortisol levels and osteocalcin levels as markers of corticosteroid absorption. Results indicated that FP had a greater effect on the two markers of the HPA axis (TCM and morning serum cortisol levels) than BUD, although neither difference was significant. Conversely, BUD was associated with a significant difference in reduced osteocalcin concentration levels in both healthy and asthmatic participants relative to FP.

There have also been cases of adrenal crisis associated with ICS use documented in the literature.[100;101] A survey of the frequency of adrenal crisis associated with ICS use[100] showed that from an initial 2912 questionnaires, 33 cases of adrenal crisis were identified. Twenty-eight of the cases were identified in children and five in adults. Of these 33 patients who had received ICS in the range of 500-2000µg per day, 30 (1%) had received FP, one (3%) FP and BUD, and two (6%) BDP. In all these patients except one, the duration of oral corticosteroid therapy in the previous 12 months was estimated to be less than 21 days.

Overall, although the biochemical changes in markers of HPA axis suppression are unequivocal, their clinical importance remains unclear, and even at high doses of ICS there remains significant inter-individual variability with many patients demonstrating little or no evidence of adrenal suppression.[93;94]

The effect of ICS on *growth in children* has been a controversial issue. A number of short-term studies using knemometry (measurement of lower limb length using highly accurate measures) have demonstrated that high dose ICS use is associated with short-term growth suppression.[102-104] Although the exact mechanism of action is not known, it is thought to be secondary to subnormal androgen secretion followed by suppression of growth hormone production.[105] However, the majority of studies have only assessed short term linear growth and have not assessed long term growth and the effects on final adult height. A number of other factors also make assessment of the effects of ICS use on short term growth rates difficult, including the fact that nutritional status, growth hormones and sex hormones will affect growth to a different extent at various ages, growth can be slower in winter when the requirement for ICS treatment may be increased, the type of inhalation device used may influence lung deposition and systemic availability, and poorly controlled asthma is known to inhibit growth rates.[103;106;107] Longer term studies that have assessed final adult height have indicated that although growth may temporarily be suppressed, there was no association between ICS use and final adult height attained.[103;107]

One of the major concerns of long-term ICS use is the potential for adverse effects on bone turnover, resulting in an increased risk for *osteoporosis and fracture*. This is mediated through the inhibition of osteoblast function (bone formation) and by increasing osteoclast function (leading to increased bone resorption). These act indirectly by inhibiting intestinal calcium absorption and renal calcium re-absorption, causing secondary hyperparathyroidism. A number of studies have assessed the effects of high dose ICS use on markers of serum osteoclastin and urinary hydroxyproline.[108;109] These studies have shown mixed results with some demonstrating decreased bone formation and increased bone re-absorption in a dose dependent manner,[108;109] whilst others have shown no effects on plasma osteoclastin concentrations at doses of BDP and BUD as high as 2000µg per day.[110] Similarly, high doses of both BDP and BUD have also not shown any effect on urinary calcium excretion, intestinal calcium absorption, serum calcium, phosphate or parathyroid hormone levels.[111;112] In relation to bone density, there is limited evidence from two studies that high dose ICS use for a duration of three years was associated with an 18% reduction in lumbar spine density[112]and a reduction in both lumbar spine and femoral neck density.[113] However, in both of these studies all subjects had previously received treatment with oral corticosteroids. Additional evidence from a cross-sectional study of patients treated with ICS at a median cumulative dose of 876µg/day over a six-year period, indicated that there was a negative association between cumulative steroid dose and bone-mineral density at the lumbar spine, femoral neck, Ward's triangle, and trochanter, both before and after the adjustment for the effects of age and sex.[114] A doubling of the dose of ICS was associated with a decrease in bone-mineral density at the lumbar spine of 0.16 SD (95% CI: 0.04; 0.28). Decreases of a similar magnitude were observed at the femoral neck, Ward's triangle, and trochanter. The majority of the study participants were from a primary-care population with relatively mild asthma, so that potentially neither the underlying disease itself not a substantial use of oral corticosteroids were probable confounders. Additionally, the study participants were between 20 and 40 years of age, so that the confounding effects of age and menopausal status were minimised. However, the exact implications of the findings of an association between cumulative dose of ICS and reductions in bone mineral density from the study would need to be verified in a longitudinal study, particularly since bone loss with oral corticosteroid therapy is time dependent and most rapid in the first 12-24 months of treatment duration.[115]

Three further studies conducted in children, have shown that doses of BDP and BUD up to 800µg per day did not affect bone density,[116;117] and the lumbar spine density of children receiving BDP 300 to 400 µg/day for six months was not different from that of the control group.[118] Overall, the long term consequences of administering ICS for many decades from early childhood are not known.

There is evidence that the use of high dose ICS is associated with *skin thinning and easy bruising*.[119;120] One study showed that skin thickness measured by an ultrasound scan was significantly reduced by 15% to 19% in subjects on BDP 1,000 to 2,250µg per day compared to controls.[119] In addition the prevalence of bruising was significantly higher at 48% in this patient population compared to 12% in the control population.[119] The results of a further survey also indicated that easy bruising was the commonest reported symptom with the use of ICS occurring in almost half of the individuals.[120] The relative risk of easy bruising was more than double that of a population of a similar age and sex distribution not taking ICS. This risk also increased with age, dose, and duration of therapy.[120] The presence of skin bruising can be considered a visible marker of the adverse effects of ICS therapy on collagen turnover in connective tissue. However, it is unclear whether early susceptibility to skin bruising relates to effects on collagen in other systemic tissues such as bone.[121] Therefore the absence of skin bruising cannot necessarily be taken as a guide to the safety of a given dose of ICS.

- *Posterior subcapsular cataract* (PSC) is a well recognised complication of treatment with oral corticosteroids with the incidence increasing with both dose and duration of treatment.[122;123] The incidence also depends on the individual's age (particularly in children) and ethnic origin, with Hispanic people being more susceptible to development of PSCs.[122] However, the evidence of an association between ICS use and development of a PSC is equivocal and often confounded by previous exposure to oral corticosteroid therapy. Three studies have reported no association between long-term low and high dose ICS therapy in adults and the prevalence of PSCs.[124-126] A further population based survey reported that after adjustment for age and sex, the relative prevalence ratio for corticosteroid versus no corticosteroid exposure was 1.9 (95% CI: 1.3, 1.9) for posterior subcapsular, 1.5 (95% CI: 1.2, 1.9) for nuclear, and 1.1 (95% CI: 0.9, 1.3) for cortical cataracts.[127] The relative prevalence ratio of posterior subcapsular cataracts for a lifetime dose of BDP greater than 2000µg per day was 5.5 (95% CI: 2.3, 13.0).[127]

  Due to the fact that cataracts in children are very rare, even large increases in risk may be missed in studies of children and adolescents.[128] The results of one study found no increased risk for the development of cataracts after an average of five years of follow-up,[125] and when cataracts have been found in studies, participants have had numerous courses of oral corticosteroids.[126]

- There have also been case reports suggesting that ICS use may be associated with the development of *ocular hypertension or open-angle glaucoma*.[129;130] The results of one case-control study showed that after adjustment for age, sex, diabetes, systemic hypertension, and the use of ophthalmic or oral corticosteroids, there was no association between current use of inhaled or intranasal corticosteroids and an increased risk for ocular hypertension or open-angle glaucoma. However, those individuals who were using high doses of corticosteroid on a regular basis for three or more months were at a small, significantly increased risk; odds ratio of 1.44 (95% CI: 1.10, 2.06).[131]

3.4.2 Long-acting beta$_2$-agonists

Products available

There are currently two long-acting beta$_2$-agonists (LABAs) licensed for use in children in England and Wales.

- *Salmeterol (SAL)* is available in MDIs with CFC-propellants (Serevent® [Allen & Hanburys]) and in DPIs (Accuhaler® [Allen & Hanburys] and Diskhaler® [Allen & Hanburys].
- *Formoterol Fumarate (FF)* (previously known as eformoterol) is available in MDIs with non-CFC propellants (Altimos Modulite® [Trinity-Chiesi]) and in DPIs (Oxis® Turbohaler [AstraZeneca] and Foradil® [Novartis]).

Combination products available

Both of these products are licensed for use in combination with an ICS in the following combinations:

- *BUD and FF* is available in DPIs (Symbicort® Turbohaler [AstraZeneca]).
- *FP and SAL* is available in MDIs with non-CFC propellants (Seretide® Evohaler [Allen & Hanburys]) and DPIs (Seretide® Accuhaler [Allen & Hanburys]).

BUD/FF is licensed for use in children over six years, and FP/SAL in children over the age of four.

3.4.2.1 Mechanisms of action of LABAs

LABAs produce sustained bronchodilation (relaxation of the airways), improving airflow in and out of the lungs. In contrast to SABAs (e.g. salbutamol, terbutaline) which are used for quick relief of symptoms, these compounds are administered on a regular basis for long-term symptom control.

3.4.2.2 Pharmacology

The two currently available LABAs (SAL and FF) are highly selective beta$_2$ adrenoceptor agonists which produce a bronchodilator effect lasting for at least 12 hours after a single inhalation. They act principally on smooth muscle beta$_2$-adrenoceptors which are widely distributed throughout the bronchial tree; the highest density of beta$_2$ adrenoceptors is found in the alveoli.[132] Both agents are highly potent (i.e. they are effective at low concentrations). Comparative studies suggest that the potency ratio is approximately 5:1 (FF:SAL) both for systemic side effects seen in healthy volunteers[133;134] and bronchodilator effects seen in people with asthma.[135] Onset of bronchodilation with FF is within 2-3 minutes whereas the onset of bronchodilation with SAL takes approximately 10 minutes and the maximal effect may not be apparent for several hours.[136] FF is more lipophilic than SAL and has a much higher degree of intrinsic agonist activity.[137] In addition to bronchodilator effects, LABAs also provide protection from a number of stimuli causing bronchial hyperresponsiveness e.g. methacholine, cold air, exercise, hyperventilation and histamine.[138] Despite some indication of anti-inflammatory activity in laboratory experiments, neither SAL nor FF have been shown to have anti-inflammatory effects in individuals with asthma,[139;140] although preliminary evidence suggests that LABAs might have some mild anti-inflammatory effects when given in combination with ICS (see section 3.4.2.3) as a result of inadvertent potentiation of the effects of the ICS.[141] The main adverse effects of LABAs relate to their systemic activity (see section 3.4.2.3). Both drugs are relatively well tolerated at recommended doses but their therapeutic window is fairly narrow.[133]

3.4.2.3 Adverse events

Most adverse events related to the use of LABAs are a result of systemic absorption (due to stimulation of $beta_2$-adrenoceptors in the heart, peripheral vasculature and skeletal muscle) and are dose-related. At standard doses, adverse events such as tachycardia, increase in the QTc interval, hypokalemia, hyperglycaemia and tremor are minimal in most individuals.[138] At higher doses (which may be relevant during an acute asthma attack), both SAL and FF produce dose-related effects on heart rate, diastolic and systolic blood pressure, QTc interval and plasma potassium levels.[133]

3.4.2.4 Tolerance

Tolerance to the effects of regular LABA exposure, as a result of down-regulation of $beta_2$-adrenoceptors, may result in a diminution of response and associated worsening of disease control. This has been the subject of much basic and clinical research.[142-147] Whilst down-regulation of $beta_2$-adrenoceptors has been demonstrated in laboratory studies, most large clinical trials of LABAs have shown that tolerance to the bronchodilator effects of LABAs is not a significant clinical problem.[137] Tolerance to the bronchoprotective effects of LABAs against bronchoconstrictor stimuli such as methacholine challenge or exercise has been demonstrated in clinical studies.[148-151] Although bronchoconstrictor challenges are considered to be a surrogate for conditions during an asthma exacerbation, whether these laboratory-conducted studies are relevant to the every-day treatment of asthma with LABAs is unclear. There is also some evidence to suggest that during regular LABA therapy there might be a reduced response to SABAs, although some of the studies in this area are difficult to interpret.[137;138]

3.4.3 Combination inhalers

3.4.3.1 Pharmacology

LABAs and ICS affect different aspects of asthma control; several studies have demonstrated the superiority of the combination of agents over increasing the dose of ICS.[152-154] Whether the combined effect is additive or synergistic (i.e. the combined effect is greater than the sum of the effects due to the individual agents) has been the subject of much research, both basic and clinical, and remains controversial.[155-157]

There are no apparent differences in systemic pharmacodynamics or pharmacokinetics when inhaled SAL and FP are given separately or in combination.[158]

3.4.3.2 Effect of LABAs on life threatening asthma attacks and asthma related deaths

Concerns have been raised in the literature regarding the association between treatment with a LABA and an increased risk of death due to asthma. This association, however, has remained uncertain, since it can be suggested that a high level of beta$_2$-agonist use is probably directly correlated with severity of asthma, and that those with more severe asthma are at greater risk of death.[159] Two post marketing surveillance studies have therefore assessed the safety of SAL and salbutamol either versus each other or placebo,[160;161] and the US Food and Drug Administration (FDA) have re-analysed data from three clinical trials[162;163] submitted in support of the approval of Foradil Aerolizer for marketing in the United States.[164]

Salmeterol Nationwide Surveillance study (SNS)

The SNS study conducted in the United Kingdom in 1990-1991, randomised 25,180 patients with asthma who were considered to require regular bronchodilator treatment.[160] Patients were randomised to receive either SAL 50μg twice daily (n=16,787) or salbutamol, 200μg four times daily (n=8,393) in combination with their previously prescribed asthma drugs for 16 weeks. Approximately three quarters of the patients were taking either an oral or ICS. The incidence of drug-related serious adverse events was similar in both groups (1.19% versus 1.15% respectively), but a significantly lower rate of severe, non-fatal asthma-related adverse events was observed in the SAL group compared with the salbutamol group (9.9% versus 1.6% respectively). The incidence of the combined trial endpoint of respiratory and asthma-related deaths was not significantly different between the SAL and salbutamol treatment groups (0.07% versus 0.02% respectively).[160]

Salmeterol Multicentre Asthma Research Trial (SMART)

The Salmeterol Multicentre Asthma Research Trial (SMART) was a randomised, placebo controlled study that compared the effects of adding SAL to usual asthma therapy.[161] Patients were randomised to receive either SAL, 42μg twice daily via an MDI or placebo twice daily for a duration of 28 weeks. The planned safety interim analysis was conducted after 26,355 patients had been randomised. At this point the trial was terminated as it was found that the overall rate of death was higher in patients treated with SAL compared with placebo. The interim analysis indicated that the occurrence of the primary outcome (combined respiratory-related deaths or life-threatening asthma attacks) was low and not significantly different between the groups. However, there was a small but significant increase in respiratory related deaths (24 versus 11) and asthma-related deaths (13 versus 3) in patients receiving SAL compared with placebo. Further post-hoc analysis showed that compared to placebo, a higher rate of asthma-related deaths occurred in the SAL group in both whites (0.01% versus 0.07%) and African Americans (0.04% versus 0.31%) respectively. However, the overall estimates of excess deaths attributable to SAL were greater in the African American trial patients due to a higher event rate. It was also observed that the occurrence of asthma-related deaths and life-threatening experiences were similar in both groups in those patients using ICS at baseline (16 versus 13 respectively). However, overall the trial was not designed or conducted in a manner that allows for any conclusions to be drawn regarding whether or not ICS significantly modify the risk of death or experiencing a life threatening episode purportedly associated with the use of SAL.[161]

Combined FF trials

Three pivotal randomised, placebo controlled, double-blind trials submitted to the FDA by Novartis Pharmaceuticals Corporation in support of the approval of Foradil Aerolizer for marketing in the US have been assessed for reports of serious asthma exacerbations.[162;163] Two of the trials were conducted in adults and one in a paediatric population. The two 12-weeks trials that were conducted in adults compared the effects of FF 12µg twice daily or 24µg twice daily, with either albuterol 180µg four times daily or placebo. Both the 12µg and 24µg twice daily doses of FF were significantly more beneficial in terms of improvement in the primary endpoint of FEV_1 at 12 week follow-up. Neither of the trials showed a statistically significant benefit for FF, 24µg twice daily compared with FF 12µg twice daily. However, the rate of serious asthma exacerbations was higher in the FF 24µg twice daily dose group compared with the groups receiving placebo or albuterol, or the group randomised to 12µg twice daily of FF. In the two 12 week trials in adults/adolescents, 9 patients in the FF 24µg twice daily group experienced a serious asthma exacerbation, all of which required hospitalization. One patient died due to a cardiorespiratory arrest. In comparison, two placebo group patients experienced a serious but non-fatal asthma exacerbation, both of which required hospitalization. In the trial that was conducted in a paediatric population for the duration of one year, 11 patients in the FF 24µg twice daily group had a serious nonfatal asthma exacerbation, compared with 8 patients in the FF 12µg twice daily group, and no patients in the placebo group.

Summary of the risk of mortality or serious asthma exacerbation associated with LABA use

The results from trials and post marketing surveillance studies provide conflicting evidence on any increased risk of mortality or serious asthma exacerbations associated with the use of a LABA. The majority of prospective trials show a decrease in exacerbation rates with the use of a LABA either in addition to an ICS, or used alone. Additionally, there is no significant excess in mortality or the rate of severe exacerbations generally observed. However, the majority of these trials are relatively short term and are usually not powered to detect relatively rare adverse events. In contrast post marketing surveillance studies have showed mixed results regarding an increased risk of either severe adverse events or mortality with LABA use. The results of the SNS[160] indicated that there were fewer severe non-fatal adverse events with the use of SAL compared with salbutamol, whilst there were no significant differences in the mortality rates between the groups. In contrast the results of SMART[161] showed that there was a significantly higher rate of respiratory and asthma-related deaths in the SAL group compared to the placebo group. No difference in the primary composite outcome was observed between the groups. Likewise, the three trials that have assessed the use of FF have indicated that there is an excess risk of severe exacerbation associated with higher doses of FF (24µg twice daily,) compared with either lower doses of FF (12µg twice daily), albuterol or placebo.

Overall it is difficult to quantify the excess risk of severe exacerbation associated with the use of either SAL or FF, but it appears to be reasonably rare. However, the degree to which this reflects the use of a LABA alone, and may be attenuated by the use of combination ICS plus LABA therapy warrants further investigation in future post marketing surveillance studies.

FDA actions on the use of LABAs

The FDA has recently asked for a 'black box' warning to appear on the labels of products containing SAL. The labelling includes a warning about a small, but significant, increased risk of life-threatening asthma episodes or asthma-related deaths with the use of SAL. A similar warning has also been included in the prescribing information. The labelling for FF remains unchanged.

3.5 Economic aspects of asthma

The research literature on economic aspects of asthma is large and diverse. While it is dominated by economic evaluations comparing the cost-effectiveness of alternative treatments for asthma, it also comprises: cost-of-illness studies; cost analyses of particular treatments; longitudinal studies; regression analyses of claims databases; and other studies to elicit patient preferences about different types of treatment and care provision.

Our aim in the following sections is to (i) give a broad overview of those economic aspects of asthma that have been identified in the research literature, focussing especially on studies conducted in the UK and/or focussing on asthma in children, and (ii) attempt to identify the key causal relationships and trade-offs that seem to exist between resource use and the nature of chronic and acute asthma in children, in order to best characterise the current decision problem and model structure. It is not, therefore, intended to be comprehensive either in terms of the economic issues covered or the research literature included on each issue.

3.5.1 NHS cost impacts of asthma

Children with asthma place various demands on the NHS budget, ranging from the cost of prescribed asthma medications, to various levels of health service use (e.g. GP and nurse consultations, accident & emergency department visits, and hospital admissions). There is some evidence that children with asthma place relatively greater demands on health services than adults with asthma.

Cost-of-illness studies of asthma consistently show relatively high “indirect costs” (including for example, the estimated cost of lost days of work or school) compared with the direct health care costs of service use.[165] They sometimes also show the dominant role of people with severe asthma in generating the bulk of asthma-related heath care costs.

Gupta and colleagues have published the most recent well-conducted cost-of-illness study of asthma in the UK.[166] Overall, they estimate that the cost to the NHS of asthma in 2000 was £754 million, of which almost 78.9% (£594 million) was due to community-dispensed prescriptions, 12.7% (£96 million) was due to GP consultations, and 8.4% (£63 million) was due to hospital admissions. This contrasts with most international studies, in which hospital costs account for a higher proportion of the costs associated with health care use.[165] Of the NHS costs associated with hospital admissions, over 86% (£54.7 million) were due to non-elective admissions (i.e. probably to treat asthma exacerbations). More recent estimates by the UK’s *Lung and Asthma Information Agency* (and cited in the *Asthma UK Cymru* report on “Asthma in Wales today”) suggest this cost to the NHS has increased to £889 million annually.[167] In a different study, cited in the same Asthma UK report, difficult-to-control asthma was estimated to cost the NHS £680 million a year.

Other data in the study by Gupta and colleagues suggests that, compared to children, adults (aged 15 and over) contribute proportionately less to both primary care and secondary care NHS costs (*Table 3*). Amongst adults there was one hospital admission for asthma for every 13 to 15 GP consultations (for asthma), whereas amongst children there was an asthma-related hospital admission for every eight GP consultations.

TABLE 3 *GP consultations and hospital admissions for asthma in UK*

Age-group	**Weekly number of GP consultations (per 100,000 in age-group) in 2002**	**Annual number of hospital admissions (per 100,000 in age-group) in 2000/2001**
0 – 14 years	46	292
15 – 44 years	25	84
45+ years	21	83
Source: Gupta and colleagues[166]		

The Prescriptions Cost Analysis database[168] details the number and cost of all prescriptions dispensed in the community in England. Listing of drug classes (by 317 BNF sub-paragraphs) shows that expenditure in 2005 on corticosteroids for respiratory conditions cost the NHS £436 million. Although only 15th in terms of the number of prescriptions, this is the third largest component of the total cost of community-dispensed drugs in England (after lipid-regulating drugs £625 million, and proton pump inhibitors £446 million). Corticosteroids for respiratory conditions cost the NHS more than double the amount spent on many other major drug classes, such as ACE inhibitors, anti-psychotic drugs and intermediate and long-term insulins.

Of the £436 million spent on respiratory corticosteroids, £276 million was spent on combination inhalers (Symbicort® and Seretide®) (*Figure 6*).

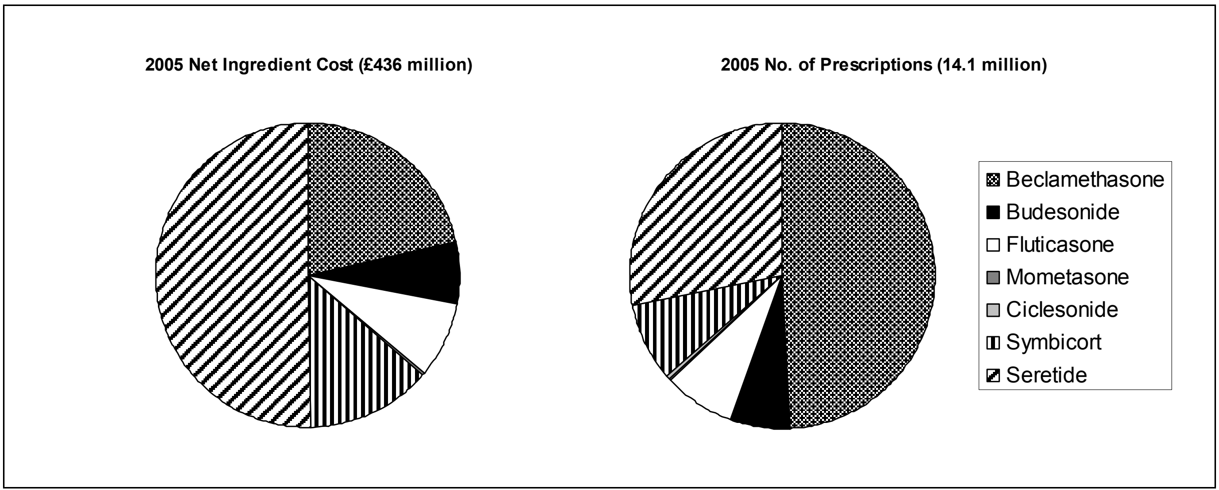


FIGURE 6 *Number and cost of community-dispensed prescriptions for ICS in England 2005*

Source: Prescriptions Cost Analysis Database[168]

Effective drug treatment for asthma relies upon the correct use of various inhaler devices (see section 3.4.1.1). It is therefore conspicuous that the cost of related education and support has usually not been included in economic analyses comparing drug treatments (for example, respiratory nurse education on the correct use of pMDIs). This omission may be particularly important in younger age groups.

3.5.2 Cost to individuals with asthma, their carers and society

3.5.2.1 Financial cost of medicines

Asthma is not a condition exempt from NHS prescription charges although, as children under 16 are exempt from all charges, they will not be required to pay for asthma medications. The financial cost of medicines should not therefore be a factor in children not receiving their prescribed dose of medication.

3.5.2.2 Other financial costs

Economic evaluations and cost-of-illness studies have not usually measured the use of resources such as medical equipment and consumables to support asthma self-medication and self-monitoring (such as nebulisers, inhalers and peak flow meters).[169] People with asthma also inevitably have to pay more of the various costs of attending more frequent primary care or hospital consultations, for example for travel, car parking, and child care.

3.5.2.3 Indirect costs to individuals with asthma, carers and society

Cost-of-illness studies in a number of countries suggest that a significant proportion – usually 50% or more – of all costs due to asthma are due to the “indirect costs” of lost days at work (or school), which may be estimated by asthma morbidity and treatment, and/or by premature deaths due to asthma.[165] Adults may lose work days as a result of their own asthma, or due to looking after children or other dependents with asthma. Two early studies estimated the annual number of working days lost due to asthma in the UK to be 5.7 million or 7 million, corresponding to an estimated 50% and 90% of all asthma costs.[170;171]

Other time costs of individuals with asthma and carers include healthy time lost (either work or leisure), the time individuals with asthma put into the process of receiving health care, and the time carers put into caring for friends and relatives with asthma.[172] Reduced school attendance due to poor asthma control may also lead to a reduction in the educational level achieved and hence the future earning potential of individuals. These costs are in principle measurable, but much harder to value, for example there is debate surrounding whether some “time costs”, such as lost leisure time, should be counted as a reduction in quality of life or as a monetary input.

A costing study by Stevens and colleagues, in the context of a UK-based RCT, estimated the mean annual costs per family with pre-school children with asthma to be £562 (comprising £32 for family-borne costs, £47 for lost non-waged time, £55 for lost waged time, and £428 for health service costs; 1999 costs).[173] Approximately half of the family-borne costs were due to “regular family expenditure” (such as extra heating, childminder costs for caring at home), and a third were associated with inpatient stays. Most of the families’ non-waged time costs were due to attending primary care consultations or inpatient stays. In contrast two-thirds of waged time cost was associated with inpatient stays. Also, a study into the loss of work days by caregivers, for French children with persistent asthma (GINA grade 2+, aged 6 to 16), showed that almost a third of caregivers lost work days during the study year. Thirteen percent of caregivers lost more than five days.[174]

3.5.3 Health care resource use and asthma severity

There are some published studies which have specifically examined the relationship between asthma severity and resource use and costs. However, we are aware of few UK-based studies that have studied this relationship. Nevertheless, the positive association between asthma severity, whether defined by GINA class or other methods, and health care costs seems strong in a variety of health systems.[175;176]

A study of 713 British children (0-15 years olds, identified with respiratory symptoms through a postal survey to parents in 1993), 381 of whom were identified as "likely asthmatics", examined the incidence of medical consultations for different reasons.[177] In a two year reference period, higher respiratory symptom and allergy history scores were associated with higher proportions of children having medical consultations (for upper and lower respiratory conditions), higher proportions having home visits, and higher proportions receiving respiratory prescriptions. These associations remained statistically significant when data for children aged under five years were analysed separately. The 381 children who were "likely asthmatics" had 934 GP consultations for a respiratory problem during the two years (a mean of 1.23 consultations per child per year). Unfortunately this study did not distinguish routine/review consultations from urgent or patient-initiated consultations in primary care. The investigators did, however, highlight the very low rates of secondary care consultation for respiratory problems, indication that in the UK most exacerbations are managed at home or with the support of primary care services.

Laforest and colleagues, in a recent one-year study of various factors amongst 261 French children with asthma (aged 6 to 16), used clear definitions of asthma severity and control in the same analysis.[178] Interestingly they found that *within severity classes*, there was only an association between the cost of medical resource use and asthma symptom control for children with severe asthma; for children with mild and moderate asthma severity (in the six month pre-study period) there was no significant association between control and asthma costs.

3.5.4 Health care resource use and asthma symptom control

Although some asthma medication is prescribed as prophylactic therapy, and some asthma-related health care consultations are for routine clinical reviews, a sizeable proportion of medication use and many consultations occur in response to worsening symptoms. It is therefore possible that there might be a strong relationship between degree of asthma (symptom) control and resource use. As a result, the level of use of healthcare resources is sometimes suggested as a possible measure of effectiveness of asthma treatments.[169]

A key indicator of poor symptom control is a greater frequency of use of reliever medication (e.g. inhaled salbutamol), which has implications for medication costs. Also, anecdotal reports suggest that poor asthma symptom control may prompt better adherence to prophylactic medication.

The key driver of the higher costs of poor symptom control appears to the resource consequences of asthma exacerbations.

3.5.5 Exacerbations and health care resource use

Asthma exacerbations (or asthma "attacks") are one of the key acute events which lead to the consumption of additional medications, or to patient-initiated health care consultations. They are also the likely cause of more expensive types of asthma-related health care use, such as A&E attendances and hospital admissions.

For example, in a UK-wide cohort study of 12,203 people with asthma followed for one year, those who experienced an attack incurred over three times as much health care costs as those who did not (£381 vs. £108, 1997 NHS costs).[179] Further breakdown of these costs showed that most of this difference was due to hospital stays (£169 vs. £7, over the year) and medication costs (£129 vs. £75).

It should be noted that many of these published studies predate the existence of NHS Direct, NHS Walk-in Centres and GP out-of-hours cooperatives. In the UK these services now provide either a new pathway to some of the more long-standing providers of acute care (e.g. general practitioners, Accident & Emergency departments), or provide emergency care and advice in their own right. It is possible that these services, by being better publicised and more accessible than traditional models of healthcare delivery, have made it easier for people with asthma to obtain care or advice when they experience symptoms or have other asthma-related queries.

3.5.6 Health care resource use and other factors

In addition to asthma severity and level of asthma symptom control, there are other published studies which have documented a relationship between asthma-related resource use and:

- Co-morbidities (such as allergic rhinitis, diabetes)[180;181]

- Sex (females being more likely to use care for asthma)
- Self-management programmes
- Health service organisation and accessibility (e.g. balance of primary care provided by nurses versus GPs, availability and use of telephone advice lines)[181;182]
- Health-related quality of life[181;183;184]

3.5.7 Summary points on economic impact of asthma

- Asthma has considerable economic impacts beyond the resources used in providing health care. These impacts comprise days lost from work for individuals with asthma and their families, and days lost from school amongst children.
- Of the costs incurred for providing health care for children with asthma, a high proportion is associated with the use of hospital services. Asthma exacerbations, both their frequency and their severity, appear to be the major driver of the cost of using health services amongst children and adults.
- As asthma severity increases and as level of asthma control decreases, the costs to the health system increase. There may be interaction effects, but we are not aware that they have been explicitly studied (e.g. poorly controlled severe asthma may lead to more consumption of health care resources than the separate effects added). People with difficult-to-control asthma may be another sub-group which generate more health care costs, but they have been less studied.
- While there has been a great deal of research to examine the cost-effectiveness of switching to alternative treatments for people with poorly controlled asthma, there do not appear to have been any economic evaluations of stepping down treatment in individuals whose asthma is well controlled.
- In the last ten years there have been considerable changes in the range of available NHS services for people with asthma, especially those for urgent care and advice – such as NHS Direct, Walk-in centres and GP After-Hours Cooperatives. These may have changed the pathways by which people access health care, and perhaps also altered the balance of self-care and formal care. In addition, the cost or cost-effectiveness of allergen avoidance strategies to reduce asthma symptoms have not been studied.

- There are some dynamic interrelationships between resource use (costs) and the level of actual or perceived symptom control. For example, patient charges for medication may be a factor in poor concordance with prophylactic therapy, and therefore symptom deterioration (and ultimately higher health care costs). Also, the lack of perceived symptoms may encourage a gradual reduction in the use of prophylactic therapies resulting in a costly exacerbation of asthma symptoms.

4. Decision problems

4.1 Aims and objectives

Assessment aim

The aim of this health technology assessment is to assess the clinical and cost-effectiveness of ICS, used alone or in combination with a LABA, for the treatment of chronic asthma in children under the age of 12 years and to provide guidance to the NHS in England and Wales

Objectives

- To identify, appraise and synthesise, where appropriate, the current evidence base which addresses the specific research questions on clinical effectiveness listed above.
- To identify the costs associated with the different treatments.
- To identify, appraise and synthesise, where appropriate, the current evidence base which addresses the specific research questions on cost-effectiveness listed above.
- To provide estimates of cost-effectiveness, where possible, of the different treatment options.

4.2 Definition of the decision problems

There are three inhaled corticosteroids available as licensed preparations in this population: BDP, BUD and FP. The drugs may all be administered via different devices, including pMDIs, with or without a spacer, and DPIs. Assessment of the effect of device on the dose of corticosteroid delivered to the airways, and, by extension, the effect of device on the clinical effectiveness of ICS, is not included in this report. Similarly, the effect of the propellant (CFC versus HFA) used in the MDIs is not considered.

In addition, two of the corticosteroids under consideration are available as licensed preparations in combination with LABA: FP used in combination with SAL (Seretide) and BUD used in combination with FF (Symbicort).

For each ICS, the appropriate comparators are the other ICS. For each combination inhaler, the appropriate comparators are ICS alone, ICS and LABA in separate inhalers, and the other combination inhaler.

The BTS/SIGN Guidelines[1] are the context in which the decision problem is set. These are outlined in section 3.3.1. Using the steps in the guidelines, the following specific review questions were identified:

1. At low doses (200 – 400µg BDP per day or equivalent), which is the most clinically and cost-effective of the three ICS? (Step 2 of the guidelines)

   The relevant population for which this intervention should be considered is children with asthma who have been treated at Step 1 or Step 2 of the guidelines i.e. they have either not been treated with corticosteroids previously or have received low doses (as defined above) of ICS.

2. At high doses (400-800µg BDP per day or equivalent), which is the most clinically and cost-effective of the three ICS? (Step 4 of the guidelines)

   The relevant population for which this intervention should be considered is children with asthma who have been treated at Step 2-3 of the guidelines i.e. they have been treated with ICS previously in conjunction with other treatments such as LABAs. They should not be steroid-naïve.

3. Which is the more clinically and cost-effective approach to introducing a LABA into a treatment regimen:

   a. To increase the dose of ICS alone or to add a LABA to treatment with ICS? (Steps 2-3 of the guidelines)

   b. To continue with an ICS alone or to add a LABA to treatment with a similar dose of ICS using a combination inhaler? (Steps 2-3 of the guidelines)

The relevant population for which this intervention should be considered is children with asthma who have been treated at Step 2 of the guidelines i.e. they have been treated with low dose ICS previously. They should not be steroid-naïve.

Question 3a is viewed as the more clinically relevant of the two sub-questions, because if patients remain uncontrolled on lower dose ICS alone, treatment protocols in line with the BTS/SIGN Guidelines would indicate that either the ICS dose is increased, or a LABA is added to the lower dose of ICS. However, the literature searches conducted for the present assessment also identified trials in which a LABA was added to the ICS treatment regimen without the dose of ICS alone being increased. Whilst this treatment strategy is not in line with that advocated in the BTS/SIGN Guidelines for completeness these studies are included in the clinical effectiveness review as a separate sub-question. This sub-question is not addressed in the cost-effectiveness evaluation.

4. Which is the more clinically and cost-effective treatment:

   FP and SAL in a combination inhaler or given in separate inhalers?

   BUD and FF in a combination inhaler or given in separate inhalers?

5. Which is the more clinically and cost-effective treatment: FP/SAL in a combination inhaler or BUD/FF in a combination inhaler? (Step 3 of the guidelines)

   The relevant population for which these interventions should be considered is children with asthma who have been treated at Step 2 of the guidelines i.e. they have been treated with low dose ICS previously. They should not be steroid-naïve.

Within the context of the BTS/SIGN guidelines, it is generally accepted that the following are clinically equivalent doses: BDP 400µg, BUD 400µg, and FP 200µg. Studies which compare these drugs at these dose ratios, delivered through similar devices, are thus the most appropriate method for testing this hypothesis.

The clinical effectiveness of treatments for asthma can be assessed against a wide variety of outcome measures, which can be broadly divided into the following categories:

- Objective measures of lung function e.g. FEV_1, PEFR

- Symptoms e.g. Nocturnal waking, morning cough, symptom-free days and nights, symptom scores
- Use of rescue medication e.g. SABAs, short courses of oral corticosteroids
- Acute exacerbations, defined in a number of ways e.g. increase in symptoms, increased use of rescue medication or contact with health services
- Adverse events
- Health-related quality of life (HRQoL)
- Mortality

Whilst there is some evidence of the minimally perceived change in PEFR considered to be clinically relevant by patients, for the majority of the above outcome measures it is unclear for which, if any, there is a generally accepted definition of the minimum level of change that is clinically significant.

5. Assessment of clinical effectiveness

SECTION CONTENTS

5.1 Methods for reviewing effectiveness

A peer-reviewed protocol was published in May 2006 on NICE's website and circulated amongst the Consultees, outlining the agreed scope and methodology for this assessment.[185] This was based upon the scope of the appraisal as published by NICE.[186]

The scope proposed that the assessment be conducted within the context of the stepwise approach as advocated by the BTS/SIGN Guidelines.[1] As far as possible these guidelines have been taken into account in the assessment of clinical effectiveness.

An over-arching philosophy of the assessment of clinical effectiveness was the need to capitalise, where possible, on existing evidence syntheses of the effectiveness of ICS and LABAs for chronic asthma. A number of systematic reviews have been published on The Cochrane Database of Systematic Reviews, some of which are relevant to the scope of this assessment,[187-191] although their aims and inclusion criteria vary in places to those of the current assessment. Where relevant we have built upon the data presented in these reviews.

5.1.1 Identification of studies

A search strategy for electronic bibliographic databases was devised and tested by an experienced information scientist (Appendix 3). Once finalised it was applied to a number of databases including: The Cochrane Database of Systematic Reviews (CDSR); The Cochrane Central Register of Controlled Trials; Database of Abstracts of Reviews of Effectiveness (DARE); the NHS Economic Evaluation Database (NHS EED); Medline (Ovid); Embase (Ovid); National Research Register; Current Controlled Trials; ISI Proceedings (Web of Knowledge); Science Citation Index (Web of Knowledge); and BIOSIS.

Searches were run up to February/March 2006, and were restricted to studies published in English. An update search was conducted in October 2006 to identify any relevant studies published since the original search.

The drug manufacturers' submissions to NICE, which we received in August 2006, were also searched for potentially relevant trials.

All identified studies were downloaded into a Reference Manager database for storage and retrieval as necessary. A keywording system was devised to enable each reference to be categorised according to pre-specified inclusion and exclusion criteria (see Section 5.1.2).

5.1.2 Inclusion and exclusion criteria

The inclusion and exclusion criteria were specified *a priori* based on the scope issued by NICE,[186] as agreed in the published protocol[185]

5.1.2.1 Intervention

Trials reporting evaluations of the following ICS were included:

- BDP
- BUD
- FP

Trials reporting evaluations of the following ICS combined with LABAs in the same inhaler (i.e. combination inhalers) were included:

- BUD/FF (in children over six years)
- FP/SAL (as xinafoate) (in children over four years)

Trials reporting ICS delivered by pMDIs and DPIs were included, those using nebulisers were excluded.

To be included the intervention had to last for more than four weeks.

5.1.2.2 Comparators

The ICS were compared with each other.

The combination inhalers were compared with: each other; and with ICS only. They were also compared with ICS and LABAs administered in separate inhalers.

Trials testing only different doses of the same agent were not included as these were outside the scope of the assessment. (NB. Cochrane systematic reviews of different doses of BUD,[192] BDP[193] and FP[194] are available). Trials which compared more than one dose of an ICS with a different ICS were included.

Trials testing different drugs by different inhalers or propellants were not included (e.g. DPI vs pMDI, or HFA pMDI vs CFC pMDI). The role of delivery device has been assessed by a published systematic review,[195;196] which found that there was no evidence for differences in effectiveness between different types of hand held inhaler. However, some clinical trials of different ICS identified in our literature search were specifically designed to demonstrate superiority of one device over another, or in some cases that one inhaler device can be used to achieve comparable asthma control at a lower ICS dose than an alternative device. For this reason we chose to limit the review to comparisons of different ICS via the same type of inhaler or propellant in order to reduce any potential confounding associated with devices.

Trials reporting comparisons between ICS and placebo were sought and included in order potentially to support economic modelling (e.g. to provide estimates for model parameters). Details of these studies are not reported in the clinical effectiveness review.

5.1.2.3 Types of studies

Fully published randomised controlled trials (RCTs) or systematic reviews of RCTs. Double blinding was not a pre-requisite for inclusion, although blinding was assessed as part of critical appraisal (see Section 5.1.4). Indicators of a 'systematic' review include: explicit search strategy, inclusion criteria, data extraction and assessment of quality.

Trials reported in abstracts or conference presentations from 2004 onwards were retrieved, however their details were not extracted, critically appraised or analysed (however, details were extracted where an abstract was available which provided data supplementary to a fully published trial report of a particular study; this occurred in a handful of cases).

Where unpublished full trial reports were available (e.g. as supplied by the drug manufacturers in their submissions to NICE) these were included.

5.1.2.4 Population

Children aged under 12 years diagnosed with chronic asthma (NB. the mean age of the study population had to be 12 years or under). Studies in which the patient group was asthmatics with a specific related co-morbidity (e.g. cystic fibrosis) were not included.

Studies reporting the treatment of acute exacerbations of asthma were not included.

Trials reporting the effectiveness of ICS with LABAs were only included if the patients had been previously treated with an ICS. Trials assessing the effectiveness of initiating treatment with ICS in combination with LABAs in steroid naïve patients are not within the context of the BTS/SIGN Guidelines.

5.1.2.5 Outcomes

At the screening stage studies reporting one or more of the following outcomes were included:

- objective measures of lung function (e.g. FEV_1, PEFR)
- symptoms (e.g. symptom-free days and nights)
- incidence of mild and severe acute exacerbations (e.g. mild – requiring unscheduled contact with healthcare professional; severe – requiring hospitalisation, systemic corticosteroids or visit to accident and emergency department).
- use of systemic corticosteroids
- adverse effects of treatment
- health-related quality of life
- mortality

A list of specific measures for each of these outcomes was devised for the data analysis (see Section 5.1.5.1).

Titles and abstracts of studies identified by the searches were screened by one reviewer based on the above inclusion/exclusion criteria. A second reviewer checked a random 10% of these. Any discrepancies were resolved through discussion and involvement of a third reviewer where necessary.

Full papers of studies included on title or abstract were requested for further assessment. All full papers were screened independently by one reviewer and checked by a second. Any discrepancies were resolved by discussion with involvement of a third reviewer where necessary.

All included papers were keyworded in the Reference Manager database as to their intervention and comparator, and were coded for the synthesis framework (see Section 5.1.5) to enable efficient retrieval of sub-sets of studies for analysis.

As far as possible all included papers describing a particular trial were linked together to form a 'set' of studies. One of the papers (usually the seminal journal article reporting the key efficacy and safety results) was designated as the primary publication, with the remaining papers classed as secondary publications.

All included trials were cross-referenced with the relevant Cochrane reviews to ascertain whether or not they had already been included in the reviews.[187-191] Those that were included were keyworded in our Reference Manager database accordingly. Conversely, the bibliography of included studies in the relevant Cochrane reviews were cross-referenced with our list of included studies and our inclusion criteria to ascertain whether there were any relevant studies in those reviews that had not been identified by our search.

5.1.3 Data extraction strategy

All trials, except those included in the relevant Cochrane reviews, were fully data extracted. Data were entered into a structured template by one reviewer and checked by a second. Any discrepancies between the data extracted and the original trial report were resolved and the data extraction finalised (see Appendix 4). Data on the studies that met our inclusion criteria and which were also included in the Cochrane reviews are available from the reviews themselves.[187-191]

5.1.4 Critical appraisal strategy

The methodological quality of the trials supplemental to the Cochrane reviews was assessed according to criteria specified by the Centre for Reviews and Dissemination (CRD) .[197] (see Appendix 4). Quality was assessed by one reviewer and their judgements were checked by a second. Where there was disagreement a third reviewer was consulted and a final judgement agreed. Judgements about the quality of the trials included in the Cochrane reviews can be found by consulting the relevant review.[187-191]

5.1.5 Methods of data synthesis

Results of the included trials were synthesised narratively (see Section 5.1.5.1) with use of meta-analyses where possible and appropriate (see Section 5.1.5.2). A framework was devised for the analysis and presentation of results, based on the step wise approach recommended in the BTS/SIGN Guidelines.[1]

The review questions were:

1. Which ICS is the most effective at low doses (200 – 400μg per day BDP/BUD equivalent[*]) (Step 2 of the guidelines)

2. Which ICS is the most effective at high doses (400 to 800μg per day BDP/BUD equivalent[†]) (Step 4 of the guidelines)

3. Which is more effective – an ICS or a combination inhaler containing an ICS and a LABA? (Step 2/Step 3 of the guidelines)

   This question is sub-divided based on two categories of trials:

   3a. where the dose of the ICS is higher when used alone, compared to the dose in the combination inhaler.

   3b. where the dose of the ICS is the same/similar in both treatments

4. Which is more effective – an ICS and a LABA administered in separate inhalers or in a combination inhaler?

5. Which is the more effective – a combination inhaler containing FF and BUD, or a combination inhaler containing SAL and FP?

Each included trial was coded according to which of the review questions it was relevant to. For example, a trial comparing 200μg per day of BDP with 200μg per day of BUD was assigned to review question 1, as it evaluated low dose ICS. Some trials were relevant to more than one review question as they tested multiple doses of inhaled steroids, some of which were relevant to review question 1 (i.e. low dose), and some which were relevant to question 2 (i.e. high dose).

[*] For FP the equivalent doses are 100 to 200μg per day (children over 4 years).

[†] For FP high dose is up to 200μg to 400μg per day (children over 4 years).

Each review question was stratified according to a number of pair-wise comparisons of the inhaled steroids and, where relevant, LABAs (where evidence allows). In addition, some trials were included in more than one pair-wise comparison as they evaluated two or more ICS (e.g. a three arm trial comparing FP with BUD and BDP).

Trials were also divided according to whether or not a parallel-group or cross-over design was used. It is generally considered inappropriate to pool these designs together within meta-analyses.[198] Where necessary trials were then further divided according to the nominal dose ratio employed, following the approach used in the Cochrane review of FP compared to BUD or BDP.[188] Some trials aimed to test the equipotency of different inhaled steroids, particularly newer steroids such as FP compared to the older steroids such as BDP and BUD. Therefore dose ratios of 1:2 or higher are common in the literature. Separate analyses of the ratios was necessary to reduce the risk of confounding associated with comparing trials with differing doses.

In summary, the framework comprised sets of trials grouped according to which review question, pair-wise comparison, study design and dose ratio they related to. For example:

- Review question1: low dose ICS
  - Pair-wise comparison: BDP versus FP
    - Parallel-group trial 1:1 ratio
    - Parallel-group trial 1:2 ratio
    - Cross-over trial 1:1 ratio
    - Cross-over trial 1:2 ratio

It was anticipated that this framework would result in generally smaller sets of studies in each analysis, as opposed to a larger set with potentially more statistical power to identify effects. However, a framework such as this was essential in order to embed the review within the context of the BTS/SIGN Guidelines[1] (as stipulated in the scope for the appraisal issued by NICE) and to reduce the likelihood of confounding due to differences in trial design and dose ratio.

5.1.5.1 Narrative synthesis

As described above, the narrative synthesis comprises a framework whereby trials are summarised according to which review question, pair-wise comparison, study design and dose ratio they were relevant to. The results sections are organised according to this framework.

Within each pair-wise comparison all included trials were tabulated for their key characteristics, and described in the text (e.g. trial duration, patient profile, outcome measures, methodological quality). In addition, more detailed data on the trials are available in Appendix 5, for those trials which were supplemental to the Cochrane reviews and which underwent full data extraction. Further details of the remaining studies are available in the relevant Cochrane reviews. Each outcome measure is presented in turn and the key results are reported in the text.

There are numerous ways of measuring and reporting outcomes from asthma trials. For brevity we only report the following measures:

- Lung function - FEV_1 litres; FEV % predicted; morning/evening PEFR (litres per minute).
- Symptoms - Days/nights without symptoms; total daily symptom scores
- Health related quality of life - Total HRQoL scores
- Use of rescue medication - Mean number of puffs per day of SABA
- Exacerbations: Number and/or rate of exacerbations, where author's definition of exacerbations is not covered by one of our existing outcomes.
- Adverse events - Number and/or rate of adverse events; number and/or rate of serious adverse events; number and/or rate of withdrawals due to adverse events; urinary/serum cortisol; bone mineral density; growth.

5.1.5.2 Meta-analysis

The feasibility and appropriateness of meta-analysis was considered once narrative syntheses had been completed. The decision to pool was influenced by the likelihood that the trials were clinically homogeneous, and that the necessary data were available. Potential clinical heterogeneity was assumed if there were differences between trials in:

- Dose
- Disease severity
- Treatment duration

To some extent the potential for clinical heterogeneity was reduced by virtue of the framework used for the review, whereby studies were grouped into sets according to whether a high or a low dose of ICS was used. Nonetheless, even within the low and high dose review questions the dose ranges can be relatively wide. It could also be argued that dose is a proxy for severity, with less severe asthmatics treated with lower doses, and vice versa, although this is a generalisation. It was therefore important to consider severity as a potential source of heterogeneity. Furthermore, the influence of trial duration cannot be discounted. Whilst trials lasting around three months are common, some are designed to evaluate longer term effects on asthma control and adverse effects. Such trials are likely to have differing aims and consequently, if they appeared to be diverse in terms of the above factors, they were not pooled.

5.2 Results

5.2.1 Quantity and quality of research available

A total of 5,175 records of publications were identified through literature searching. Of these, 4,365 were excluded on title and abstract. Full reports for the remaining 807 were requested for more in-depth screening. Of these, 34 records describing 25 studies were included. Searches for this report were combined with the accompanying report on ICS in adults and children aged 12 years and over. Consequently, a proportion of the 807 papers screened were included in that report.[199]

Of the 25 studies:

- 3 were conference abstracts published from 2004 onwards (Bibliographic details of these are listed in Appendix 6).
- 6 were systematic reviews (of which 5 were Cochrane reviews) (These are reported in Section 5.2.8).
- 16 were fully published RCTs (of which 12 had been included in the Cochrane reviews)

Updated searches conducted in October 2006 yielded a total of 245 records of publications, of which 26 were inspected on full report. Of these two studies (one RCT, one systematic review) appear relevant and would be eligible for inclusion in any future update and their bibliographic details are listed in Appendix 5). In all but one of the 16 RCTs the mean age was under 12, in line with our inclusion criteria. The exception was the study by O'Byrne and colleagues,[200] in which mean age was 36 years (range 4-79). Approximately 12% of participants were under the age of 12 and results for growth and cortisol levels are reported separately for this group. The age range in the RCTs varied, but generally ranged from four to 19 years. It should therefore be acknowledged that there is a slight overlap with some of the studies in adolescents over the age of 12 included in the accompanying report on ICS in adults and children over the age of 12.[199] Notably absent from the evidence base are studies in children and infants aged under four years.

Table 4 to *Table 9* provide a breakdown of the number of RCTs for each pair-wise comparison between the three ICS within each review question. There are equal numbers of trials reporting on low and high dose ICS (seven in each case). There is very little evidence for the efficacy and safety of ICS in combination with LABAs.

TABLE 4 *Breakdown of studies for Review Question 1 – low dose ICS*

Pair-wise comparison	**Number of RCTs included**
BDP and BUD	1
FP and BDP	2
FP and BUD	2
Total	5

TABLE 5 *Breakdown of studies for Review Question 2 – high dose ICS*

Pair-wise comparison	**Number of RCTs included**
BDP and BUD	1
FP and BDP	3
FP and BUD	3
Total	7

TABLE 6 *Breakdown of studies for Review Question 3a – ICS vs ICS + LABA (ICS dose higher when used alone)*

Pair-wise comparison	Number of RCTs included
BUD vs BUD + FF	1
Total	1

TABLE 7 *Breakdown of studies for Review Question 3b – ICS vs ICS + LABA (ICS dose similar in both treatments)*

Pair-wise comparison	Number of RCTs included
FP vs FP + SAL	1
BUD vs BUD + FF	1
Total	2

TABLE 8 *Breakdown of studies for Review Question 4 – combination inhaler vs separate inhalers*

Pair-wise comparison	Number of RCTs included
FP/SAL (combination) vs FP + SAL (separate)	1
Total	1

TABLE 9 *Breakdown of studies for Review Question 5 – combination inhaler vs combination inhaler*

Pair-wise comparison	Number of RCTs included
FP/SAL (combination) vs BUD + FF (combination)	0
Total	0

The 16 RCTs are described in the following sections in terms of their characteristics and results.

5.2.2 Q1: Effectiveness of low dose ICS

5.2.2.1 Low dose ICS: BDP and BUD

5.2.2.1.1 Study characteristics

Only one RCT, published in 1988, evaluated the effects of BUD compared to BDP in children[201] (*Table 10*). It was a small, multi-centre study conducted in six centres in Denmark, and involving 41 children. The trial was a double-blind, parallel-group design, containing two arms.

The trial incorporated a stepwise increase in ICS, and consisted of three four-week periods with successive daily doses of 200µg, 400µg, and 800µg of either BDP or BUD. Thus, the comparison of the two drugs was at a dose ratio of 1:1 throughout the study. Although 800 µg is regarded as a high dose of BDP and BUD, the comparison by Bisgaard and colleagues[201] is included in this (low-dose) review question as opposed to question 2, because two-thirds of the treatment duration involved lower doses (200 µg and 400 µg), and effects of the higher dose would not have been independent of the preceding lower doses. The drugs were both delivered via an aerosol pMDI inhaler device (BDP was purchased commercially and it is not stated explicitly, but can be deduced from the text that BUD was provided by AstraZeneca Pharmaceutical). The treatment period was three months in total (four weeks for each of three successive doses).

Children who completed the trial were aged between 5-17 years, with a mean age of about 11 years. Although all the children were using SABAs and almost half were using theophylline daily, none had used ICS therapy during the preceding six months. The severity of asthma was not specifically stated and baseline FEV_1 % predicted was not reported.

The rationale of the study was primarily to evaluate the effect of ICS in varying doses on adrenal function (as an indicator of systemic effects). A secondary aim was to investigate whether BUD offered an improved ratio between the beneficial ICS effect and undesirable systemic activity compared to BDP. The primary outcome was a measure of adrenal function using biochemical measurements.

TABLE 10 *Study characteristics (BDP and BUD)*

Study ID	Design	Intervention	Patients	Outcomes
Bisgaard et al. (1998)[201]	RCT Multi-centre Parallel-group Dose-escalation Double-blind	*Drugs:* 1. BDP step-wise increased doses: 200, 400, 800µg/daily 2. BUD step-wise increased doses: 200, 400, 800µg/daily Successive doses (200, 400, 800µg/d) were given for 4 week periods in succession with no washout between each dose. *Delivery device:* 1. pMDI (purchased commercially, no other details reported) 2. pMDI (Pulmicort, Astra Pharmaceutical*) *Duration:* 3 mths *Run in period:* 2 wks	*Number randomised* 41 *Age range* 7-15 years *Baseline FEV_1 % predicted* Not reported *Previous ICS treatment (drug and dose)* None during previous 6 mths	*Outcomes* Adrenal function evaluated by: 24 hr urinary free cortisol excretion urinary cortisol metabolites plasma cortisol 30 min post 125µg iv tetracosactrin (nmol/L) PEFR % predicted am & pm Rescue SABA use Adverse effects
* not stated explicitly, deduced from the text				

In terms of methodological quality, details of the randomisation procedure were not reported, and thus concealment of allocation was unknown. The study did not perform intention-to-treat analysis as the analysis was only carried out on all children completing the trial (n=30). The eligibility criteria were not adequately specified. The trial was double-blind, although due to the dose variation, the trial was blind to drug but not dose.

5.2.2.1.2 Results

Lung function

The study did not present any values for lung function. However, the authors reported that the morning and evening PEFR was not different between treatment groups (presented as the average PEFR during the last 10 days of the first trial period (200μg/day)), nor did it change significantly with the increase in ICS dose (p>0.1).

Symptoms

The trial did not report symptom scores as an outcome measure.

Use of rescue medication

As for lung function, the study did not present any data for rescue medication use, but did state that there were no differences between the two drugs. Similarly, the use of SABAs did not change significantly with the increase in ICS dose (p>0.1).

Exacerbations

The trial did not report the incidence of asthma exacerbations as a specific outcome measure. However, two children withdrew from the study due to a severe exacerbation of asthma (one in each treatment group).

Adverse events

The authors stated that there were very few adverse effects in the two groups, with no dose-related trend. Six of the eleven children who withdrew from the study did so because of adverse events (two BDP, four BUD).

There was no significant difference (*p*=0.207) between treatments in suppression of diurnal urinary free cortisol when doses were ignored, whereas differences between doses were highly significant when treatment was ignored (*p*=0.004). Data (extracted from a graph by the reviewers) indicate that the mean urinary free cortisol concentrations after the treatment with 200µg, 400µg and 800µg doses respectively were (approximately) 82 nmol/g, 72 nmol/g and 54 nmol/g for BDP and 76 nmol/g, 56 nmol/g and 69 nmol/g for BUD. Confidence intervals or error bars were given for these data but cannot be interpreted as their units were ambiguous.

5.2.2.1.3 Summary

Only one small, multi-centre, parallel-group trial evaluated the effects of BUD compared to BDP in children. Treatment with increasing doses of BDP, but not BUD, resulted in a significant decline of adrenal function, but the overall effect on adrenal function did not differ significantly between the groups. The groups were also similar in terms of the effects on lung function (PEFR), use of rescue medication and safety.

5.2.2.2 Low dose ICS: FP and BDP

5.2.2.2.1 Study characteristics

There are two trials in this section, by Gustaffson and colleagues[202] and Rao and colleagues[203] (*Table 11*). Both trials were parallel group studies, comparing FP 200µg /day with BDP 400µg /day (i.e. a dose ratio of 1:2). The studies both had two active treatment arms, but the study by Rao and colleagues[203] also had a placebo arm. Duration of the trials ranged from six weeks[202] to 20 months.[203] The six-week study by Gustafsson and colleagues[202] was a large multi-centre trial (32 centres in 11 countries) with 398 children aged from four to 19 years, who were inadequately controlled on current treatment. The other trial was smaller, and the number of centres was not reported. Rao and colleagues[203] recruited 23 steroid naïve children with moderately severe asthma aged five to 10 years.

TABLE 11 *Study characteristics (FP and BDP)*

Study ID	Design	Intervention	Patients	Outcomes
Gustafsson et al. (1993)[202]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP 100µg b.i.d. (daily total 200µg) 2. BDP 200µg b.i.d. (daily total 400µg) *Delivery device:* 1, 2. MDI +large volume spacer (no further details about devices reported) *Duration:* 6 wks *Run in period:* 2 wks (usual medication)	*Number randomised* 398 1. 197 2. 201 *Mean age (range)* 1. 10 (4-19) years 2. 11 (4-18) years *Mean baseline FEV_1 % predicted* 1. 88.9 % 2. 87.8 % *Previous ICS treatment (drug and dose)* Either received ICS up to 400µg or received a bronchodilator, ketotifen or sodium cromoglycate but asthma inadequately controlled.	*Outcomes* Change in FEV_1 (L) Change in FEV_1 (% predicted) Change in clinic PEFR (% predicted) Change in am & pm PEFR (% predicted) Diurnal variation in PEFR % symptom-free days % symptom-free nights % SABA free days Adverse events

Study ID	Design	Intervention	Patients	Outcomes
Rao *et al.*(1999)[203]	RCT Parallel-group Double-blind	*Drugs:* 1. FP 100µg b.i.d. (daily total 200µg) 2. BDP 200µg b.i.d. (daily total 400µg) 3. Placebo (for 10 wks before merging with the FP arm) *Delivery device:* 1. + 2. MDI + spacer (no further details about devices reported) *Duration:* 20 mths *Run in period:* 2 wks	*Number randomised* 23 (not broken down by group) *Mean (SEM) age* 1. 6.68 (0.57) years 2. 6.93 (0.61) years 3. 6.77 (0.61) years *Mean (SEM) baseline FEV_1 % predicted* 1. 90.8 (4.7) % 2. 79.3 (5.5) % 3. 94.4 (4.7) % *Previous ICS treatment (drug and dose)* Steroid naïve	*Outcomes* FEV_1 (% predicted) $FEF_{25\text{-}75}$ Post exercise fall in FEV_1 AM plasma cortisol Log PC_{20} for Histamine (the provocative concentration of histamine causing a 20% fall in FEV_1) Daily asthma symptom score Bone mineral density by dual energy x-ray absorptometry Serum & urine markers of bone turnover Height assessment

Participants in both trials used a MDI and spacer (no further details about the devices were reported).

Both studies were described as being double-blind and randomised, but no details were given on the randomisation procedure, concealment of allocation or blinding. Only Gustafsson and colleagues[202] reported a power calculation (the outcome used was PEFR) and neither of the trials stated that they used an intention-to-treat analysis. In the study by Rao and colleagues,[203] the three arms ran for 10 weeks. After this period, the placebo arm merged with the FP arm as it was considered unethical to continue the placebo for longer, thus breaking randomisation. Therefore we only report results for the first 10 weeks, where data were available in the trial report. Unfortunately the number of children originally randomised to the three groups was not stated; when merged there were 15 children in the FP arm and eight in the BDP arm.

The participants were similar at baseline in the study by Gustafsson and colleagues[202] and withdrawals were described (nine patients in total, four from the FP arm and five from the BDP arm). All patients in Rao and colleagues'[203] study completed the initial 10 weeks and were well matched (except for immunoglobulin E levels, which were significantly higher in the BDP group).

The overall aim of the study by Gustafsson and colleagues[202] was to compare the efficacy and safety of FP with BDP. Rao and colleagues[203] were predominantly interested in comparing the effect of FP with BDP on growth and bone turnover.

5.2.2.2.2 Results

All results refer to parallel 1:2 dose ratio comparisons. Meta-analysis was not possible due to different outcomes being reported in each study.

Lung function

FEV_1 (L)

FEV_1 at end-point (week 6) reported by Gustafsson and colleagues[202] was 2.19 L for the FP group (n=190) and 2.26 L for the BDP group (n=198) but it was not reported whether this difference between the groups was statistically significant. No data on FEV_1 during the first 10 weeks were given by Rao and colleagues.[203]

Only Gustafsson and colleagues[202] reported the FEV_1 change from baseline. This was 0.12 L in the FP group and 0.15 L in the BDP group, adjusted for baseline, age and country. Neither of these changes from baseline was statistically significant. It was not reported whether these changes from baseline differed significantly between the groups.

FEV_1 % predicted

The FEV_1 % predicted reported by Gustafsson and colleagues[202] at end-point (week 6) was 94.1% in the FP group (n=190) and 94.1% in the BDP group (n=193). These identical mean values imply no difference between the groups (no statistics were reported for this comparison).

Rao and colleagues[203] presented the FEV_1 % predicted data in a graph, from which the data at 10 weeks have been extracted by the reviewers (after 10 weeks, the FP group was merged with the placebo group). In the FP group the baseline mean ± SEM was estimated to be 90% ± 10% and the end-point (10-week) value was 96% ± 12%. In the BDP group the corresponding baseline and end-point values were 80% ± 12% and 81% ± 12% respectively. No statistical tests of the difference between groups at 10 weeks are available.

Morning PEFR L/min

In the study by Gustafsson and colleagues,[202] the mean baseline morning PEFR and the change in morning PEFR from baseline for the FP group were 318 L/min and 24 L/min respectively. For the BDP group the respective values were 329 L/min and 19 L/min. No variances or *p*-values for these differences were presented. Rao and colleagues[203] did not report this outcome measure.

Evening PEFR L/min

In the study by Gustafsson and colleagues,[202] the mean baseline evening PEFR and the change in evening PEFR from baseline for the FP group were 326 L/min and 21 L/min respectively. For the BDP group the respective values were 340 L/min and 16 L/min. As with the morning PEFR, no statistical information was provided for these differences. Rao and colleagues[203] did not report this outcome measure.

Symptoms

Rao and colleagues[203] presented daily summary scores for the entire 82-week study period but not for the initial 10 week period of interest. Gustafsson and colleagues[202] did not present daily summary scores as an outcome measure, but did report that there were no statistically significant differences between treatments in the percentage of symptom-free days or nights (no data or significance values were reported).

Use of rescue medication

Neither of the studies presented data in terms of mean number of inhalations per day.

Exacerbations

Only Gustafsson and colleagues[202] reported this outcome. They did not present the total number of exacerbations; however, three patients from each group withdrew because of exacerbations.

Adverse events

In the study by Gustafsson and colleagues,[202] 99 patients reported 155 adverse events (three described as serious) in the FP group and 95 patients reported 153 adverse events (two described as serious) in the BDP group. Rao and colleagues[203] did not present any data on adverse events. They measured growth and bone density and reported a significantly higher growth rate in the FP-treated group (difference 0.81 cm/year, 95% CI 0.45 to 1.16 cm/year, no *p*-value given). However, the timing of these measurements is not relevant to the initial 10 week period of interest (bone density was measured over 20 months), or was unclear (the timing of the growth measurements was not stated).

Gustafsson and colleagues[202] found no significant difference between the two treatments in the effect on plasma cortisol. They reported that the ratio of FP to BDP [sic] was 1.00 (95%CI 0.91 to 1.09; p=0.989), but the meaning of this statement is unclear. In the study by

Rao and colleagues,[203] there was a significant drop in the plasma cortisol from baseline to 10 weeks in the BDP group (95% CI for the difference 44.64 to 254.50 nmol/L^{-1}, *p*=0.010), although the absolute values were still within the normal range. The corresponding 95% CI for the difference in the FP group was -149.91 to 260.25, *p*=0.52. Statistics for the between group differences were not presented.

5.2.2.2.3 Summary

Two studies compared the efficacy and safety of FP and BDP in children. These studies differed considerably in their size and patient populations: one was with steroid-naive patients, the other with patients on ICS that inadequately controlled their asthma. The studies tended to report different outcomes which precluded meta-analysis. Only one of them presented statistical information about differences between the drugs. Overall, these studies do not appear to support the superiority of either FP or BDP. The adverse effects profiles appear similar for the two drugs, although one study found a statistically significant drop in plasma cortisol levels in the BDP arm (but with absolute values within the normal range), but a similar change was not seen in the BDP arm.

5.2.2.3 Low dose ICS: FP and BUD

5.2.2.3.1 Study characteristics

Two RCTs, by Agertoft and Pedersen[204] and Altintas and colleagues,[205] investigated the effectiveness of BUD versus FP in children (*Table 12*). The studies were published in 1997[204] and 2005.[205] Both trials used a parallel group design (assumed from the text rather than explicitly stated in one trial[205]). The trials varied in sample sizes from 30 to 217 patients, and both were single-centre studies.

Altintas and colleagues[205] conducted a three-armed study, using a control group, but no details were supplied about the group. The study by Agertoft and Pedersen[204] contained two arms. The former study[205] compared total daily doses of 250μg of FP and 400μg of BUD, approximating a nominal dose ratio of 1:2. The latter study[204] used a starting total daily dose of 200μg or 400μg for both drug treatments, equivalent to a 1:1 ratio, with dose reductions of 50% at five-week intervals.

TABLE 12 *Characteristics of studies (FP and BUD)*

Study ID	Design	Intervention	Patients	Outcomes
Agertoft & Pedersen (1997)[204]	RCT Parallel-group Double-blind, double-dummy	*Drugs:* 1. FP 100µg or 200µg b.i.d.* (daily total 200µg or 400µg) 2. BUD 100µg or 200µg b.i.d.* (daily total 200µg or 400µg) *After 5 wks reduced to 100µg b.i.d. - reduced by 50% every 5 wks until deterioration in asthma control or acceptable asthma control achieved *Delivery device:* 1. Diskhaler DPI 2. Turbuhaler DPI (no further details about devices were reported) *Duration:* Varied among patients up to 15 wks. Data for most outcomes reported for 5 wks. *Run in period:* 2 wks	*Number randomised* 217 *Mean age (range)* 1. 9.9 (5-15) years 2. 10.1 (5-16) years *Mean ± SD baseline FEV_1 % predicted* 1. 91.9 ± 14.6 % 2. 93.8 ± 13.3 % *Previous ICS treatment (drug and dose)* BUD 400 or 800µg/daily from pMDI with large volume spacer (Nebuhaler)	*Outcomes* AM & PM PEFR FEV_1 FEF_{25-75} Dose reduction steps from baseline Minimal effective ICS dose (µg daily) Asthma symptom scores Rescue SABA use Urine cortisol excretion

Study ID	Design	Intervention	Patients	Outcomes
Altintas et al (2005)[205]	RCT Parallel-group	*Drugs:* 1. FP 250µg/q.d 2. BUD 400µg/daily 3. (non randomised) control group *Delivery device:* 1, 2. no details of device reported *Duration:* 12 mths *Run in period:* Not reported	*Number randomised* 30 *Mean age (range)* 1. 9.6 ± 2.4* (6-12) years 2. 10.6 ± 2.1* (7-13) years *Mean baseline FEV_1 % predicted* 1. 60.6 ± 9.4* % 2. 60.6 ± 9.4* % *statistics (not stated) are assumed to be SD *Previous ICS treatment (drug and dose)* Children with moderate asthma	*Outcomes* Anthropometric measurements: Body mass index Growth rate Pulmonary functions: FVC PEFR FEV_1 Bone metabolism: Serum calcium Serum phosphorus Serum ALP Bone mineral density Adrenal functions: Basal am serum cortisol level Free cortisol in 24hr urine collection Urine & calcium 7 creatinine ration ACTH stimulation test Symptom score

Altintas and colleagues[205] used pMDI devices for both drugs (no further details on devices were reported). The Agertoft and Pedersen[204] study used a Turbuhaler for BUD and a Diskhaler for FP (both branded forms of DPI). The former study[205] had a treatment duration of 12 months, but the duration of the latter[204] varied among patients, with dose reductions by 50% at five-week intervals until deterioration in asthma control or acceptable asthma control was seen. Data on most of the outcomes reported in that study were presented only for the first five weeks.

There was some variation in terms of the aims of the studies. Altintas and colleagues[205] did not specifically state whether the intention was to assess equivalence or superiority between treatments. Rather, the focus was on the adverse effects of ICS therapy on growth in children. Agertoft and Pedersen[204] aimed to determine the equipotency of the inhaled steroids, whilst also defining the minimal effective doses with these delivery systems.

The age range of children in the RCTs was five to 16 years, and mean ages were in the range 9.6 to 10.6 years. Agertoft and Pedersen[204] reported children as having been treated previously with either 400 or 800µg of BUD, but no previous treatment details were reported by Altintas and colleagues.[205] The mean baseline levels for FEV_1 ranged from 60%[205] to around 90%.[204] One trial included children with moderate asthma,[205] but the other did not report asthma severity.[204] Neither of the studies specifically stated their primary outcomes.

The study by Agertoft and Pedersen[204] reported an adequate method of randomisation, but no details of the randomisation procedure were reported by Altintas and colleagues.[205] Neither of the studies reported an intention-to-treat analysis.

5.2.2.3.2 Results

Lung function

Both of the trials reported measures of lung function. However, pooling results for meta-analysis was not possible due to the differences in study design and methodology.

Parallel 1:1 dose ratio studies

Agertoft and Pedersen[204] reported a mean change from baseline to the end of the first treatment period (five weeks) in FEV_1 of 0.1 L for the FP group and <0.1 L for the BUD group. This difference between the groups was not statistically significant (95% CI -0.07 to 0.03, *p*=0.77).

The change in PEFR from baseline was presented as the difference between the mean PEFR at baseline and the mean PEFR during the last two weeks of the first five weeks of treatment (i.e. treatment weeks four and five). The change from baseline in morning PEFR was 7.6 L/min for FP recipients and 1.9 L/min for BUD recipients. This difference between groups was not statistically significant (95% -12.0 to 0.7, *p*=0.06). The corresponding results for evening PEFR were 5.1 L/min for FP recipients and -0.7 L/min for BUD recipients. This difference between groups was also not statistically significant (95% CI -12.1 to 0.6, *p*=0.06).

Parallel 1:2 dose ratio studies

Altintas and colleagues[205] provided data showing improvements after one year in FEV_1 % predicted for both BUD and FP. However, due to an error in reporting (identical data were presented for both groups), these results cannot be used.

Symptoms

Parallel 1:1 dose ratio studies

Agertoft and Pedersen[204] measured day-time and night-time symptom scores on a four-point scale (0=none, 3=severe, no reference supplied). The change from baseline in symptom scores was presented as the difference between the mean score at baseline and the mean score during the last two weeks of the first five weeks of treatment (i.e. treatment weeks four and five). The change in day-time asthma symptom scores was -0.11 for the FP group and -0.05 for the BUD group. This difference between the groups was not statistically significant (95% CI -0.08 to 0.20, *p*=0.37). The change in night-time asthma symptoms was -0.04 for patients on FP and -0.03 for patients on BUD. This difference between the groups was also not statistically significant (95% CI -0.07 to 0.09, *p*=0.75).

Parallel 1:2 dose ratio studies

Altintas and colleagues[205] provided data showing improvements in symptom scores after one year for both BUD and FP. However, due to an error in reporting (identical data were presented for both groups), these results cannot be used.

Use of rescue medication

Only Agertoft and Pedersen[204] reported use of rescue medication as an outcome. They presented data on the daily use of SABAs, but did not state whether these were the number of inhaler sessions per day or the number of puffs per day. The change from baseline was reported as the difference between the mean SABA use at baseline and the mean use in weeks four and five. SABA use remained relatively unchanged, with values of 0.02 for the FP group and 0.01 for the BUD group. This difference between the groups was not statistically significant (95% CI -0.20 to 0.18, p=0.87).

Exacerbations

Neither of the trials reported exacerbations of asthma as an outcome measure.

Adverse events

Neither of the studies reported the number of adverse events experienced by each treatment group, but other measures of safety or side effects were reported.

Parallel 1:1 dose ratio studies

Agertoft and Pedersen[204] reported the change in 24-hour urine cortisol excretion from baseline to five weeks. This was 6.6 nmol for the FP group and 1.8 nmol for the BUD group. The difference between the groups is not statistically significant (95% CI -10.9 to 1.3, p=0.13).

Parallel 1:2 dose ratio studies

Altintas and colleagues[205] reported growth rate (cm in one year). Growth increased at a similar rate and did not differ significantly between the groups (FP 8.2 cm/year, BUD 8.4 cm/year, $p>0.05$). In the same study, morning serum cortisol levels decreased in both groups at 12 months, with no statistically significant difference between BUD and FP ($p>0.05$). Bone mineral density was also comparable between groups, with no statistically significant difference ($p>0.05$).

5.2.2.3.3 Summary

Two studies compared the efficacy and safety of FP and BDP among children. These RCTs had different designs and used different nominal dose ratios (1:1 and 1:2). The more detailed of these studies was only five weeks in duration, with some outcomes reported as mean values for weeks four and five. No statistically significant differences were observed in measures of lung function when patients were treated with FP compared to treatment with BUD. Only one of the studies reported reliable symptom scores and a measure of safety (urine cortisol). Neither of these outcomes differed significantly between the treatment groups.

5.2.2.4 Summary of Q1: relative effectiveness of low dose ICS

BDP versus BUD, n=1 RCT

<table>
<tr><th rowspan="3">Daily dose</th><th rowspan="3">Studies, design, duration, device, number randomised</th><th rowspan="3">ICS in each trial arm</th><th colspan="12">Results</th></tr>
<tr><th colspan="3">Lung function</th><th colspan="4">Symptoms</th><th rowspan="2">HRQoL</th><th rowspan="2">Rescue medication</th><th rowspan="2">Exacerbations</th><th rowspan="2">Adverse events, % of patients</th><th rowspan="2">Adrenal markers</th></tr>
<tr><th>FEV$_1$</th><th>PEFR morning</th><th>PEFR evening</th><th>NW</th><th>SFD</th><th>SFN</th><th>SS</th></tr>
<tr><td rowspan="2">step-wise increased doses: 200, 400, 800µg/d</td><td rowspan="2">Bisgaard, 12w (3 x 4 wk) Parallel group, double-blind MDI; n=41</td><td>BDP</td><td></td><td rowspan="2">C</td><td rowspan="2">C</td><td></td><td></td><td></td><td></td><td></td><td rowspan="2">C</td><td></td><td>2 withdrawals</td><td rowspan="2">NSD</td></tr>
<tr><td>BUD</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>4 withdrawals</td></tr>
<tr><td colspan="15">NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies); C = stated to be comparable between trial arms but no tests of statistical significance reported. Blank cells signify no data reported on that outcome.</td></tr>
</table>

FP versus BDP n=2 RCTs

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results											
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients	Adrenal markers
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS					
200µg vs 400 µg	Gustafsson,* 6w Parallel group, double-blind MDI; n=398	FP					NSD	NSD					50% (3 serious)	NSD
		BDP	F *										47% (2 serious)	
	Rao,* 20m Parallel group, double-blind MDI; n=23	FP†	F											F
		BDP												

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies); N = number of events; NSD = no significant difference between trial arms; F = results appear favour treatment group, but no tests of statistical significance reported. Blank cells signify no data reported on outcome.

* Gustafsson *et al* reported within-group differences for measures of lung function, rather than between-group comparisons. Rao *et al.* presented FEV_1 data graphically with no between group comparisons; only symptom scores for the entire period (not for the initial 10 wk period of interest) were reported; AE outcomes were related to growth and bone turnover, therefore no usable data can be reported in the table. †This study had a third arm where patients received placebo for 10 wks and were then merged with the FP arm. * refers to FEV_1 L. Study also reports data for FEV_1% predicted, where the values were identical in both groups.

BUD versus FP n=2 RCTs

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results											
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients	Adrenal markers
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS					
200 or 400µg vs 200 or 400µg*	Agertoft, variable* Parallel group, double-blind DPI; n=217	FP	NSD	NSD	NSD				NSD		NSD			NSD
		BUD												
250µg vs 400µg	Altintas,[†] 12m Parallel group Device not reported; n=30	FP												NSD
		BUD												

NW = nocturnal waking; SFD = symptom-free days; SFN =symptom-free nights; SS = symptom score (varies between studies); N = number of events; NSD = no significant difference between trial arms. Blank cells signify no data reported on that outcome.

* starting daily dose of 200 or 400µg for 5 wks with dose reductions by 50% at 5 wk intervals.

† Altintas et al. did not analyse differences between groups; the focus was on the adverse effects of ICS therapy on growth, therefore no usable data can be reported in the table.

5.2.3 Q2: Effectiveness of high dose ICS

5.2.3.1 High dose ICS: BDP and BUD

5.2.3.1.1 Study characteristics

Only one study, by Pedersen & Fuglsang[206] published in 1988, compared the effects of BUD and BDP in children (*Table 13*). It was a small, single-centre study conducted in Denmark, involving 31 children. The trial was an open label, cross-over design with no washout period, containing two arms. It focused on systemic adverse effects rather than clinical effectiveness.

The total daily dose of ICS varied between 800 and 1200 µg/d, with a mean of 900 µg/d. The dose was equal to that normally used by the child, and was the same in both the BUD and BDP treatment periods. Thus the comparison of the two drugs was at a dose ratio of 1:1 throughout the study. The drugs were both delivered via an MDI, with or without a volume spacer (make or manufacturer of device not reported). The aim of the study was to determine if there were any differences between the two drugs in adverse systemic effects on adrenal function. For this purpose, cortisol excretion was chosen as the primary outcome (it was not explicitly stated whether the intention was to test equivalence or superiority). The treatment duration was two six-week periods with no wash-out in between. However, the authors reported that no carry-over effects were found.

The trial included boys and girls aged between 5 and 15 years, with a mean age of 10 years. All the children had previously received high dose ICS therapy with either BUD or BDP. The severity of asthma was not specifically stated and baseline FEV_1 % predicted was not reported. However, it may be assumed that the participants' asthma was severe in light of the high dose ICS therapy.

The trial reported a randomisation procedure that assured true random assignment to treatment groups (a computer generated algorithm), and which was also adequately concealed. However, these details were obtained by the authors of the Cochrane review in which this trial was included, and not reported in the original paper. Although the trial was open-label, the outcome assessors were blind to the experimental dose regimen. It is not known whether the study performed an intention-to-treat analysis.

TABLE 13 *Study characteristics (BDP and BUD)*

Study ID	Design	Intervention	Patients	Outcomes
Pedersen & Fuglsang (1988)[206]	RCT Single-centre Cross-over (no wash-out) Open-label	*Drug(s):* 1. BDP total 800-1200 µg/daily 2. BUD total 800-1200 µg/daily Taken b.i.d. as: BDP 50, 100, or 250µg per actuation; BUD 50 or 200µg per actuation, & remaining constant throughout the trial *Delivery device:* 1,2. MDI ± spacer (Volumatic or Nebuhaler, no other details about devices reported) *Duration:* 2 x 6 wks *Run in period:* None	*Number randomised* 31 *Mean age* 10.2 (range 5-15) years *Baseline FEV_1 % predicted* Not reported *Previous ICS treatment (drug and dose)* BDP or BUD 800-1200 µg/daily	*Outcomes* Adrenal function (as measured by 24hr free cortisol excretion in urine) FEV_1 Adverse effects

5.2.3.1.2 Results

Lung function

Pedersen and colleagues[206] reported limited data on efficacy in terms of lung function parameters as this was not the main purpose of the study. The authors reported that FEV_1 at the end of each period was 2.35 L (range 0.9 – 3.8 L) for BDP compared to 2.26 L (range 0.8 – 3.9 L) for BUD. The difference was not statistically significant.

Symptoms, use of rescue medication, exacerbations

The trial did not report symptoms, use of rescue medication, or exacerbations as outcome measures.

Adverse events

The authors stated that no side effects were reported. However, one participant during the period on BUD was withdrawn from the study because of an acute exacerbation of asthma.

The excretion of urinary cortisol was statistically significantly higher during BUD treatment (76.3 (range 25 – 215) nmol/day) than during BDP treatment (53.7 (range 6 – 118) nmol/day) (p<0.01). The difference was reported to be more pronounced in children treated with 1000-1200 µg/d (n=8) than in those treated with 800 µg/d (n=22). Cortisol excretion was below the normal range during the period on BDP for four children and during the period on BUD one child.

Summary

Only one small, single-centre, cross-over trial evaluated the effects of BUD compared to BDP in children receiving high dose ICS therapy. The study focused on adverse systemic effects on adrenal function but also reported FEV_1 at the end of each period. The FEV_1 did not differ significantly between the BDP and BUD periods. However, treatment with BUD resulted in significantly higher 24hr free cortisol excretion compared to BDP.

5.2.3.2 High dose ICS: FP and BDP

5.2.3.2.1 Study characteristics

Three RCTs compared the effects of high doses of FP and BDP in children. These trials, published between 1997 and 2001, were by Yiallouros and colleagues,[207] Fitzgerald and colleagues,[208] and de Benedictis and Colleagues.[209] (*Table 14*). One study used a parallel group design,[209] whilst the other two studies used a cross-over design. The study sizes ranged from 34 patients[207;207] to 343 patients.[209] Two of the trials were single-centre studies[207;208] and one trial was a multi-centre study.

All three RCTs contained two arms. There was variability in the doses used in the trials. Fitzgerald and colleagues[208] used a daily dose of 750µg FP and 1500µg of BDP. In the study by Yiallouros and colleagues[207] participants had been receiving between 400µg to 900µg per day of BUD/BDP (median 519 µg/m^2/day BUD, 588 µg/m^2/day). They were randomised to receive either an equal dose of BDP or an equipotent (half the dose) of FP daily. De Benedictis and colleagues[209] used a daily dose of 400µg for both FP and BDP. Thus, two studies used dose ratios of 1:2[207;208] (FP: BDP) and one study used a dose ratio of 1:1.[209] Two of the trials used MDI devices with spacers[207;208] (the only device details provided are by Yiallouros and colleagues, in that the devices were provided by Glaxo Group Research), whist the third trial used a dry powder Diskhaler (no further details about the device were reported) .[209] Two RCTs treated for 12 weeks,[207;208] whilst the third RCT lasted for 52 weeks.[209] A range of efficacy outcomes were measured, as well as safety, with two measuring adrenal function[207;208] (one of which was powered specifically to detect differences on this outcome[208]), and one measuring growth.[209]

All three RCTs contained two arms. There was variability in the doses used in the trials. Fitzgerald and colleagues[208] used a daily dose of 750µg FP and 1500µg of BDP. Yiallouros and colleagues[207] used a daily dose of 200µg of FP and 400µg of BDP, whist de Benedictis and colleagues[209] used a daily dose of 400µg for both FP and BDP. Thus, two studies used dose ratios of 1:2[207;208] and one study of 1:1.[209] Two of the trials used MDI devices with spacers[207;208] (the only device details provided are by Yiallouros and colleagues, in that the devices were provided by Glaxo Group Research), whist the third trial used a dry powder Diskhaler (no details about the device were reported) .[209]

TABLE 14 *Study characteristics (BDP and FP)*

Study ID	Design	Intervention	Patients	Outcomes
Fitzgerald *et al.*(1998)[208]	RCT Cross-over (no washout) Double-blind	*Drugs:* 1. FP 375µg/b.i.d. (daily total 750µg) 2. BDP 750µg/b.i.d. (daily total 1500µg) *Delivery device:* 1, 2. MDI + volume spacer (no further details about devices reported) *Duration:* 12 wks *Run in period:* 4 wks	*Number randomised* 34 *Mean ± SD age (range)* 1. 10.5 ± 2.5 (6-15) years 2. 9.4 ± 2.9 (5-13) years *Baseline FEV_1 % predicted (range)* 1. 86 (82-90) % 2. 86 (82-90) % *Previous ICS treatment (drug and dose)* FP 750µg/daily or BDP 1500µg/daily	*Primary outcomes* PEFR (am & pm) Symptom scores (day & night) *Secondary outcomes* 24 hour urinary cortisol levels Growth Adverse effects: No. of asthma exacerbations No. of asthma exacerbations requiring oral steroids Patient assessed efficacy scale Physician assessed efficacy scale Plasma ACTH 8 am plasma cortisol Plasma cortisol 1 hour post synthetic ACTH (synacthen) (0.5µg/1.73m^2 body surface area)

Study ID	Design	Intervention	Patients	Outcomes
Yiallouros et al (1997)[207]	RCT Cross-over (no washout) Double-blind	*Drugs:* 1. BDP: dose equal to pre-study ICS 2. FP at half daily µg dose of pre study ICS *Delivery device:* 1, 2. MDI + spacer (GlaxoSmithKline*) *Duration:* 12 wks *Run in period:* 2 wks	*Number randomised* 34 (comprising 2 groups, A and B, before randomisation) *Median age (range)* A. 7.3 (5-12.4) years B. 8.8 (6-13.1) years *Baseline FEV_1 % predicted* Not reported *Previous ICS treatment (drug and median dose)* A. BUD 519µg/d. B. BDP 588µg/d. (for ≥ 3 months before randomisation)	*Outcomes* Urinary cortisol Urinary cortisol metabolites PEFR (am & pm) Symptom sores Rescue SABA use (day & night)
de Benedictis et al (2001)[209]	RCT Multi-centre Parallel-group Double-blind	1. FP 200µg/b.i.d. (daily total 400µg) 2. BDP 200µg /b.i.d. (daily total 400µg) *Delivery device:* 1. DPI (Flixotide Diskhaler, GlaxoSmithKline*) 2. DPI (Diskhaler, GlaxoSmithKline*) *Duration:* 52 wks *Run in period:* 2 wks	*Number randomised* 343 *Mean ± SD age (range)* 1. 7.6 ± 1.7 (4-11) years 2. 7.6 ± 2.0 (4-11) years *Baseline FEV_1 % predicted* No reported *Previous ICS treatment (drug and dose)* FP 100 to 200µg/daily or BDP or BUD 200 to 500µg/daily	*Primary outcome* Growth velocity *Secondary outcomes* Symptom scores Rescue medication PEFR (am and pm) FEV_1
* not stated explicitly, but deduced from the text				

Two RCTs had a treatment duration of 12 weeks,[207;208] whilst the third RCT lasted 52 weeks.[209] All three RCTs assessed the equivalence of the two treatments, two of these focused on adrenal function[207;208] and the third study on growth in children.[209]

The age range of children included in the RCTs varied from four to 15 years, with mean ages from seven[207;209] to nine years.[208] One trial reported children as having been previously treated with 1000 to 2000μg daily of BDP or BUD,[208] while the second trial reported a daily median dose of 519μg BUD or 588μg BDP.[207] In the third trial children had previously been treated with 100 to 200μg daily of FP or 200 to 500μg daily of BDP or BUD.[209] Fitzgerald and colleagues[208] reported mean baseline levels for FEV_1 at 80%. The other two studies reported measuring baseline levels for FEV_1, but provided no further details.[207;209] De Benedictis and colleagues[209] described children as suffering with mild to moderate asthma, whist the other two trials described children as suffering with persistent severe[208] or severe chronic asthma.[207]

De Benedictis and colleagues[209] reported their primary outcome as growth velocity, whilst Fitzgerald and colleagues[208] specified their primary efficacy variables as PEFR, as well as day and night symptom scores. Yiallouros and colleagues[207] did not specify a primary outcome. Fitzgerald and colleagues[210] powered their study to detect a mean daily difference in PEFR of 5% (15 L/min in 10-year-old children) whilst de Benedictis and colleagues powered their study to detect a difference in growth rate of 1cm/year. Yiallouros and colleagues[207] did not report statistical power or details of their randomisation procedure, whilst allocation concealment was also unclear in two of the studies.[207;208] Only two of the studies reported an intention-to-treat analysis,[208;209] and only one study[209] reported the proportion of eligible patients that were not randomised (20 / 403, of which 10 were due to adverse events, four for failure to return and six for withdrawal of consent). Both of the cross-over trials[207;208] had no wash-out period between treatments due to asthma severity, however both these trials reported that there were no carry-over effects.

5.2.3.2.2 Results

Parallel design, 1:1 dose ratio

The following data were obtained by the reviewers from the primary publication[209] and, in some cases, also from the Cochrane review.[188] De Benedictis and colleagues[209] reported mean ± SD end-point data for FEV_1 in the FP group to be 1.75 ± 0.29 L and in the BDP group to be 1.63 ± 0.31 L. This was shown to be statistically significantly different in favour of FP, $p<0.001$. Mean ± SD morning PEFR in this trial was 251.30 ± 29.81 L/min at end-point in the FP group compared to 242.80 ± 31.38 L/min in the BDP group. The difference between groups (8.5 L/min) was statistically significant (95% CI 2.8 to 14.2, $p=0.004$). Mean ± SD evening PEFR was 255.10 ± 28.52 L/min at end-point in the FP group compared to 246.50 ± 30.08) L/min in the BDP group, with the difference between groups (8.6 L/min) also statistically significant (95% CI 3.0 to 14.1, $p=0.003$).

Cross-over design, 1:2 dose ratio

Fitzgerald and colleagues[208] demonstrated no statistically significant differences between FP and BDP in mean morning PEFR (FP 311 L/min, BDP 308 L/min, treatment difference 2.6 L/min (95% CI -1.8 to 7.0 L/min). Results in the trial were adjusted to take account of a significant period effect and patient differences in the sequence groups. To investigate a possible carry-over effect the analysis was repeated for the last month of treatment (month three). The results were similar with no differences demonstrated between the two treatment groups. Yiallouros and colleagues[207] also demonstrated no statistically significant differences between FP and BDP in mean morning PEFR (both groups 268 L/min). The trial also reports that no statistically significant carryover effect was detected ($p=0.144$).

Similarly no statistically significant differences between the two groups were shown in mean evening PEFR (FP 316 L/min, BDP 312 L/min, treatment difference 4.2 L/min (95% CI -1.2, 9.5 L/min) in the Fitzgerald and colleagues[208] trial. Results were adjusted to take account of a significant period effect and patient differences in sequence groups. Yiallouros and colleagues[207] also reported that there was no statistically significant differences between the two drugs for the mean evening PEFR (no results were presented but commented that there was a trend towards a carry-over effect ($p=0.096$)).

Symptoms / health related quality of life

Parallel design, 1:1 dose ratio

De Benedictis and colleagues[209] reported that there were no significant differences between treatment groups with respect to diary-card symptoms, but no data are presented to support this.

Cross-over design, 1:2 dose ratio

Symptom scores were reported on a four-point scale (0= no symptoms, 3= unable to carry out activities due to shortness of breath) in the trial by Fitzgerald and colleagues[208] (no reference supplied). Daytime and night-time symptom scores (adjusted to take account of a significant period effect and patient differences in sequence groups) were reported (without *p*-values) as being not statistically significantly different at end-point between the FP treated patients and the BDP treated patients. The daytime scores were (0.3 for FP and 0.4 for BDP, with a treatment difference of -0.1 (95% CI -0.8 to 0.02). Night-time symptom scores were 0.3 for both drugs, with a treatment difference of -0.05 (95% CI -0.14 to 0.03).

Use of rescue medication

Parallel design, 1:1 dose ratio

De Benedictis and colleagues[209] reported that there were no significant differences between treatment groups with respect to the need for rescue medication but no data were presented to support this.

Cross-over design, 1:2 dose ratio

Yiallouros and colleagues[207] report that there were no statistically significant differences between FP and BDP treatments with respect to the need for rescue medication but no data are presented to support this.

Exacerbations

Parallel design, 1:1 dose ratio

The total number of exacerbations in the FP group was 47 compared to 52 in the BDP group of the De Benedictis and colleagues[209] trial. The percentage of patients experiencing at least one exacerbation was 16% in the FP group compared to 19% in the BDP group. No statistical significance testing was reported for these outcomes.

Cross-over design, 1:2 dose ratio

The total number of exacerbations in the trial by Fitzgerald and colleagues[208] was 33 during treatment with FP and 35 during treatment with BDP. This is reported to be not statistically significant although no *p*-value is reported. Overall the study reports that 16 of these exacerbations were in the group who received FP first whereas 52 exacerbations were in the group who received BDP first. This difference was shown to be statistically significant (p<0.001) and the authors suggest that a greater proportion of less stable cases were placed in this latter treatment sequence.

Adverse events

Parallel design, 1:1 dose ratio

Adverse events were experienced at similar rates in the FP and BDP arms of the De Benedictis and colleagues[209] trial (around 80% in both groups). Mean ± SEM growth rates for the ITT populations were 4.76 ± 0.28 cm/year in the FP-treated group and 4.06 ± 0.29 cm/year in the BDP-treated group. This difference (0.7 cm/year) was statistically significant (95% CI 0.13 to 1.26 cm/year, p<0.02).

In the same study,[209] there were no statistically significant differences in changes from baseline morning serum cortisol levels between treatment groups (FP 8.1 µg/dl; BDP 7.1 µg/dl, p=0.12). There were no statistically significant differences in changes from baseline overnight urinary cortisol levels (FP 14.0 µg/dl; BDP 12.6 µg/dl, p=0.32).

Cross-over design, 1:2 dose ratio

Fitzgerald and colleagues[208] report that there were no differences in the number of adverse events between the FP and BDP treatment phases in their study, but no data are presented. Similarly, Yiallouros and colleagues[207] report that the incidence of adverse events was similar in the two groups, but no data are presented.

One patient discontinued during treatment with FP and three during treatment with BDP in the Yiallouros and colleagues[207] trial.

Fitzgerald and colleagues[208] commented that there was no evidence of growth suppression (based on height standard deviation scores) and no evidence of a significant effect of drug treatment on growth, which remained normal (no *p*-values were provided).

There were no statistically significant differences in adjusted mean urinary free cortisol levels between the FP and BDP treatment groups in the Fitzgerald and colleagues[208] trial (25.3 nmol/24h FP versus 25.2 nmol/24h, treatment difference –0.1 (95% CI –6.0, 6.3). Similarly, in the Yiallouros and colleagues[207] trial, there were no statistically significant differences in adjusted total cortisol between the two study medications (FP 1315 μg/dl, BDP 1254 μg/dl, p=0.55).

5.2.3.2.3 Summary

Parallel design, 1:1 dose ratio

Patients treated with FP improved more than patients treated with BDP on measures of lung function. However, differences between the groups on measures of symptoms, use of rescue medication and exacerbations were not statistically significant, although reported data were limited on these outcomes. Similar rates of adverse events were noted between the two treatments, except that the BDP treated group had a significantly lower growth rate.

Cross-over design, 1:2 dose ratio

On measures of lung function no significant differences were observed between groups treated with FP and groups treated with BDP. No differences between the two treatments were observed on symptoms, use of rescue medications or exacerbation rates where data was reported. The adverse event profiles of the two drugs were similar.

5.2.3.3 High dose ICS: FP and BUD

5.2.3.3.1 Study characteristics

Three parallel group RCTs[211-213] evaluated the effectiveness of BUD compared to FP, published between 1996 and 2002 (*Table 15*). One study[213] reported additional data in a secondary publication.[214]

TABLE 15 *Characteristics of studies (BUD and FP)*

Study ID	Design	Intervention	Patients	Outcomes
Hoekx et al (1996)[211]	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP 100μg 2 puffs b.i.d. (daily total 400μg) + placebo 2. BUD 200μg 1 puff b.i.d. (daily total 400μg) + placebo *Delivery device:* 1. DPI Diskhaler (Flixotide, GlaxoSmithKline) 2. DPI Turbuhaler (Pulmicort, AstraZeneca) *Duration:* 8 wks *Run in period:* 2 wks	*Number randomised* 229 *Age range* 4 -13 years *Baseline FEV_1 % predicted* Not reported *Previous ICS treatment (drug and dose)* Mild-to-moderate asthma (all taking ICS but no details of drug or dose)	*Outcomes* FEV_1 Clinic PEFR Am & pm PEFR Daytime asthma symptom score % symptom-free days % symptom-free nights Days missed from school (patients) Days missed from work (parents) Parent completed, patient-centred assessment of physical & social activity Morning serum cortisol Biochemical markers of bone turnover

Study ID	Design	Intervention	Patients	Outcomes
Ferguson et al (1999)[212]	RCT Multi-centre Parallel-group Double-blind	*Drug(s):* 1. FP 400μg daily 2. BUD 800μg daily *Delivery device:* 1. DPI Diskhaler® (Flixotide, GlaxoSmithKline) 2. DPI Turbuhaler® (Pulmicort, AstraZeneca) *Duration:* 20 wks *Run in period:* 2 wks	*Number randomised* 333 *Mean age* 1. 8.2 ±2 years 2. 7.9 ± 2 years *Baseline FEV_1 % predicted* Not reported *Previous ICS treatment (drug and dose)* All taking ICS but no details of drug or dose	*Outcomes* Am PEFR Change in daytime & night-time symptom score Daytime SABA use Change in height compared Change in morning plasma cortisol Asthma exacerbations Oro-pharyngeal side effects Height assessment

Study ID	Design	Intervention	Patients	Outcomes
Kannisto et al (2002)[213;214]	RCT Parallel-group Open-label	*Drugs:* 1. FP 250μg b.i.d. (daily total 500μg) – 200μg daily after 2mths 2. BUD 400μg b.i.d. (daily total 800μg) - 400μg/daily after 2mths 3. Cromolyn 200μg t.i.d. (daily total 600μg or Nedocromil 40μg t.i.d. (daily total (120μg) Only groups 1 and 2 relevant here *Delivery device:* 1. DPI Diskus® (Flixotide, GlaxoSmithKline) 2. DPI Turbuhaler® (Pulmicort, AstraZeneca) *Duration:* 16 wks *Run in period:* Not reported	*Number randomised* 60 for group 1 & 2 (75 in total) *Age range* 5.5-14.7 years *Baseline FEV_1 % predicted (± SD)* 1. 92± 11 2. 92±15 *Previous ICS treatment (drug and dose)* None	*Outcomes* FEV_1 % change from baseline No. with fall in FEV_1 Rescue medication usage: doses /wk Changes in height

Two studies were multi-centre studies where study sample sizes ranged between 229 and 333 participants, while the third study was a single centre pilot study where the sample size was 60.[213] Only one of the trials reported undertaking a power calculation, where adequate power in the sample was met.[212]

All three included trials had two-arm comparisons of BUD versus FP. One trial compared FP 400µg with BUD 400µg, a nominal dose ratio of 1:1.[211] Two trials compared FP with BUD at a nominal dose ratio of 1:2.[212;213] One compared 400µg per day of FP with 800µg per day of BUD,[212] the second compared FP 500µg per day with BUD 800µg per day.[213] This latter study reduced doses after two months to 200 and 400µg per day respectively. This study also had a third, non-randomised comparison group, who were prescribed cromones (not discussed here). The devices used in all three studies were DPIs for BUD respectively (Diskhalers: Flixotide, GlaxoSmithKline; Turbuhalers: Pulmicort, AstraZeneca). The treatment duration in the 1:1 dose ratio study was eight weeks.[211] The treatment duration for the two 1:2 dose ratio studies were similar at 16 weeks and 20 weeks for the Kannisto and colleagues[213] and Ferguson and colleagues[212] study respectively.

All three included trials aimed to compare the clinical efficacy of the two drugs, administered in a DPI. The outcomes used to measure clinical efficacy differed between the groups. The one trial using equal doses of the two comparator drugs[211] aimed to compare the efficacy and effects on serum cortisol and serum and urinary indices of bone metabolism. The trial by Ferguson and colleagues[212] was reported to be an equivalence trial, assessing morning PEFR as their primary outcome. The third trial,[213] reported as a pilot study, aimed to measure clinical efficacy using FEV_1 as the primary outcome.

The ages of participants in the trials are likely to be similar. Two trials report age ranges that lie between 4-15 years[211;213] and one trial reports mean ages between 7.9-8.2 years.[212] The severity of asthma varied across the three studies. In the 1:1 dose ratio study participants were described as mild to moderate in severity.[211] In the two 1:2 dose ratio studies participants were moderate to severe,[212] and newly diagnosed[213] respectively. In the Hoekx and colleagues[211] and Ferguson and colleagues[212] trials all patients were already prescribed ICS. Baseline FEV_1 % predicted was reported in only one of the included trials and was similar across the comparison arms at 92%.[213]

The method of randomisation and allocation concealment was assessed to be adequate in the Hoekx and colleagues[211] trial. In the Ferguson and colleagues trial[212] and the Kannisto and colleagues[213] trial no method of randomisation was reported and allocation concealment was also unclear. These two factors reduce the risk of selection bias and therefore care is required when interpreting the latter two trials. Only the trial by Ferguson and colleagues[212] reports that data were analysed using an intention-to-treat principle although, as it appears that some participants were excluded from the data analysis, reporting is not considered accurate.

5.2.3.3.2 Results

Lung function

Parallel design, 1:1 dose ratio

Hoekx and colleagues[211] presented data on morning and evening PEFR as the mean of available data during a period of 1-8 weeks of treatment. They also presented this as an adjusted mean to account for differences in baseline gender, age and country. During the treatment period (weeks 1-8) the adjusted mean morning PEFR was 274 L/min in the FP group compared to 267 L/min in the BUD group, which was statistically significant, p=0.019. The adjusted mean evening PEFR did not differ significantly between the groups (FP 279 L/min, BUD 273 L/min, p=0.054). No measures of variance were reported.

Parallel design, 1:2 dose ratio

After 20 weeks of treatment the adjusted mean morning PEFR for the FP group in the Ferguson and colleagues[212] trial was 271 (± SD 82) L/min compared to 259 (± SD 75) L/min in the BUD arm. The treatment regimens were shown not to be equivalent as determined by an *a priori* calculation of the 90% CI. The difference was shown to be statistically significantly different, p=0.002 in favour of FP. Evening PEFR was not statistically significantly different between the two groups (FP 271 (± SD 104) L/min, BUD 259 (± SD 103) L/min, mean difference 12 [95% CI -11.12, 35.12]).

The Ferguson and colleagues[212] study reports a comparable improvement from baseline to end of treatment in FEV_1 between the groups (FP 1.74 (± SD 0.51), BUD 1.66 (± SD 0.44), *p*=0.183). Kannisto and colleagues[213] report that change in FEV_1 % predicted was 5.5% (± SD 11.83) for the FP group and 6.7% (± SD 13.25) for the BUD group. These changes from baseline were reported to be not statistically significantly different but no *p*-value was reported.

Symptoms / health related quality of life

Parallel design, 1:1 dose ratio

Although Hoekx and colleagues[211] report some data on symptoms, inadequate information was provided for the purposes of the present review.

Parallel design, 1:2 dose ratio

The Ferguson and colleagues[212] trial report that there were no differences between the FP and BUD groups on change in daytime symptom scores but no data are presented to support this.

Use of rescue medication

Parallel design, 1:1 dose ratio

No data on use of rescue medication in terms of puffs per day were reported in the included trial[211] in this category.

Parallel design, 1:2 dose ratio

The Ferguson and colleagues[212] trial report that there were no differences between the FP and BUD groups on the need for rescue medication but no data are presented to support this. Kannisto and colleagues[213] showed at end-point that rescue medication usage in terms of puffs per day was lower in the FP group (1.70 (± SD 3.45) compared to the BUD group (3.75 (± SD 7.50) but this was not statistically significantly different (mean difference -2.05 [95% CI -5.00, 0.90]).

Exacerbations

Parallel design, 1:1 dose ratio

No data on exacerbation rates were reported in the included trial in this category.

Parallel design, 1:2 dose ratio

No data on exacerbation rates were reported in either included trial in this category.

Adverse events

Parallel design, 1:1 dose ratio

The proportion of patients with an adverse event ≥ 5% were similar in the FP group and BUD groups in the Hoekx and colleagues[211] trial (63% versus 69%, respectively). Two patients from the FP group and three from the BUD group in the Hoekx and colleagues[211] trial discontinued due to adverse events. One patient from each treatment group had a serious adverse event. The mean value of serum cortisol concentration rose from 248 nmol/L[1] (baseline) to 291 nmol/L[1] (after 8 weeks) for those on FP treatment, and from 214 nmol/L[1] (baseline) to 246 nmol/L[1] (after 8 weeks) for those on BUD treatment. A FP/BUD ratio of change in mean cortisol level was shown to be statistically significantly different between the two groups at four weeks (p=0.022) but not statistically significantly different between the two groups at eight weeks (p=0.074).

Parallel design, 1:2 dose ratio

Ferguson and colleagues[212] report that there were no significant differences in the number of children who experienced an adverse event between the two treatment groups (FP 144/166, BUD 145/167 patients, OR 0.99 [95% CI 0.53, 1.87]). Serious adverse events were experienced by 4/166 children in the FP group and 10/167 children in the BUD group. Four patients in the FP treatment group and one in the BUD treatment group discontinued due to adverse events. The study by Kannisto and colleagues[213] did not report proportions of patients experiencing adverse events other than growth and serum cortisol changes.

Kannisto and colleagues[213] reported that the decrease in height SD scores differed significantly between the treatment groups (p<0.05). In the FP group, 8 patients (27%) experienced a decrease in the height SD score (absolute risk increase 7%, 95% CI 13 to 67%). In the BUD group, the decrease affected 18 patients (60%) (absolute risk increase 40%, 95% CI -19 to 33%).

In the study by Ferguson and colleagues,[212] the adjusted mean growth from end of run-in to 20 weeks was 3.31 cm in FP-treated subjects and 1.99 cm in BUD-treated subjects. This difference (1.32 cm) was statistically significant (90% CI 0.48 to 2.17, p=0.002).

Kannisto and colleagues[213] reported that the cortisol response decreased in five patients (17%) in the FP group (absolute risk increase 17%, 95% CI 4 to 30%) and in nine patients (30%) in the BUD group (absolute risk increase 30%, 95% CI 14 to 47%). This difference between the drugs is not statistically significant (p>0.05).

In the study by Ferguson and colleagues,[212] adjusted geometric mean serum cortisol concentrations at the end of treatment were 199 mmol/L in the FP-treated group and 183 mmol/L in the BUD-treated group. The ratio of these means (1.09) does not differ significantly from 1.0 (95% CI 0.98 to 1.21, p=0.172).

5.2.3.3.3 Summary

Parallel design, 1:1 dose ratio

Limited available data suggests that on measures of lung function there were greater improvements in the FP treated groups compared to the BUD treated groups, although this was not always statistically significant. Rates of adverse events and discontinuations were similar between the two treatment groups.

Parallel design, 1:2 dose ratio

On measures of lung function, one trial demonstrated superiority of FP over BUD on morning PEFR, but similarity between the two groups on evening PEFR. The other trial showed comparable improvement between groups on FEV_1. No differences between FP and BUD were seen on measures of symptoms or use of rescue medication. Growth was significantly lower in BUD-treated patients in both trials and more adverse events were experienced by

BUD-treated children in one of the trials. The adverse event profiles, including changes in cortisol concentrations, were otherwise similar between the two drugs. Data on most outcomes were limited.

5.2.3.4 Summary of Q2: relative effectiveness of high dose ICS

BDP versus BUD, n= 1 RCT

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results											
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients	Adrenal markers
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS					
800 - 1200 µg*	Pederson, 12w Cross-over, open-label MDI; n=31	BDP	NSD											+
		BUD												

NW = nocturnal waking; SFD = symptom-free days; SFN = symptom-free nights; SS = symptom score (varies between studies); N = number of events; NSD = no significant difference between trial arms. Blank cells signify no data reported on that outcome.

* same in each group and remaining constant throughout study period.

FP versus BDP, n= 3 RCTs

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results											
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients	Adrenal markers
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS					
1500 vs 750µg	Fitzgerald, 12w Cross-over, double-blind MDI; n=34	BDP		NSD	NSD				NSD*			NSD	81%	NSD
		FP											80%	
400 vs 200µg	Yiallouros, 12w Cross-over, double-blind MDI; n=34	BDP		NSD	NSD						NSD		C	NSD
		FP												
400 vs 400µg	De Bendictis, 52w Parallel, double-blind DPI; n=343	BDP							NSD†		NSD	C	C	
		FP	+	+	+									

NW = nocturnal waking; SFD = symptom-free days; SFN = symptom-free nights; SS = symptom score (varies between studies); N = number of events; NSD = no significant difference between trial arms; C = stated to be comparable between trial arms but statistical tests not reported; + indicates results significantly favour this trial arm. Blank cells signify no data reported on that outcome.

* day-time symptom scores

† diary card symptoms

FP versus BUD, n=3 RCTs

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results: Lung function FEV$_1$	Lung function PEFR morning	Lung function PEFR evening	Symptoms NW	Symptoms SFD	Symptoms SFN	Symptoms SS	HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients	Adrenal markers
400 vs 400µg	Hoekx, 8w Parallel, double-blind DPI; n=229	BUD											69%	NSD
		FP		+	F[a]								63%	
800 vs 400µg	Ferguson, 20w Parallel, double-blind DPI; n=333	BUD	NSD		NSD				C[b]		C		NSD	NSD
		FP		+										
800 vs 500µg*	Kannisto, 16w Parallel, open-label DPI; n=60 (75 total)	BUD	NSD								NSD		NSD	NSD
		FP†												

NW = nocturnal waking; SFD = symptom-free days; SFN = symptom-free nights; SS = symptom score (varies between studies); NSD = no significant difference between trial arms; C = stated to be comparable between trial arms but statistical tests not reported; + indicates results significantly favour this trial arm. Blank cells signify no data reported on that outcome.

* doses reduced after 2 mths to 400µg BUD vs 200µg FP

† this study had a third non-randomised arm receiving cromones.

[a] borderline statistical significance (*p*=0.054)

[b] day-time symptom scores

5.2.4 Q3a: ICS/LABA or higher-dose ICS

No RCTs of this comparison with an exclusively child patient population were identified. However, one RCT, included in our accompanying report on inhaled corticosteroids,[199] included around 12% of patients under the age of 12.[200] Results for growth and plasma cortisol only are reported separately for children and are presented here. A further brief summary of the results from the overall trial population for both adults and children is also presented.

The study by O'Byrne and colleagues[200] (*Table 16*) was published in 2005 and evaluated the combination of BUD/FF in a single inhaler with higher doses of BUD alone. It was a multi-centre study conducted in 246 centres across 22 countries. Of the 2,760 participants, 341 (12%) were children aged 4-11 years. The trial was a double-blind parallel group design, containing three arms. The first arm was 80µg BUD/4.5µg FF twice daily with the combination inhaler as reliever. The second arm was 80µg BUD/4.5µg FF twice daily with terbutaline as reliever, and the final arm was 320µg BUD twice daily with terbutaline as reliever. Children were given half the maintenance dose once daily at night. All study medication was delivered by Turbohaler (BUD - Pulmicort Turbuhaler®, AstraZeneca).

The rationale of the trial was to test superiority of combined treatment, and the treatment duration was 12 months. The time to first severe asthma exacerbation was the primary outcome measure. The age range of all patients was from 4 to 79 years, with a mean of around 36 years. The mean baseline FEV_1% predicted was 73. Prior to entry, children had to be treated with 200 to 500µg per day of inhaled corticosteroid. The trial was of reasonable methodological quality. A computer generated random number list was used (they were randomised in balanced blocks and there were separate lists for children and adults), and the treatment delivery devices were indistinguishable – no other details were available. The study reported using intention-to-treat analysis.

TABLE 16 *Study characteristics (BUD vs. BUD + FF)*

Study ID	Design	Intervention	Patients	Outcomes
O'Byrne et al (2005)[200]	RCT Multi-centre Parallel-group Double-blind *N.B. This trial also examines the effects of the combination inhaler as a reliever. 12% are children (4-11 yrs)*	1. BUD + FF 80µg + 4.5µg b.i.d. plus 80µg + 4.5µg as needed (daily total 160µg + 9µg) + combination inhaler as reliever 2. BUD + FF 80µg + 4.5µg b.i.d. (daily total 160µg + 9µg) + terbutaline as reliever as needed 3. BUD 320µg b.i.d. (daily total 640µg) + terbutaline as reliever as needed Children were given half the maintenance dose once daily. *Delivery device:* 1, 2, 3. DPI (Pulmicort Turbuhaler®, AstraZeneca) *Duration:* 12 mths *Run in period:* 14-18 days	*Number randomised* 2760 (341 children) *Mean (years) age (range)* 1. 35 (4-77) 2. 36 (4-79) 3. 36 (4-79) *Baseline mean FEV_1 % predicted (range)* 1. 73 (43-108) 2. 73 (46-108) 3. 73 (49-100) *Previous ICS treatment (drug and dose)* Adults 400-1000µg q.d. - children 200-500µg q.d.	*Primary outcome* The time to first severe asthma exacerbation. *Secondary outcomes* FEV_1 PEFR (am & pm) Asthma symptom scores (day/night) Awakenings Reliever medication use Symptom-free days Rescue medication free days Asthma control days Study drug use Adverse events Height (children) Morning plasma cortisol Mild exacerbations

The majority of results (pertaining to adults) are presented in our accompanying assessment report on the efficacy and safety of ICS in adults.[199] However, for clarity a summary of the overall results is reported here for the total trial population and the safety results which were reported separately for children are reported in full.

Summary of trial results for overall population

Treatment with BUD/FF combination used as maintenance and reliever therapy significantly prolonged the time to first severe and mild exacerbation compared to treatment with either BUD/FF plus terbutaline or BUD plus terbutaline. Furthermore, treatment with combination therapy as both maintenance and reliever, was associated with significantly reduced reliever medication use, improvements in both morning and evening PEFR and FEV_1, and the number of night-time awakenings compared to the two other treatment groups.

Adverse Events

Children in both BUD/FF groups grew significantly more than those in the BUD group. There was an adjusted mean difference in growth of 1.0cm between children treated with BUD/FF as maintenance and reliever compared to BUD (95% CI 0.3 to 1.7, *p*=0.0054), and a difference of 0.9cm between BUD/FF with terbutaline reliever compared to BUD (95% CI 0.2 to 1.6, *p*=0.0099).

Data was also presented for mean change in morning plasma cortisol. The between group differences were 11% (95% CI -7% to 33%) for BUD/FF with terbutaline reliever vs BUD, 1% (95% CI -15% to 21%) for BUD/FF as maintenance and reliever vs BUD, and -9% (95% CI -23% to 9%) for the two BUD/FF groups. The differences were not statistically significant.

5.2.4.1 Summary of Q3a: ICS/LABA or higher-dose ICS

BUD versus BUD/FF, n=1 RCT

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results											
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients	Adrenal markers
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS					
	O'Byrne *et al* Parallel, 12 months DPI N= 2760 (341 children)	1. BUD												NSD 2 vs 1 3 vs 1
		2. BUD/FF*												
		3. BUD/FF**												

NW = nocturnal waking; SFD = symptom-free days; SFN = symptom-free nights; SS = symptom score (varies between studies); C = stated to be comparable between trial arms but statistical tests not reported; F = results favour this trial arm but statistical tests not reported. Blank cells signify no data reported on that outcome.

* BUD/FF with terbutaline as a reliever when needed

** BUD/FF used for both maintenance and relief

5.2.5 Q3b: ICS/LABA or similar dose ICS

5.2.5.1 FP/SAL *versus* FP

5.2.5.1.1 Study Characteristics

Only one RCT, published in 2005, evaluated the combination of SAL and FP compared to FP alone[215](*Table 17*). It was a multi-centre study conducted in 79 sites across the USA and Canada, and involving 203 children. The trial was a double-blind, parallel group design, containing two arms.

The total daily dose of FP was 200µg and was the same in both arms. The total daily dose of SAL was 100µg. The drugs were both delivered via a Diskus inhaler device (FP - Flovent, GlaxoSmithKline), with the FP/SAL drugs delivered in combination via a single inhaler (Advair, GlaxoSmithKline).

The rationale of the study appeared to be whether the addition of a LABA to the ICS (as opposed to increasing the dose of ICS) is as safe as treatment with ICS alone. It is not explicitly stated whether the intention was to test equivalence or superiority of safety measures. The treatment period of the trial lasted for 12 weeks.

The study included boys and premenarchal girls aged between 4-11 years, with a mean age of eight years. All patients had previously received a range of ICS therapy at a consistent dose, with FP being the most commonly used ICS in each group (70-74% of patients used FP). The severity of asthma was not specifically stated, but the mean baseline FEV_1 % predicted was approximately 80%.

Whilst the primary objective of the trial was to compare the safety profile of the two treatments, some measures of efficacy were obtained. However, these were reported in separate abstract publications.[216;217]

TABLE 17 *Study characteristics (FP vs FP + SAL)*

Study ID	Design	Intervention	Patients	Outcomes
Malone et al. (2005)[215]	RCT Multi-centre Parallel-group Double-blind Active-controlled	*Drugs:* 1. FP/SAL 100/50μg b.i.d. (total dose 200/100μg) 2. FP 100μg b.i.d. (total dose 200μg) *Delivery device:* 1. Diskus (Advair, GlaxoSmithKline) 2. Diskus (Flovent, GlaxoSmithKline) *Duration:* 12 wks *Run in period:* 2 wks	*Number randomised* 203 *Mean age* 1. 8.0 2. 8.1 *Baseline FEV_1 % predicted* 1. 80.9 2. 80.0 *Previous ICS treatment (drug and dose)* BDP 252-336μg daily, triamcinolone acetonide 600-1,000μg daily, flunisolide 1,000μg daily, FP 88-250μg daily, or BUD 200-400μg daily consistent dose for 1mth prior to study	*Primary outcome* Safety measures (adverse events) *Secondary outcomes* FEV_1 (for aged 6-11yr) Am & pm PEFR 2-hr serial post-dose FEV_1 (for aged 6-11 yr) or 2-hr serial post-dose PEFR (for aged 4 -5yr) after the first dose of study medication on treatment day 1 Daytime asthma scores 24-hr rescue medication use Asthma exacerbations or worsening asthma

On the whole, the study was of adequate quality with regard to the reporting of methodological details. The study used an intention-to-treat analysis which included all subjects who received at least one dose of study drug. However, details of the randomisation procedure and concealment of allocation were lacking. The eligibility criteria were adequately specified, and the supplemental paper[217] described withdrawals and drop-outs, with reasons and numbers reported for each treatment group.

5.2.5.1.2 Results

Lung function

The main publication for this trial[215] did not report any values for lung function as this was a safety study and was not designed to evaluate efficacy differences between treatment groups. However, the authors did report that the FP/SAL group showed greater improvements in FEV_1 and in morning and evening PEFR compared to FP alone.

In one of the abstract publications for the study,[216] FEV_1 (L) at end-point was reported for a sub-group of children aged 6-11 years, and was 1.88 vs 1.77 for FP/SAL vs FP respectively. No *p*-values were reported. A second abstract linked to this study[217] reported a mean change (± SE) from baseline in morning PEFR (L/min) of 21.5±2.79 vs 16.9±2.85, and evening PEFR of 21.5±2.43 vs 15.1±2.83 for FP/SAL and FP respectively. Again, statistical significance was not reported. Caution is advised as these data are taken from conference abstracts and have not been subjected to academic journal peer-review.

Symptoms

Daytime asthma symptom scores were based on a Likert scale which is a five point rating scale (0=none, 5=severe, no reference supplied), and were recorded by the parent or guardian on a daily diary card. The asthma symptom scores improved to a similar degree in both treatment groups (-0.6±0.10 vs -0.5±0.12 [mean±SE]) for FP/SAL vs FP respectively).

Use of rescue medication

The mean reduction from baseline in the use of albuterol (number of puffs per day) was similar in both treatment groups (-0.5±0.22 vs -0.4±0.19 [mean±SE]) for FP/SAL vs FP respectively).

Exacerbations

The trial reported that children treated with FP/SAL had a lower incidence of asthma exacerbations than children treated with FP alone, occurring in three (3%) and eight (8%) patients respectively. Withdrawal from the study due to asthma exacerbations occurred in two (2%) children treated with FP /SAL and five (5%) children treated with FP alone.

Adverse events

The overall incidence of adverse events was similar in the two treatment groups, with 59% in the FP/SAL group compared to 57% of FP treated patients experiencing any adverse event (occurring at a rate of ≥ 3% during treatment). Slightly more patients in the FP/SAL group experienced at least one adverse event that was potentially related to the study drug (13% vs 9% for FP/SAL and FP respectively). Similarly, addition of a LABA resulted in three (3%) patients having adverse events leading to premature study withdrawal compared to none with FP alone. There were no serious drug-related adverse events in either group.

Summary

Only one multi-centre, parallel group trial evaluated FP compared to SAL and FP delivered in combination via a single inhaler. Children in the SAL/FP group showed apparent greater improvements in lung function compared to FP alone, although no statistical data were reported. Furthermore, addition of a LABA to FP appeared to be as safe as treatment with FP alone.

5.2.5.2 ICS versus ICS + LABA (BUD vs BUD/FF)

5.2.5.2.1 Study characteristics

Tal and colleagues (2002)[218] was the only RCT which evaluated the effectiveness of the combination of FF and BUD compared to BUD alone in children (*Table 18*). It was an international, multi-centre study conducted in 48 centres in seven countries (Belgium, the Czech Republic, Hungary, Israel, South Africa, Spain and the UK), and involving 286 children. The trial was a double-blind, parallel group design, containing two arms.

Patients in the BUD/FF group received 80/4.5μg, compared to BUD 100μg, both taken as two puffs twice daily. The doses of BUD in each treatment group were equivalent (differences are explained by labelling changes for new inhaled drugs which require the delivered dose rather than the metered dose to be reported). The total daily dose of BUD was 400μg in each group, and both groups used the Turbuhaler® device (Symbicort® & Pulmicort®, both AstraZeneca) for drug administration. The hypothesis of the study was that the combination of BUD/FF would lead to improved lung function compared to treatment with BUD alone. The treatment period of the trial lasted for 12 weeks.

The trial included asymptomatic children aged between 4-17 years, with a mean age of 11 years. All the children had previously received a range of ICS therapy at a constant dose. The severity of asthma was described by the authors as moderate, and the mean baseline FEV_1 % predicted was approximately 75%.

The primary outcome was morning and evening PEFR, and this reflected the rationale of the study which was that addition of a LABA to ICS would lead to improved lung function compared to ICS therapy alone.

Methodological quality was generally adequate. The trial reported a randomisation procedure that assured true random assignment to treatment groups (a computer-generated block-randomisation list), and which was also adequately concealed. A double-dummy technique was used for drug administration, as well as a double-blind procedure, and the study used an intention-to-treat analysis with all available data.

TABLE 18 *Study characteristics (BUD vs BUD/FF)*

Study ID	Design	Intervention	Patients	Outcomes
Tal et al. (2002)[218]	RCT Multi-centre Parallel-group Double-blind Double-dummy	*Drugs:* 1. BUD/FF 80/4.5µg 2 puffs b.i.d. actuation (daily total 400/18µg) 2. BUD 100 µg 2 puffs b.i.d (daily total 400µg) *Delivery device:* 1.Turbuhaler (Symbicort®, AstraZeneca) 2. Turbuhaler (Pulmicort®, AstraZeneca) *Duration:* 12 wks *Run in period:* 2-4 wks	*Number randomised* 286 *Mean age (range)* 1. 11 (4-17) 2. 11 (5-17) *Baseline FEV_1 % predicted (range)* 1. 74 (40-114) 2. 76 (40-100) *Previous ICS treatment (drug and dose)* ICS at constant dose for at least 6 wks prior to study (≥ 400µg BUD Turbuhaler®, ≥ 600µg BUD via pMDI, ≥ 375µg FP, or ≥ 600µg CFC-BDP)	*Outcomes* morning and evening PEFR FEV_1 Symptom scores Daily use of rescue medication Adverse events

5.2.5.2.2 Results

Lung function

Relative to baseline, children treated with BUD/FF exhibited significantly greater increases in FEV_1 % predicted compared to BUD alone (86.77% vs 83.02%, $p<0.05$). A beneficial effect of adding a LABA was further seen in terms of improvement in morning PEFR (% predicted), with the mean increase from baseline being significantly greater in the BUD /FF group compared to BUD alone (7.22% vs 3.45%, $p<0.001$). Evening PEFR also increased significantly with BUD/FF (6.13% vs 2.73%, $p<0.001$).

Symptoms

The severity of daytime and nocturnal asthma symptoms were recorded using a four-point rating scale (0=none, 3=severe, no reference supplied). There were no significant differences in asthma symptoms between the two groups at the end of treatment. The % of symptom-free days (defined as a night and day without symptoms and no asthma-related nocturnal awakenings) was determined as an overall measure of symptom control. The % symptom-free days was slightly greater in the BUD/FF group (77.5%) compared to the BUD group (75.1%), but this difference was not significant.

Use of rescue medication

Similar improvements in the use of inhaled terbutaline or salbutamol (number of puffs per day) were observed in both treatment groups.

Exacerbations

Tal and colleagues[218] did not report asthma exacerbations as a specific outcome measure. However, it was reported that five children in the BUD /FF group had an exacerbation of asthma that was classed as a serious adverse event requiring admission to hospital. It is assumed from the text that there were no asthma exacerbations in the BUD group.

Adverse events

The two treatment groups were reported to be similar in terms of adverse event profiles, with similar proportions of patients in each group experiencing the most common adverse events. Seven patients (4.7%) in the BUD /FF group had a serious adverse event requiring admission to hospital. A total of 18 children withdrew from treatment - nine children (6.1%) in the BUD /FF group and nine (6.5%) in the BUD group.

Summary

Only one trial evaluated the effectiveness of BUD/FF delivered in combination via a single inhaler compared to BUD alone. It was a large, international, multi-centre study, of parallel group design and high methodological quality. The combination of FF and BUD resulted in statistically significant improvements in lung function compared to BUD therapy alone. The safety profile of the two groups appeared to be similar, as was the improvement in symptoms and use of rescue medication.

5.2.5.3 Summary of Q3b: ICS/LABA or similar dose ICS

FP vs FP/SAL, n=1 RCT

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results											
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients	Adrenal markers
			FEV$_1$	PEFR morning	PEFR evening	NW	SFD	SFN	SS					
200 vs 200/100µg	Malone, 12w Parallel, double-blind DPI; n=203	FP							C*		C		C	
		FP/S	F	F	F							F		

NW = nocturnal waking; SFD = symptom-free days; SFN = symptom-free nights; SS = symptom score (varies between studies); C = stated to be comparable between trial arms but statistical tests not reported; F = results favour this trial arm but statistical tests not reported. Blank cells signify no data reported on outcome.

* day-time symptom scores

BUD versus BUD/FF, n=1 RCT

Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	Results											
			Lung function			Symptoms				HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients	Adrenal markers
			FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS					
400 vs 400/18μg	Tal, 12w Parallel, double-blind DPI; n=286	BUD					NSD*		NSD		C		C	
		BUD/FF	+	+	+									

NW = nocturnal waking; SFD = symptom-free days; SFN = symptom-free nights; SS = symptom score (varies between studies); + indicates results significantly favour this trial arm; NSD = no significant difference between trial arms; C = stated to be comparable between trial arms but statistical tests not reported. Blank cells signify no data reported on that outcome.

* defined as a night and day without symptoms and no asthma-related nocturnal awakenings

5.2.6 Q4: ICS/LABA administered in separate or combination inhalers

5.2.6.1 FP/S in combination inhaler *versus* FP+S in separate inhalers

5.2.6.1.1 Study characteristics

One parallel group RCT[219] evaluated the effectiveness of FP/ SAL in combination compared to FP plus SAL taken concurrently and was published in 2000 (*Table 19*). This study was a multi-centre trial with 35 centres and the study sample size was 257 participants. No power calculation to ascertain an adequate sample size was reported.

The trial compared FP/SAL 200/100μg per day via Diskus inhaler (Seretide™, GlaxoSmithKline) in one trial arm with FP 200μg per day plus SAL 100μg per day also via Diskus inhalers (it is not explicitly stated, but can be deduced from the text that devices were supplied by GlaxoSmithKline) in the second trial arm. The treatment duration was 12 weeks. The aim of the study was to compare safety and efficacy of a combination of the two groups with that of the two drugs separately in children with asthma that was poorly controlled by ICS alone.

The mean age of the participants in the trial was 7.6 years. The children were all poorly controlled by ICS therapy alone (BDP or BUD or flunisolide 400-500μg per day, or FP 200-250μg per day). The mean baseline FEV_1 % predicted in was 86% in the combination therapy arm and 84% in the concurrent therapy arm respectively.

The quality of reporting and methodology of the study was generally inadequate. The method of randomisation and allocation concealment was not reported. The study did however report that data were analysed on an intention-to-treat population, but the method undertaken to achieve this was assessed to be inadequate.

TABLE 19 *Study characteristics (FP/SAL combination vs separate inhalers)*

Study ID	Design	Intervention	Patients	Outcomes
Van den Berg et al (2000)	RCT Multi-centre Parallel-group Double-blind	*Drugs:* 1. FP/SAL 100/50µg b.i.d. (daily total 200/100µg) + placebo 2. FP + SAL 100 + 50µg b.i.d. (daily total 200 + 100µg) *Delivery device:* 1. Diskus™ (Seretide™, GlaxoSmithKline*) + Diskus™ 2. Diskus™ (Flixotide, GlaxoSmithKline*) *Duration:* 12 wks *Run in period:* 2 wks	*Number randomised* 257 *Mean age* 7.6 (4 – 11) yrs *Baseline FEV_1 % predicted* Not reported *Previous ICS treatment (drug and dose)* BDP, BUD 400-500µg/daily, flunisolide 200-250µg/daily constant for 4wks prior to study	*Outcomes* FEV_1 Mean am & pm PEFR Adverse events
* not stated explicitly, but deduced from the text				

5.2.6.1.2 Results

Lung function

The Van den Berg and colleagues[219] trial present data on the adjusted mean change from baseline in FEV_1. At 12 weeks this was 0.21 L in the SAL/FP combination group and 0.13 L in the FP plus SAL group (difference -0.08 L, 95% CI -0.14, -0.01. *p*=0.052) suggesting the difference is of borderline significance.

For morning PEFR, the adjusted mean change from baseline was 33 L/min in the combination therapy group compared to 28 L/min in the concurrent therapy group. The mean difference between groups (separate inhalers – combination inhaler) (-5 L/min, 90% CI -10,0 L/min, *p*=0.103) was shown to be within the defined limits for equivalence (the criterion being ± 15 L/min). Similar, non-statistically significant differences were seen with adjusted mean change in evening PEFR (FP/SAL 29 L/min, FP plus SAL 25 L/min, *p*=0.164).

Symptoms / health related quality of life

Symptom-free days were reported to be similar between groups in the Van den Berg and colleagues[219] trial but no data were reported in the publication to support this.

Use of rescue medication

The Van den Berg and colleagues[219] trial report that there were no differences between the FP/SAL and the FP plus SAL groups on the need for rescue medication but no data are presented to support this.

Exacerbations

No data on exacerbations were reported.

Adverse events

There were 13 children with adverse events in the FP/SAL group and 6 in the FP + SAL group of the Van den Berg and colleagues[219] trial. No analysis for statistical significance was undertaken on this data.

5.2.6.1.3 Summary

In this multi-centre trial no differences between treatment with FP/SAL in a combination inhaler and FP plus SAL in separate inhalers were observed on measures of lung function, symptoms, use of rescue medication or adverse events.

5.2.6.2 Summary of Q4: ICS/LABA administered in separate or combination inhalers

FP/SAL versus separate FP + SAL, n=1 RCT

			Results											
			Lung function			Symptoms								
Daily dose	Studies, design, duration, device, number randomised	ICS in each trial arm	FEV_1	PEFR morning	PEFR evening	NW	SFD	SFN	SS	HRQoL	Rescue medication	Exacerbations	Adverse events, % of patients	Adrenal markers
200/100µg vs 200 + 100µg	Van den Berg, 12w Parallel, double-blind DPI; n=257	FP/S	NSD*	NSD NID	NSD		C				C		C	
		FP+S												

NW = nocturnal waking; SFD = symptom-free days; SFN = symptom-free nights; SS = symptom score (varies between studies); NSD = no significant difference between trial arms; C = stated to be comparable between trial arms but statistical tests not reported; NID = Non-inferiority / equivalence demonstrated. Blank cells signify no data reported on that outcome.

* *p*=0.052

5.2.7 Q5: Combination inhaler compared to combination inhaler

No RCTs of this comparison were identified.

5.2.8 Cochrane systematic reviews

Five Cochrane systematic reviews[187-191] evaluating various ICS treatments for chronic asthma in adults and children were identified in searches. The reviews were published between 2000 and 2006 and are briefly described individually below.

It is important to note that these reviews had slightly different inclusion criteria to the current assessment (e.g. when comparing ICS and LABA to ICS alone, the former could be delivered in separate inhalers as well as combination inhalers). Further, only a relatively small proportion of the included studies in each review comprised children under 12 years. Their results are provided here as context within which to interpret the results of the current assessment.

Adams and colleagues[188] – FP versus BDP or BUD

This review[188] evaluated the effectiveness and safety of three inhaled corticosteroids - FP was compared with either BDP or BUD. The review was first published in Issue 1, 2001 and was last updated in May 2005 (searches up to January 2005). The review included prospective RCTs of parallel or cross-over design in both adults and children (>2 years) with chronic asthma. The interventions included any dose of FP compared to any dose of BDP or BUD, with a treatment period of one week or longer.

The review found 57 studies which met the inclusion criteria, involving a total of 12,614 participants. Fourteen of the studies were in children, with the remaining studies conducted in adolescents and adults. The asthma severity of the participants in the trials varied from mild (8 studies), mild to moderate (12 studies), moderate (12 studies), moderate to severe (16 studies), severe (6 studies), and mild to severe (two studies), with severity being unclear in one trial. In the majority of studies, some or all of the participants were using regular inhaled corticosteroids at the time of enrolment.

Results

Dose ratio 1:2

FP resulted in a significantly greater absolute FEV_1 compared to BDP/BUD (mean difference 0.09 litres, 95% CI 0.03 to 0.15 litres). However, when reported as change from baseline, there was no significant difference between groups (mean difference 0.01 litres, 95% CI -0.02 to 0.05 litres). Similarly, there was no significant difference between groups in absolute FEV_1 % predicted (mean difference 0.50%, 95% CI -1.28 to 2.28%) or change from baseline FEV_1 % predicted (mean difference -1.04%, 95% CI -3.55 to 1.47%).

Treatment with FP led to a significantly greater morning PEFR compared to BDP/BUD (mean difference 9.32 L/min, 95% CI 5.96 to 12.69 L/min), but not evening PEFR (mean difference 4.67 L/min, 95% CI -1.36 to 10.7 L/min). When reported as change from baseline, there was no significant difference between groups (mean difference 1.68 L/min, 95% CI -1.93 to 5.29 L/min).

Symptoms and rescue medication use were widely reported but differences in the reporting of these outcomes precluded the pooling of data for meta-analysis. The review only reported on specific adverse events, and data on morning plasma cortisol and 24-hour urinary cortisol was limited. No significant differences were observed between FP and BDP/BUD for trial withdrawals (OR 0.76, 95% CI 0.53 to 1.09, 12 studies), or in the likelihood of experiencing an asthma exacerbation (OR 0.75, 95% CI 0.52 to 1.08, three studies).

Dose ratio 1:1

A significant difference in absolute FEV_1 was found in favour of FP (mean difference 0.09 litres, 95% CI 0.02 to 0.17 litres). However, when reported as change from baseline, there was no significant difference between groups (mean difference 0.04 litres, 95% CI -0.03 to 0.11 litres).

Morning PEFR was significantly better with FP compared with BDP (mean difference 8.78 L/min, 95% CI 5.14 to 12.41 L/min). Evening PEFR was also significantly better with FP (mean difference 6.37 L/min, 95% CI 2.75 to 9.99 L/min).

Treatment with FP resulted in a significant reduction in the odds of an asthma exacerbation (OR 0.77, 95% CI 0.59 to 0.99, four studies). However, when a random effects model was applied to the meta-analysis due to study heterogeneity, the difference became insignificant. No significant differences were observed between FP and BDP/BUD for trial withdrawals (OR 0.72, 95% CI 0.38 to 1.35, five studies). Differences in the reporting of measures of symptoms and rescue medication use meant that only limited studies could be included in a meta-analysis. There was no significant difference between groups in the proportion of symptom-free days (three studies), day time or night-time score (two studies), the number of participants experiencing symptom-free days or nights (two studies), or the use of rescue medication use (two studies).

Lasserson and colleagues[191] – FP versus HFA-BDP for chronic asthma in adults and children

This review[191] aimed to determine the efficacy of FP compared to HFA-BDP. The review was first published in Issue 4, 2005 and was last updated in January 2006 (searches up to January 2006). The review included RCTs of parallel or cross-over design in both adults and children with chronic asthma. The interventions included CFC- or HFA-FP compared to HFA-BDP.

The review found eight studies which met the inclusion criteria, involving a total of 1,260 participants. Only one of the studies was conducted in children. The HFA-BDP used in all the studies was extra fine, and all the studies had a nominal dose ratio of 1:1. Treatment duration ranged from three to twelve weeks. The majority of participants were adults with baseline symptoms and lung function indicating moderate asthma.

Results

Parallel trials

No significant difference in change in FEV_1 was observed between the HFA-BDP and FP groups (WMD 0.04 litres, 95% CI -0.03 to 0.11). Similarly, no significant difference was observed in change from baseline in morning PEFR (WMD -2.31 L/min, 95% CI -12.53 to 7.91).

Differences in the way data was reported meant that meta-analysis was not undertaken for most of the other outcome measures. Individual studies reported no significant differences between treatment groups for symptom scores, health-related quality of life, nor asthma exacerbations. Whilst three trials found no difference in the use of rescue medication (reported in various ways), one trial reported a significant difference in the medians which favoured FP (0.28 vs 0 puffs/day, p=0.04). No significant difference was found in the rate of any adverse event (RR 0.88, 95% CI 0.72 to 1.08).

Cross-over trials

Of the three RCTs of cross-over design, one was a fully published paper and two were conference abstracts only. Therefore, there is limited data to report in this category.

One trial reported no significant difference between FP and HFA-BDP in FEV_1 % predicted or morning PEFR. One trial also reported in the text that there were no differences between treatment groups in FEV_1 or morning PEFR but did not present any data. The third study did not indicate whether reported FEV_1 data were significantly different.

The trials in this category did not report any data on symptoms, quality of life, rescue medication use, asthma exacerbations or withdrawals.

Ni Chroinin and colleagues[190] – $LABA_s$ versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma

This review[190] assessed the effectiveness and safety of adding a LABA to inhaled corticosteroids compared to inhaled corticosteroids alone. The review was first published in Issue 4, 2005 and was last updated in June 2005 (searches up to April 2004). The review included RCTs of parallel or cross-over design in both adults and children (>2 years) with chronic asthma who had previously received ICS therapy. The interventions included a LABA (SAL or FF) or placebo administered daily for at least 30 days, added to ICS (e.g. FP, BDP, BUD, triamcinolone acetonide). The dose of ICS had to be the same in both the LABA and ICS alone groups.

The review included 26 studies involving 8,147 participants which met the inclusion criteria and provided data in sufficient detail. Eight of the studies were in children, with the remaining studies conducted in adolescents and adults. LABA was added to BUD in seven trials, to BDP in three trials, to BDP or BUD in one trial, to FP in four trials, with the ICS being unspecified in 11 studies. Most of the studies used separate inhaler devices for ICS and LABA (n=19), and study duration was four months or less in most trials. Participants in the majority of trials had inadequate asthma control, and the severity of asthma was mild (n=8 trials) or moderate (n=18 trials). In adult studies, the mean age of participants ranged from 35 to 48 years, whilst in children the mean age ranged from 8.5 to 14 years.

Results

Compared to ICS alone, the addition of LABA to ICS provided significantly greater improvement in change from baseline FEV_1 (WMD 0.170 litres, 95% CI 0.11 to 0.24 litres) and change in FEV_1 % predicted (WMD 2.79%, 95% CI 1.89 to 3.69%). Similarly, treatment with LABA + ICS led to a significantly greater improvement in change from baseline in morning PEFR (WMD 23.28 L/min, 95% CI 18.38 to 28.18 L/min) and evening PEFR (WMD 21.33 L/min, 95% CI 14.53 to 28.12 L/min).

Use of LABA + ICS significantly reduced day time symptoms (SMD -0.34, 95% CI -0.44 to -0.23, five studies), night-time symptoms (SMD -0.18, 95% CI -0.31 to -0.05, two studies), and overall 24-hour symptoms (SMD -0.28, 95% CI -0.45 to -0.11, two studies). The addition of LABA was also significantly more favourable in terms of change from baseline in symptom-free days (WMD 17.21%, 95% CI 12.06 to 22.36%, six studies) and symptom-free nights (SMD 0.51, 95% CI 0.28 to 0.74, four studies). There were no significant differences between groups in change in percentage of nights with no awakenings or in night-time awakenings.

The addition of LABA to ICS significantly reduced the need for rescue-medication use in terms of the change in overall 24-hour use (WMD -0.81 puffs/day, 95% CI -1.17 to -0.44, eight studies). The addition of LABA also significantly reduced the risk of asthma exacerbations requiring systemic steroids by 19% (RR 0.81, 95% CI 0.73 to 0.90, 17 studies). There was no group difference in the risk of overall adverse events (RR 0.98, 95% CI 0.92 to 1.05, 11 studies), serious adverse events (RR 1.16, 95% CI 0.30 to 4.42, four studies) or withdrawals due to adverse events (RR 1.29, 95% CI 0.96 to 1.75, 23 studies).

Adams and colleagues[187] – BDP versus BUD for chronic asthma

This review assessed clinical outcomes in studies which compared BDP with BUD delivered at the same nominal daily dose. The review was published in Issue 1, 2000 and was last updated in November 1999 (searches up to 1999, month not specified). The review included RCTs of either parallel-group or cross-over design. Studies were eligible for inclusion if they included adults or children over two years old with chronic asthma. The drugs could be delivered by different devices (pMDI, MDI+spacer, DPI), and there does not appear to have been any restriction on the length of treatment period.

The review found 24 studies (5 parallel-group and 19 cross-over trials) published between 1982 and 1988 which met the inclusion criteria. Four of these were only available in abstract form and did not report any outcome data. Two of the citations were not assessed for the review as they required translation. Eighteen of the studies were conducted in adults, and six studies were in children, with a total of 1174 participants in the included trials. The level of asthma control at randomisation was not well described in the majority of studies, and asthma severity at baseline was not well documented. One study stated that patients had asthma of moderate severity, one described patients as having fairly severe asthma, and two reported severe asthma. In 20 of the studies, patients were not previous regular users of oral corticosteroids (OCS). In three of the studies, prior OCS use was an inclusion criterion, and a proportion of patients in another trial had received OCS treatment at the time of enrolment. Twelve studies lasted from two to four weeks, ten treated patients from six to 12 weeks, and one study treated patients for two years. One of the studies had a complex trial design with treatment periods of variable length. Only two of the cross-over trials had a washout period. The majority of trials assessed daily doses of 400µg/day (n=10) or 800µg/day (n=7), although one study assessed doses of 200µg/day and two studies used higher doses of 1500-1600µg/day. An MDI device was used to deliver both drugs in eight of the studies, but the other 16 used different delivery devices for each drug.

Results

Meta-analysis by Adams and colleagues[187] found no statistically significant differences between BDP and BUD for any of the outcome measures relevant to the present review. Results were presented separately for cross-over trials with no prior OCS, parallel-group trials, and cross-over trials with prior OCS. Comparisons reported below were for BDP vs. BUD.

FEV_1 was reported by six cross-over studies of people with no prior OCS and two parallel-group studies. The weighted mean difference was -0.08L [-0.27, 0.12] in the cross-over studies of people with no prior OCS and -0.02 [-0.23, 0.20] in the parallel-group studies. FEV_1 predicted was also reported by two cross-over studies of people with no prior OCS (WMD -5.04L[-11.98, 1.89]). Morning and evening PEFR reported in diary cards also showed no statistically significant difference between the two drugs. The pooled cross-over trials where patients had no prior OCS had a WMD of -2.99L/min [-28.43, 22.45] for morning PEFR (six trials) and -5.47L/min [-31.50, 20.56] for the five trials reporting evening PEFR. Similar, non-statistically significant differences were observed in three cross-over trials whose patients had previously received OCS. Corresponding analysis for one parallel-group RCT found a WMD of -18.00 L/min [-54.76, 18.76] for morning PEFR and -8.00 L/min [-49.29, 33.29] for evening PEFR.

The studies reported asthma symptoms using a range of measures, and no significant differences between treatments were reported for any of these measures. Meta-analysis of daily symptom score in five studies found no statistically significant difference between BDP and BUD (SMD 0.08 [95% CI -0.22, 0.39]). Similarly, use of rescue medication was not reported to differ statistically significantly between the two drugs. Adverse events were not pooled due to lack of clear reporting in the original trials. One parallel-group study reported a relative risk of 1.76 (BDP vs. BUD) for withdrawal due to an asthma exacerbation (95% CI 0.44, 7.10).

Greenstone and colleagues[189] – Combination of LABA and ICS vs. higher dose ICS in children and adults with persistent asthma

This review assessed clinical outcomes in studies which compared combination treatment of twice daily LABA and ICS against use of a higher dose of ICS. The review was published in Issue 4, 2005 and was last updated in July 2005 (searches up to April 2004). The review included RCTs of adults or children over two years old with chronic asthma, with a minimum duration of 30 days' treatment.

The review found 42 studies published as 26 full-text papers and 16 abstracts, 13 of which provided insufficient data to be included in the meta-analysis. One of the trials had two intervention groups compared to a control group, and these were analysed as separate trials, so the review was therefore based on data from 30 trials with a total of 9509 participants. One trial was a cross-over study, and the rest were of parallel-group design. The majority of trials (n=27) were based on adult participants, and three of the studies focussed on children. Participants' asthma was generally of moderate severity, and was inadequately controlled at baseline in all but two of the studies. Patients were required to have used ICS for at least one to three months before entry to all but one of the trials.

SAL was used as the LABA in 24 of the trials, with FF being used in the other eight trials. Standard doses of LABA were used in the majority of trials (n=27). Most of the trials (n=25) used the same ICS in both the LABA and control groups; 11 used CFC-BDP; four used BUD and ten FP. Three trials compared FP and LABA to CFC-BDP, BUD or HFA-BDP. One study compared the combination of LABA and the patients' usual ICS to additional FP in the higher ICS study arm, and one study compared BUD and LABA to FP. The median ICS dose in the combined LABA group was 400µg/day (range 200-1000µg/day) and 1000µg/day (range 400-2000µg/day) in the higher ICS dose group. ICS and LABA drugs were delivered via separate devices in 22 trials, but eight trials used a single device to deliver the drugs. Most of the trials lasted for 12 or 24 weeks (n=14, n=9), with others lasting four weeks (n=1), six weeks (n=1), 52 weeks (n=3) or 54 weeks (n=1).

Results

The review's main outcome measure was the risk of exacerbation requiring systemic corticosteroids, and this was reported by 15 of the trials. Pooled data gave a relative risk of 0.88 (95% CI 0.77, 1.02), with no significant group difference (RD=2% [95% CI 0% to 4%). Although the similarity between treatments did not meet Greenstone and colleagues'[189] *a priori* definition of equivalence, the upper confidence interval was reported to exclude the likelihood of a higher rate of exacerbations in patients who received LABA. Planned subgroup analyses found no effect of age group (children vs. adult), average baseline severity, type of LABA, ICS dose difference between groups, ICS dose associated with LABA, and trial duration. However, meta-regression of 13 trials found two independent variables which significantly reduced the risk of exacerbation (low ICS dose used in combination with LABA [*p*=0.046] and trial duration of 24 weeks or less [*p*=0.01]).

Lung function showed a statistically significantly greater improvement in the combination LABA and ICS groups than in the high dose ICS group. Using pooled data from nine trials, the weighted mean difference in FEV_1 at endpoint was 0.13 L (p5% CI 0.08, 0.19). Similarly, change from baseline FEV_1 showed a WMD of 0.10L (95% CI 0.07, 0.12; n=7 trials) and FEV_1 % predicted at endpoint had a WMD of 3.93% (95% CI 1.33, 6.53; n=4 trials). The WMDs for morning and evening PEFR at endpoint were 27.33L/min (95% CI 21.39, 33.26; n=14 trials) and 20.18L/min (95% CI 12.75, 27.62; n=3 trials), respectively.

Patients treated with a combination of ICS and LABA had statistically significantly better changes from baseline total asthma symptom scores. Data from five trials were pooled, giving a SMD of -0.23 (95% CI -0.41, -0.05). The percent of symptom-free days at endpoint also favoured combination therapy in pooled analysis of eight trials (WMD=11.9%, 95% CI 7.37, 16.44). Change in rescue inhalations over 24 hours favoured the combination treatment group (ICS+LABA) over the high dose ICS group. Data from eight trials were pooled to give a SMD of -0.22 (95% CI -0.29, -0.14). There were no statistically significant differences between the groups in daytime symptoms at endpoint, nighttime symptoms, percentage of symptom-free days at endpoint, change from baseline in nighttime awakenings, and QoL as measured by the Juniper Questionnaire. There were no group differences in overall side effects (RR=0.93 (95%CI 0.84, 1.03]; n=15 trials), serious adverse events (RR=1.54 [95% CI 0.72, 3.21]; n=5 trials) or withdrawals due to adverse events (RR=0.94 [95% CI 0.71, 1.24]; n=18 trials).

6. Economic Analyses

SECTION CONTENTS

6.1 Aim of the assessment of economic evaluations

The following section provides a detailed overview of existing cost-effectiveness evaluations that have aimed to assess the cost-effectiveness of the inhaled corticosteroids BDP, BUD and FP used alone or in combination with a LABA, SAL or FF within their licensed indications, and within the appropriate step of the BTS/SIGN Guidelines,[1] for the treatment of chronic asthma in children less than 12 years of age. This section reviews existing cost-effectiveness evaluations and those submitted by industry to NICE through the appraisal process, and examines the quality of these evaluations and the relevance of the data from the perspective of the UK NHS and PSS.

6.2 Systematic review of cost-effectiveness studies

A systematic review of existing cost-effectiveness studies was undertaken.

6.2.1 Search Strategy and Critical Appraisal Methods

MEDLINE, EMBASE and the Cochrane Library (Issue 1, 2006) were searched for cost-effectiveness studies that assessed the cost-effectiveness of BDP, BUD, and FP dipropionate used alone or in combination with a LABA, SAL or FF within their licensed indications and the appropriate step of the BTS/SIGN Guidelines.[1] The full search strategy is displayed in Appendix 3.

A total of 723 titles and abstracts were screened for inclusion in the review. This included studies that were potentially relevant to the present assessment, and also those relevant to a linked assessment on the effectiveness and cost-effectiveness of inhaled corticosteroids and LABAs for the treatment of chronic asthma in adults. Of the titles and abstracts screened, 58 were ordered as full papers and assessed in detail.

6.2.1.1 Inclusion and exclusion criteria

Cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses and cost-consequence analyses were eligible for inclusion in the cost-effectiveness review. In addition, separate submissions were received from GlaxoSmithKline, AstraZeneca, Meda Pharmaceuticals Ltd, and Trinity-Chiesi Pharmaceuticals Ltd as part of the NICE technology appraisals process.

6.2.1.2 Published cost-effectiveness studies

No cost-effectiveness studies for the relevant comparators in the treatment of chronic asthma in children less than 12 years of age were identified.

6.3 Cost-effectiveness studies provided by industry

Four submissions to NICE included cost-effectiveness analysis. Two of these included cost-effectiveness analysis (CEA) and two included cost minimisation analysis (CMA). Submissions were made by GlaxoSmithKline, Astra-Zeneca, Meda Pharmaceuticals, and Trinity-Chiesi. *Table 20* below shows a summary of the submissions received by industry through the appraisal process.

TABLE 20 *Summary of the submissions received by industry through the appraisal process*

Manufacturer	Product	Type of analysis
GlaxoSmithKline	Becotide® Flixotide® Seretide®	CEA
Astra-Zeneca	Pulmicort® Symbicort®	CEA
Meda Pharmaceuticals Ltd	Novolizer®	CMA
Trinity-Chiesi Pharmaceuticals Ltd	Modulite®	CMA

Below an outline review of each of the manufacturer's submissions (CEA, CMA) is presented. This outline review is based on a checklist suggested for critical appraisal of cost-effectiveness analysis (Drummond and colleagues, 1997) ,[220] and the requirements of NICE for submissions on cost-effectiveness analysis (reference case) (NICE 2004),[221] and where appropriate a suggested guideline for good-practice in cost-effectiveness models (Philips and colleagues, 2004).[222]

6.4 Review of the submission by GlaxoSmithKline (GSK)

6.4.1 Overview

The submission by GSK to NICE includes an economics commentary and cost-effectiveness analysis to support three GSK products; BDP (Becotide®), FP (Flixotide®), and a combination inhaler containing FP/SAL xinafoate in combination) (Seretide®).

The submission includes some commentary on the clinical equivalence of ICS products, and the presentation of some price estimates. The submission does not include any cost-effectiveness analysis for BDP and FP versus other ICS products, with a cost-minimisation approach assumed due to clinical equivalence across these products. This is justified in the submission on the basis of assumed equivalence. The submission also does not include any cost-effectiveness analysis for Seretide versus Symbicort, as the submission states there is an absence of head to head comparisons of the clinical effectiveness of these products.

The submission is focused on four specific research questions, which are:

Q1: For patients taking ICS alone, is FP the most clinically effective ICS?

Q2: For patients uncontrolled on ICS alone, is switching to Seretide more clinically effective than remaining on the same dose or increasing the dose of ICS alone?

Q3: Where a LABA and ICS are to be co-prescribed, is Seretide more clinically effective than ICS and LABA delivered in separate inhalers?

Q4: In patients where combination therapy is appropriate what is the relative clinical effectiveness of Seretide compared to Symbicort?

The submission presents outline detail of a systematic search of the literature on cost-effectiveness analyses for treatment of asthma. Appendix 9 of the submission provides information on this review, but the literature is not considered relevant. The submission presents specific cost-effectiveness analyses, and a generic cost-effectiveness model to address questions 2 and 3. Question 1 is not covered further (as above, a CMA approach is assumed) and question 4 is addressed via a comparison of product costs only.

6.4.2 Model on cost-effectiveness of Seretide

In the submission a new model is developed by GSK to estimate cost-effectiveness of the alternative treatment scenarios. A common model is used for the analysis of both adult and child treatment for asthma. Below we outline the approach taken for the GSK model, and provide an outline review.

The model presented is a simple two state model applying effectiveness data on the percentage of symptom-free days (% SFDs), cost and outcome data associated with the two health states of 'symptom-free' and 'with symptoms'. The model is essentially a spreadsheet calculation to estimate cost-effectiveness from this related data across alternative treatments. In the model, at a given point in time, patients are either (1) symptom-free, or (2) with symptoms. Death is not included in the model (due to an assumption of no differential effect of treatments). Exacerbations are not included in the model. The model is not a disease progression model, and does not involve transitions between the two health states over time. The model presents a scenario, showing occupancy of states 'conditional on treatment choice' on the basis of a meta-analysis of the % SFD at trial endpoint. This endpoint is chosen as it was (1) commonly reported and considered, (2) based on clinical opinion, (3) judged to be more appropriate than lung function for representing patients clinical response to treatment. This reported endpoint (% SFD) was taken to represent the proportion of time spent in the symptom-free state. The model used effectiveness data from four trials; two for Seretide versus the same dose of FP, one for Seretide versus an increased dose of FP, and one for Seretide versus the same dose delivered via separate products.

The model is based on a range of assumptions, including the assumptions that:

- Alternative therapies have the same mortality profile and the same toxicity profile (including long-term effects).
- The differential proportion of time patients spend in the symptom-free state over their treatment lifetime would be the same as the differential proportion observed during the trial period (even though clinical trials are mainly 12-weeks)
- Trial based data is generalisable to wider patient populations
- There is no difference in the effectiveness between different inhaler devices.

The submission states that the time horizon is "nominally one year, corresponding to the duration of the GOAL trial used to estimate costs and utilities." However, given the nature of the model, it is a 'snap-shot' or cross-sectional approach to estimating cost-effectiveness analysis.

The model uses health state values of 0.97 for the 'symptom-free' health state, and 0.85 for the 'with symptoms' health state, a utility decrement of 0.12. These values are cited from the CEA study for the GOAL RCT reported by Briggs and colleagues (2006) .[223] However, this study does not provide information on the methods used for estimating utility weights, citing a personal communication only, for a study mapping AQLQ to EQ-5D. The model works by placing proportions of patients (or patient time) in each health state, according to the effectiveness data, and calculating QALY differences as the product of these data [(e.g. a 12.29% difference in % SFDs (low dose Seretide versus FP 200µg/day), results in a difference in QALYs between treatments of 0.014748)].

Whilst the data from the GOAL clinical trial are based on an adult patient group, the GSK submission states that these data are considered to be the most appropriate for use in the paediatric analysis. No justification is provided in the submission to support this.

Costs are comprised of mean acquisition costs for products and an estimate of the annual mean 'other health service' costs for symptom-free time and time with symptoms. This latter 'other' cost excludes primary treatment costs. The cost estimates used for the health states are based on data from the GOAL clinical trial, which comprised resource use against secondary care visits, primary care visits and rescue medication used. The submission uses a linear regression model to estimate a mean annual cost, which is £79.83 for the health state 'with symptoms' and £1.57 for 'symptom-free'. The cost differences between alternatives is as per the above example for QALY differences, with estimated difference in costs for strategies multiplied by the percentage difference in SFDs.

The model is developed for use in both adult and child patient groups, and is arranged around 21 specific cost-effectiveness questions (5 for children, 16 for adults). All costs are reported as UK (£) sterling 2006.

6.4.3 Model / Cost-effectiveness Results

The cost-effectiveness analysis is arranged around the comparison of Seretide (200 FP/100 SX µg/day) to (i) the same dose of ICS alone (FP), (ii) a higher dose of ICS alone (FP400µg/day), and (iii) ICS + LABA in separate inhalers (at same dose). The analysis also considers a comparison with Symbicort (at 400 BUD/FF100µg/day). The submission reports results for different product costs for Seretide (for Evohaler and Accuhaler), and against two different ICS product costs (FP & BDP). Therefore the analysis results in approximately 10 different summary statistics. These are summarised below:

Q1: Seretide 200/100µg/day versus the same dose of ICS minus a LABA (FP 200µg/day) – ICERs range: Seretide £31,388 (Evohaler, versus comparator price at £91.31) – to £72,702 per additional QALY. For all scenarios incremental effect is 3.61% in % SFDs, incremental QALYs are 0.0043, and 'other costs' are reduced by -£2.83. Incremental drug/treatment costs range from £138 to £317.

Q2: Seretide 200/100µg/day versus a higher dose ICS alone (FP 400µg/day) - ICERs range: Seretide at £15,739 (Evohaler, versus comparator price at £178.97) to Seretide at £63,736 per QALY (with comparator price at £178.97). For all scenarios incremental effect is 2.60% in % SFDs, incremental QALYs are 0.0031, and 'other costs' are reduced by -£2.03. Incremental drug/treatment costs range from £51 to £201.

Q3: Seretide 200/100µg/day versus FP 200+SX 100µg/day (separate inhalers) - ICERs: Seretide dominates for all comparisons (cost saving and greater effect). For all scenarios incremental effect at 1.90% in % SFDs, incremental QALYs are 0.0023, 'other costs' reduced by -£1.49. Drug/treatment costs for comparators all lower for Seretide, from -£47.48 to -£226.45.

Q4: Seretide 200/100µg/day versus Symbicort [BUD 400µg/day, (inhaler type100/6)] – No CEA undertaken, acquisition cost comparisons only, with Seretide Evohaler at £230.11 versus £401.78, and Accuhaler at £379.86 versus. £401.78, both presented as Seretide being cost saving (acquisition costs).

A number of factors are considered in the analysis (e.g. dose, price) resulting in a range of cost-effectiveness results. The TAR team suggest that policy makers should take note of the specific inputs for analysis and consider the interpretation of results. For example, estimated cost savings and estimated incremental QALYs are very small, and some consideration should be given to their significance and/or meaningfulness.

6.4.4 Outline appraisal of the cost-effectiveness analysis undertaken

TABLE 21 Critical appraisal checklist of economic evaluation by GSK

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	Yes	4 clinical questions stated (2 of which covered in CEA)
Is there a clear description of alternatives?	Yes	Seretide versus comparators (various options stated with comparisons against the same dose of FP alone, an increased dose of FP alone, single versus combination inhaler and Symbicort. Analysis against comparable dose of BDP alone was presented as a sensitivity analysis)
Has the correct patient group / population of interest been clearly stated?	Partial	Children under 12-years is the patient group under consideration, however much of the data is from adult patient groups (aged 12+)
Is the correct comparator used?	Yes	Sensitivity analysis undertaken for BDP versus Seretide. This is appropriate as it is the other single comparator under consideration with the same inhaler and propellant type (i.e. pMDI with HFA)
Is the study type reasonable?	Yes	CEA model used (CUA results presented)
Is the perspective of the analysis clearly stated?	Yes	Perspective stated as UK NHS
Is the perspective employed appropriate?	Cost: Yes Outcomes: Partial	Submission appears to adopt a UK NHS and PSS perspective for costs (consistent with NICE reference case). Perspective on outcomes is that of the patient, but not all effects considered
Is effectiveness of the intervention established?	Yes	The CEA is based on clinical effectiveness data from a small number of trials reporting the chosen economic endpoint (%SFDs) – mainly over 12-weeks. Whilst the study demonstrates effectiveness over this one endpoint it does not discuss, in context of CEA, the other effectiveness endpoints across treatments. Study assumes differences seen in trials can be generalised to the lifetime treatment period.
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	No	Nominal 1-year time horizon used (not lifetime) ICERs are based on 1-year cost and QALY differences
Are the costs and consequences consistent with the perspective employed? *	Partial	Costs appear to be consistent with perspective employed, but limited justification provided. Consequences limited to consequences of SFDs?
Is differential timing considered?	No	Nominal 1-year time frame used

Item	Critical Appraisal	Reviewer Comment
Is incremental analysis performed?	Yes	
Is sensitivity analysis undertaken and presented clearly?	Yes	Yes sensitivity analysis included, including probabilistic sensitivity analysis. No scenario analyses undertaken to consider different mean input parameters.
* More on data inputs for costs and consequences in the review of modelling methods below		

TABLE 22 *NICE reference case requirements – GSK submission*

NICE reference case requirement		Reviewer comment
Decision problem: As per the scope developed by NICE (esp. technologies & patient group)	Partial	
Comparator: Alternative therapies routinely used in the UK NHS	Yes	
Perspective on costs: NHS and PSS	Yes	
Perspective on outcomes: All health effects on individuals	No	Only symptom-free days were used to consider QALY values
Type of economic evaluation: Cost-effectiveness analysis	Yes	
Synthesis of evidence on outcomes: Based on a systematic review	Yes	
Measure of health benefits: QALYs	Yes	
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	Unclear	Method for estimating health state utilities is unclear
Method of preference elicitation for health state values: Choice-based method (e.g. TTO, SG, not rating scale).	Unclear	Method of preference elicitation is not reported
Source of preference data: Representative sample of the UK public	Unclear	
Discount rate: 3.5% pa for costs and health effects	N/A	
N/A=not applicable		

6.4.4.1 Model structure / assumptions

The model structure is based around the clinical endpoint in the GOAL trial of differences in the percentage of symptom-free days, and this is assumed, in the submission, to be a reasonable reflection of relative treatment effectiveness. This may not be a reasonable assumption, as this endpoint only reflects part of the effectiveness profile of asthma treatments. Other important elements of asthma control include night time disturbances (and data presented in the submission indicates differences between SFNs may be smaller than % SFDs), lung function and exacerbations. The model presented does not directly capture these items The model structure used is stated to be based on the CEA for the GOAL clinical trial presented by Briggs and colleagues.(2006)[223] However, the model differs from the approach of Briggs and colleagues in a number of ways. Firstly the model presented by Briggs uses patient level data to derive transition probabilities, secondly, their study uses a composite measure of asthma control, and lastly they also model the state of exacerbation. The estimates of cost-effectiveness presented by GSK are simple spreadsheet calculations combining data on % SFDs and data estimated for relative costs and QALYs for patients in the health states used. The model uses a two-state approach covering time in a symptom-free state, and time with symptoms. This is a simplification of the disease process for asthma, and is stated to be driven by the availability of data for comparative purposes, and on a review of the general literature on modelling asthma treatment. However, it may be that the endpoint chosen is more favourable for comparison of Seretide with other alternative strategies. For example, the effect of Seretide will be more immediate on SFDs than it will be from ICS alone (where any treatment benefit will accrue more slowly over time). No discussion of other outcomes, in the context of the CEA, is provided for the discussion on the model structure, although a brief statement on the potential use of lung function as an alternative approach is provided.

When considering the above points it is important to acknowledge that the literature on modelling cost-effectiveness in asthma treatment is sparse, and whilst there are guidelines for the treatment of asthma (e.g. BTS/SIGN) it is generally difficult (given the current evidence base) to structure and populate a model which reflects such guidelines.

6.4.4.2 Data inputs

The primary data inputs for effectiveness, costs and outcomes are presented in the submission. In the analysis, there is a lack of transparency in the calculations for 'other costs', and there are concerns with the methods used to identify and measure the 'other costs'. The data used on the resource for 'other costs' are taken from one clinical trial, the GOAL trial, Bateman and colleagues (2004),[224] but the specific data used are not presented in the submission. Furthermore, the generalisability of this study (a multi-national RCT, covering 44 countries) to the current analysis is not discussed. The GOAL CEA used data on resource use from all 44 countries in the trial, using a UK indicator variable in the analysis presented. However, the issue of how generalisable the GOAL study is to the UK context and also to a paediatric population is not discussed in the context of the current analysis. Unit costs for the resource use are taken from appropriate data sources. The submission uses a regression model to estimate other costs, based on an expected cost per week of £1.53 for people with asthma symptoms, a mean annual cost of £79.83. Where people with asthma are symptom-free this is reduced to £0.03, a mean annual cost of £1.57. These cost estimates appear to be very low and the submission does not offer the opportunity to consider the appropriateness of the resource use to the UK treatment group. The submission has referred to the economic evaluation undertaken alongside the GOAL trial, Briggs et al.(2006),[223] however the publication for that particular evaluation does not offer detail on resource use. The regression analysis employed in the submission also differs from that presented by Briggs and colleagues(2006).

The cost for Seretide is based on its availability in two different inhaler devices (Accuhaler and Evohaler), with both prices from the Drug Tariff, together with an average price, used to generate a range of data on cost-effectiveness. A drug 'cost per day' is estimated for all treatment options. For example, in the model the estimated cost per day for Seretide 200/100μg/day via Accuhaler and Seretide 200/100μg/day via Evohaler + spacer, are set at £1.04 and £0.63 respectively. For Symbicort 400 (100/6μg/day), and ICS alone (FP 200μg/day), the daily costs are estimated at £1.10 and £0.25 respectively. There are a range of approaches that can be taken to estimate daily costs, and the approach taken in the submission appears reasonable for the current analysis (Appendix 9 of the submission presents the methods used).

There is a lack of transparency over the calculation of health state utilities used in the model (with a citation to a personal communication). The general literature available to inform on health state values for asthma is sparse and undeveloped, and whilst the values used for symptom-free in the analysis seems relatively high (compared to some general population age-related values), the important issue is the incremental difference of 0.12, used between the health state of with symptoms and symptom-free.

The effectiveness data used in the CEA are from a limited number of available trials (as above, two for Seretide versus same dose FP, one for Seretide versus increased dose FP, and one for Seretide versus the same dose of separate products), and this is justified in the submission on the basis of a lack of consistency in the reporting of common outcomes across relevant trials. The use of this limited data may introduce bias to the estimates used, but this has not been discussed or considered in the sensitivity analysis. Effectiveness data from the trials presented are assumed to be generalisable to the treatment group in England and Wales that are the focus of policy analysis. Likewise, the treatment effect from short term trials (mainly of a 12-week duration) is assumed to be appropriate over longer time periods (e.g. one-year).

6.4.4.3 Assessment of uncertainty

Uncertainty in the analyses is addressed using probabilistic sensitivity analysis (PSA). The PSA considered parameter uncertainty for the mean treatment effect, and for 'other cost' and utility model inputs. The report submitted does not present discussion on the results of the sensitivity analysis (additional material was submitted, providing a cost-effectiveness plane and CEAC for each of the 80+ analyses undertaken). Additionally, the report does not present any deterministic sensitivity analysis, or address structural uncertainties via sensitivity analyses. Also heterogeneity of the treatment group has not been considered against any defined sub-groups.

6.4.4.4 Model validation

The submission states that checks were undertaken to consider the validity of the model, with a re-build undertaken using a different software package. This presents evidence of the internal consistency (logic) of the model structure and data structure used.

6.4.5 Summary of general comments on the submission:

- The focus on % SFDs as a measure of asthma control, and treatment effect, may be limited and may not capture other important aspects of asthma control and/or effectiveness data (e.g. exacerbations, quality of life).
- The use of a limited evidence base to populate the model (e.g. only six trials used to derive effectiveness estimates).

- The assumptions over the generalisability of trial data on effectiveness to a UK paediatric population and extrapolation of the treatment effect are not discussed.
- Concerns over the methods used and estimates used for ‘other costs’.
- Concerns over the lack of transparency in estimating health state utilities, and other cost estimates.
- Data assumed to be generalisable to a paediatric analysis, and assume that:
  - Resource use data from the GOAL clinical trial are generalisable to a UK treatment group (under 12 years).
  - Health state utility values cited from the GOAL CEA (Briggs et al. 2006) are generalisable to a UK treatment group under 12-years.

6.5 Review of the submission by Astra-Zeneca (AZ)

6.5.1 Overview

The submission by AZ to NICE includes economics commentary and cost-effectiveness analysis to support two AZ products; Pulmicort® (BUD) and Symbicort® (BUD/FF in combination).

The submission includes some commentary on the clinical equivalence of BUD with other ICS products, and the presentation of some price estimates. It does not include any cost-effectiveness analysis for BUD versus other ICS products. There is limited discussion of the relative cost-effectiveness of different ICS products, with a cost minimisation approach taken due to assumed clinical equivalence between products.

The cost-effectiveness analysis presented in the submission is to support the use of Symbicort (BUD/FF in combination). The submission refers to Symbicort fixed dose (FD), and Symbicort adjustable maintenance dosing (AMD). The submission uses Symbicort FD as the base case for the cost-effectiveness analysis, working on the basis that Symbicort AMD has been shown to be superior to Symbicort FD. The submission compares Symbicort (Symbicort FD & AMD) to the use of ICS alone (high dose), BUD and FF in separate inhalers, and to Seretide (GSK combination product). However, there is no cost-effectiveness analysis presented for Symbicort versus Seretide.

The submission consists of a brief discussion on relevant literature (covering CEAs, and modelling studies), and the presentation of the methods and results for a cost-effectiveness model developed for the submission to NICE.

A literature search is reported that aimed to identify CEAs on Symbicort. In total nine studies were identified, all of which are stated to show Symbicort AMD or Symbicort SMART (Symbicort as both maintenance and reliever therapy) at an equivalent or increased efficacy compared to Symbicort FD (four studies), separate inhalers (three studies), high dose FP (ICS alone) (one study), or Seretide (one study). All except one of these identified studies is stated to show cost savings from the use of Symbicort. None of the identified studies covered the population of children aged 4 to 11 years.

6.5.2 Model on cost-effectiveness of Symbicort

The submission states that the approach presented by Price & Briggs (2000)[225] was most appropriate for the analysis of Symbicort. However, it is also stated to have a number of limitations and a new model is developed by AZ for their submission. Below we outline the approach taken for the AZ model, and provide an outline review.

A model was developed to capture the difference in exacerbations between comparisons, and the difference in time spent in a non-exacerbation health state. It is a Markov-type model with four health states: non-exacerbation, mild-exacerbation, severe-exacerbation, and treatment change. This latter state is a form of absorbing state which reflects withdrawal from the treatment allocated. Where patients withdraw from treatment (undergo treatment change) they are subject to a second-line treatment regimen and are modelled in a parallel process to the main (first-line) model. When treatment is changed, it is in line with recommendations in the BTS/SIGN Guidelines. The model uses a cycle of four weeks, and has a time horizon of one year (with a five-year time horizon considered in sensitivity analysis). The model uses transition probabilities derived from two clinical trials, Pohunek and colleagues (2004)[226] and Tal and colleagues (2002).[218] One of these trials[226] is available as a published abstract only. The trials were both 12-week RCTs conducted in children aged 4 to 11 years[226] and children and adolescents aged 4 to 17 years.[218] Transition probabilities were from combined data from trial arms of Symbicort FD and the BUD+FF arm (administered as separate inhalers) assuming equivalent efficacy. Data on the relative effect (relative risks for severe exacerbation, mild exacerbation, and treatment change) of ICS alone (and Symbicort AMD) were derived from clinical trial data for these comparators (two RCTs for ICS alone).[218;226] Patient level trial data (over 12-weeks) allow the use of different transition probabilities for Symbicort over months 1-3, and thereafter a constant transition probability matrix is used based on events occurring during months 1-3. Analysis is presented for an asthma treatment group aged under 12 (4 to 11 years). In the model all persons start in the 'non-exacerbation' (controlled) health state. The perspective of the analysis is stated as UK NHS & PSS. Prices for asthma treatment are at a 2005/06 price year.

Health state utilities used for the model are based on EQ-5D tariff values. Health state descriptions covering the health states used in the model were collected from a sample of asthma patients, and EQ-5D tariff values for these states were applied (citing Kind et al 1999, for tariff values). The values used for the child (4 to 11 years) patient group were ***CIC removed*** for 'non-exacerbation' (no SABA use), ***CIC removed*** for 'non-exacerbation' (SABA use), (with proportions for SABA and non-SABA use applied to calculate a weighted utility value at ***CIC removed*** for 'mild exacerbation', and ***CIC removed*** for 'severe exacerbation'. The model assumes that exacerbations affect costs and utilities for one week only, with the remaining three weeks in that cycle based on non-exacerbation status. Therefore utility values for the mild exacerbation and severe exacerbation states were weighted accordingly, at ***CIC removed*** respectively, based on one week of the exacerbation related value, plus three weeks at a non-exacerbation value.

A monthly cost is applied in the model based on asthma medication costs and health service consultations and hospitalisations. Primary care NHS resource use (consultations) are assumed to be the same for each of the treatment options, and are not included in the model. The cost of managing a mild exacerbation is estimated at £49.46 and for severe exacerbation between £333 - £1,751.

6.5.3 Model / Cost-effectiveness results

The submission presents summary results for outcomes and costs separately, in table 9 and 10 respectively, and in an incremental analysis in table 11.

The submission presents results indicating that over a 12-month period Symbicort FD is dominated by the ICS alone treatment option (Symbicort with greater cost and less QALYs), dominated by Seretide (no difference in effect and Symbicort with greater cost), and Symbicort is dominant over ICS+LABA in separate inhalers (no difference in effect and Symbicort with lower cost).

In the opinion of the TAR team, it would appear that any comparison rests on the incremental costs associated with ‘maintenance costs’ (drug/treatment acquisition costs).

6.5.4 Outline appraisal of the cost-effectiveness analysis undertaken

TABLE 23 *Critical appraisal checklist of economic evaluation by AZ*

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	Yes	
Is there a clear description of alternatives?	Yes	Symbicort versus comparators (various options stated).
Has the correct patient group / population of interest been clearly stated?	Yes	Children 4-11 years. All patients in model start in non-exacerbation state (this may not be the case in practice with a proportion of patients being in an ‘uncontrolled’ asthma state)
Is the correct comparator used?	Yes	Comparators used are all appropriate, however other additional comparators could also be used.
Is the study type reasonable?	Yes	CEA model used (CUA results presented).
Is the perspective of the analysis clearly stated?	Yes	Perspective stated as UK NHS & PSS
Is the perspective employed appropriate?	Partial Cost: Yes Outcomes: partial	Submission appears to adopt a UK NHS and PSS perspective for costs (consistent with NICE reference case). Perspective on outcomes is that of the patient, but not all effects considered (the focus is on ‘non- exacerbation’ state, and exacerbation events, with no symptom based measures used)
Is effectiveness of the intervention established?	Partial	The CEA is based on clinical effectiveness data from a limited number of trials reporting the chosen economic endpoint (exacerbation related states/outcomes) – mainly over 12-weeks. Primary effectiveness data from 2 RCTs form model transits. Study assumes differences seen in trials can be generalised to the lifetime treatment period.
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	No	1-year time horizon used (not lifetime) ICERs are based on 1-year cost and QALY differences. 5-yr horizon in sensitivity analysis
Are the costs and consequences consistent with the perspective employed? *	Partial	Costs appear to be consistent with perspective employed, but limited justification provided, and may not include all relevant costs (e.g. primary care not included) Consequences limited to exacerbations, and non-exacerbation months. Interpretation of non-exacerbation state from limited clinical evidence.
Is differential timing considered?	No	1-year time frame used – no discounting. (In sensitivity analysis 3.5% discount rate used)
Is incremental analysis performed?	Yes	

Item	Critical Appraisal	Reviewer Comment
Is sensitivity analysis undertaken and presented clearly?	Yes	Yes sensitivity analysis is undertaken, probabilistic analysis.
* More on data inputs for costs and consequences in the review of modelling methods below		

TABLE 24 *NICE reference case requirements – AZ submission*

NICE reference case requirement		Reviewer comment
Decision problem: As per the scope developed by NICE (esp. technologies & patient group)	Yes	
Comparator: Alternative therapies routinely used in the UK NHS	Yes	
Perspective on costs: NHS and PSS	Yes	
Perspective on outcomes: All health effects on individuals	Partial	Health effects were limited to effect of treatment on exacerbation status / rate
Type of economic evaluation: Cost-effectiveness analysis	Yes	
Synthesis of evidence on outcomes: Based on a systematic review	Yes	
Measure of health benefits: QALYs	Yes	
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	Unclear	Method for estimating health state utilities is unclear
Method of preference elicitation for health state values: Choice-based method (e.g. TTO, SG, not rating scale).	Partial	Method of preference elicitation is explicit ***CIC removed***
Source of preference data: Representative sample of the UK public	Yes	
Discount rate: 3.5% pa for costs and health effects	N/A	The base case is 1-year analysis and therefore no discounting is necessary. Sensitivity analysis at 5-years, with 3.5% rate used for costs and effects
N/A=not applicable		

6.5.4.1 Model structure / assumptions

The model structure is driven by the use of exacerbation data, and the characterisation of a 'non-exacerbation' health state, using clinical trial data. The structure is not discussed and justified in the context of a coherent theory of asthma, and the model is essentially based around the availability of data surrounding exacerbations for Symbicort and comparators. It may be that AZ have adopted this approach due to the more positive profile of Symbicort (against exacerbation rates), when use of an outcome related more directly to control, such as percentage of symptom-free days, may have seemed more favourable for comparator products (e.g. Seretide). The submission indicates that a review of published modelling studies was undertaken, but no discussion is presented on alternative approaches. Given the prominence in the clinical and economic literature of outcome measures around lung function and symptoms, it would have been useful for some discussion of competing approaches for the modelling of asthma treatment and cost-effectiveness to have been presented.

The non-exacerbation health state presented is made up of patients that are without symptoms and those patients with symptoms, but not requiring any intervention from a health care professional. However, it is not clear how the data have been interpreted from different clinical trials, where the trial methods may not have been homogeneous. Much of the data to inform the model transitions have been taken from a limited evidence base, with citations to two published RCTs, with data on patient location in those RCTs over time being presented in C.I.C. format only.

The cycle length and time horizon are justified (in the submission) on the basis of data available and an assumption that mortality effects (longer term outcomes) are similar across comparison treatments. Both of these assumptions seem reasonable. However, treatment effect is based primarily on 12-week trial data, and the submission does not discuss the assumption that this treatment effect is assumed to continue for the time period of the model (one year in the base case analysis), nor the generalisability of the trial data to the broader treatment population.

Whilst not stated in the submission the model assumes ***CIC removed*** toxicity profile for treatments, and ***CIC removed*** profile for any longer-term adverse effects.

There is no statement in the submission on the evaluation of the internal consistency of the model.

When interpreting the above points it is also important to acknowledge that the literature on modelling cost-effectiveness in asthma treatment is indeed sparse, and whilst there are guidelines for the treatment of asthma (e.g. BTS/SIGN) it is generally difficult (given the current evidence base) to develop and populate a model which is driven by such guidelines.

6.5.4.2 Data inputs

The primary data inputs for effectiveness, costs and outcomes are presented in the submission. Medication costs are based on trial data for the number of inhalations per day, and drug costs from the Drug Tariff or eMIMs, and a weighted average cost per inhalation was estimated across the various drug formulations (mean inhalation per day for Symbicort FD (100/6), dose of 400/24, was 3.86, same data for ICS (400 per day), and ICS + LABA (400/24 per day). The 'base case' mean cost per day applied for Symbicort FD is £1.06, with cost per day for Seretide (200/100), ICS alone (400), and ICS+LABA (separate inhalers), at ***CIC removed*** £0.18, and £1.12. Data on 'other costs' are presented clearly, and whilst including a number of assumptions, the methods used appear reasonable. The estimated cost for managing a mild exacerbation was £49.46. The estimated cost for the management of a severe exacerbation ranged between £333 and £1,751 (dependent on need for hospitalisation); with proportion having hospitalisation at ***CIC removed***

Whilst there may be some methodological limitations with the health state utility study (as with many studies of this nature) presented to inform the model, data on health state utilities are consistent with the preferred approach of NICE, and CIC data are provided in support. The general literature available to inform the health state values for asthma is sparse and undeveloped.

When considering methods for calculation of transition probabilities, a small clinical evidence based has been used, and within the trial data used there are only a small number of reported events occurring (from a sample of n=565). One of the two RCTs used to estimate transition probabilities is available in abstract form only.[226] Data presented indicates that in the trial populations there were ***CIC removed*** hospitalisations over 12-wks, ***CIC removed*** events requiring oral corticosteroids, and ***CIC removed*** severe exacerbations (presumably hospitalisations) (Appendix 6). Relative treatment effect is estimated for the ICS alone treatment comparison, from two RCTs (as above, one available as an abstract only). There is no assessment of relative treatment effect for Symbicort versus Seretide.

6.5.4.3 Assessment of uncertainty

Uncertainty is addressed in the submission using deterministic sensitivity analysis and probabilistic sensitivity analysis. Probabilistic analysis has addressed parameter uncertainty in a number of cases (number of inhalations, utility values, transition probabilities, relative risks). However, although the choice of distributions would seem to follow accepted methods, in many cases the uncertainty around parameter inputs is very small, with standard errors (around the mean) being very small (e.g. for a mean number of inhalations of 3.86, the SE was ***CIC removed***, and for the health utility for non exacerbation at ***CIC removed***, the SE was ***CIC removed***). The report (Appendix 6) refers to the use of probabilistic methods for transition probabilities. However, it is unclear how probabilities were sampled (whether they were either re-scaled to sum to 1.00, or sampled via a correlation matrix) and the submission only reports that they were "normalised to give a sum of one" (p99).

The assessment of uncertainty does not address any issue of heterogeneity in the treatment group, and certain structural and methodological uncertainties are not addressed in the sensitivity analysis (e.g. impact of exacerbations on patients).

The deterministic analysis presented indicates very little difference in the summary status on cost-effectiveness comparisons, however the variations in many of the parameter inputs are often very small.

6.5.5 Summary of general comments on the submission:

- The focus on exacerbation (rate), and non-exacerbation defined control status may not capture other important aspects of asthma control and/or effectiveness data (e.g. broader symptoms, QOL, lung function).
- The use of a limited evidence base for effectiveness to populate the model (the transition probabilities were derived from data from only two trials, in which the event rate was low) with one of the trials being reported in abstract form only).
- The relative treatment effect applied for the ICS alone comparator option was also based upon the data from only two RCTs conducted in children one including children aged 4-11 years and the other including children and adolescents between the ages of 4-17 years. In addition no relative treatment effect and no cost-effectiveness analysis for Symbicort versus Seretide was presented (due to lack of head-to-head data).

- Assumptions over the generalisability of the trial data, and extrapolation of treatment effect are not discussed.
- The analysis contains a large amount of data that is classified as 'in confidence', some of which is not transparent in the submission.

6.6 Review of the submission by Meda pharmaceuticals Ltd

6.6.1 Overview

The submission by Meda pharmaceuticals Ltd to NICE includes evidence summaries of the Novolizer® DPI device's technical performance, tolerability, and acceptability to patients as well as general discussion on the burden of asthma and the role of BUD in asthma treatment. The emphasis throughout their report, including in the cost minimisation analysis, is on the documented or estimated patient benefits and NHS savings of the Novolizer device compared to its main DPI competitor product, the Turbohaler. The majority of the submitted material, and the whole of the economic analysis, is therefore outside the scope of the NICE appraisal which is focused on ICS drug compounds and selected 'add-on' therapies, rather then different formulations of the same compound and different delivery devices.

Nevertheless, the submission does provide further useful insight into the mediating role of inhaler devices in the effectiveness of ICS and other inhaled asthma medications.

For completeness we outline the approach taken in the submission and provide an outline review.

TABLE 25 *Critical appraisal checklist of economic evaluation by Meda Pharmaceuticals Ltd.*

Item	**Critical Appraisal**	**Reviewer Comment**
Is there a well defined question?	No	Implicitly compare the two device types
Is there a clear description of alternatives?	Yes	Novolizer (BUD) vs. Turbohaler (BUD) both at a dose of 400µg daily (or 200µg bd)
Has the correct patient group / population of interest been clearly stated?	Yes	Implicitly children from daily doses
Is the correct comparator used?	No	Comparison of devices not a part of NICE scope
Is the study type reasonable?	Yes - CMA	Assuming that claim of therapeutic equivalence with Turbohaler is valid
Is the perspective of the analysis clearly stated?	No	But implicitly NHS perspective
Is the perspective employed appropriate?	Yes	
Is effectiveness of the intervention established?	Yes(?)	Depending on the quality of RCT by Chuchalin et al. in Respiration 2002; 69(6): 502-508
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	No	CMA projects 1 year costs
Are the costs consistent with the perspective employed?	Yes	Only drug provision costs are included
Are the consequences consistent with the perspective employed?	N/A	
Is differential timing considered?	N/A	
Is incremental analysis performed?	Yes	Calculates per person annual NHS savings of switching from Turbohaler to Novolizer
Is sensitivity analysis undertaken and presented clearly?	No	

TABLE 26 *NICE reference case requirements – Meda Pharmaceuticals Ltd submission*

NICE reference case requirement		**Reviewer comment**
Decision problem: As per the scope developed by NICE (esp. technologies & patient group)	No	Inhaler devices compared, (i.e. not BUD with other ICS or ICS+LABAs)
Comparator: Alternative therapies routinely used in the UK NHS	Yes	BUT assessing inhaler devices outside NICE scope
Perspective on costs: NHS and PSS	Yes	Implicitly (source of costs = eMIMS)
Perspective on outcomes: All health effects on individuals	N/A	CMA
Type of economic evaluation: Cost-effectiveness analysis	CMA	
Synthesis of evidence on outcomes: Based on a systematic review	Yes(?)	PubMed search obtained 1 trial; no stated inclusion or exclusion criteria
Measure of health benefits: QALYs	N/A	CMA
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	N/A	CMA
Method of preference elicitation for health state values: Choice-based method (e.g. TTO, SG, not rating scale).	N/A	CMA
Source of preference data: Representative sample of the UK public	N/A	CMA
Discount rate: 3.5% pa for costs and health effects	No	

N/A=not applicable
* Health effects – just symptom-free days, used to consider QALY values
** Method for estimating health state utilities is unclear

6.7 Review of the submission by Trinity-Chiesi Pharmaceuticals Ltd

6.7.1 Overview

The submission by Trinity-Chiesi to NICE focuses on clinical effectiveness and cost of the following HFA-propelled BDP product for use with pMDIs:

6.7.1.1 Clenil® Modulite®

The submission includes some discussion of the clinical equivalence of this product and the main CFC-propelled equivalent product that is licensed for use in children, and the presentation of some price estimates. There is also some discussion on the changing regulatory environment for these and related products, specifically the progressive banning of CFC-propelled asthma medications under the Montreal Protocol.[227;228]

The submission is based on a systematic search of the literature on a range of topics that include clinical effectiveness, tolerability and safety, and costs-effectiveness of the product. Appendix 9 of the submission provides information on this review. The literature is deemed unhelpful for the current submission, and the submission presents specific cost comparisons for selected products. For completeness an outline review of the approach taken in the submission is presented.

6.7.1.2 Analysis of cost of Clenil® Modulite® (BDP)

Based on evidence summarised elsewhere in the submission (one published study, two unpublished Phase III studies) the cost-effectiveness section assumes the clinical equivalence of Clenil® Modulite® with Becotide®, which is the main alternative BDP preparation for children that is for inhalation via pMDI devices. It then proceeds with a cost comparison between Clenil® Modulite® and the following three BDP products that are licensed for use in children in the UK:

Becotide® (= BDP, via CFC pMDI)

Asmabec® (= BDP, via Clickhaler® DPI)

Becodisks® (= BDP, via Diskhaler® DPI)

The submission uses a time horizon of a year and calculates the per patient incremental (NHS) medication costs of Clenil® Modulite®, Asmabec®, and Becodisks® compared with Becotide®, at both 100µg twice-daily and 200µg twice-daily (Tables 12 and 13 in the submission's Appendix).

Given regulatory changes towards the banning of CFC-propelled ICS, it is questionable whether the cost or cost-effectiveness of any products should now be compared with CFC-propelled products like Becotide®. More appropriate comparators would be products which combine other well-established ICS compounds (such as BUD or FP) that similarly use HFA-propellants for use with pMDI devices.

Cost-effectiveness results

Below we summarise the annual incremental cost of the three comparator BDP preparations with Becotide®.

TABLE 27 *Annual incremental cost of the three comparator BDP preparations with Becotide®*

Product	At 100µg twice-daily		200µg twice-daily	
	Annual cost (£)	**Incremental cost (£)**	**Annual cost (£)**	**Incremental cost (£)**
Becotide®	10.18	-	29.71	-
Clenil® Modulite®	28.18	18.00	61.43	31.72
Asmabec®	35.81	25.63	71.61	41.90
Becodisks®	73.00	62.82	139.13	109.42

6.7.2 Appraisal of the submitted cost-minimisation analysis

TABLE 28 *Critical appraisal checklist of economic evaluation by Trinity-Chiesi Pharmaceuticals Ltd.*

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	No	But, the implicit question is: which of the currently licensed non-CFC-propelled BDP products for use in children is the cheapest?
Is there a clear description of alternatives?	Yes	However, although equivalence is demonstrated with Becotide®, the cost comparison includes two other BDP products that are delivered by DPI (Asmabec® Clickhaler®, and Becodisk® Diskhaler®)
Has the correct patient group / population of interest been clearly stated?	No	Although implicitly their analysis applies to children aged under 12 years (or 6 years and over, which is the licence for some of the products compared). Note that the main trial used to demonstrate clinical equivalence with Becotide® recruited children aged six to 16 years old.
Is the correct comparator used?	No	Both in terms of accordance with NICE scope, and the fact that the proper comparator should probably be other ICS compounds delivered via pMDIs using HFA propellants
Is the study type reasonable?	Yes	
Is the perspective of the analysis clearly stated?	No	But, implicitly NHS perspective (implied by source of unit costs)
Is the perspective employed appropriate?	Yes	
Is effectiveness of the intervention established?	Yes	Equivalence to Becotide®, but not to the other two products included in the cost comparison
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	No	CMA for 1 year
Are the costs consistent with the perspective employed?	Yes	
Are the consequences consistent with the perspective employed?	N/A	
Is differential timing considered?	N/A	
Is incremental analysis performed?	N/A	
Is sensitivity analysis undertaken and presented clearly?	N/A	

TABLE 29 *NICE reference case requirements - Trinity-Chiesi Pharmaceuticals Ltd*

NICE reference case requirement		**Reviewer comment**
Decision problem: As per the scope developed by NICE (especially technologies & patient group)	No	Product was compared with same ICS with different pMDI propellant (Becotide®) and with same ICS for use DPI devices (Asmabec® Clickhaler®, and Becodisk® Diskhaler®). Therefore it is outside the scope of the present appraisal.
Comparator: Alternative therapies routinely used in the UK NHS	Yes	(see above). However, Becotide® will soon be obsolete due to implementation of Montreal Protocol, so rationale for this being the main comparator for cost-effectiveness purposes is questionable.
Perspective on costs: NHS and PSS	Yes	
Perspective on outcomes: All health effects on individuals	No	CMA
Type of economic evaluation: Cost-effectiveness analysis	CMA	
Synthesis of evidence on outcomes: Based on a systematic review		Search criteria supplied
Measure of health benefits: QALYs	N/A	CMA
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	N/A	CMA
Method of preference elicitation for health state values: Choice-based method (e.g. TTO, SG, not rating scale).	N/A	CMA
Source of preference data: Representative sample of the UK public	N/A	CMA
Discount rate: 3.5% pa for costs and health effects	No	

N/A = not applicable; CMA = Cost-minimisation Analysis; TTO = Time Trade-Off technique; SG = Standard Gamble technique; PSS = Personal Social Services; BNF = British National Formulary; eMIMS = Electronic Monthly Index of Medical Specialities; PSA = Probabilistic Sensitivity Analysis; CEACs = Cost-effectiveness Acceptability Curves.

6.8 Summary of findings from the cost-effectiveness review

The review of economic evaluations identified a number of limitations in both the literature and the industry submissions. Most notably, no published economic evaluations were identified that had assessed the use of the inhaled corticosteroids, BDP, BEC or FP, used alone or in combination with a LABA, SAL or FF in children. Additionally the review of the industry submissions highlighted a number of further concerns.

None of the submissions compared the cost-effectiveness of all three of the ICS products licensed for use in children. All four submissions presented a cost minimisation analysis with a general assumption of an equivalent level of clinical effectiveness across ICS products being made. The submissions by Meda Pharmaceuticals Ltd and Trinity-Chiesi Pharmaceuticals Ltd, were both limited to a presentation of the costs of their respective BDP products, Novolizer® and Modulite®. The submissions by GSK and AZ for the cost-effectiveness of ICS products were limited to a cost minimisation analysis. The cost-effectiveness of the products included in the current appraisal was not apparent. Moreover, the methods used for estimating the product costs varied across the submissions, and were not transparent. This is particularly pertinent, as the majority of the different ICS named preparations are usually sold in a variety of dose-strengths (e.g. 100µg, 200µg or 400µg per dose). Therefore there are a number of ways of achieving any given daily dose of a particular drug, with the method used to derive the dose affecting cost.

For the combination therapies of Seretide (FP+S; GSK) and Symbicort (BUD+FF; AZ) more complex cost-effectiveness models were presented. However, once again both of the models were developed from a product-specific view of cost-effectiveness analysis. The model developed by GSK was presented as a 'generic' model, but the focus was entirely on Seretide, with no formal comparison being made with Symbicort. Conversely, the model developed by AZ was based only on trial data for Symbicort, and again no formal comparisons were made with Seretide. In both submissions the lack of direct head-to-head trial evidence between Seretide and Symbicort in children was highlighted.

6.9 Approach to modelling cost-effectiveness for this review

As discussed above, the review of the cost-effectiveness literature on asthma did not identify any studies that were applicable to the research questions of interest in the UK context.

Similarly, the limitations of published models of asthma meant they were not applicable in the context of this review. We therefore developed our own model to address the specific research questions outlined previously, in the context of a UK paediatric population and of the BTS/SIGN guidelines.[1]

To use the model to estimate the relative cost-effectiveness of the three ICS drugs at low or high dose required an estimate of their relative treatment effects. Despite of the number of trials identified, it was not possible to derive such an estimate, either from direct trial evidence of head to head comparisons of the three ICS, or from meta-analyses combining the trial data, or from synthesising the data using a mixed treatment comparison model. The trial data have been presented in the clinical effectiveness review and the reasons for this lack of an overall treatment effect are discussed in detail in the discussion below. Briefly, our inability to pool or compare treatment effects lies in the heterogeneous nature of the trials and lack of consistency in measuring and reporting outcomes, making comparison and combination extremely difficult.

For questions one and two, as the clinical effectiveness review did not establish any clear or consistent differences in effectiveness or safety between the three ICS drugs at their accepted clinically equivalent doses, clinical equivalence in terms of effectiveness and safety could reasonably be assumed and a cost comparison was undertaken (see section 5.2.2 and 5.2.3).

For question three, no trials were identified that assessed the treatment strategy of either increasing the dose of ICS alone if control remained inadequate at doses within the Step 2 range of the guidelines, or the addition of a LABA to a lower dose of ICS in children.

As it is improbable from a clinical view point that the two treatment strategies would provide comparable benefits in terms of treatment effect and associated adverse events, equivalence in outcomes between the two strategies could not be assumed. We were therefore unable to undertake a cost comparison for the costs associated with these two treatment strategies due to lack of relevant clinical trial evidence. An exploratory cost-offset analysis based on costs only was therefore undertaken for the higher dose ICS compared to each of the available combination preparations in a dose ratio of 2:1 for the ICS dose delivered either alone or in combination. The assumption was made that this represented the most usual clinical decision facing clinicians when considering options for treating children whose asthma is inadequately controlled on low dose ICS alone.

For the comparison of both combination inhalers with the same drugs delivered in separate inhalers, clinical equivalence between the treatment strategies could be assumed from the results of the clinical effectiveness analysis. A cost comparison was therefore undertaken and is presented in section 6.11.

For question five, no trials were identified that compared the effectiveness of a combination inhaler containing BUD/FF with a combination inhaler containing FP/S in children. Due to the lack of evidence on the relative cost-effectiveness of using either combination inhaler, a cost comparison was undertaken. This was deemed appropriate due to the lack of evidence of non-equivalence between the two comparators. The methods employed and results of the cost comparison are presented in Section 6.10.

6.10 Cost-comparison methods

6.10.1 Rationale

Cost-comparison analysis should normally be used when there is valid and reliable evidence of equivalent effectiveness of the alternative technologies being compared.[220] However, as previous sections of this report have concluded, amongst different ICS for asthma there is little conclusive evidence of equivalence, and more often instead, inconclusive evidence concerning differential effectiveness. Furthermore, the evidence of differential effectiveness due to adding a LABA to treatment with ICS is also ambiguous, and largely restricted to studies in adults.

However, performing a cost-comparison analysis is not straightforward, as it is far from simple to derive a single ‘representative’ cost figure for each ICS. This is because each drug is typically available in a range of named preparations (e.g. from different manufacturers, or for different inhaler devices), and also because each named preparation is usually sold in a variety of dose-strengths (e.g. 100µg, 200µg or 400µg per dose). There can therefore be a wide variety of ways of achieving any given daily dose of a particular drug. This is especially an issue for long-established drugs like BDP and BUD.

In order to generate single cost figures for each drug, we have made use of standard assumed ratios regarding dose equivalence and made some other simplifying assumptions to enable pooling of cost estimates. Also, given the likely withdrawal of CFC-containing products in the near future, we have also calculated cost estimates both including and excluding currently available CFC-containing products (this is an issue for BDP and BUD preparations only). During the period when CFC-containing products are withdrawn from sale in the UK, it is likely that the relative market shares of different named preparations will also alter, because many patients will need to switch between products, new products may simultaneously enter the market, and pack prices may also change.

Given the issues outlined above, what we present below should be viewed as an exploration of the current and future relative costs of different classes of ICS and combination products.

6.10.2 Methods

First, we have calculated the mean annual per patient cost of taking each specific named preparation of each drug (or each combination of drugs), in order to achieve a given level of daily dosage. For each named preparation, this is calculated as:

£ per dose × doses per day × No. days in year

= (BNF £ pack price ÷ doses per pack)

× (Target daily dose ÷ No. μg BDP-CFC equivalent per dose)

× 365

Where BNF £ pack price is the specific British National Formulary per pack price for a specific preparation (e.g. 50, 100, or 200μg per dose). The doses per day are the number of doses of a given preparation needed to achieve a particular target daily dose level (e.g. 400μg/day of BDP-CFC equivalent ICS; see below).

Assumptions about target daily dosage

For child patients with asthma, we have estimated costs for two ‘low levels’ and one ‘high level’ of daily dosage of ICS. The low level dosages we have costed are:

LD_{start}: Low dose starting dosage = 200μg CFC-BDP (or equivalent) per day

LD_{max}: Low dose maximum dosage = 400µg CFC-BDP (or equivalent) per day

Respectively, these equate to: the recommended starting dose for child patients stepping up from mild intermittent asthma managed primarily by SABAs (i.e. those changing from Step 1 to Step 2 of the BTS/SIGN Guidelines), and; the recommended maximum daily dose of ICS for children before an add-on therapy (such as a LABA) should be tried (i.e. Step 3 'Add-on therapy').

The 'high level' daily dosage we have costed is either 800µg BDP-CFC (or equivalent) per day. This is assumed to approximate to the median ICS dose of people being treated at Step 4 of the BTS/SIGN Guidelines.

Assumptions about number of doses per day/dose of preparations

For simplicity, and unless otherwise recommended in the BNF, we assumed that the required daily dose of an ICS was achieved as either one dose taken twice daily or two doses twice daily. These base case assumptions are summarised in *Table 30* below.

TABLE 30 *Daily patterns of ICS dose-taking to achieve target daily dose*

Daily dosage (BDP-CFC equivalent)	**taken either as**	**or as**
200µg	50µg* × 4 doses	100µg* × 2 doses
400µg	100µg* × 4 doses	200µg* × 2 doses
800µg	200µg* × 4 doses	400µg* × 2 doses
* BDP-CFC or equivalent (see multipliers in table in following section)		

Assumptions about dose-equivalence with CFC-BDP

In order to compare the cost of alternative ICS preparations it is necessary to make some assumptions about the likely equivalent dose that would be required if controlled patients were switching between preparations. Because of product 'potency' characteristics, related to particle size and mode of action, the same quantities of different active ingredients achieve different clinical effectiveness. For the practical purposes of informing dosage decisions when switching patients between ICS products, both the GINA Guidelines and the BTS/SIGN Guidelines have published ratios of dose-equivalence. These are shown below in *Table 31*.

TABLE 31 *Published and assumed dose-equivalence ratios of different ICS preparations*

Drug	Equivalent amount of BDP-CFC (BTS/SIGN Guidelines)	Equivalent amount of BDP-CFC (GINA Pocket Guide to Asthma)	Ratio used in CMA
BDP-HFA-propelled[a]	× 2	× 2	× 2
BUD	Approx. × 1	Not shown	× 1
BUD-DPI	Approx. × 1[b]	Approx. × 1	× 1
FP	× 2	× 2	× 2

Sources: section 4.2.3 of BTS/SIGN Guideline, and; Figure 7, p.19 of the GINA Pocket Guide 2005.

[a] except Clenil Modulite, which has been designed to have equivalent potency to BDP-CFC preparations.

[b] Despite some evidence that BUD-DPI via turbohaler is more effective than same dose of BDP-CFC.

It should be noted that these effectiveness equivalence ratios are fairly crude 'rules of thumb', for the main purpose of aiding doctors in deciding the starting dose of any new ICS drug when switching between drug types. They may not necessarily, therefore, reflect the relative doses actually used in the body of trials that have examined the clinical effectiveness of the different ICS drugs. Nor would they be likely to reflect possible differences in de facto effectiveness within and between drugs due to different concordance or ease of use associated with different inhaler devices. In any case, it should be remembered that after a switch between drug treatments, clinical guidelines recommend that the dose be adjusted upwards or downwards until the minimum dose required to maintain effective control is found.

However, to perform a cost-comparison analysis we have to make use of these assumptions about how much of alternative ICS preparation people would probably need to take in order to maintain the same level of symptom control.

Assumptions about the mix of brands/named preparations within each ICS drug class

For some of the ICS drug (notably BDP) there is a wide range of named preparations, available in different physical form (aerosol versus dry powder), for different inhaler devices, and either propelled by CFC-containing or non-CFC propellants (e.g. HFA preparations). To compare between ICS drugs it is therefore necessary to generate a single, average cost for a given level of daily dosage.

We have used two methods for doing this: (i) using an unweighted mean annual cost, and; (ii) using a weighted mean annual cost, weighted according to the current (2005) market share in terms of quantity of doses sold (in BDP-CFC equivalent units).

The unweighted mean annual cost is calculated as follows. First, for a given dose level (e.g. LDstart = 200μg BDP-CFC equivalent) calculate the annual cost of achieving this daily dosage (e.g. all products available as 50μg BDP-CFC equivalent doses and/or 100μg BDP-CFC equivalent doses). Second, sum the annual costs for these preparations. Third, divide by the number of preparations available at these doses (i.e. the number of annual costs summed in step two).

The weighted mean annual cost is calculated as follows:

First, the adjusted annual quantity sold of each product for each drug is calculated. For a product sold in 200 dose packs, in a drug where most products are available in 200 dose packs, this will simply be the quantity of packs sold (in thousands, as listed in the Prescriptions Cost Analysis database for 2005). However, for a product of this drug sold in a 100 dose pack, this PCA quantity sold will be multiplied by 0.5 (=100/200); similarly, for any products sold in 120 dose packs the PCA quantity sold will be multiplied by 0.6 (=120/200).

Second, using these adjusted sale quantities, total quantities are summed for each drug. For each drug, total quantities are also calculated for three groupings of products: CFC-propelled aerosols (pMDI-CFC), HFA-propelled aerosols (pMDI-HFA) and products for DPIs. These total quantities are used as the denominators for the weighted mean percentages, and to calculate the proportion of adjusted sales of each subgroup of products (e.g. pMDI-HFA only, DPI only) accounted for by each product.

This has enabled the calculation of several different (weighted and unweighted) mean annual costs by broad inhaler type, and also according to whether the product contains a CFC propellant or not. This is particularly critical for estimating the mean annual cost of BDP and BUD, since CFC-containing products account for a substantial market share of these drugs. However, these products will probably be withdrawn from the market in the near future.

For each of the three ICS drugs that are licensed for use in children, and for each of the three dose levels, we have therefore estimated both a weighted and an unweighted mean annual cost of:

- All relevant CFC-propelled (pMDI) products (where they exist)
- All relevant HFA-propelled (pMDI) products (where they exist)
- All relevant dry powder (capsule and loose powder) products
- All relevant products for the ICS (including CFC-propelled products)
- All relevant products for the ICS (excluding CFC-propelled products)

By 'relevant' products we mean those that achieve the specified daily dose in two or four doses per day.

Note that because the combination inhaler products are only available in two named preparations (Symbicort and Seretide), and only the lowest dose-strength of each product is recommended in children, we have simply calculated the cost for each low-dose product.

6.11 Cost comparison analysis results

6.11.1 Research Question 1: What is the cheapest ICS at Step 2

The cost comparison results presented below are justified on the basis that **we found no consistent evidence of differential effectiveness in trials comparing the three comparators of interest** (see section 5.2.2.4).

Table 32 and *Table 33* below summarise the unweighted and weighted mean annual cost of taking the three main ICS drug classes, by inhaler and propellant type, at the ***typical starting daily dose*** for children of 200µg BDP-CFC (equivalent) per day. The *Figure 7* and *Figure 8* on the following pages then summarise some of this data, together with data on the cheapest and most expensive drug in each ICS drug class for achieving this target daily dosage.

They show that overall BDP appears to be the current cheapest class of ICS drug at starting low doses for children (200µg BDP-CFC equivalent per day), costing on average £30 per year (weighted mean) or £32 per year (unweighted mean). If CFC-propelled products are excluded from the available products, BDP is still the cheapest but at a higher annual cost. Excluding CFC-propelled products, and using current prices, causes a significant increase in the mean annual cost of taking BDP at this dose level since CFC-propelled products still account for over half of the product types and quantities of BDP sold. In contrast for FP, no currently available products are CFC-propelled, so their exclusion does not alter the calculated mean annual cost. BUD is the most expensive of the class of drug when weighted means are considered. When CFC-propelled products are excluded FP is significantly cheaper (weighted means) than either BDP or BUD; this is because there is a relatively cheap HFA-propelled preparation of FP (Flixotide Evohaler 50µg, £5.44 for 120 dose pack = £33 per year) which accounts for a large proportion (79% of 50µg FP doses) of current sales of the three 50µg FP products available to children.

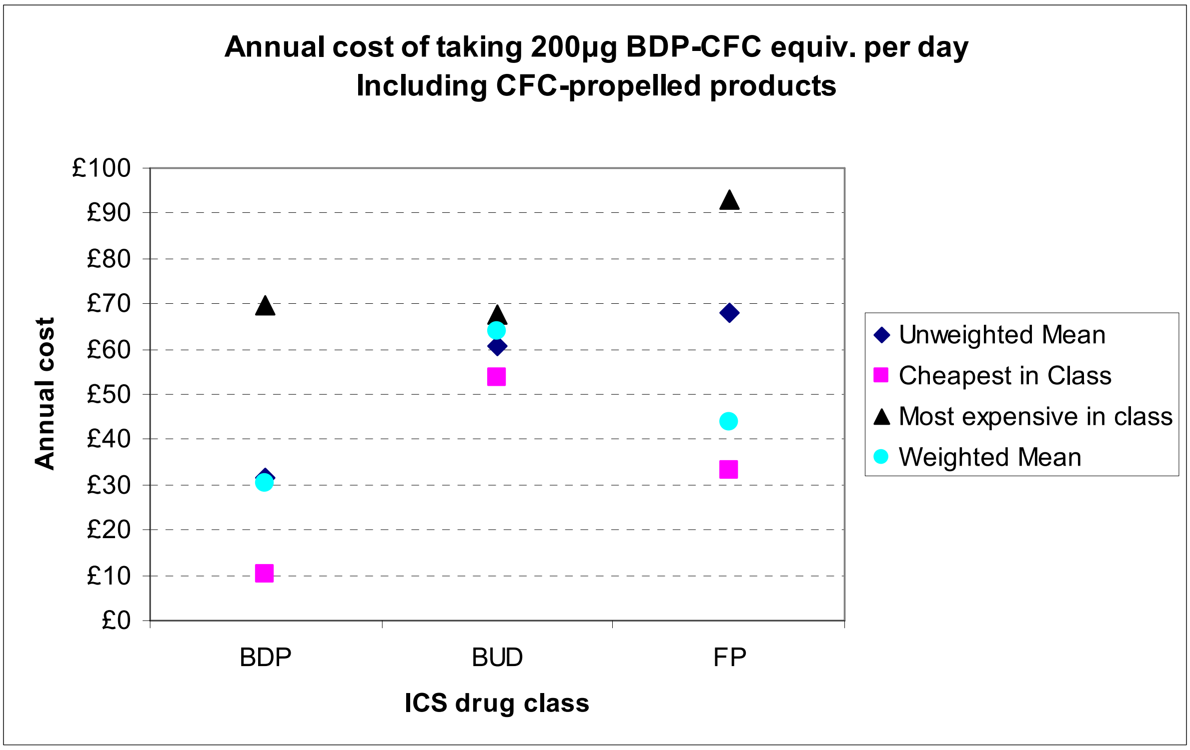
TABLE 32 *Unweighted mean annual cost of ICS by drug if on 200µg BDP equivalent per day*

	Preparations with same inhaler and propellant type (2006 £)			**All preparations in drug class (2006 £)**	
	pMDI with CFC	**pMDI with HFA**	**DPI**	**Including CFC-propelled**	**Excluding CFC-propelled**
BDP	26	28	48	32	42
BUD	54	N/A	68	61	68
FP	N/A	33	85	68	68

TABLE 33 *Weighted mean annual cost of ICS by drug if on 200µg BDP equivalent per day*

	Preparations with same inhaler and propellant type (2006 £)			**All preparations in drug class (2006 £)**	
	pMDI with CFC	**pMDI with HFA**	**DPI**	**Including CFC-propelled**	**Excluding CFC-propelled**
BDP	28	N/A*	60	30	60
BUD	54	N/A	68	64	68
FP	N/A	33	85	44	44

* There is currently only one pMDI with HFA product recommended for use in children (Clenil Modulite); its current market share is not known.

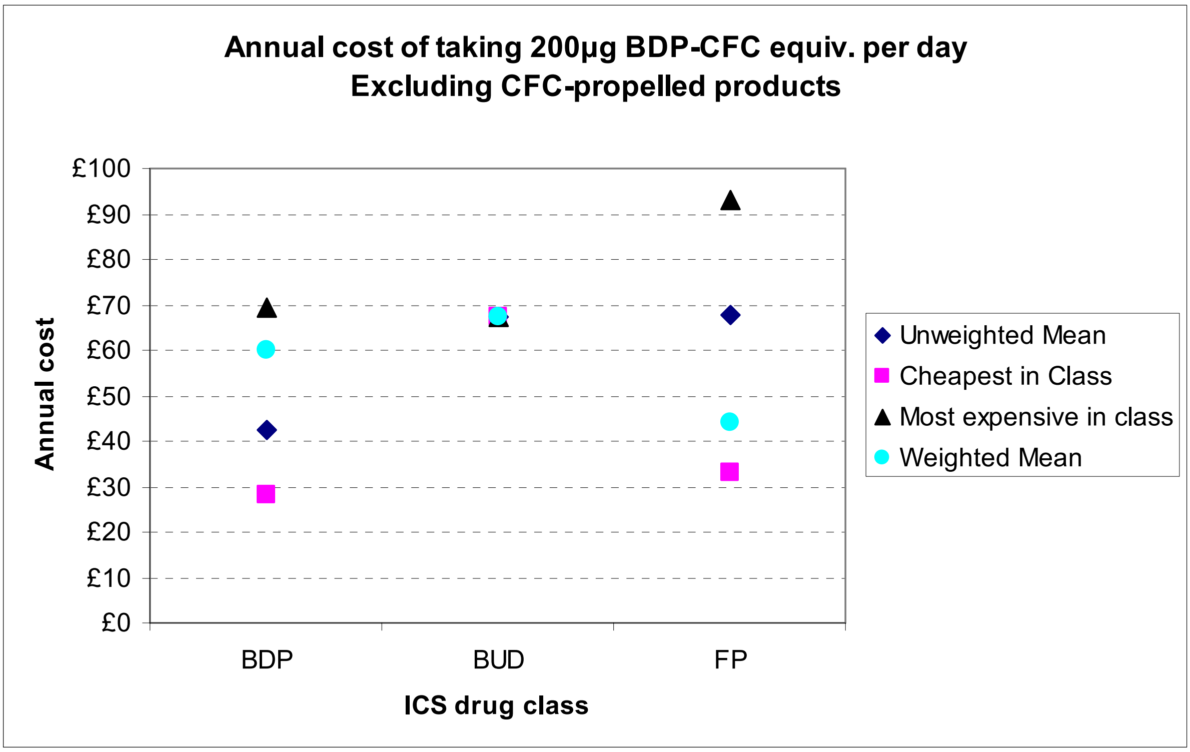


Notes: Cheapest in class products: BDP = Becotide 100µg (200 D); BUD = Pulmicort L.S. 50µg (200 D); FP = Flixotide Evohaler 50µg (120 D).

Most expensive in class products: BDP = Becodisks Disk 100µg (120 D Ref.); BUD = Pulmicort Turbohaler 100µg (200 D); FP = Flixotide Disk 50µg (60 D Ref.).

D = number of doses in pack; Ref. = Refill pack price (where the same preparation is also available with inhaler device included).

FIGURE 7 *Annual cost of 200µg ICS per day by drug class, and including all products*



Notes: Cheapest in class products: BDP = Clenil Modulite 50μg (200 D); BUD = Pulmicort Turbohaler 100μg (200 D); FP = Flixotide Evohaler 50μg (120 D).

Most expensive in class products: BDP = Becodisks Disk 100μg (120 D Ref.); BUD = Pulmicort Turbohaler 100μg 200; FP = Flixotide Disk 50μg (60 D Ref.).

D = number of doses in pack; Ref. = Refill pack price (where the same preparation is also available with inhaler device included).

FIGURE 8 *Annual cost of 200μg ICS per day by drug class, and excluding CFC-propelled products*

Table 34 and *Table 35* below summarise the unweighted and weighted cost of mean annual cost of taking the three main ICS drug classes, by inhaler and propellant type, at the ***typical maximum daily dose*** for children of 400μg BDP-CFC (equivalent) per day. The *Figure 9* and *Figure 10* on the following pages then summarise some of this data, together with data on the cheapest and most expensive drug in each ICS drug class for achieving this target daily dosage.

They show that, overall at this dose level, BDP appears to be the current cheapest class of ICS drug, costing on average £63 per year (weighted mean) or £68 per year (unweighted mean). If CFC-propelled products are excluded from the available products, BDP is still the cheapest according to both the unweighted and unweighted means. Excluding CFC-propelled products, and using current prices, causes a substantial increase in the weighted mean annual cost of taking BDP at this dose level, since typically cheaper CFC-propelled products still account for over half of the product types and quantities of BDP sold. In contrast for FP, no currently available products are CFC-propelled, so their exclusion does not alter the calculated mean annual cost. Overall, under most assumptions, FP products are the most expensive drug class (weighted/unweighted means when including CFC-propelled products), except that they are similar in cost to CFC-free BUD products. In fact, if only CFC-propelled products are considered, the weighted mean annual cost of the three ICS drug classes varies between only £122 and £133.

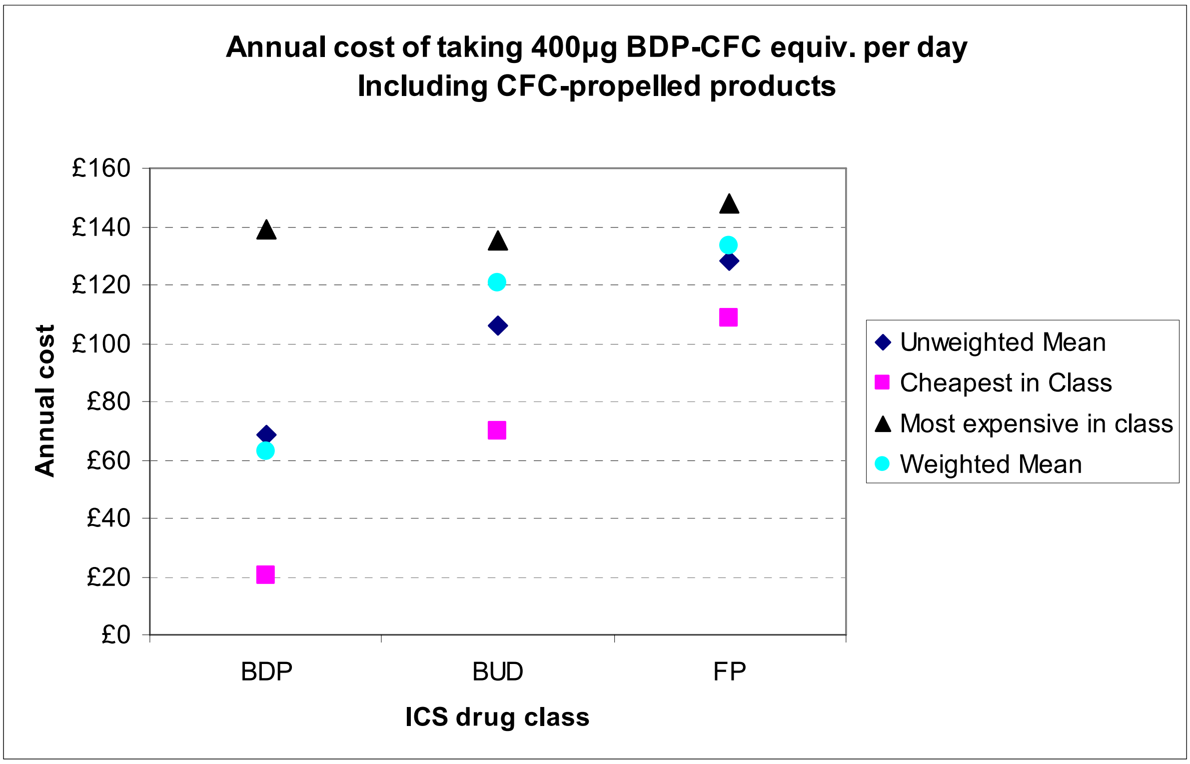
TABLE 34 *Unweighted mean annual cost of ICS by drug if on 400µg BDP equivalent per day*

	Preparations with same inhaler and propellant type (2006 £)			**All preparations in drug class (2006 £)**	
	pMDI with CFC	**pMDI with HFA**	**DPI**	**Including CFC-propelled**	**Excluding CFC-propelled**
BDP	47	56	98	68	92
BUD	76	N/A	113	106	113
FP	N/A	N/A	128	128	128

TABLE 35 *Weighted mean annual cost of ICS by drug if on 400µg BDP equivalent per day*

	Preparations with same inhaler and propellant type (2006 £)			**All preparations in drug class (2006 £)**	
	pMDI with CFC	**pMDI with HFA**	**DPI**	**Including CFC-propelled**	**Excluding CFC-propelled**
BDP	51	N/A*	122	63	122
BUD	76	N/A	134	120	134
FP	N/A	N/A	133	133	133

* There is currently only one pMDI with HFA product recommended for use in children (Clenil Modulite); its current market share is not known.

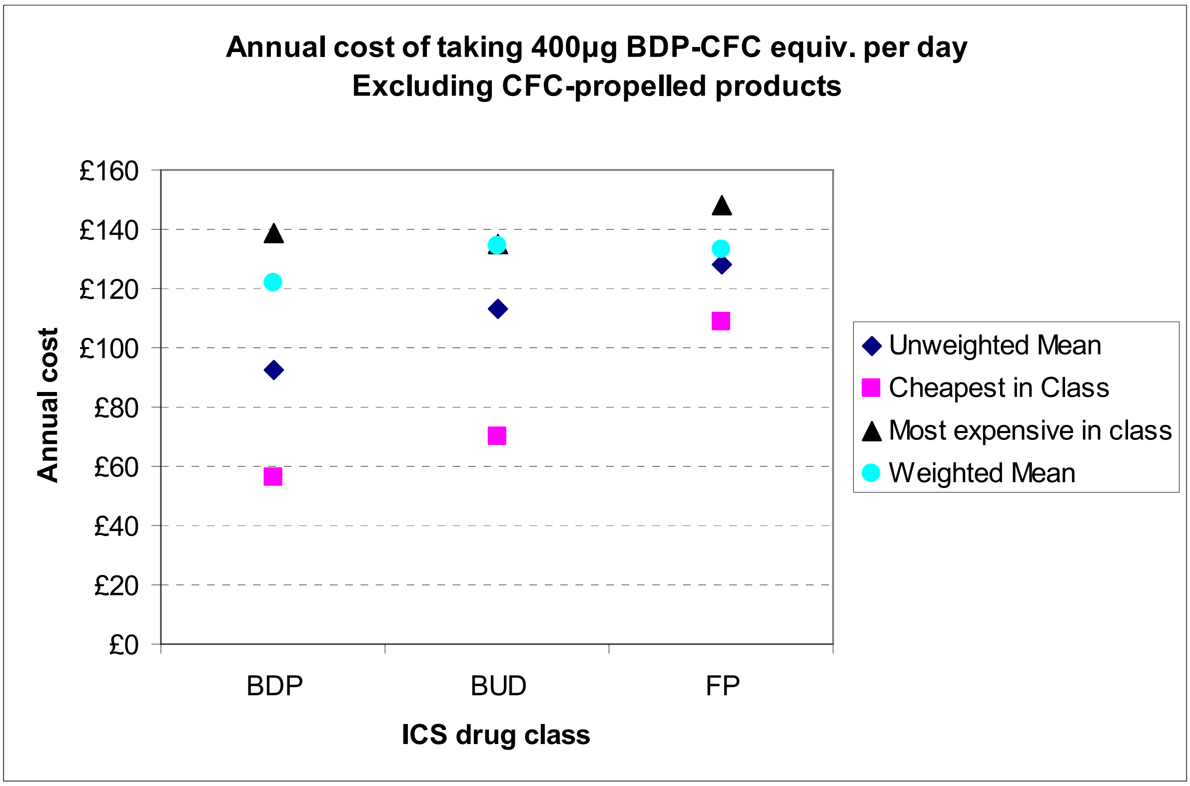


Notes: Cheapest in class products: BDP = Becotide 100µg (200 D); BUD = Novolizer 200µg (100 D ref.); FP = Flixotide Accuhaler 100µg (60 D with device).

Most expensive in class products: BDP = Becodisks Disk 100µg (120 D Ref.); BUD = Pulmicort Turbohaler 100µg (200 D); FP = Flixotide Disk 100µg 60 D Ref.).

D = number of doses in pack; Ref. = Refill pack price (where the same preparation is also available with inhaler device included).

FIGURE 9 *Annual cost of 400µg ICS per day by drug class and including all products*



Notes: Cheapest in class products: BDP = Clenil Modulite 100µg (200 D); BUD = Novolizer 200µg (100 D Ref.); FP = Flixotide Accuhaler 100µg (60 D with device).

Most expensive in class products: BDP = Becodisks Disk 100µg (120 D Ref.); BUD = Pulmicort Turbohaler 100µg (200 D); FP = Flixotide Disk 100µg (60 D Ref.).

D = number of doses in pack; Ref. = Refill pack price (where the same preparation is also available with inhaler device included).

FIGURE 10 *Annual cost of 400µg ICS per day by drug class excluding CFC-propelled products*

6.11.2 Research Question 2: What is the cheapest ICS at Step 4?

The cost comparison results presented below are justified on the basis that **we found no consistent evidence of differential effectiveness in trials comparing the five comparators of interest at this dose level** (see section 5.2.3.4**)**

For this question we have assumed that for children a maximum daily dose of ICS when at treatment Step 4 of the BTS/SIGN Guidelines is 800µg BDP-CFC equivalent. Since the new BDP product Clenil Modulite® is listed in the BNF under standard-dose inhalers, we have assumed that this product is not currently recommended for use in children at these high doses.

Table 36 and *Table 37* below summarise the unweighted and weighted cost of mean annual cost of taking the three main ICS drug classes for children, by inhaler and propellant type, at the ***typical maximum daily dose*** for children of 800µg BDP-CFC (equivalent) per day. The *Figure 11* and *Figure 12* on the following pages then summarise some of this data, together with data on the cheapest and most expensive drug in each ICS drug class for achieving this target daily dosage.

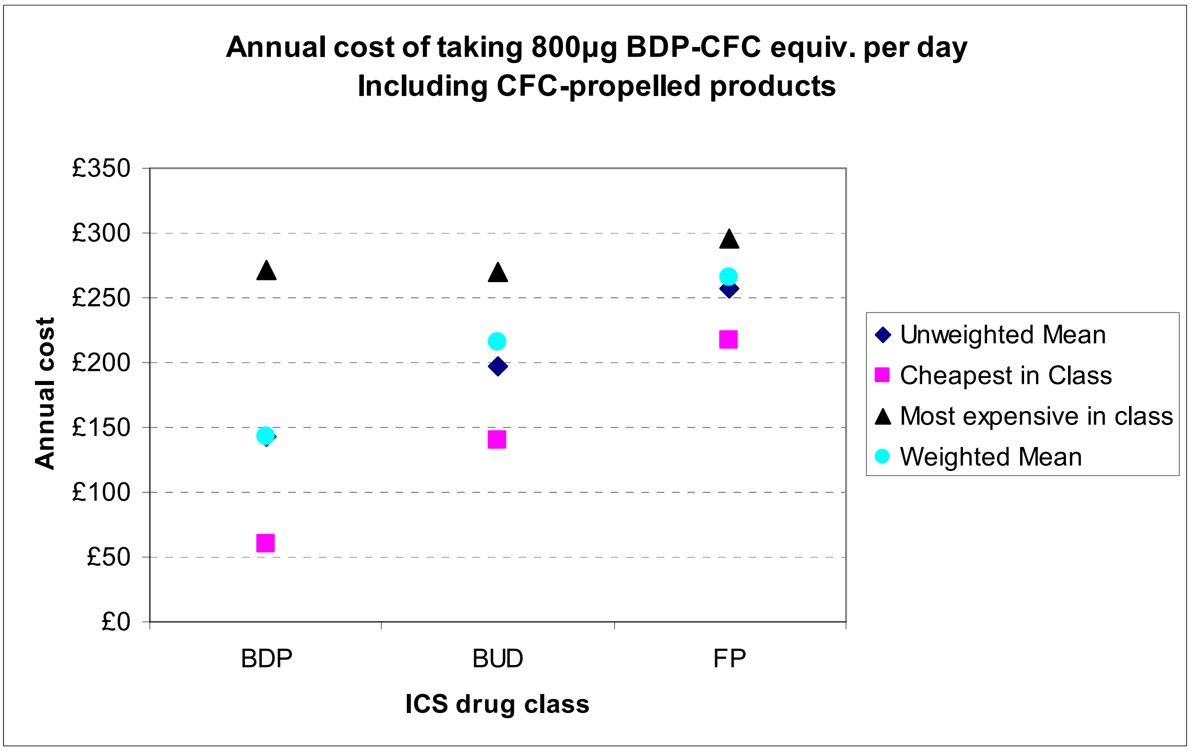
They show that, overall at this dose level, BDP appears to be the current cheapest class of ICS drug, costing on average £142 per year (weighted mean) or £143 per year (unweighted mean). If CFC-propelled products are excluded from the available products, BDP is still the cheapest according to both the unweighted and unweighted means. Excluding CFC-propelled products, and using current prices, causes a substantial increase in the weighted mean annual cost of taking BDP at this dose level, since the cheaper CFC-propelled products still account for over half of the product types and quantities of BDP sold (for children and adults). In contrast for FP, no currently available products are CFC-propelled, so their exclusion does not alter the calculated mean annual cost. Overall, under most assumptions, FP products are currently the most expensive drug class (weighted/unweighted means when including CFC-propelled products). However, FP products are similar in cost to CFC-free BUD products when weighted according to current market share. If only CFC-propelled products are considered, the weighted mean annual cost of the three ICS drug classes varies between only £247 and £266.

TABLE 36 *Unweighted mean annual cost of ICS by drug if on 800µg BDP equivalent per day*

	Preparations with same inhaler and propellant type (2006 £)			All preparations in drug class (2006 £)	
	pMDI with CFC	pMDI with HFA	DPI	Including CFC-propelled	Excluding CFC-propelled
BDP	59	N/A	199	143	199
BUD	153	N/A	212	197	212
FP	N/A	N/A	257	257	257

TABLE 37 *Weighted mean annual cost of ICS by drug if on 800µg BDP equivalent per day*

	Preparations with same inhaler and propellant type (2006 £)			All preparations in drug class (2006 £)	
	pMDI with CFC	pMDI with HFA	DPI	Including CFC-propelled	Excluding CFC-propelled
BDP	59	N/A*	247	142	247
BUD	153	N/A	269	216	269
FP	N/A	N/A	266	266	266

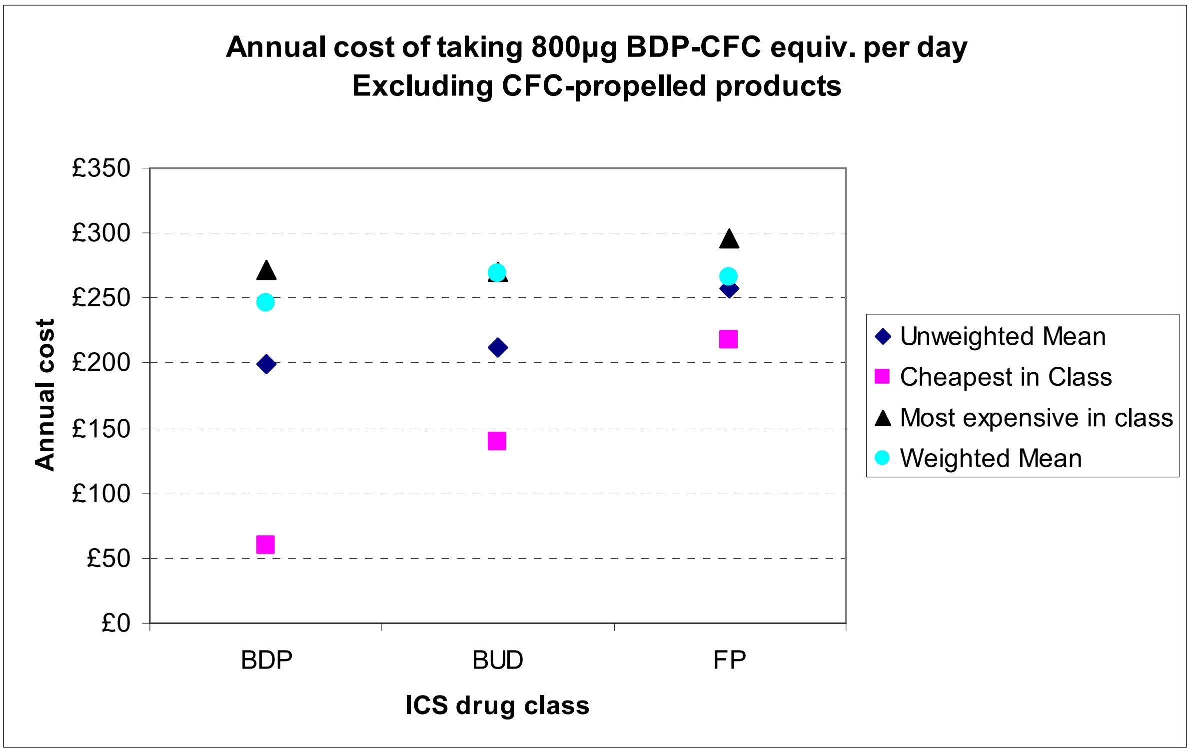


Notes: Cheapest in class products: BDP = Beclazone 200µg (200 D); BUD = Novolizer 200µg (100 D ref.); FP = Flixotide Accuhaler 100µg (60 D with device).

Most expensive in class products: BDP = Becodisks Disk 200µg (120 D Ref.); BUD = Pulmicort Turbohaler 200µg (100 D); FP = Flixotide Disk 100µg 60 D Ref.).

D = number of doses in pack; Ref. = Refill pack price (where the same preparation is also available with inhaler device included).

FIGURE 11 *Annual cost of 800µg ICS per day by drug class and including all products*



Notes: Cheapest in class products: BDP = Beclomet Dipropionate 200µg (200 D); BUD = Novolizer 200µg (100 D ref.); FP = Flixotide Accuhaler 100µg (60 D with device).

Most expensive in class products: BDP = Becodisks Disk 200µg (120 D Ref.); BUD = Pulmicort Turbohaler 200µg (100 D); FP = Flixotide Disk 100µg 60 D Ref.).

D = number of doses in pack; Ref. = Refill pack price (where the same preparation is also available with inhaler device included).

FIGURE 12 *Annual cost of 800µg ICS per day by drug class excluding CFC-propelled products*

6.11.3 Research Question 3: Increase ICS dose or add LABA to a lower ICS dose?

We have **not** performed a cost-comparison analysis of this research question because **we found no reliable evidence that would enable us to conclude, or reasonably assume, equivalence between ICS and ICS plus a LABA** (see section 5.2.4). Therefore below we set out the costs and cost differences between products and present the results of a speculative threshold analysis to examine the number of exacerbations that would need to be avoided for the more expensive product to achieve NHS cost-savings.

6.11.3.1 Exploratory cost-savings analysis of combination inhalers *versus* ICS monotherapy

Given the lack of any evidence on the relative effectiveness of combination inhalers compared with an increased dose ICS, but also the known differences in costs between different products, it is possible to calculate some threshold levels of effectiveness – in terms of exacerbations avoided – that would need to be achieved for the more expensive product to achieve NHS cost-savings. These are based upon an estimated mean cost of a hospital-managed exacerbation of £1056 (assumed range £500 to £2000) or the estimated cost of a GP-managed exacerbation of £24 (assumed range £20 to £40). (The estimation of these costs is shown in *Table 42* and *Table 43* at the end of this section.) In general therefore, averting one hospital-managed exacerbation is much more likely to generate cost-savings than averting a GP-managed exacerbation.

The calculations for these exploratory analyses are shown in *Table 38* to *Table 41*. *Table 38* and *Table 39* compare the cost of Seretide® and Symbicort® products with the weighted mean cost of an increased dose of each type of ICS drug. *Table 40* and *Table 41* compare the cost of Seretide® and Symbicort® products with an increased dose of the cheapest product for each ICS drug. Where the annual cost of either Seretide® or Symbicort® exceeds the cost of the increased dose ICS, we have calculated the annual number of either hospital-managed exacerbations or the annual number of GP-managed exacerbations that would have to be averted in order to compensate for the additional costs of the combination preventer medication.

Both Seretide Evohaler® (100µg/50µg FP/S per day) and Symbicort Turbohaler® (200µg/6µg BUD/FF per day) are slightly cheaper than the **weighted mean cost** of all types of ICS at increased dose except BDP 400µg/day (including CFC-propelled products). Compared with BDP-CFC products at 400µg/day, taking these two combination products costs £56 and £53 extra per year. If the cost of a hospital-managed exacerbation lies somewhere between £500 and £2000, then in order to be cost-saving these combination inhalers would annually need to avert at least one hospital-managed exacerbation in between 9 and 33 people who are using these inhalers compared to BDP. However, treatment with these combination inhalers would annually need to avert between 1.3 and 2.8 GP-managed exacerbations per person to cover the extra drug treatment costs.

Compared with the **lowest cost preparation** for each ICS drug, the combination inhalers are always more expensive than these ICS products at increased dose. The greatest cost difference is between taking Symbicort Turbohaler® (200µg/12µg per day = £201 per year) and BDP 400µg/day (as Becotide® 100µg = £20 per year). To compensate for these extra annual medication costs, the combination inhaler would annually need to avert at least one hospital-managed exacerbation in 3 to 11 people taking the drug. In contrast, between 4.5 and 9 GP-managed exacerbations per person would need to be averted annually to compensate for the extra cost of taking this combination inhaler, compared to increasing the dose of Becotide to 400µg/day.

However, since Becotide® and other CFC-propelled products will soon be withdrawn from sale in the UK, it is now probably more realistic to compare the cost of the combination inhalers with CFC-free ICS products. Compared with the cheapest CFC-free products of each ICS drug, the combination inhalers are between £10 and £145 more costly per year (see *Table 40* and *Table 41*). With a £10 extra annual cost of Seretide Evohaler® 100/50 per day over FP 200µg per day only a GP-managed exacerbation would have to be avoided every two to four years to cover the additional drug cost. In contrast, to cover the £145 extra annual cost of Symbicort® Turbohaler (200/12 per day) compared with increasing the dose of BDP (CFC-free) to 400µg per day, at least one hospital-managed exacerbation would have to be avoided per year for every 3 to 14 patients on the combination inhaler.

In summary, the extra annual cost to the NHS of combination inhalers, compared with an increased dose of the different ICS drugs as monotherapy varies enormously depending on the exact ICS product used. For the more expensive ICS products, their use at higher dose is more expensive than some of the combination inhaler products. However, for the cheapest ICS products the additional cost implied by using a combination inhaler (instead of increasing the ICS dose) will often be £100 or more per year. While this does not, perhaps, appear to be a large difference, this exploratory analysis shows that to achieve cost savings the combination inhaler would need to at least avert approximately four GP-managed exacerbations, or avert one hospital-managed exacerbation amongst 10 people on the drug for a year.

We appreciate that this basic 'cost-savings' or 'cost-offset analysis' does not take into account the other important benefits to individuals and their families of avoiding exacerbations, or having generally improved asthma control in between exacerbations. Nor does it capture the longer term cost impact of avoiding exacerbations on reducing the likelihood over time of treatment step-up. However, given the paucity of other reliable sources of effectiveness data we hope it is a useful illustration of how much more effective combination inhalers would need to be in order to be cost-saving compared with increasing ICS dose.

This illustration should also be read in the context of how likely these absolute differences in exacerbation rates could be for each of the different treatment options under consideration, given background exacerbation rates which may already be low. The results from the clinical effectiveness review highlighted there are currently no trials that have compared the effectiveness of increasing the dose of ICS alone to the addition of a LABA to a lower dose of ICS in a paediatric population. Therefore it is impossible to comment on the likely exacerbation rates associated with each of the treatment options, except to say that in adults these rates are typically fairly low.

TABLE 38 *Exploratory cost-savings analysis: Annual exacerbations avoided to cover extra cost of FP/S compared with weighted mean cost of ICS*

	Weighted mean annual cost of ICS	**Seretide Evohaler 100/50 FP/S per day**	**Cost Difference per year**	**Cost of a hospital-managed exacerbation**			**Cost of a GP-managed exacerbation**		
				£500	**£1,056**	**£2,000**	**£20**	**£24**	**£40**
BDP 400/day	£63	£119	£56	0.11	0.05	0.03	2.80	2.33	1.40
BUD 400/day	£120	£119	-£1	Seretide Evohaler cheaper than higher dose ICS					
FP 200/day (all CFC-free)	£133	£119	-£14	Seretide Evohaler cheaper than higher dose ICS					
BDP 400/day (excl. CFC-propelled)	£122	£119	-£3	Seretide Evohaler cheaper than higher dose ICS					
BUD 400/day (excl. CFC-propelled)	£134	£119	-£15	Seretide Evohaler cheaper than higher dose ICS					
		Seretide Accuhaler 100/50 FP/S per day							
BDP 400/day	£63	£190	£127	0.25	0.12	0.06	6.35	5.29	3.18
BUD 400/day	£120	£190	£70	0.14	0.07	0.04	3.50	2.92	1.75
FP 200/day (all CFC-free)	£133	£190	£57	0.11	0.05	0.03	2.85	2.38	1.43
BDP 400/day (excl. CFC-propelled)	£122	£190	£68	0.14	0.06	0.03	3.40	2.83	1.70
BUD 400/day (excl. CFC-propelled)	£134	£190	£56	0.11	0.05	0.03	2.80	2.33	1.40

TABLE 39 *Exploratory cost-savings analysis: Annual exacerbations avoided to cover extra cost of BUD/FF compared with weighted mean cost of ICS*

	Weighted mean annual cost of ICS	**Symbicort Turbohaler 200/12 BUD/FF per day**	**Cost Difference per year**	**Cost of a hospital-managed exacerbation**			**Cost of a GP-managed exacerbation**		
BDP 400/day	£63	£201	£138	0.28	0.13	0.07	6.90	5.75	3.45
BUD 400/day	£120	£201	£81	0.16	0.08	0.04	4.05	3.38	2.03
FP 200/day (all CFC-free)	£133	£201	£68	0.14	0.06	0.03	3.40	2.83	1.70
BDP 400/day (excl. CFC-propelled)	£122	£201	£79	0.16	0.07	0.04	3.95	3.29	1.98
BUD 400/day (excl. CFC-propelled)	£134	£201	£67	0.13	0.06	0.03	3.35	2.79	1.68
		Symbicort Turbohaler 200/6 BUD/FF per day							
BDP 400/day	£63	£116	£53	0.11	0.05	0.03	2.65	2.21	1.33
BUD 400/day	£120	£116	-£4	Symbicort Turbohaler cheaper than higher dose ICS					
FP 200/day (all CFC-free)	£133	£116	-£17	Symbicort Turbohaler cheaper than higher dose ICS					
BDP 400/day (excl. CFC-propelled)	£122	£116	-£6	Symbicort Turbohaler cheaper than higher dose ICS					
BUD 400/day (excl. CFC-propelled)	£134	£116	-£18	Symbicort Turbohaler cheaper than higher dose ICS					

TABLE 40 *Exploratory cost-savings analysis: Annual exacerbations avoided to cover extra cost of FP/S compared with cheapest ICS product for each drug*

	Annual cost of cheapest ICS	**Seretide Evohaler 100/50 FP/S per day**	**Cost Difference per year**	**Cost of a hospital-managed exacerbation**			**Cost of a GP-managed exacerbation**		
				£500	**£1,056**	**£2,000**	**£20**	**£24**	**£40**
BDP 400/day	£20	£119	£99	0.20	0.09	0.05	4.95	4.13	2.48
BUD 400/day (all CFC-free)	£70	£119	£49	0.10	0.05	0.02	2.45	2.04	1.23
FP 200/day (all CFC-free)	£109	£119	£10	0.02	0.01	0.01	0.50	0.42	0.25
BDP 400/day (excl. CFC-propelled)	£56	£119	£63	0.13	0.06	0.03	3.15	2.63	1.58
		Seretide Accuhaler 100/50 FP/S per day							
BDP 400/day	£20	£190	£170	0.34	0.16	0.09	8.50	7.08	4.25
BUD 400/day (all CFC-free)	£70	£190	£120	0.24	0.11	0.06	6.00	5.00	3.00
FP 200/day (all CFC-free)	£109	£190	£81	0.16	0.08	0.04	4.05	3.38	2.03
BDP 400/day (excl. CFC-propelled)	£56	£190	£134	0.27	0.13	0.07	6.70	5.58	3.35

TABLE 41 *Exploratory cost-savings analysis: Annual exacerbations avoided to cover extra cost of BUD/FF compared with cheapest ICS product for each drug*

	Annual cost of cheapest ICS	Symbicort Turbohaler 200/12 BUD/FF per day	Cost Difference per year	Cost of a hospital-managed exacerbation			Cost of a GP-managed exacerbation		
				£500	**£1,056**	**£2,000**	**£20**	**£24**	**£40**
BDP 400/day	£20	£201	£181	0.36	0.17	0.09	9.05	7.54	4.53
BUD 400/day (all CFC-free)	£70	£201	£131	0.26	0.12	0.07	6.55	5.46	3.28
FP 200/day (all CFC-free)	£109	£201	£92	0.18	0.09	0.05	4.60	3.83	2.30
BDP 400/day (excl. CFC-propelled)	£56	£201	£145	0.29	0.14	0.07	7.25	6.04	3.63
		Symbicort Turbohaler 200/6 BUD/FF per day							
BDP 400/day	£20	£116	£96	0.19	0.09	0.05	4.80	4.00	2.40
BUD 400/day (all CFC-free)	£70	£116	£46	0.09	0.04	0.02	2.30	1.92	1.15
FP 200/day (all CFC-free)	£109	£116	£7	0.01	0.01	0.00	0.35	0.29	0.18
BDP 400/day (excl. CFC-propelled)	£56	£116	£60	0.12	0.06	0.03	3.00	2.50	1.50

TABLE 42 *Estimated cost of a hospital-managed exacerbation for children with asthma*

Resource type	**Unit cost**	**Source**			**Cost**
Oral steroids (prednisolone 2 × 25mg per day for 10 days, as per BTS/SIGN Guidelines)	17.27p per dose	BNF	20 doses		3.45
Child asthma patients discharged from A & E:					
% of those with exacerbations who are discharged			39% [b]		
Arriving by ambulance/paramedic services	£169	NSRC	39%	23% [b]	15.10
A & E Other high cost investigations	£100	NSRC	39%	11% [b]	4.30
A & E low cost investigations	£74	NSRC	39%	18% [b]	5.20
A & E No investigations	£62	NSRC	39%	71% [b]	17.22
Post discharge GP follow-up	£20	UCHSC	39%	64% [b]	4.97
Child asthma patients admitted from A & E:					
% of those with exacerbations who are admitted to hospital via A & E department			28% [b]		
Arriving by ambulance/paramedic services	£169	NSRC	28%	41% [b]	19.50
A & E Other high cost investigations	£151	NSRC	28%	18% [b]	7.65
A & E low cost investigations	£118	NSRC	28%	14% [b]	4.63
A & E No investigations	£112	NSRC	28%	68% [b]	21.46
Hospital episode for treating asthma (paediatric)	£721	NSRC	28%		202.75
ICU costs (3 bed-days in ICU, for 25% of those admitted via A & E)	£1910	NSRC	28%	3[b] × 25% [b]	403.01
Child asthma patients admitted following GP referral:					
% admitted to hospital via GP referral			33% [b]		
GP appointment	£20	UCHSC	33%		6.60
Hospital episode for treating asthma (paediatric)	£721	NSRC	33%		237.77
ICU costs (mean = 1 bed-days in ICU, for 10% of those admitted via GP referral)	£1910	NSRC	33%	1[b] × 10%[b]	63.01
All child asthma patients admitted to hospital:					
Post discharge GP follow-up	£20	UCHSC	61%	50%[a]	6.11
Post discharge hospital outpatient follow-up	£111	NSRC	61%	50% [a]	33.83
NHS cost per hospital-managed exacerbation					**£1056.56**

BNF = British national Formulary No. 51 (March 2006) ;[229] NSRC = National Schedule of Reference Costs 2005;[230] UCHSC = Unit Costs of Health and Social Care 2005.[231]

[a] authors' assumption

[b] administrative records of Royal Devon & Exeter NHS Trust and/or Southampton University Hospitals Trust

TABLE 43 *Estimated cost of a GP-managed exacerbation for children with asthma*

Resource type	Unit cost	Source			Cost
Oral steroids (prednisolone 2 × 25mg per day for 5 days, as per BTS/SIGN Guideline)	17.27p per dose	BNF	10 doses		1.73
% of consultations that are in surgery hours:			80% [b]		
In-hours GP visit (half see GP)	£20	UCHSC	80% [b]	50% [b]	8.00
In-hours GP visit (half see practice nurse)	£9	UCHSC	80% [b]	50% [b]	3.60
Out-of-hours GP telephone consultation (all out-of-hours)	£22	UCHSC	20% [b]	100% [a]	4.40
Out-of-hours GP visit (half of those calling out-of hours)	£59	UCHSC	20% [b]	50% [a]	5.90
NHS cost per GP-managed exacerbation					**£23.63**

BNF = British National Formulary No. 51 (March 2006) ;[229] UCHSC = Unit Costs of Health and Social Care 2005.[231]

[a] authors' assumption

[b] clinical expert opinion/estimate

6.11.4 Research Question 4: Combination versus separate inhalers at Step 3?

The cost comparison results presented below are justified on the basis that **we found no consistent evidence of differential effectiveness in trials comparing the comparators of interest** (see section 5.2.6)

Table 44 and

Table **45** below show, for both the currently available combination products (Seretide and Serevent), the combination ICS-with-LABA product is always cheaper than taking the same drugs in separate inhalers. For taking BUD with FF, using Symbicort via Turbohaler is always cheaper than taking Pulmicort via Turbohaler (at the same BUD dose) and taking FF separately. The estimated annual savings vary between £57 and £190 depending on the exact preparation of FF used and the daily dose of BUD required.

For taking FP with SAL, using Seretide via Accuhaler is always cheaper than taking Flixotide Accuhaler (at the same FP dose) and SAL separately. The estimated annual savings vary from £132 (if on 200µg FP per day) to £244 (if on 100µg FP per day). Similarly, using Seretide via Evohaler is always either £185 or £270 cheaper than taking Flixotide via Evohaler (at the same FP dose) and taking SAL separately.

TABLE 44 Annual cost of combination versus separate inhalers: BUD with FF added

		Annual cost (£) by daily dose of BUD	
Combination or BUD	**FF**	**200µg per day**	**400µg per day**
Symbicort Turbohaler (combination product)		201	402
Separate inhalers: Pulmicort Turbohaler, plus:	Oxis 4.5µg (or 9µg)*	369	437
	Foradil 12µg	391	458
Difference in annual cost (separate less combination):			
Separate inhalers: Pulmicort Turbohaler, plus:	Oxis 4.5µg or 9µg	+169	+35
	Foradil 12µg	+190	+57

* Oxis® 4.5µg and 9µg are the same price per dose.

TABLE 45 Annual cost of combination vs separate inhalers: FP with SAL added

		Annual cost (£) by daily dose of FP	
Preparation	**Taken as**	**100µg per day**	**200µg per day**
As dry powder:			
Flixotide Accuhaler	2 blisters/day	78	155
Serevent Accuhaler (or aerosol inhaler)#	2 blisters/day*	356	356
Both (total):		434	511
Seretide Accuhaler (FP and S combined)	2 blisters/day*	190	379
Difference in annual cost:		+244	+132
As aerosol:			
Flixotide Evohaler	4 puffs/day	33	66
Serevent aerosol Inhaler	4 puffs/day*	356	356
Both (total):		389	422
Seretide Evohaler (FP and S combined)	4 puffs/day*	119	237
Difference in annual cost:		+270	+185

* Each blister contains 50µg of SAL, and each puff contains 25µg of SAL

\# Seretide Accuhaler and aerosol inhaler are the same price per µg.

Comparisons with SAL delivered as Serevent Diskhaler are not shown. However, two blisters of Serevent diskhaler per day costs £428 per year (£72 more than Serevent Accuhaler or Serevent inhaler), and therefore the difference in annual cost between separate and combination inhalers would be even greater.

6.11.5 Research Question 5: FP/S vs BUD/FF at Step 3?

The cost comparison results presented below are justified on the basis that **we found no consistent evidence of differential effectiveness in trials comparing the comparators of interest** (see section 5.2.7)

Table 46 below compares the cost of taking ICS with LABA in the two currently licensed combination inhalers, Seretide® and Symbicort®. In making the comparison between these products we have assumed that 200µg and 400µg of BUD is equivalent to 100µg and 200µg of FP, respectively.

Symbicort is more expensive than both of the Seretide preparations that are recommended for use in children. The estimated annual savings to the NHS of using Symbicort instead of Seretide may be between £11 and £164. However, these differences rely heavily on the assumed 2:1 dose-equivalence between BUD and FP, which is a rather crude rule of thumb (and not, for example, derived from a meta-analysis of trials of the relevant products in children). It should also be noted that the assumed equivalence of Symbicort to Seretide at half the ICS dose, is based on only four head-to-head trials in adults, and in all these trials the Seretide comparator product was Seretide Diskus (which is marketed as Accuhaler in the UK) and all the trials were in adults and of doses that would not be recommended in children (typically comparing 500µg/100µg FP/S per day with 800, 1600 or 400µg /12µg of BUD/FF per day).

TABLE 46 *Comparison of the cost of currently available combination products*

Combination product		**200µg BUD per day**	**400µg BUD per day**
Symbicort Turbohaler (100µg:6µg of BUD:FF combined)	1 or 2 puffs/day	201	402
		100µg FP per day	**200µg FP per day**
Seretide Accuhaler (100µg:50µg of FP:S combined)	1 or 2 blisters/day*	190	379
Seretide Evohaler (50µg:25µg of FP:S combined)	2 or 4 puffs/day*	119	237

6.12 Summary of cost comparisons

What is the cheapest type of ICS?

For research question 1, the weighted mean annual cost of taking an ICS drug at 200µg BDP-CFC (or equivalent) varies from £30 for BDP to £64 for BUD. In contrast, the weighted mean annual cost of taking an ICS drug at a higher dose of 400µg BDP-CFC (or equivalent) varies over two-fold from £63 for BDP to £133 for FP. At this higher dose level, currently available BUD preparations cost on average £120 per year; only slightly less expensive than FP.

CFC-containing products are often considerably cheaper than the dry powder or HFA-propelled alternatives within the same drug class. As a consequence, and assuming pack prices and relative market shares remain the same, when CFC-containing products are withdrawn the weighted mean annual cost of taking BDP will increase from £30 to £60 (at a 200µg ICS/day dose level) and from £63 to £122 (at a 400µg ICS/day dose level). Although the difference in mean price between CFC-containing and non-CFC-containing BUD products is also substantial (weighted means £76 vs £159), the CFC-containing products currently account for a much smaller proportion of BUD product sales and the dry powder products are relatively cheap. As a consequence, the exclusion of CFC-containing products causes an increase in the weighted mean annual cost of BUD (at 400µg per day) of only £14 (from £120 to £134).

What these weighted averages often conceal, however, is very wide variations in the cost of individual preparations within each class of drug. This is an issue particularly for BDP, BUD and FP products. For example currently, the cheapest way of obtaining 400µg of BDP per day is taking Becotide 100µg four times daily (1.39p per dose = £20.37 per year); the most expensive way is to use Becodisks 100µg four times daily (9.52p per dose = £138.94 per year). Similarly, for obtaining 400µg of BUD per day, the cheapest product is Novolizer BUD 200µg taken twice daily (9.59p per dose = £70.00 per year); the most expensive product is Pulmicort Turbohaler 100µg and 200µg (9.25p and 18.5p per dose = £135.05 per year).

Which is cheapest – taking ICS with LABAs in combination or separate inhalers?

Overall, taking ICS with LABAs as either of the two currently available combination products is cheaper than taking the relevant ingredient drugs in separate inhalers. Taking Symbicort Turbohaler instead of the same drugs in separate inhalers saves the NHS between £35 and £190 per patient per year. Taking Seretide Accuhaler or Evohaler instead of the same drugs in separate inhalers saves the NHS between £132 and £270 per patient per year.

Which combination inhaler is the cheapest?

Noting that this comparison crudely assumes that 200µg and 400µg of BUD are equivalent to 100µg and 200µg of FP, respectively, and also that 12µg of FF per day has effectiveness equivalent to 100µg of SAL per day, the Seretide Evohaler appears considerably cheaper than either Seretide Accuhaler or Symbicort Turbohaler). At the lower daily dose of 200µg BUD or 100µg FP per day, Seretide Evohaler is over £70 cheaper per year than both Seretide Accuhaler and Symbicort Turbohaler, and when taking 400µg BUD or 500µg FP per day, it is over £140 cheaper than these alternatives.

All of the comparisons described above have involved a number of simplifying assumptions including (i) the relative doses of different products which are assumed to have equivalent effectiveness (ii) the combinations of products which are used to achieve any particular daily dose level of ICS or ICS-with-LABA, and (iii) using 2005 community prescription sales as a way of producing a weighted mean annual cost for each class of drugs. For these reasons - and because the range of available ICS and combination products is currently undergoing considerable change (with CFC-containing products being phased out, and some new HFA-propelled products recently entering the market) - the conclusions should be viewed with appropriate caution.

7. Factors relevant to the NHS and other parties

Asthma is one of the most common chronic conditions in the UK with a prevalence of approximately 5.2 milllion.[22] Therefore the economic burden of asthma in both direct and in-direct costs to the NHS is high. In 2005 expenditure on corticosteroids for respiratory conditions cost the NHS £436 million. Although this was only 15th in terms of the number of prescriptions issued, this is the third largest component of the total cost of community-dispensed drugs in England.

Estimates of the prevalence of treated asthma in children vary somewhat according to the source used to obtain them. However, estimates from the General Practice Research Database indicate that the prevalence of children being treated for asthma ranges from approximately 9.5% to 13.5% for boys and 6.0% to 10.5% for girls. In both cases the age ranges used in these estimates were age 0-4 years and 5-15 years, and in both sexes the prevalence increased with increasing age. It is not clear from these data what percentage of these children are currently using ICS or ICS plus LABA. Estimates quoted in the background, from Neville and colleagues, suggest that around a third of children under 5 years old and 20-25% of children aged 5 to 15 are treated at Step 1 of the BTS/SIGN Guidelines or below. These very rough estimates suggest that the majority of children with asthma are treated with ICS, either alone or in combination with other drugs. As these data are fairly old (1994/5), it is likely that this proportion is currently higher.

Children with asthma place various demands on the NHS budget, ranging from the cost of prescribed asthma medications, to various levels of health service use including GP and nurse consultations, accident and emergency department visits, and hospital admissions. Each of these is associated with a varying level of cost.

7.1 ICS therapy alone

The cost comparisons presented in this review indicate there are presently considerable differences in the mean annual cost between the different ICS preparations, as well as large cost differences between individual products of each ICS drug. These differences do not appear to be associated with any additional treatment benefit which would off-set the additional cost of the more expensive options. Therefore there may be little justification for the considerable cost differences between the three licensed comparators. There are potential cost savings to be made for the NHS if patients who are currently treated with the more expensive ICS drugs or preparations were switched to a cheaper option. Currently the largest cost savings would be associated with switching all patients to BDP-CFC propelled devices at all dose ranges. However, this is not a realistic treatment strategy as CFC-propelled devices are due to be phased out in the near future, and there are additional GP consultation costs associated with a review to switch patients between treatment strategies and drugs. With the phasing out of CFC-propelled products the cost of providing ICS therapy to the NHS is likely to increase. Additional costs will be associated with switching patients who are currently on CFC-propelled formulations to new preparations and the higher costs associated with all non-CFC propelled preparations of ICS. The exact cost implications to the NHS are difficult to project, as it is likely that as CFC-propelled formulations are removed from the market, the relative market share of non-CFC formulations will change and new products will enter the market. In order to realise any potential cost savings it may be important to review patients ICS therapy in routine GP or nurse consultations and examine whether switches can potentially be made to cheaper preparations of the same product, obviously which has an associated cost in terms of patient education, follow-up and any further treatment changes that may need to be made if the treatment regimen is unsuitable.

Additionally it must be noted that any potential cost savings of switching patients between either products or preparations can easily be off-set by the costs incurred by potentially higher exacerbation rates. The BTS/SIGN Guidelines states that patients and clinicians should choose the preparation that most suits the individual patient. This will be based not only on the preparation, but also the device and the complexity of the treatment regimen. It is therefore necessary that any potential switches to cheaper preparations, should be done bearing in mind the patient's ability to use different inhaler types. This is particularly pertinent within a paediatric population as a higher percentage of exacerbations are managed either within an Accident and Emergency Department or by an in-patient hospital stay compared with the adult population. Both of these incur considerable costs to the NHS.

7.2 ICS plus LABA

There are potential direct savings to the NHS with a switch to combination ICS/LABA products delivered in the same inhaler from the same drugs delivered in separate inhalers. Taking Symbicort via Turbohaler is associated with an estimated annual saving between £57 and £190 depending on the exact preparation of FF used and the daily dose of BUD required compared to taking Pulmicort via Turbohaler and taking FF separately.

Taking Seretide via Accuhaler is associated with an estimated annual saving of between £132 to £244 (depending on the dose of FP) compared to taking Flixotide via Evohaler and taking SAL separately. Likewise, using Seretide via Evohaler is between £185 and £270 cheaper than taking the constituent drugs separately.

However, it is not clear to what extent the drugs are currently prescribed in separate inhalers. Given the concerns that the clinicians consulted for this report have expressed about the potential hazards of using LABAs without ICS, it is likely that most ICS plus LABA therapy is now prescribed in combination inhalers and so the potential for cost savings in this area may be limited.

We are also aware from discussions with clinicians for this report that there is an increasing tendency to prescribe ICS and LABA in combination inhalers instead of ICS alone at Step 2 of the BTS/SIGN Guidelines. Reasons given for this practice include ease of use for patients, to get both preventer and reliever therapy in one device and concerns about over-use of reliever medication, particularly LABAs, on their own. As this practice is not in line with the guidelines, assessing the effectiveness and cost-effectiveness of this treatment strategy is outside the scope of this report and has not been investigated. It is likely, however, that a significant proportion of current prescribing cost may reflect ICS and LABA use that is not strictly according to the guidelines, making estimating potential cost savings more difficult.

8. Discussion

8.1 Assessing the effectiveness of interventions for asthma

Asthma is a common chronic condition with a number of definitions based on disease process, clinical symptoms and their pattern over time and response to external stimuli. Each definition defines different populations in terms of severity, the underlying pathological process and the likely disease trajectory. No one objective test can be used definitively to diagnose asthma in children and the diagnosis may only be made after a period of observation and trials of treatment, particularly in very young children. Asthma is also partly defined by the variation of symptoms over time, thus making the detection of changes due to interventions more difficult to identify.

In terms of outcomes of treatment for asthma, death is very uncommon and so is not an informative outcome measure for assessing the effectiveness of treatment at levels of severity within the scope of this report. The wealth of other outcome measures can broadly be divided into lung function, symptoms, acute exacerbations, use of rescue medication and adverse events. However, no standardised measures are used consistently in trials. Measures of lung function such as FEV_1 and morning and evening PEFR are among some of the most commonly reported outcomes. However, such measures are less useful in children as objective measures of lung function are often difficult to obtain and may be unreliable, particularly in young children. Additionally although FEV_1 is widely reported in trials, it may be expressed as absolute changes or % predicted. Symptoms are also widely reported, but trials do not use consistent methods for scoring symptoms or defining measures such as symptom-free days or nights. Similarly, definitions of exacerbations vary considerably. Very few trials report health related quality of life outcomes which are needed to inform cost-utility analysis, thereby making cost-effectiveness comparisons in asthma more difficult.

While lung function provides the more objective assessment of response to treatment, and probably more closely reflects the underlying disease process, the clinical significance of reported changes in lung function are not clear. Disease severity also relates to the underlying disease process, reflected in lung function and symptoms, but is most commonly defined by level of medication. Patients on substantial amounts of medication may be classified as having moderate or severe disease, but this classification will give no indication of their level of symptoms which may be well or poorly controlled.

The aim of treatment is to control symptoms and enable patients to lead as normal a life as possible, so well controlled asthma is a composite concept that varies between patients and professionals. It is dependent on any given patient's expectations for their lifestyle (e.g. being active versus sedentary or willingness to avoid known trigger factors), as well as their acceptance of a regular treatment regimen. Each individual therefore must balance these factors to allow them to achieve an acceptable level of symptoms and medication. Part of this balance is the extent to which patients will adhere to a medication regimen when they are symptom-free; many will adhere while they are symptomatic, but choose to reduce treatment levels once symptom-free. This step down in treatment may be appropriate in response to symptoms, but it may happen too quickly and lead to a return of symptoms or an exacerbation. Mild exacerbations may be managed either by the patient alone by increasing medication use, or managed within a primary care setting, leading to the wide variation in definition referred to above. From the perspective of assessing cost-effectiveness, however, it is particularly important to be able to identify the health care resource use associated with more severe exacerbations. These are usually defined as those exacerbations requiring hospital admissions or attendance in emergency departments, but many non-clinical factors influence admission to hospital, particularly for young children.

Assessing differences in health care costs for the treatment of asthma is difficult, because of the difficulty in deriving a single representative cost for each drug. There are a range of alternative products, available in a range of doses and delivered by different devices for each drug. Therefore there can be a number of ways of achieving any given daily dose of a particular drug, with significant consequences for the cost of delivering that dose. In order to make any comparisons in terms of costs between the different drugs, assumptions have to be made regarding dose equivalence and the way in which the target daily dose is achieved.

A further assumption must be made regarding the context of the BTS/SIGN Guidelines for assessing intervention effects of the different comparators under consideration. Whilst the Guidelines are well established and have been used for a number of years within the UK, it is clear that many clinical trials are not set within their context, and the treatment regimens assessed do not fit neatly into the Guideline steps.

8.2 Limitations of the evidence base

This review identified a very limited evidence base of trials including children under the age of 12 years and none including children under the age of five years. We have only identified eight trials that have been conducted solely on child populations under the age of 12 years: the rest include children over 12 and all exclude children under five years old. In those trials with a mixed adult and child population, the proportion of children under 12 years in the study is usually not specified, nor are the results reported separately. The trials that have been identified are generally of short duration (less than six months), with a treatment period of 12 to 24 weeks. These trials do not capture long-term outcomes, such as growth and impact on bone mineral density that may be of most interest to clinicians and patients. A number of trials report various measures of adrenal function, but it is not clear how these results can be extrapolated to periods of treatment lasting years or decades rather than the weeks that the trials last. It is also not clear what the minimal clinically significant change is for many of the reported outcomes such as lung function, symptoms or exacerbations. The wide range of possible outcome measures, most with no widely accepted and standardised method of measuring them, makes comparison across studies difficult and combining studies in a meta-analysis largely inappropriate. Trials have also been conducted for a variety of reasons and are not necessarily powered to detect superiority of one ICS over another. It is also not always clear how well blinding is maintained when drugs are delivered through different devices, although some trials report the use of placebo devices. Reporting of baseline population characteristics and outcome measures is frequently poor or selective.

8.2 Review of clinical effectiveness

Out of the 16 RCTs identified as relevant to this assessment, 12 have been included in published Cochrane systematic reviews. This assessment adds to this body of evidence, providing a systematic synthesis of these drugs within the context of a comprehensive and recognised care pathway. Below we discuss the key findings according to Steps 2 to 4 of the Guideline, embedded within our five review questions.

Review question 1: *Which inhaled corticosteroid is the most effective at low doses? (200 – 400µg per day BDP/BUD equivalent*)? (Step 2 of the guidelines)*

Five relevant RCTs of the efficacy and safety of ICS at doses up to 400µg per day (BDP/BUD or equivalent, corresponding to the BTS/SIGN Guidelines)[1] were included.

In general all three of the ICS were associated with favourable changes across a range of outcomes. However, limited findings are reported, particularly in terms of statistical significance tests. Where such tests were reported there were few statistically significant differences between them when evaluated in pairwise comparisons. The steroids might therefore be considered generally equivalent in clinical terms, although few studies explicitly aimed to assess clinical equivalence / non-inferiority.

The BTS/SIGN Guidelines note that BDP and BUD are approximately equivalent in clinical practice.[1] Similarly, the Cochrane review of BDP and BUD[187] noted few significant differences between them. In the current assessment, only one small trial of BUD compared to BDP was included. The trial was designed to evaluate the impact of step-wise increases in doses on adrenal function, as opposed to efficacy outcomes. That said, the trial did report that the treatments were comparable in terms of morning and evening PEFR and use of rescue medication, although no statistical tests were reported. There was no significant difference between the groups in suppression of diurnal urinary free cortisol (irrespective of dose).

The BTS/SIGN Guidelines also note that FP provides equal clinical activity to BDP and BUD at half the dose.[1] This is based on a reported higher potency for FP. In the Cochrane review of FP compared to BEC or BUD[188] (of which 14 of the 57 included RCTs were in children), the only significant differences between the drugs when administered at a 1:2 dose ratio (FP: BDP/BUD) were for FEV_1 and morning PEFR, in favour of FP. There were few differences between the drugs on other outcome measures, although limitations in the reported data prohibited meta-analysis of these outcomes. Only two studies comparing FP with BEC were included in the current assessment (a further three were included in the 'high' dose

[*] For FP the equivalent doses are 100 to 200µg per day (children over 4 years).

comparison of the two drugs, discussed under Review question 2, below). Both of them tested the drugs in a 1:2 dose ratio (FP:BEC). Differences between them in size, length and outcomes measured make it hard to draw comparisons. The findings generally do not support the superiority of either drug. Where statistical comparisons were reported they showed no significant differences between groups. This was the case for symptom-free days and nights, and for plasma cortisol. The proportion of patients experiencing an adverse event was similar between the treatments in the one trial that reported this outcome.

There were only two studies comparing FP with BUD (again, a further three were included in the 'high' dose comparison, below). One was a large study in which the dose of both drugs (dose ratio 1:1) was reduced by 50% every five weeks until asthma was controlled. The other was a much smaller trial focusing on long term safety over 12 months (dose ratio 1:2). There were no statistically significant differences between the treatments on any of the outcomes, including safety measures such as 24 hour urine cortisol, bone mineral density and growth over 12 months.

In summary, from the limited evidence available low dose ICS, when evaluated in pairwise fashion, appear similar in effects, with no statistically significant differences between them where statistical tests have been reported.

Review question 2: *Which inhaled corticosteroid is the most effective at high doses? (400 - 800µg per day BDP/BUD equivalent[*]) (Step 4 of the BTS/SIGN Guidelines)*

Seven RCTs of the efficacy and safety of ICS at 'high' doses in excess of 400µg per day (BDP/BUD or equivalent, corresponding to the BTS/SIGN Guidelines[1]) were included. Although in general doses were within the 400µg to 800µg dose range, in some studies they reached as high as 1500µg per day for BEC, 1200µg per day for BUD, and 750µg per day for FP.

The results of comparisons of ICS at high doses were similar to those of comparisons of ICS at low doses in demonstrating few statistically significant differences between the steroids.

[*] For FP high dose is greater than 200µg per day.

For the comparison of BDP with BUD, there was just one small short-term cross-over RCT. The primary outcome was to examine any differences in systemic effects, principally adrenal function. Urinary cortisol excretion was statistically significantly higher with BUD. There was no significant difference between the drugs for FEV_1.

Three RCTs compared FP with BDP, ranging from 12 weeks to one year in length. Results for lung function were inconsistent between different dose ratios, although for one of the dose ratios there was only one trial. When compared at a nominal 1:1 dose ratio (as measured in one trial), FP was significantly favourable for FEV_1, as well as morning and evening PEFR. There were no significant differences for symptoms or use of rescue medication. The incidence of exacerbations was similar and there were no statistically significant differences between the drugs for changes in morning serum cortisol and overnight urinary cortisol levels. There was a significant difference in growth rates, favouring FP. At a nominal 1:2 dose ratio (FP:BDP), measured in two small cross-over trials, there were no statistically significant differences between the drugs on any efficacy measures, including exacerbations. Rates of adverse events appeared similar, and there were no statistically significant differences in mean urinary free cortisol levels and total cortisol levels.

There were also three RCTs comparing FP with BUD. In common with the comparison of FP with BEC, there was one nominal 1:2 dose ratio comparison and two 1:2 dose ratio comparisons (FP:BUD). Results were mixed, with FP significantly better in term of lung function in two trials at dose ratio of 1:1 (not the accepted clinically equivalent dose ratio), but not for other outcomes. At a dose ratio of 1:2, one trial also reported a significantly favourable outcome for FP in terms of morning PEFR, but not for other outcomes. The proportion of patients experiencing adverse events was similar between the drugs, with no significant differences in one trial. There was no significant difference in changes in serum cortisol between groups in the one trial that reported this measure. FP was significantly favourable in terms of changes in growth/height.

In summary, when evaluated in pairwise fashion, there were few statistically significant differences between the high dose ICS in efficacy outcomes. Where significant differences did exist they tended to favour FP, but this is largely at 1:1 dose ratios; where only comparisons of the accepted clinically equivalent dose ratios are considered, even fewer significant differences are reported. There was no consistent pattern in effects across different dose ratios, although the small number of trials limits what can be concluded about this. Perhaps more importantly, there were few significant differences between the ICS in measures of adrenal suppression, which is of particular interest when ICS are prescribed at high doses in children. However, the trials did not appear to be adequately powered to detect differences on this outcome.

Review question 3: *Which is more effective: an ICS or a combination inhaler containing an ICS and a LABA? (step2/Step 3 of the BTS/SIGN Guidelines)*

The clinical effectiveness review concentrated on the comparison of ICS alone versus ICS and LABA where the ICS dose in the monotherapy arm was higher than in the combination arm, as this comparison appeared to be most relevant to the clinical decision at Step 2 of the guidelines, of whether to increase the dose of ICS or add in a LABA. However, the review identified trials comparing ICS alone to combination ICS and LABA where the ICS doses are similar in each arm. They are included and commented on below.

ICS+LABA where the dose of the ICS is higher when used alone, compared to the dose in the combination inhaler

For patients who are inadequately controlled on low dose ICS, the options include increasing the dose of the ICS, either within or beyond the 400μg per day dose threshold, or adding in a supplemental treatment. The BTS/SIGN Guidelines[1] recommend a trial of an add-on therapy for such patients, before increasing the ICS dose. In children aged five to 12 years the first choice is a LABA. For children aged two to five years, a trial of a leukotriene receptor agonist is recommended. However, the scope of this assessment does not include add-on therapies other than LABAs and therefore we cannot comment on the efficacy and safety of such strategies in children of this age group.

Only one trial where the dose of ICS was higher than the dose in the combination inhaler arm was identified and included. This was a large multi-centre trial of over 2000 patients. However, only around 12% were children under 12 years. The only results that are reported separately for children are for growth rates and plasma cortisol (our accompanying assessment report in adults and children over 12 years reports the efficacy results for the full population). There was a significant difference in favour of the combination inhaler for growth, but there were no significant differences for plasma cortisol.

A Cochrane review of this treatment modality[189] found that combination therapy led to greater improvement in lung function, symptoms and use of rescue medication. It was also associated with fewer withdrawals due to poor asthma control. There was no significant difference between treatments in terms of reducing exacerbations requiring systemic corticosteroids. However, caution is advised in any extrapolation from this evidence base as only three of the 30 studies were in paediatric populations, and only eight of the studies used a combination inhaler (the remaining studies using separate inhalers to deliver ICS and LABA). Clearly more RCTs evaluating this treatment strategy are needed in children, with a particular focus on impact on exacerbations, health related quality of life and long-term safety.

ICS+LABA where the dose of the ICS is the similar in both treatments

As discussed, the BTS/SIGN Guidelines recommend either increasing the dose of ICS or adding in a supplemental drug, such as a LABA for patients uncontrolled on low doses of ICS. However, a body of evidence exists, mainly in adult patients, comparing ICS with ICS and LABA where the ICS dose is similar in both strategies. These trials were conducted to evaluate the safety and efficacy of the combination inhalers compared to standard treatment with ICS.

In this assessment two such trials were included, both multi-centre trials of reasonable size. One compared FP against FP/S in a combination inhaler, the other comparing BUD against BUD/FF in a combination inhaler.

The trial that compared FP against FP/S was designed to primarily to evaluate safety. The limited, unpublished, data for efficacy outcomes suggested that the combination inhaler was favourable for lung function outcomes, and exacerbations, although it is not clear whether the there were statistically significant differences. The treatments appeared similar for symptoms and use of rescue medication and adverse events.

When BUD was compared against BUD/FF in a combination inhaler, the latter was statistically significantly more favourable for changes in FEV_1, and morning and evening PEFR. For other outcomes, such as symptoms, use of rescue medication and adverse events, the combination inhaler was either favourable or the treatments appeared similar, but no significance testing was reported.

Review question 4: *ICS and LABA administered in a combination inhaler compared to separate inhalers*

The scope for this assessment, as set by NICE, includes the use of ICS and LABA in a combination inhaler, but not in separate inhalers. It should therefore be acknowledged that there is a wider evidence base for the use of ICS and LABA in separate inhalers compared to ICS alone, although mainly in adults, as summarised by the Cochrane Collaboration.[189;190] The scope does, however, cover the use of ICS + LABA in a combination inhaler compared to the two in separate inhalers.

In this assessment only one such trial was identified, a multi-centre RCT of over 200 children. The key findings were that there were no statistically significant differences between the two treatment modalities for measures of lung function, and the mean difference in morning PEFR was within a defined range for clinical equivalence. They were similar for symptoms, use of rescue medication and exacerbations, but no statistical data were reported.

In practice decisions about whether a combination inhaler or whether separate inhalers are used will be based on factors such as ease of use, convenience and the likelihood of concordance. Expert clinical opinion suggests that one of the advantages of combination inhalers is that the risk of patients failing to take their ICS is reduced. When ICS and LABA are prescribed separately it is suggested that the rapid symptom relief provided by the LABA may mean that some patients are less likely to routinely take their ICS. The LABA will not have reduced the underlying inflammation and patients may be at increased risk of exacerbation. The BTS/SIGN Guidelines[1] make it clear that LABAs should not be used without ICS.

Review question 5: *Combination inhaler compared to combination inhaler ? (FP/S versus BUD/FF)*

No trials were identified which compared the two combination trials head to head in children. We are therefore unable to comment on the relative efficacy and safety of the two inhalers. Clearly RCTs assessing the two combination inhaler therapies head-to-head with a focus on exacerbation rates, symptom-free days and safety are needed.

8.3 Estimates of cost-effectiveness

We decided that it was not possible to develop a valid and credible cost-utility model for the treatment of asthma with an ICS used either alone or in combination with a LABA at the appropriate step of the BTS/SIGN Guidelines in a paediatric population. The main reason for this was the lack of direct head-to-head trial data for the three ICS comparators considered in questions one and two, ICS versus other ICS, and the lack of relevant trial data in questions three, four and five. Poor reporting of trial results, where they existed, meant that the reported data could not be used because of incomplete information.

As the results from the clinical effectiveness review did not demonstrate any consistent or significant differences in effectiveness between the comparators at the assumed clinically equivalent doses, we therefore undertook a cost comparison for questions one, two, four and five. No trials were identified that had assessed the treatment strategy in question three, of whether it is more effective to increase the dose of ICS alone if control is not adequate at doses within step two of the guidelines, or to add a LABA to an ICS. As there was no prior assumption of clinical equivalence between ICS only and LABA plus ICS strategies, neither equivalence nor consistent differences in effects between the two strategies could be assumed in the absence of any trial data. It was therefore considered inappropriate on methodological grounds to undertake a cost comparison analysis since this implies some clinical equivalence. We therefore undertook an exploratory cost-offset analysis to examine the number of hospital or GP managed exacerbations that would need to be avoided in order to off-set any cost differences between the different treatment strategies.

Discussion of cost comparisons

These cost comparisons have been shown in section 6. They relied upon a range of assumptions for arriving at each mean annual cost of taking a particular ICS or combination inhaler. In particular, they used the conventional (GINA and BTS/SIGN) dose-equivalence ratios for different ICS drugs and/or propellants, and use the 2005 community-dispensed prescription sales data for weighting the cost of different products within each drug type. For these reasons they should probably be viewed as a form of illustrative economic 'what if' analysis: 'If they were equally effective, what would be the likely differences in the annual cost of treatment?'

There are considerable differences in weighted mean annual cost between the different ICS, as well as large cost differences between different preparations of the same ICS. The annual cost varies seven-fold between different preparations of BDP to less than three-fold between different FP preparations. The cost differences between different BDP preparations are smaller, however, if the (typically cheaper) CFC-propelled preparations are excluded from the analysis. Our systematic review of the published research evidence has highlighted the fact that there is little demonstrated difference in effectiveness between the different ICS comparators under trial conditions. Therefore there appears to be little justification for the sometimes considerable cost differences between different products containing the three licensed drugs. However, other differences between the products – for example inhaler device characteristics and propellant taste, will probably influence how effectively or easily they are used. Yet in most clinical trials assessing the effectiveness of an ICS, only those participants who are already able to use the inhaler device type being trialled effectively and who are willing to tolerate other properties of the propellant will actually be eligible for inclusion.

It is well recognised that a large proportion of the asthmatic population has difficulty in using particular inhaler devices. This difficulty relates particularly to pMDIs and to a lesser extent to DPIs. Both require the ability to coordinate inhalation with activation of the inhaler. All trial evidence of the effectiveness of inhaled treatment for asthma should therefore be considered carefully for its generalisability to the general population with asthma rather than the subgroup able to use the trial devices.

In applying these cautions on the ease of use of inhaler devices to the results of the cost comparison analysis, the cost savings that could be realised by using the cheapest ICS via the cheapest device (a pMDI) might well result in an increase in other health care resource use through an increase in exacerbations resulting from poorer control of asthma from lack of adherence to treatment regimens or inability to use a pMDI. While we cannot quantify this likely increase, concordance with treatment in trials is around 80%, while in the general population of children with asthma, it may be that less than 50% take the full amount of prescribed medication (see Background). Addition of a spacer device to the pMDI, or choosing a more expensive delivery device that the patient prefers and is able to use easily might well improve concordance, thus minimising other health care resource use.

Summary of the cost comparison analyses

At the present time it is clear that BDP CFC-propelled products are the cheapest product available for the treatment of asthma in children. However, as CFC-propelled products are phased out, the cost of ICS treatment is likely to increase considerably. When non CFC-propelled products are considered, then there is less variation in the costs between the three ICS, although BDP still appears to be marginally cheaper than either BUD or FP. When considering the cost-effectiveness of increasing the dose of ICS alone or adding a LABA to a lower dose of ICS, it is clear that the extra annual cost of combination therapy varies enormously depending on the exact ICS product used. For the more expensive ICS products, their use at higher dose is more expensive than some of the combination inhaler products, whilst the use of cheaper ICS products in preference to a combination inhaler will be cost saving. Overall it should be noted that whilst the use of weighted averages can provide a useful way of representing the major differences between the different ICS drugs and LABAs, they conceal the wide variations in the cost of individual products. This means that any generic conclusions about cost-effectiveness, at the level of each ICS drug either versus another ICS or an ICS/LABA combination are not possible as they are confounded by the sheer number and differences in price of the products available for each drug.

All of the comparisons described above have also involved a number of simplifying assumptions including (i) the relative doses of different products which are assumed to have equivalent effectiveness (ii) the combinations of products which are used to achieve any particular daily dose level of ICS or ICS-with-LABA, and (iii) using 2005 community prescription sales as a way of producing a weighted mean annual cost for each group of drug preparations. For these reasons - and because the range of available ICS and combination products is currently undergoing considerable change (with CFC-containing products being phased out, and some new HFA-propelled products recently entering the market) - the conclusions should be viewed with appropriate caution.

Brief comments on the results of the submissions received by GSK and AZ for the treatment strategy reviewed in question 3

We were unable to produce results from the available trial data from which to assess the relative cost-effectiveness of increasing the dose of ICS alone if control is not adequate at

Step 2 of the Guidelines, compared to adding a LABA to a lower dose of ICS. Therefore in line with a request from NICE, we provide a short commentary below on the trial data used to address this question in the industry submissions received as part of the appraisal process from both GSK and AZ. A more comprehensive appraisal of both of the submissions has previously been outlined in section 6.4 and 6.5. The submission received from GSK was product-specific and aimed to assess whether for patients uncontrolled on ICS alone (FP), switching to FP/S (Seretide) is more cost-effective than increasing the dose of FP alone. The submission therefore, unlike the present assessment, did not aim to examine the cost-effectiveness of other alternative treatment strategies such as increasing the dose of BUD alone or switching to the combination of BUD/F. Therefore for question 3, the clinical trial data used in the model were from only one trial and did not take account of other available trial data.

Overall, the results presented appear to be reasonable. However, it should be noted that the exploratory cost-utility analysis from the assessment team's model for the linked report on the cost-effectiveness of ICS and LABAs for the treatment of asthma in adults, indicated that the results were very sensitive to any differentials in the utility values assigned to the different treatment arms. There was insufficient data reported in the submission to assess the likely effect of applying differential utility weights between the trial arms on the resulting reported ICERs.

The submission presented by AZ was also product-specific and aimed to examine whether for patients uncontrolled on ICS alone (BUD), it is more cost-effective to switch to combination therapy (BUD/F) or to remain on BUD alone. Therefore again, unlike the present assessment, this submission did not aim to examine the cost-effectiveness of alternative treatment strategies such as increasing the dose of FP or switching to a combination of FP/S. Additionally, the treatment strategy that was assessed differed from that of the assessment report, which aimed to assess whether it is more cost-effective to increase the dose of ICS alone or add a LABA to a lower dose of ICS. The strategy that was assessed in the AZ submission was that of whether it is more cost-effective to add a LABA in addition to an ICS, or remain on the same dose of ICS alone. The two clinical trials that were used to populate the economic model both reflected this treatment strategy, comparing Symbicort FD (400/24µg/day) and BUD plus F in separate inhalers (400/24µg/day) with BUD

400μg/day.[218;226] The treatment strategies presented in the AZ submission was therefore not comparable with that assessed within the present report.

8.4 Strengths and limitations of the review

The systematic review has the following strengths:

The systematic review builds on the relevant trial evidence from existing Cochrane reviews as well as further identified studies and synthesises the evidence on the effectiveness of BUD, BDP and FP used alone or in combination with either SAL or FF within the appropriate step of the BTS/SIGN Guidelines[1] for the treatment of chronic asthma in children aged under 12 years of age.

The review was guided by explicit principles for undertaking systematic reviews. The methods were set out in a research protocol (Appendix 2), which was open within the NICE appraisal process and commented on by an advisory group. The protocol defined the inclusion criteria, validity assessment methods, data extraction process, and the methods used to undertake the different stages of the review.

The effect of inhaler devices was outside the scope of the present assessment. However, in order to reduce any potential confounding in the assessment of the different comparators under consideration, only trials in which the inhaler type and propellant were the same in each of the trial arms were included in the systematic review.

And some significant limitations:

Owing to the time constraints placed upon the project, there was a lack of follow-up with authors of studies to clarify methodological details and results from the primary studies. This is particularly pertinent since in a large number of trials a measure of variance had not been reported for many of the outcome measures.

It was not possible to report every outcome measure reported in each of the included trials. As discussed earlier, there are numerous ways of measuring and reporting measures of asthma control. To achieve brevity we prioritised key measures from each of the relevant outcomes. For example, of the various ways of measuring lung function we only reported

FEV_1, and morning and evening PEFR, as these appeared to be the most commonly used and clinically meaningful. Consequently, in some trials the primary outcome has not been reported in this assessment if it was not a measure that had been prioritised. Furthermore, some of the outcomes that have been reported here were secondary outcomes that the trials were not necessarily powered to detect differences in. This should be kept in mind when interpreting the findings.

It was not possible to conduct meta-analysis in order to provide a quantitative estimate of treatment effect. This would have provided greater statistical power to show differences. Differences between studies in length and dose meant that it was not appropriate to pool studies. In cases where pooling was appropriate, poor reporting prohibited quantitative synthesis.

The majority of the included trials tended to be of short duration, so do not provide data on the long-term consequences of treatment for chronic asthma or the longer term side effects associated with therapy.

No trials of treatment in children under 5 have been identified for this review. It is not clear whether this is because there are none, or because they have not met our inclusion criteria. The latter may reflect both the tendency of very young children to be treated with nebulised drugs (nebulisers were excluded from our review) and the reliance on SABA therapy in this population. Conducting trials in young children can be problematic in terms of obtaining consent and assessing outcomes such as lung function and symptoms. Since asthma in this population may well respond differently to ICS and other treatment options, it is of concern that there does not appear to be a direct formal evidence base on which to base clinical decisions. It was therefore not possible to provide a stratified analysis to examine the effects of ICS and/or LABA use in infants and young children as requested in the assessment scope.

No trials have been conducted in a paediatric population that have assessed the effectiveness of a combination inhaler containing FP/S versus BUD/FF. Therefore it is not possible to compare the relative effectiveness and cost-effectiveness of these treatments for chronic childhood asthma.

Grounding the review within the context of the BTS/SIGN Guidelines placed a number of limitations on the comparisons between different treatment strategies that could be assessed. For example, the strategy of adding a LABA to an ICS at Step 2 rather than Step 3 was outside the scope of the present assessment. Such a strategy would involve the instigation of combination therapy in a potentially steroid naïve population that have been treated predominantly with a SABA. At the present time such strategies are outside the recommended guidance in the BTS/SIGN Guidelines.

Despite of extensive literature searches, we did not identify any published cost-effectiveness evaluations for treatment with either an ICS or an ICS used in combination with a LABA that had been conducted in children.

The majority of the literature that has examined the costs associated with living with asthma, such as the costs associated with treating exacerbations of differing severity, has been conducted in adults and there are few data to inform accurately on resource use within a paediatric population.

Economic analysis has been severely restricted as we were unable to combine the relevant trial data to simultaneously compare the effects of all the comparators under consideration for both questions one and two of the present assessment. Further restrictions were imposed due to the lack of relevant clinical trial data to populate the cost-utility model to assess the cost-effectiveness of:

i. increasing the dose of ICS alone or the addition of a LABA to a lower dose of ICS if control remains inadequate at doses within Step 2 of the BTS/SIGN Guidelines.

ii. combination therapy with FP/S versus BUD/F

Therefore all comparisons have focused on an analysis of the costs associated with the annual treatment costs for each ICS.

The cost comparison approach we adopted was a pragmatic response to both the lack of evidence generally and the lack of evidence of differential effectiveness for some of the review questions. In the absence of a formal cost-effectiveness analysis, these comparisons illustrate the wide variation in possible cost for each ICS drug, and how these vary by product type/strength, daily dose and inhaler type. Althought we have chosen to present averages for each ICS, we have put them in context be showing both weighted and unweighted mean and also the cheapest and most expensive product for each ICS at each dose level. With a view to other changes currently taking place in the UK market for asthma drugs, we have also generated estimates with and without CFC-propelled products included. Finally, for the comparison of combined ICS with LABA versus ICS alone, our simple cost-consequence analysis at least presents the main clinical effectiveness review findings alongside their estimated costs in a disaggregated form.

9. Conclusions

The literature on the clinical and cost-effectiveness of the three inhaled corticosteroids, BUD, BDP and FP used alone or in combination with a LABA in the treatment of chronic asthma in children under 12 years is limited. The RCTs included in this review were predominantly of one ICS comparator versus another, used at doses within the range of steps two to four of the BTS/SIGN Guidelines. There was no evidence available on whether the addition of a LABA to a dose of ICS at a range within step two of the guidelines, is more effective than increasing the dose of ICS alone. No trials were identified that assessed the relative effectiveness of the combination treatments of ICS plus LABA (Symbicort and Seretide) currently licensed for use in children.

No evidence is available on the clinical effectiveness of any of these treatments for children under the age of five.

ICS *versus* ICS

From the available evidence, the clinical effectiveness and short-term safety of the three inhaled corticosteroids, used at either low (step two) or high (step four) dose is similar. As no cost-utility model could be used to estimate cost-effectiveness across all technologies, cost comparisons were undertaken between the different ICS drugs. At the starting dose of 200µg/day BDP tends to be the cheapest ICS available, although when CFC-propelled products are exluded FP products can be the cheapest. At the higher doses of 400µg/day and 800µg/day it remains the cheapest. When non-CFC propelled products are considered the mean annual cost of ICS therapy increases for all three ICS, but overall cost differences between the drugs diminishes. However, the use of weighted averages to represent the cost associated with each ICS tends to conceal the wide variations in costs apparent between the individual preparations of each drug, and the wide overlap in costs between the drugs.

ICS *versus* ICS+LABA

No evidence is available on clinical effectiveness of ICS on its own *versus* ICS+LABA at a lower dose of ICS. There is limited evidence that ICS+LABA in a combination inhaler is more effective than the same dose of ICS on its own.

The combination inhaler preparations tend to be cheaper than an ICS on its own at double the clinically equivalent dose in the combination inhaler when based on comparisons made in relevant trials. Further evidence on the relative clinical effectiveness of these alternative treatment strategies should be sought to confirm the use of combination inhalers as the cost-effective option.

ICS plus LABA versus ICS plus LABA

From the limited evidence available, there were no significant differences in the clinical effectiveness of ICS plus LABA delivered concurrently compared to delivery in separate inhalers. Cost comparison between the two regimens showed that taking an ICS with a LABA as either of two currently available combination products (Symbicort and Seretide) is usually cheaper than taking the relevant ingredient drugs in separate inhalers.

The use of single inhaler therapy not only provides a simpler treatment regimen, but may also enhance concordance with maintenance ICS therapy and diminish the potential use of a LABA on its own. From this review there appear to be no significant clinical differences in effects between the two modes of treatment delivery, and potential cost savings to the NHS with use of a combination inhaler compared with separate inhalers.

9.1 Research recommendations

There is a clear lack of research in a number of areas that have been covered in the present assessment on the effectiveness and cost-effectiveness of ICS used alone or in combination with a LABA for the treatment of chronic asthma in children under 12 years of age.

The diagnosis of asthma in young children is extremely difficult, as viral wheeze is common in young children. However, a scoping review, using broad inclusion criteria, followed by research synthesis as appropriate, is required to assess the requirements for additional primary research on the clinical effectiveness of treatment for asthma in children under 5 years. Such a review could also usefully include all treatment options, pharmacological and non-pharmacological, for asthma.

There is currently no trial evidence available to inform the relative effectiveness of the two combination inhalers of FP/S and BUD/FF within a paediatric population. The results of the current assessment suggest that for FP/S there are no significant differences in effectiveness in terms of whether the drugs are delivered in a single inhaler or concurrently in two separate inhalers. However, as ease of treatment regimen may potentially affect concordance then a direct head-to-head trial that compares the two combination therapies of FP/S and BUD/FF is warranted.

No trials have assessed the relative effects of increasing the dose of ICS or adding a LABA to a lower dose of ICS if control is not maintained at doses within Step 2 of the BTS/SIGN Guidelines. It is therefore important that the relative effects of these two treatment strategies are compared within a paediatric population, particularly given concerns about the adverse effects of long-term ICS use. Given the chronic nature of asthma and that treatment may be necessary on a long-term basis from childhood, it is important to assess whether the addition of a LABA to a lower dose of ICS could potentially be as effective as an increased dose of ICS alone, but also be steroid sparing.

There is a need for the long-term adverse events associated with ICS use to be assessed systematically. Initial searches undertaken for this assessment indicate that there are presently no good quality systematic reviews available that have assessed all potential long-term adverse events associated with the three different ICS comparators. Present published reviews have tended to focus upon the use of short-term RCT safety data with a length of follow-up between one and two years. Therefore to adequately assess the longer term sequel of ICS use future reviews should aim to examine studies of longer term follow-up, and use appropriate data sources such as cohort, case control studies and registry data where available.

Need for standardisation of outcome measures and reporting

The evidence base that was assessed in the current review was highly heterogeneous both in terms of the way that outcome measures had been defined and measured, but also in the detail in which results were reported. Future trials of treatment for chronic asthma in children should aim to further standardise the way in which outcome measures are defined. There should be a greater focus on patient-centred outcomes such as HRQOL and symptoms. This will provide a more meaningful estimation of the impact of treatment on asthma control.

Methods of reporting also require standardisation. In particular where statistical results are presented means and standard deviations should be provided. This will enable such studies to be included in quantitative meta-analysis. The statistical methods of analysis should also be explicitly stated. In addition, the overall trial methods should be explicitly documented and reported with adherence to the CONSORT statement[232] standard of reporting being made a priority.

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Appendices

APPENDIX 1 : Expert advisory group

Dr Nick Adams	Consultant Physician	
Dr Alan Cade	Consultant Paediatrician	Plymouth Hospitals NHS Trust
Dr Chris Cates	Co-ordinating Editor	Cochrane Airways Review Group
Dr Tim Harrison	Consultant Physician (pharmacotherapy)	Nottingham City Hospital
Prof Stephen Holgate	MRC Clinical Professor of Immunopharmacology	Southampton General Hospital
Ms Emily Lancsar	Lecturer Economics	University of Newcastle-upon-Tyne
Ms Sarah Lewis	Reader in Medical Statistics	Division of Respiratory Medicine, Nottingham City Hospital
Dr David Mabin	Consultant Paediatrician	RD&E NHS Foundation Trust
Dr David Seamark	General Practitioner	Honiton Medical Practice
Dr David Sinclair	Consultant Physician, Respiratory Medicine	Torbay District Hospital
Prof Anne Tattersfield	Emeritus Professor of Respiratory Medicine	
Prof John Warner	Professor of Child Health	Dept. of Child Health, University of Southampton

APPENDIX 2 : Assessment protocol

Technology Assessment Report commissioned by the NHS R&D HTA Programme on behalf of the National Institute for Health and Clinical Excellence – FINAL PROTOCOL

May 4th 2006

1. Title of the project

Inhaled corticosteroids and long-acting $beta_2$ agonists for the treatment of chronic asthma in children under the age of 12 years

2. Name of TAR teams and 'leads'

Southampton Health Technology Assessment Centre (SHTAC)

Peninsula Technology Assessment Group (PenTAG)

3. Plain English Summary

Chronic asthma is a condition that affects around 5 million children and adults in the UK. The symptoms can include wheezing, shortness of breath, and general difficulties in breathing, and can significantly disrupt daytime activity and the ability to sleep well at night. Symptoms occur as a result of tightening of the muscles surrounding the airways and inflammation of the airway lining. People with asthma need to maintain good control of the condition to prevent worsening of symptoms or 'asthma attacks'. This can be achieved by following a healthy lifestyle, reducing contact with substances likely to aggravate asthma, and regular and correct use of prescribed drugs. People with mild asthma can usually manage the condition through use of an inhaler device containing a short-acting $beta_2$ agonist (e.g. salbutamol) on an as needed basis. Short-acting $beta_2$ agonists are known as bronchodilators and work by relaxing the airway muscles to improve the passage of air into the lungs. When this is not enough to prevent worsening of symptoms patients may be prescribed one of the five available corticosteroids, usually via a hand-held inhaler. A corticosteroid works to reduce inflammation in the airways. The corticosteroid is usually inhaled twice a day for a given period of months or longer (in addition to the inhaled short-acting $beta_2$ agonist, as needed) until asthma is stabilised, at which time it may be gradually reduced. Often a low, regular dose of inhaled corticosteroid is needed to control symptoms.

Where asthma symptoms continue to be difficult to control the daily dose of inhaled corticosteroid may be increased, or a third drug may be prescribed. Inhaled long-acting $beta_2$ agonists, of which there are two, are commonly used in these situations. They may be given separately or in a combined inhaler containing the inhaled corticosteroid. Other drugs may be given in cases where control is still not adequate.

There are a number of different inhaled corticosteroids and long-acting $beta_2$ agonists available, in different combinations and via different inhalers. This study will systematically summarise the results of clinical trials which compare the different inhaled corticosteroids with each other; trials which compare inhaled corticosteroids combined with long-acting $beta_2$ agonists with use of inhaled corticosteroids only; and trials which compare the two different combinations of inhaled corticosteroids and long-acting $beta_2$ agonists. The report will include an economic evaluation, to compare the costs and benefits of the different drugs to indicate whether they represent good value for money from the NHS and personal social services perspective.

4. Decision problem

The aim of this health technology assessment is to assess the clinical-effectiveness and cost-effectiveness of inhaled corticosteroids (ICS), and inhaled corticosteroids in combination with long-acting $beta_2$ agonists (LABA), in the treatment of chronic asthma in children aged under 12 years.

4.1 Background to asthma

Asthma is a condition characterised by inflammation and narrowing of the bronchial airways leading to wheezing, cough, chest tightness, shortness of breath and general difficulties in breathing. Symptoms vary from mild intermittent wheezing or coughing to severe attacks requiring hospital treatment. Severity can be defined on the basis of symptoms, lung function, and incidence of exacerbations. Definitions vary but a classification system has been proposed by the Global Initiative for Asthma (GINA)[P1;P2]. Asthma can be triggered by a number of stimuli, including allergens (e.g. animals, house dust mite), environmental factors (e.g. dust, pollution, tobacco smoke) and exercise. Family history of asthma and low birth weight may pre-dispose people to the condition. Other risk factors include increasing age, lower social class, and urban dwelling[P3]. Although common in children and young adults, asthma can affect people at any time of life.

Asthma is distinguished from other related conditions such as chronic obstructive pulmonary disease (COPD) or emphysema through reversible rather than progressive airway narrowing (although evidence is emerging that people with asthma do have some degree of decline in lung function over time). In young children it is often not possible to measure lung function in order to confirm variable airway obstruction; diagnosis is then usually made on careful clinical history and examination

Prevalence has increased considerably over recent decades, in both developed and developing countries. Reasons are complex, reflecting environmental and lifestyle factors. In the UK there are 5.2 million people (9%) with asthma, including 590,000 teenagers. In England and Wales the number of people affected is around 4.7 million. Whilst severe exacerbations of asthma may cause death, mortality from the condition is relatively low compared to other respiratory diseases such as COPD. Respiratory disease accounts for greater mortality in the UK (24% of total deaths) than coronary heart disease (21%) or non-respiratory cancer (19%). However, asthma is responsible for only 1% of respiratory deaths[P3].

4.2 Management

The management of asthma includes several inter-linked approaches including medication (e.g. (bronchodilators, corticosteroids), lifestyle modification, environmental changes (e.g. minimising the impact of allergens in the home or workplace), patient education (e.g. to encourage self-management and improve concordance with medication), and regular monitoring to assess disease control. Management is primarily the responsibility of the general practitioner in collaboration with the patient, although specialist intervention may be required in severe cases. The aims of treatment are to relieve symptoms (e.g. wheeze, cough), improve health related quality of life (including ability to work, study or sleep), improve lung function (i.e. Forced Expiratory Volume 1, (FEV_1); Peak Expiratory Flow Rate, (PEFR)), minimise the requirement for relief (e.g. short-acting $beta_2$ agonists) and rescue (oral corticosteroids) medication and reduce adverse effects associated with medication.

The British Thoracic Society (BTS), in collaboration with the Scottish Intercollegiate Guidelines Network (SIGN), have published clinical guidelines on asthma[P4;P5]. The guidelines cover a variety of aspects of management, including pharmacological management. They propose a stepwise approach to achieving symptom control (Appendix 9.1). Treatment is initiated at the step most appropriate to the initial severity of asthma and the person's day to day needs, with the aim of achieving early control of symptoms. Control is maintained by stepping up treatment as necessary and stepping down when control is good.

First line treatment in mild intermittent asthma is with an inhaled short-acting $beta_2$ agonist, as required for symptom relief (e.g. salbutamol, or terbutaline). Treatment is stepped up with the introduction of regular preventer therapy with ICS in addition to symptomatic use of an inhaled short-acting $beta_2$ agonist (Step 2). If necessary a long-acting $beta_2$ agonist (LABA) is added (but not in children under the age of four in whom a leukotriene receptor agonist should be considered, and in children under 2 years referral to a respiratory paediatrician should be considered) (Step 3). If control is still not adequate the dose of the inhaled corticosteroid can be increased, in addition to introduction of a fourth drug such as an theophylline or a leukotriene receptor agonist (children aged 5 to 12) (Step 4). For children aged under 5 years, Step 4 involves referral to a respiratory paediatrician. For children aged 5 to 12, if response remains poor specialist care may be initiated with regular use of oral corticosteroids (e.g. prednisolone), in addition to the other drugs (Step 5).

In 2000 NICE issued guidance to the health service in England and Wales on the use of inhaler devices in children with chronic asthma aged under five (Guidance number 10), and in 2002 guidance for older children (aged 5-15, Guidance number 38).

For children under the age of 5 years with chronic stable asthma both corticosteroids and bronchodilator therapy should be routinely delivered by a pressurised metered dose inhaler (pMDI) and a spacer system, with a facemask where necessary. Where this combination is not clinically effective for the child and depending on the child's condition, nebulised therapy may be considered. In the case of children aged 3 to 5 years, a dry powder inhaler (DPI) may also be considered.

For children aged 5 to 15 years a press-and-breathe pressurised metered dose inhaler (pMDI) and suitable spacer device is recommended as the first-line choice for the delivery of inhaled corticosteroids. If adherence is likely to be poor then other alternatives should be considered. For bronchodilators a wider range of devices should be considered to take account of their more frequent spontaneous use, the greater need for portability, and the clear feedback that symptom response provides to the device user. Over-arching principles when choosing an inhaler include the therapeutic need for the particular drug, the ability of the child to develop and maintain an effective technique with the specific device, the suitability of a device for the child's and carer's lifestyles, considering factors such as portability and convenience and the child's preference for and willingness to use a particular device.

A planned update of both sets of guidance in 2005 was not undertaken as it was found that little new evidence had emerged since the first guidance. They have both now been moved to the Institute's 'static' list of appraisals, which will not routinely be updated.

4.2.1 Inhaled corticosteroids (ICs)

ICS work to reduce bronchial inflammation. They are recommended for prophylactic treatment of asthma when patients are using a short-acting beta$_2$ agonist more than three times a week or if symptoms disturb sleep more than once a week, or if the patient has suffered exacerbations in the last two years requiring a systemic corticosteroid or a nebulised bronchodilator. Corticosteroid inhalers should be used regularly for maximum benefit.

There are currently 3 ICS licensed in the UK for children (see Appendix 9.2 for details of delivery devices. NB. High dose inhalers are not licensed in children):

- beclometasone dipropionate (AeroBec [3M], Asmabec Clickhaler [Celltech], Beclazone Easi-Breathe [IVAX], Becloforte [Allen & Hanburys], Beclometasone Cyclocaps [APS], Becodisks [Allen & Hanburys], Becotide [Allen & Hanburys], Easyhaler [Ranbaxy], Filair [3M], Pulvinal Beclometasone Dipropionate [Trinity])

- budesonide (Budesonide Cyclocaps [APS], Easyhaler [Ranbaxy], Novolizer [Viatris], Pulmicort [AstraZeneca])
- fluticasone propionate (Flixotide [Allen & Hanburys])

Beclometasone dipropionate, budesonide and fluticasone propionate have been used for some time, whilst ciclesonide is relatively newer. Ciclesonide (Alvesco [Altana]) is included in the scope issued by NICE with the expectation that it may receive an extension to its marketing authorisation to include children under the age of 12 within the time frame for the appraisal. There are a variety of delivery systems including pressurised metered-dose inhalers (pMDI), breath-activated pMDIs, dry powered formulations, and nebulisers. Chlorofluorocarbons (CFCs) have been the traditional propellant in pMDIs, but with the phasing out of CFCs they are being replaced by ozone-friendly hydrofluoroalkanes (HFAs). Spacer chambers can be attached to pMDIs to make them easier to use and improve drug delivery to the lungs.

Standard daily recommended doses of ICS in children are 100 micrograms (mcg) twice daily for budesonide and beclometasone dipropionate; and 50 mcg twice daily for fluticasone propionate[P6]. The BTS recommends titrating to the lowest dose at which effective control is maintained[P5;P7]. In children this can be up to 400 mcg per day (for budesonide or beclometasone dipropionate)[P5]. Fluticasone is considered clinically equivalent to budesonide or beclometasone dipropionate at half the dose. (However, HFA propelled beclometasone dipropionate is regarded as clinically equivalent to fluticasone at the same dose).

If maintenance therapy with an ICS does not adequately control symptoms there are a number of potential treatment options. One is to continue with the IC but to increase the dose to the higher end of the recommended range (e.g. up to 400 mcg in children aged 5 to 12 years, or 200mcg in children younger than 5 years). However, this increases the risk of adverse effects (such as growth and adrenal suppression). An alternative is to add a LABA to ICs (but not in children younger than 4 years old). Adding a LABA may be preferential as results of dose-response studies suggest that higher doses of ICS may worsen the overall therapeutic ratio (that is, the ratio of the maximally tolerated dose of a drug to the minimally curative or effective dose)[P8].

4.2.2 Long-acting beta$_2$ agonists (LABA)

Two LABAs are licensed for use in the UK, salmeterol (Serevent) and formoterol (Foradil; Oxis). Like short-acting beta$_2$ agonists, LABAs have a bronchodilatory action, expanding the bronchial airways to improve the passage of air. They are recommended in addition to existing inhaled corticosteroid therapy, rather than replacing it. They can be used in combination with inhaled corticosteroids in separate inhalers, or combined in one inhaler. There are two licensed combination inhalers in the UK:

- budesonide + formoterol fumarate (Symbicort)
- fluticasone propionate + salmeterol (as xinafoate) (Seretide)

Budesonide and formoterol fumarate can be used only in children over six years, whilst fluticasone propionate and salmeterol can be used in children as young as four. The two LABAs differ chemically, with formoterol associated with a more rapid onset of action.

A typical dose of fluticasone propionate/salmeterol in children over four is 100/50 micrograms (mcg) per day, titrated up to 200/100 mcg per day if necessary. A typical dose of budesonide/formoterol in children over six is 80/4.5 mcg once daily, titrated up to 320/18 mcg per day in severe cases.

Given the vast range of options available in the pharmacological management of chronic asthma, an assessment of clinical-effectiveness and cost-effectiveness of the various strategies is required. Specifically, an assessment is needed of the relative benefits and adverse effects of the different ICS; and of the two ICS and LABA combination inhalers. It is also necessary to assess the benefits and adverse effects of combined treatment with an ICS and a LABA compared with continuing ICS alone (including increasing the dose of the ICS) in situations of worsening asthma control.

5. Report methods for synthesis of evidence of clinical effectiveness

5.1 Search strategy

- A search strategy will be devised and tested by an experienced information scientist. The strategy will be designed to identify two different types of study: (i) studies reporting the clinical-effectiveness of inhaled corticosteroids and long-acting beta$_2$ agonists; and (ii) studies reporting the cost-effectiveness of inhaled corticosteroids and long-acting beta$_2$ agonists. The draft search strategy for Medline is in Appendix 9.3.

- A number of electronic databases will be searched including: The Cochrane Database of Systematic Reviews (CDSR); The Cochrane Central Register of Controlled Trials; NHS CRD (University of York) Database of Abstracts of Reviews of Effectiveness (DARE) and the NHS Economic Evaluation Database (NHS EED); Medline (Ovid); Embase (Ovid); National Research Register; Current Controlled Trials; ISI Proceedings; Web of Science; and BIOSIS. Bibliographies of related papers will be assessed for relevant studies where possible.
- The manufacturers' submissions to NICE will be assessed for any additional studies.
- Experts will be contacted to identify additional published and unpublished references.
- Searches will be carried out from the inception date of the database until February/March 2006 (for clinical-effectiveness and cost-effectiveness studies). All searches will be limited to the English language. The searches will be updated around October 2006.
- Searches for other evidence to inform cost-effectiveness modelling will be conducted as required (see Section 6.5b).

5.2 Inclusion and exclusion criteria

5.2.1 Intervention

Studies reporting evaluations of the following inhaled corticosteroids will be included:

- beclometasone dipropionate
- budesonide
- ciclesonide*
- fluticasone propionate

*subject to licensing

Studies reporting evaluations of the following inhaled corticosteroids combined with long-acting beta$_2$ agonists in the same inhaler (i.e. combination inhalers) will be included:

- budesonide + formoterol fumarate (in children aged 6 and over)

- fluticasone propionate + salmeterol (as xinafoate) (in children aged 4 and over)

Studies reporting treatment duration of four weeks or less will not be included.

5.2.2 Comparators

- The inhaled corticosteroids will be compared with each other.
- The combination inhalers will be compared with: each other; and with inhaled corticosteroids only. They will also be compared with inhaled corticosteroids and long-acting $beta_2$ agonists administered separately in terms of any adverse events likely to impact on costs and cost effectiveness.
- Studies testing different doses of the same agent, or the same agent delivered by different inhaler devices will not be included.

5.2.3 Types of studies

- Fully published randomised controlled trials (RCTs) or systematic reviews of RCTs. Double blinding is not a pre-requisite for inclusion, although blinding will be assessed as part of critical appraisal (see Section 5.3). Indicators of a 'systematic' review include: an explicit search strategy, and inclusion/exclusion criteria.
- Studies published as abstracts or conference presentations from 2004 onwards will be included in the primary analysis of clinical and cost-effectiveness only if sufficient details are presented to allow an appraisal of the methodology and assessment of results.

5.2.4 Population

- Children aged under 12 years with chronic asthma. Studies in which the patient group is asthmatics with a specific related co-morbidity (e.g. cystic fibrosis) will not be included.
- Where data are available clinical-effectiveness and cost-effectiveness will be reported for patient sub-groups, in terms of disease severity and age. Concordance according to different patient sub-groups will be assessed where data allow.
- Studies reporting the treatment of acute exacerbations of asthma will not be included.

5.2.5 Outcomes

- Studies reporting one or more of the following outcomes will be included:
  - objective measures of lung function (e.g. FEV_1, PEFR)
  - symptom-free days and nights
  - incidence of mild and severe acute exacerbations (e.g. mild – requiring unscheduled contact with healthcare professional; severe – requiring hospitalisation, short-term 'rescue' use of systemic corticosteroids or visit to accident and emergency department).
  - adverse effects of treatment (e.g. growth suppression)
  - health-related quality of life
  - mortality
- Titles and abstracts of studies identified by searching will be screened by one reviewer based on the above inclusion/exclusion criteria. A second reviewer will check a random 10% of these with any discrepancies resolved through discussion and involvement of a third reviewer where necessary.
- Full papers of studies which appear potentially relevant on title or abstract will be requested for further assessment. All full papers will be screened independently by one reviewer and checked by a second, and a final decision regarding inclusion will be agreed. Any discrepancy will be resolved by discussion with involvement of a third reviewer where necessary.

5.3 Critical appraisal and data extraction

- A number of recently updated Cochrane systematic reviews of the effectiveness of comparisons of ICS[P9;P10;P11], and ICS with LABA[P12] have been published. Where possible these and other high quality systematic reviews will be used to assess clinical-effectiveness. RCTs published since the reviews were last updated would be prioritised for full data extraction and critical appraisal. The findings of the systematic reviews and the supplemental RCTs will be used together to inform the assessment of clinical effectiveness.

- Data extraction and critical appraisal will be performed by one reviewer using a standardised data extraction form (see Appendix 9.4). A second reviewer will check the form for accuracy and completeness. Discrepancies will be resolved by discussion, with involvement of a third reviewer where necessary.
- The quality of included RCTs and systematic reviews will be assessed using NHS CRD (University of York) criteria[P13] (see Appendix 9.5).

5.4 Methods of analysis/synthesis

- Clinical-effectiveness studies will be synthesised through a narrative review with tabulation of results of included studies.
- Where data are of sufficient quantity, quality and homogeneity, a meta-analysis of the clinical-effectiveness studies will be performed, using appropriate software.
- To minimise clinical heterogeneity the synthesis will seek to group together studies reporting similar populations and interventions.
    - For example, comparisons of different ICS delivered via pMDI may be considered separately to those comparing different ICS delivered by dry powder formulations.
    - Similarly, comparisons of ICS where a CFC propelled pMDI is used may be grouped separately to those where the propellant is HFA, given suggested differences in potency[P11]
    - Dose equivalence will need to be taken into account as far as the evidence allows, particularly where a study compares a CFC pMDI ICS with a HFA pMDI ICS.

6. Methods for synthesising evidence of cost-effectiveness

6.1 Search strategy

Refer to Appendix 9.3 for details of the draft search strategy for Medline. The sources to be searched are similar to those used in the clinical-effectiveness review (see Section 5.1). All searches will be limited to the English language.

6.2 Inclusion and exclusion criteria

The inclusion and exclusion criteria for the systematic review of economic evaluations will be identical to those for the systematic review of clinical effectiveness, except that:

- non-randomised studies may be included (e.g. decision model based analyses or analyses of patient-level cost and effectiveness data alongside observational studies);
- full cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses and cost-consequence analyses will be included. (Economic evaluations which only report average cost-effectiveness ratios will only be included if the incremental ratios can be easily calculated from the published data);

Based on the above inclusion/exclusion criteria, study selection will be made independently by two reviewers. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

6.3 Study quality assessment

The methodological quality of the economic evaluations will be assessed using accepted frameworks such as the International consensus-developed list of criteria developed by Evers and colleagues (2005)[P4], and Drummond and colleagues (1997)[P14]. For any studies based on decision models we will also make use of the checklist for assessing good practice in decision analytic modelling (Philips and colleagues, 2004)[P15]. We will examine recent published studies which are carried out from the UK NHS and PSS perspective in more detail.

6.4 Data extraction strategy

Data will be extracted by one researcher into two summary tables: one to describe the study design of each economic evaluation and the other to describe the main results.

- The following data will be extracted into the study design table: author and year; model type or trial based; study design (e.g. cost-effectiveness analysis (CEA) or cost-utility analysis (CUA)); service setting/country; study population; comparators; research question; perspective, time horizon, and discounting; main costs included; main outcomes included; sensitivity analyses conducted; and other notable design features.

- For modelling-based economic evaluations a supplementary study design table will record further descriptions of model structure (and note its consistency with the study perspective, and knowledge of disease/treatment processes), sources of transition and chance node probabilities, sources of utility values, sources of resource use and unit costs, handling of heterogeneity in populations and evidence of validation (e.g. debugging, calibration against external data, comparison with other models).
- For each comparator in the study, the following data will be extracted into the results table: incremental cost; incremental effectiveness/utility and incremental cost effectiveness ratio(s). Comparators excluded on the basis of dominance or extended dominance will also be noted. The original authors' conclusions will be noted, and also any issues they raise concerning the generalisability of results. Finally the reviewers' comments on study quality or generalisability (in relation to the NICE scope) will be recorded.

6.5 Synthesis of evidence on costs and effectiveness

(a) Published and submitted economic evaluations

Narrative synthesis, supported by the data extraction tables, will be used to summarise the evidence base from published economic evaluations and sponsor submissions to NICE

(b) Economic Modelling

A new cost-effectiveness analysis will be carried out from the perspective of the UK NHS and Personal Social Services using a decision analytic model. The evaluation will be constrained by available evidence. If possible, the incremental cost-effectiveness of the intervention drug classes and the specified comparators will be estimated in terms of cost per Quality Adjusted Life Year (QALY) gained, as well as the cost per acute exacerbation avoided.

Model structure will be determined on the basis of research evidence and clinical expert opinion of:

- The biological disease process of chronic asthma in children (i.e. knowledge of the natural history of the disease);
- The main diagnostic and care pathways for patients in the UK NHS context (both with and without the intervention(s) of interest); and
- The disease states or events that are most important in determining patients' clinical outcomes, quality of life and consumption of NHS or PSS resources.

For example, we will need to consider developing a natural history model of chronic asthma which could reflect factors such as: patient age, asthma severity (e.g. FEV_1, PEF, frequency of acute exacerbations), whether their asthma is predominantly self-managed or GP/primary care nurse-managed. The extent to which the model *is able to* fully reflect these various factors will depend upon the available research literature. The extent to which the model *needs to* reflect these factors will depend on how plausible it is that they impact on either the effectiveness or cost impacts of the interventions.

Parameter values will be obtained from relevant research literature, including our own systematic review of clinical-effectiveness. Where required parameters are not available from good quality published studies in the relevant patient group we may use data from sponsor submissions to NICE or expert clinical opinion. Sources for parameters will be stated clearly.

Resource use will be specified and valued from the perspective of the NHS and PSS in 2005 (this is the most recent year for which NHS National Schedule of Reference Cost data will be available). Cost data will be identified from NHS and PSS reference costs or, where these are not relevant, they will be extracted from published work or sponsor submissions to NICE as appropriate. If insufficient data are retrieved from published sources, costs may be obtained from individual NHS Trusts or groups of Trusts.

To capture health-related quality of life effects, utility values will be sought either directly from the relevant research literature. Ideally utility values will be taken from studies that have been based on "public" (as opposed to patient or clinician) preferences elicited using a choice-based method.

Analysis of uncertainty will focus on cost-utility, assuming the cost per QALY can be estimated. Uncertainty will be explored through one-way sensitivity analysis and, if the data and modelling approach permit, probabilistic sensitivity analysis (PSA). The outputs of PSA will be presented both using plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.

The simulated population is likely to be separate birth cohorts of children aged between 2 and 11 years of age. Where possible the base case results will be presented separately for grouped age-bands, at least for 2- to 4-year-olds and 5- to 11-year-olds. The time horizon for our analysis will be between 1 and 5 years; sufficiently long to reflect both the chronic nature of the disease and estimate differences in rare outcomes, such as asthma-related deaths.

Searches for additional information regarding model parameters, patient preferences and other topics not covered within the clinical effectiveness and cost-effectiveness reviews will be conducted as required (e.g. health related quality of life; epidemiology and natural history). This is in accordance with the methodological discussion paper produced by InterTASC (January 2005).

7. Handling the company submission(s)

All information submitted by the manufacturers/sponsors as part of the NICE appraisal process will be considered if received by the TAR team no later than 2nd August 2006. Information arriving after this date will not be considered.

Economic evaluations included in sponsors' submission will be assessed against the NICE guidance for the Methods of Technology Appraisals (NICE, 2004) and will also be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used.

Incremental cost effectiveness ratios (ICERs) estimated from consultee models will be compared with results from the Assessment Group's analysis, and reasons for large discrepancies in estimated ICERs will be explored and, where possible, explained.

Any 'commercial in confidence' data taken from a company submission will be <u>underlined</u> and highlighted in the assessment report (followed by an indication of the relevant company name e.g. in brackets).

8. Competing interests of authors

There are no competing interests

9. Appendices

9.1 SIGN/BTS Pharmacological management pathway for chronic asthma

9.2 Inhaled steroids and devices

9.3 Medline search strategy

9.4 Data extraction form (RCTs and systematic reviews)

9.5 Quality assessment criteria (RCTs and systematic reviews)

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APPENDIX 3 : Search strategies and databases searched for the clinical and cost-effectiveness reviews

Clinical effectiveness search strategy: Corticosteroids in asthma

Databases searched:

The Cochrane Database of Systematic Reviews (CDSR)
The Cochrane Central Register of Controlled Trials
CRD (University of York) Database of Abstracts of Reviews of Effectiveness (DARE), NHS Economic Evaluation Database (NHS EED)
Medline (Ovid); Embase (Ovid)
National Research Register
Current Controlled Trials
Web of Knowledge Science Citation Index and ISI Proceedings
BIOSIS.
Ovid MEDLINE(R) <1966 – 2006 Run on 15/02/2006; update search run on 26/09/06

1 exp asthma/
2 asthma.ti,ab.
3 1 or 2
4 exp randomized controlled trials/
5 exp random allocation/
6 controlled clinical trials/
7 randomized controlled trial.pt.
8 controlled clinical trial.pt.
9 exp double blind method/
10 exp single blind method/
11 (randomiz$ or randomis$).
12 placebo.ti,ab.
13 (singl$ or doubl$ or tripl$ or trebl$ or blind$).ti,ab.
14 (trial$ or study or studies or method$).ti,ab.
15 13 or 14
16 meta analysis/

17 (meta analys?s or metaanalys?s).ab,pt,ti.
18 (systematic$ adj2 (review$ or overview$)).ti,ab.
19 or/16-18 28348
20 or/4-12,15,19
21 (letter or editorial or comment).pt.
22 20 not 21
23 3 and 22
24 beclomethasone/
25 bdp.ti,ab.
26 budesonide/
27 (beclomet?asone or budesonide or ciclesonide or fluticasone or mometasone).mp.
28 (asmabec or belclazone or cyclocaps or becodisks or becotide or filair or qvar or pulvinal or pulmicort or flixotide or aerobec or becloforte or novoliser or viatris or alvesco or asmanex or novolizer or easyhaler or symbicort or seretide or serevent or atimos or foradil).mp.
29 exp glucocorticoids/
30 (corticosteroid$ or glucocorticoid$ or steriod$).ti,ab.
31 or/24-30
32 31 not 21
33 23 and 32
34 limit 33 to (humans and english language)
35 or/24-28
36 35 not 21
37 23 and 36
38 limit 37 to (humans and english language)

Cost-effectiveness search strategy: Corticosteroids in asthma

Search strategy translated and run in:
MEDLINE (Ovid)
MEDLINE in Process (Ovid)
EMBASE (Ovid)
Cochrane Database of Systematic Reviews (CDSR)
Cochrane Central Register of Controlled Trials (CCTR)

Science Citation Index (Web of Knowledge)

CRD NHS Economic Evaluation Database, DARE and HTA databases, and EconLit.

Ovid MEDLINE(R) <1966 to March Week 1 2006>

Searched 09/03/2006; Update search 6/10/2006

1 exp Asthma/)
2 asthma.ti,ab
3 1 or 2
4 exp ECONOMICS/
5 exp ECONOMICS, HOSPITAL/
6 exp ECONOMICS, PHARMACEUTICAL/
7 exp ECONOMICS, NURSING/
8 exp ECONOMICS, DENTAL/
9 exp ECONOMICS, MEDICAL/
10 exp "Costs and Cost Analysis"/
11 Cost-Benefit Analysis/
12 VALUE OF LIFE/
13 exp MODELS, ECONOMIC/
14 exp FEES/ and CHARGES/
15 exp BUDGETS/
16 (economic$ or price$ or pricing or financ$ or fee$ or pharmacoeconomic$ or pharma economic$).tw.
17 (cost$ or costly or costing$ or costed).tw.
18 (cost$ adj2 (benefit$ or utilit$ or minim$ or effective$)).tw.
19 (expenditure$ not energy).tw.
20 (value adj2 (money or monetary)).tw.
21 budget$.tw.
22 (economic adj2 burden).tw.
23 "resource use".ti,ab.
24 or/4-22
25 news.pt.
26 letter.pt.
27 editorial.pt.
28 comment.pt.

29 or/25-28
30 24 not 29
31 3 and 30
32 Beclomethasone/
33 budesonide/
34 bdp.ti,ab.
35 (beclometasone or beclomethasone or budesonide or ciclesonide or fluticasone or mometasone).mp.
36 (pulmicort or flixotide or asmanex or novoliser or becotide or asmabec or belclazone or cyclocaps or becodisks or filair or qvar or pulvinal or aerobec or becloforte or viatris or alvesco).mp.
37 32 or 33 or 34 or 35 or 36
38 31 and 37
39 limit 38 to (humans and english language)

Quality of life search strategy: Asthma in adults and children

This search strategy was translated and run in:
MEDLINE (Ovid)
MEDLINE in Process (Ovid)
EMBASE
Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (CDSR and CCTR)
Ovid MEDLINE(R) 1966-to May Week 1 2006>. searched 11/5/2006; update search run on 6/10/06

1 exp Asthma/
2 asthma.ti,ab.
3 1 or 2
4 value of life/
5 quality adjusted life year/
6 quality adjusted life.ti,ab.
7 (qaly$ or qald$ or qale$ or qtime$).ti,ab.
8 disability adjusted life.ti,ab.

9 daly$.ti,ab.
10 health status indicators/
11 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab.
12 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab.
13 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab.
14 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab.
15 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab.
16 (euroqol or euro qol or eq5d or eq 5d).ti,ab.
17 (hql or hqol or h qol or hrqol or hr qol).ti,ab.
18 (ACQ or asthma control questionnaire$).ti,ab.
19 (AQLQ or asthma quality of life questionnaire$).ti,ab.
20 (SGRQ or (St George$ adj5 Respiratory Questionnaire$)).ti,ab.
21 (hye or hyes).ti,ab.
22 health$ year$ equivalent$.ti,ab.
23 health utilit$.ab.
24 (hui or hui1 or hui2 or hui3).ti,ab.
25 disutil$.ti,ab.
26 rosser.ti,ab.
27 quality of well being.ti,ab.
28 quality of wellbeing.ti,ab.
29 qwb.ti,ab.
30 willingness to pay.ti,ab.
31 standard gamble$.ti,ab.
32 time trade off.ti,ab.
33 time tradeoff.ti,ab.
34 tto.ti,ab. (221)
35 (index adj2 well being).mp.

36 (quality adj2 well being).mp.
37 (health adj3 utilit$ ind$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
38 ((multiattribute$ or multi attribute$) adj3 (health ind$ or theor$ or health state$ or utilit$ or analys$)).mp.
39 quality adjusted life year$.mp.
40 (15D or 15 dimension$).mp.
41 (12D or 12 dimension$).mp.
42 rating scale$.mp.
43 linear scal$.mp.
44 linear analog$.mp.
45 visual analog$.mp.
46 (categor$ adj2 scal$).mp.
47 or/4-46
48 (letter or editorial or comment).pt.
49 47 not 48
50 3 and 49
51 limit 50 to english language

Adverse events searches: Corticosteroids for asthma

This search strategy was translated and run in:
MEDLINE (Ovid)
MEDLINE in Process (Ovid)
EMBASE
Cochrane Database of Systematic Reviews
Cochrane Central Register of Controlled Trials and DARE.
Database: Ovid MEDLINE(R) <1966 to May Week 3 2006>; searched 26-05-06

1 exp Asthma/
2 asthma.ti,ab.
3 1 or 2
4 (beclometasone or beclomethasone or budesonide or ciclesonide or fluticasone or mometasone).mp.

5 (pulmicort or flixotide or asmanex or novoliser or becotide or asmabec or belclazone or cyclocaps or becodisks or filair or qvar or pulvinal or aerobec or becloforte or viatris or alvesco).mp.
6 Beclomethasone/ae, po, to
7 budesonide/ae, po, to
8 Adrenal Cortex Hormones/ad, ae, po, to [Administration & Dosage, Adverse Effects, Poisoning, Toxicity]
9 exp *Pregnenediones/ae, to [Adverse Effects, Toxicity]
10 steroid$.ti,ab.
11 (inhal$ or oral).ti,ab.
12 (toxicity or poisoning or adverse effects).fs.
13 10 and 11 and 12
14 4 and 12
15 5 and 12
16 6 or 7 or 8 or 9 or 13 or 14 or 15 (
17 (safe or safety).ti,ab.
18 side effect$.ti,ab.
19 tolerability.ti,ab.
20 toxicity.ti,ab.
21 (adverse adj3 (effect or effects or reaction or reactions or event or events or outcome or outcomes or consequence$)).ti,ab.
22 exp Dose-Response Relationship, Drug/
23 17 or 18 or 19 or 20 or 21 or 22
24 long term.ti,ab. (296250)
25 short term.ti,ab. (79427)
26 16 and 23 and 24 and 3
27 16 and 23 and 25 and 3

Healthcare resource use and asthma severity or symptom control searches

This search strategy was translated and run in (Ovid) MEDLINE , (Ovid) MEDLINE in Process and (Ovid) EMBASE

Ovid MEDLINE(R) <1966 to July Week 4 2006> Searched 02/08/2006

1	"healthcare resource use".mp.
2	exp Health Care Costs/
3	economics/ or exp resource allocation/
4	hcru.ab,ti.
5	health care utilisation.mp
6	1 or 2 or 3 or 4 or 5
7	"Anti-Asthmatic Agents"/
8	Asthma/
9	asthma$.ti,ab.
10	Asthma, Exercise-Induced/
11	7 or 8 or 9 or 10
12	"Drug Administration Schedule"/
13	"Needs Assessment"/
14	"Severity of Illness Index"/
15	(severe$ or severity).ti,ab.
16	(symptom$ adj3 control$).mp
17	(asthma adj3 control$).mp
18	exp disease management/
16	or/12-18
17	6 and 11 and 16

APPENDIX 4 : Systematic review of clinical effectiveness: Data extraction and quality assessment forms

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
Ref ID: 204 **Author:** Altintas *et al* **Year:** 2005 **Country:** Turkey **Study design:** Randomised trial **Number of centres:** 1 **Funding:** Not reported	**Random groups** **Group A:** *n* = 15 Drug(s): BUD Dose: 400µg/day Delivery: inhalation Duration: 1 yr **Group B:** *n* = 15 Drug(s): FP Dose: 250µg/day Delivery: inhalation Duration: 1 yr **A third control group** **Group C:** *n* = 30 Drug(s): NA Dose: NA Delivery: NA Duration: 1 yr **Run-in period:** Duration: NR ICS: NR Relief: NR **Additional treatment allowed:** Relief: NR Other: NR	**Number randomised:** 30 **Sample attrition/dropout:** Not reported **Sample crossovers:** Not reported **Inclusion/exclusion criteria:** ▪ Not reported. The study sample was children with moderate asthma that were followed up by the investigators. (Asthma was diagnosed according to guidelines for the diagnosis and management of asthma from the National Institutes of Health, National Heart, Lung & Blood Institute.) **Baseline characteristics:** *Summarising the group A and B, without including the third group C* ▪ Age: mean (range) = 10.1 (6-13) yr ▪ Male/female = 17/13 ▪ Symptom score = 5.6 (0.5) ▪ Pulmonary functions: mean (SE or SD) ▫ VC = 66.6 (8.7) ▫ PEFR = 62.4 (5.5) ▫ FEV_1 = 60.0 (9.4) ▪ Bone metabolism: mean ▫ Calcium (mg/dl) = 9.55 ▫ Phosphorus (mg/dl) = 4.35 ▫ ALP (IU/L) = 468.5 ▫ Bone mineral density (g/cm^2) = 0.615	**Primary measure:** ▪ Anthropometric measurements ▫ Body mass index ▫ Linear growth ▫ Growth rate ▪ Symptom score ▪ Pulmonary functions ▫ FVC ▫ PEFR ▫ FEV1 **Secondary measures:** ▪ Bone metabolism ▫ Serum calcium ▫ Serum phosphorus ▫ Serum ALP ▫ Bone mineral density ▪ Adrenal functions (basal serum cortisol level) **Method of assessing outcomes:** Not reported **Length of follow-up:** 1 yr

RESULTS

Outcomes [a]	Group A (*n*=15)	Group B (*n*=15)	*p*-value
FEV_1, % predicted values for height and age: *assuming reported as mean (SD)*	82.8 (10.0)	82.8 (10.0)	NA
PEFR, % predicted values for height and age: *assuming reported as mean (SD)*	82.5 (14.3)	82.5 (14.3)	NA
Symptom-free days			
Nocturnal awakenings			
Acute exacerbations			

RESULTS

Outcomes [a]	**Group A (n=15)**	**Group B (n=15)**	***p*-value**
Use of systemic corticosteroids			
Use of reliever medication			
Mortality			
QoL			
Adverse events – n (%) [b]			
Other [c]			
FVC, % predicted values for height and age: *assuming reported as mean (SD)*	85.3 (10.7)	85.3 (10.7)	NA
Symptom score: mean (SE or SD)	4.2 (0.4)	4.2 (0.4)	NA

[a] It looks incorrect as the symptom score and pulmonary functions before and after therapy for the two groups are identical including the SE/SD; the outcome extracted are at the end point (after treatment)

[b] Reported that the study didn't observed any side effects of ICs, and the study found that long term ICS treatment did not cause any serious side effects in children.

[c] Body mass index and weight percentiles did not change after one year in all groups (P>0.05). The mean increase in linear growth from the beginning to the first year of the therapy was statistically significant and similar in all groups (P<0.05). Growth rate (cm in 1 year) was 8.4 ± 4.6 cm (95%CI 6.07, 10.73) in group A and 8.2 ± 6.2 (95%CI 5.06, 11.34) in group B *[95%CIs were calculated by the reviewers assuming the reported values were presented as mean ± SD]. Outcomes which are not relevant to the review protocol are not extracted.*

METHODOLOGICAL COMMENTS

- **Allocation to treatment groups:** reported as randomised trial, but no further details about randomisation and allocation.
- **Blinding:** not reported
- **Comparability of treatment groups:** symptom score and pulmonary functions (VC, PEFR, and FEV1) at baseline are identical including SE or SD.
- **Method of data analysis:** used SPSS program for all statistical analysis. Analysis was performed by Mann Whitney-U and Wilcoxon tests. A P value < 0.05 was considered significant.
- **Sample size/power calculation:** not reported
- **Attrition/drop-out:** not reported

GENERAL COMMENTS

- **Generalisability:** applicable to children with moderate asthma. But not very clear as inclusion and exclusion criteria was not reported.
- **Outcome measures:** appropriate and objective
- **Inter-centre variability:** NA
- **Conflict of interests:** unknown

QUALITY CRITERIA FOR ASSESSMENT OF EXPERIMENTAL STUDIES

1. Was the assignment to the treatment groups really random?	Inadequate
2. Was the treatment allocation concealed?	Inadequate
3. Were the groups similar at baseline in terms of prognostic factors?	Inadequate (appears to be an error)
4. Were outcome assessors blinded to the treatment allocation?	Inadequate

QUALITY CRITERIA FOR ASSESSMENT OF EXPERIMENTAL STUDIES	
5. Was the care provider blinded?	Inadequate
6. Was the patient blinded?	Inadequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an intention to treat analysis?	Unknown
9. Were withdrawals and dropouts completely described?	Inadequate

From: NHS Centre for Reviews and Dissemination – Undertaking Systematic Reviews of Research on Effectiveness: Guidance for those Carrying Out or Commissioning Reviews (Report 4)
http://www.york.ac.uk/inst/crd/report4.htm

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
Ref ID: 214 **Author:** Malone *et al* **Year:** 2005 **Country:** USA and Canada **Study design:** Randomized, multi-centre, double-blind, active-controlled, parallel-group **Number of centres:** 79 **Funding:** GlaxoSmithKline	**Group A:** *n* = 101 Drug(s): FP/S Dose: 100/50µg b.i.d. Delivery: Advair Diskus Duration: 12 wks **Group B:** *n* = 102 Drug(s): FP Dose: 100µg b.i.d. Delivery: Flovent Diskus Duration: 12 wks **Run-in period:** Duration: 2wks ICS: baseline ICS was continued Relief: albuterol metered-dose inhaler for rescue use **Additional treatment allowed:** Relief: albuterol Other: not reported / unknown. (Oral or parenteral corticosteroids, cromolyn, nedocromil, or LABA were prohibited throughout the study. Also, the use of medications that could affect the course of asthma or interact with study medications, such as anticholinergics, anticonvulsants, or ß-adrenergic blockers, were prohibited throughout the study)	**Number randomised:** 203 **Sample attrition/dropout:** 35 withdrawals; 19 (19%) were from group A and 16 (16%) from group B. 7 of the 35 (2 v. 5) were due to worsening asthma. **Sample crossovers:** No **Inclusion criteria:** For screening: ▪ Age 4 – 11 yrs with asthma (defined by the American Thoracic Society criteria) ▪ History of asthma ≥2mths ▪ Were receiving ICS (BDP 252-336µg; triamcinolone acetonide 600-1000µg; flunisolide 1000µg; FP 88-250µg; or BUD 200-400µg, daily) at a consistent dose for ≥1mth before screening ▪ FEV_1 50 – 95% of the predicted for aged 6-11 yrs ▪ PEFR 50-95% of the predicted for aged 4 -5 yrs ▪ An increase in FEV_1 (for aged 6 - 11 yrs) or PEFR am (for aged 4 -5 yrs) of ≥12% within 30min of inhalation of 2-4 actuations of albuterol (180-360µg) or to have a historical documentation of ≥12% reversibility within the previous yr For randomization: ▪ A morning FEV_1 50 – 95% of the predicted for aged 6-11 yrs or a morning ▪ PEFR 50-95% of the predicted for aged 4 -5 yrs ▪ A daytime asthma symptom score of ≥1 (on a scale from 0-5) on ≥3 days or the use of albuterol on ≥3 days during the 7 days before the randomization visit ▪ Adequate compliance, defined as ≥70% compliance with diary card completion **Exclusion criteria:** ▪ A history of life-threatening asthma ▪ Hospitalization due to asthma ≥ 2	**Primary measure:** Adverse events **Secondary measures:** ▪ Asthma exacerbations or worsening asthma ▪ 2-hr serial post-dose FEV_1 (for aged 6-11 yrs) or 2-hr serial post-dose PEFR (for aged 4-5 yrs) after the first dose of study medication on treatment day 1 ▪ FEV_1 (for aged 6-11yrs) ▪ PEFR am & pm ▪ Daytime asthma scores ▪ 24-hr albuterol use **Method of assessing outcomes:** ▪ Clinic visit after 1, 2, 4, 8, and 12 wks of treatment ▪ Investigators were responsible for the detection, documentation, intensity evaluation, and causality evaluation of all adverse events ▪ Parents or guardians' diary: ▫ PEFR am & pm (measured before taking a dose of study medication or albuterol) ▫ Use of albuterol ▫ Daytime asthma symptom scores: 0 (no symptom) to 5 (severe symptoms that prevented normal daily activities) **Length of follow-up:** 12 wks

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
		times in the previous yr ▪ A significant concurrent disease (e.g. cystic fibrosis, malignancy, or immunologic compromise) ▪ Recent upper or lower respiratory tract infection ▪ Current chickenpox or recent exposure to chickenpox in a non-immune patient ▪ Severe milk protein allergy ▪ Hypersensitivity to $ß_2$-agonist, sympathomimetic, or corticosteroid therapy ▪ Clinically significant abnormal laboratory test results ▪ A history or present use of tobacco ▪ A history or current presence of glaucoma or posterior sub-capsular cataracts ▪ Not to have used oral or parenteral corticosteroids for ≥1mth before screening, cromolyn or nedocromil for ≥1wk before screening, or LABA within 48hrs of screening. **Baseline characteristics:** ▪ Age, mean y =8.05 ▫ % 4 -5 yrs = 20 ▫ % 6- 11 yrs = 80 ▪ Male/female = 127/73 ▪ White: black: other, % = 70:19:11 ▪ Duration of asthma, mean y = 5.2 ▪ Aged 6 – 11 yrs ▫ FEV_1, L = 1.68 ▫ FEV_1, mean, % predicted = 80.45 ▫ FEV_1, mean, %reversibility = 19.3 ▫ Historical reversibility, %* = 46 ▪ Aged 4 -5 yrs ▫ PEFR, L/min = 142.5 ▫ PEFR, mean, % predicted = 86.65 ▫ PEFR mean, %reversibility = 27.9 ▫ Historical reversibility, %* = 20 ▪ Run-in ICS regimen, patients/daily mean dose [§] ▫ FP = 129/ 166.5µg ▫ BUD = 45/ 380µg ▫ BDP hydrofluoroalkane = 2/240µg	

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
		▫ BDP = 1/ 252µg ▫ Triamcinolone acetonide = 3/550µg * Evaluated at screening § The total daily dose of ICS was calculated in 93 patients in group A and 89 patients in group B.	

RESULTS

Outcomes	Group A (*n*=101)	Group B (*n*=102)	*p*-value
FEV_1, L (for aged 6-11y) at 12 wks[a]	1.88 (n=80 in this age group)	1.77 (n=83 in this age group)	
a.m. PEFR (L/min), mean (SE) change from baseline[b]	21.5 (±2.79)	16.9 (±2.85)	
p.m. PEFR (L/min), mean (SE) change from baseline[b]	21.5 (±2.43)	15.1 (±2.83)	
Asthma symptom score, mean (SE) change from baseline[b]	-0.6 (±0.10)	-0.5 (±0.12)	
% symptom-free days, mean (SE) change from baseline[b]	24.4 (±4.10)	21.2 (±4.09)	
Nocturnal awakenings			
Acute exacerbations: ▪ patients with exacerbation occurred, n (%) ▪ withdrawal due to exacerbations, n (%)	 3 (3) 2 (2)	 8 (8) 5 (5)	
Use of systemic corticosteroids			
Use of reliever medication (puffs/24 hr), mean (SE) change from baseline[b]	-0.5 (±0.22)	-0.4 (±0.19)	
Mortality			
QoL			
Adverse events – n (%): [c] ▪ any adverse event ▪ patients experienced at least 1 potentially study drug-related adverse event ▪ withdrawal due to adverse event ▪ patients with orpharyngeal candidiasis occurred	 60 (59) 13 (13) 3 (3) 4 (4)	 58 (57) 9 (9) 0 (0) 0 (0)	
Other [d]			

a data taken from linked abstract [215]
b data taken from linked abstract[216]
c data on detailed types of adverse events available in table 2 in the paper.
d not relevant

METHODOLOGICAL COMMENTS

- **Allocation to treatment groups:** randomised allocation, but no further details.
- **Blinding:** double-blind. (The cardiologist accessing ECGs were blinded to treatment assignment)
- **Comparability of treatment groups:** reported as comparable at baseline with respect to patient demographics and pulmonary function.
- **Method of data analysis:** only that it was analysed on an ITT basis was reported.

METHODOLOGICAL COMMENTS
▪ **Sample size/power calculation:** no power calculations were performed (because it was a safety study); but estimated that approximately 100 patients in each treatment arm was sufficient to evaluate the safety of the treatment for group A compared to the treatment for group B. ▪ **Attrition/drop-out:** 35 withdrawals; 19 (19%) were from group A and 16 (16%) from group B. 7 of the 35 (2 v. 5) were due to worsening asthma. Intention-to-treat population (defined as all patients who were randomised and received at least one dose of study drug) was used for all demographic and safety measures except for cortisol excretion.

GENERAL COMMENTS
▪ **Generalisability:** relatively inclusive criteria; not applicable to ICS naive patients. ▪ **Outcome measures:** appropriate and objective ▪ **Inter-centre variability:** not reported; unclear whether randomisation was stratified by centre. ▪ **Conflict of interests:** study supported and 4 authors from GlaxoSmithKline.

QUALITY CRITERIA FOR ASSESSMENT OF EXPERIMENTAL STUDIES	
1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Unknown
5. Was the care provider blinded?	Adequate
6. Was the patient blinded?	Adequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an intention to treat analysis?	Adequate
9. Were withdrawals and dropouts completely described?	Adequate

From: NHS Centre for Reviews and Dissemination – Undertaking Systematic Reviews of Research on Effectiveness: Guidance for those Carrying Out or Commissioning Reviews (Report 4)
http://www.york.ac.uk/inst/crd/report4.htm

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
Ref ID: 199 **Author:** O'Byrne *et al* **Year:** 2005 **Country:** international (22 countries) **Study design:** randomised, parallel group, double-blind **Number of centres:** 246 **Funding:** AstraZeneca (Lund, Sweden)	**Group A:** *n* = 925 Drug(s): BUD/F Dose: 80/4.5µg b.i.d. 80/4.5µg as needed Children given half dose Delivery: Turbuhaler Duration: 52 wks **Group B:** *n* = 909 Drug(s): BUD/F Dose: 80/4.5µg b.i.d. terbutaline 0.4mg as needed Children given half dose Delivery: Turbuhaler Duration: 52 wks **Group C:** *n* = 926 Drug(s): BUD Dose: 320µg b.i.d. plus terbutaline 0.4mg as needed Children given half dose Delivery: Turbuhaler Duration: 52 wks **Run-in period:** Duration: 14-18 days ICS: as previously prescribed Relief: terbutaline **Additional treatment allowed:** Nasal glucocorticoids; antihistamines (except terfenadin); disodium cromoglycate and/ or nasal nedocromil sodium; immunotherapy (at constant dose during 90 days pre enrolment); other medication given at investigators discretion. Severe	**Number randomised:** 2760 Sample attrition/dropout: *n* = 412 (67 adverse events; 111 eligibility criteria not fulfilled; 47 lost to follow-up; 187 other) **Sample crossovers:** NR **Inclusion/exclusion criteria:** **Inclusion criteria:** ▪ age ≥4 ▪ 1 ≥ exacerbations in previous yr ▪ adults maintained on ICS 400 - 1000µg/day and children maintained on 200 – 500µg/day in previous yr ▪ constant dose of ICS ≥ 3 mths ▪ FEV_1 60-100% predicted ▪ reversibility: FEV_1 ≥12 ▪ For Rx ≥12 inhalations for adults and or ≥ 8 for children during last 10 days of run in. ▪ **Exclusion criteria:** ▪ During run in: ▪ For Rx10 ≥ inhalations reliever medication on any one day (7 ≥ for children) ▪ additional exacerbations **Baseline characteristics:** **Baseline characteristics:** ▪ mean age (range) = 36 (4-79) ▪ male: female = 1231:1529 ▪ 4-11 yrs, n (%): 341 (12%) ▪ mean duration of asthma = 9 yrs (range:0-69) ▪ FEV1 (L): 2.12 (range: 0.62-4.50) ▪ FEV1 (% predicted): 73 (range: 43-108) ▪ FEV1 reversibility: 21% (range: 2%-89%) ▪ ICS dose at entry (µg/day): 598-620* ▪ LABA use at entry (n): 250-258 (28%) ‡ ▪ Reliever use, number of inhalations/day: 1.69-1.74 (range: 0.0-9.4) ▪ Reliever use, number of inhalations/night: 0.72 (range: 0.0-	**Primary measure:** Time to first severe exacerbation (defined as hospitalization emergency room treatment; oral steroid treatment (or an increase in ICS and/or other additional treatment for children aged 4-11 years) or AM PEFR<= 70% of baseline on 2 consecutive days). **Secondary measures:** ▪ PEFR (am & pm) ▪ FEV_1 ▪ time to first mild exacerbation (defined as AM PEFR<= 80% of baseline, ≥2 reliever inhalations/day above baseline or awakenings caused by asthma). ▪ asthma symptom scores (day/night) ▪ rescue medication use (day/night) ▪ symptom free days ▪ rescue medication free days ▪ asthma control days ▪ nocturnal awakenings ▪ mild exacerbation days ▪ height (children only) ▪ adverse events **Method of assessing outcomes:** ▪ Clinic assessments at beginning and end of run-in and1,3,6,9,12 months ▫ PEFR (am & pm) Mimi-Wright PEFR meter ▪ FEV_1 (spirometry at clinic visits) ▪ Daily patient diaries (symptoms, awakenings, effects and extra medication) ▪ Electrocardiogram, AM plasma cortisol, vital

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
	exacerbations treated with 10-days of oral prednisone (30mg/day)	6.6) ▪ Asthma symptom scale score (0-6): 1.5 (range: 0.0-6.0) ▪ Symptom free days (%): 23.5 (range: 0.0-100) ▪ Reliever free days (%): 8.4 (range: 0.0-100) ▪ Asthma control days (%): 5.6 (range: 0.0-90) ▪ Awakenings (% of nights): 20.9 (range: 0.0-100) * values=combination of metered and delivered doses ▪ ‡ includes combinations of ICS/LABA and LABA	signs (at clinic visits) ▪ Height measured using local procedures (before run-in, 6 and 12 months of treatment) **Length of follow-up:** none beyond 12 mths treatment period

RESULTS

Outcomes	**Group A (*n*=925)**	**Group B (*n*=909)**	**Group C (*n*=926)**	***p*-value**
FEV_1, mean[a] over 12 mths treatment period	2.51	2.43	2.41	<0.001[b]; <0.001[c]; 0.09[d;]
PEFR (L/min), mean[a] over 12 mths treatment period AM: PM:	 355 360	 346 349	 339 345	<0.001[b]; <0.001[c]; <0.001[d] <0.001[b;] <0.001[c]; <0.001[d]
Symptom-free days (%) mean[a] over 12 month treatment period	54	53	46	0.52[b]; <0.001[c]; <0.001[d]
Nocturnal awakenings, (% of nights) mean[a] over 12 month treatment period	9	12	12	<0.001[b]; <0.001[c]; 0.60[d]
Severe exacerbations including PEFR falls: patients with event (%)[e] Severe exacerbations resulting in medical intervention: patients with event (%)[e]	16 11	27 21	28 19	<0.001[b]; <0.001[c]; 0.74[d] <0.001[b]; <0.001[c]; 0.37[d]
Use of reliever (inhalations/day) mean over 12mths Use of reliever (inhalations/night) mean over 12mths	0.73 0.28	0.84 0.37	1.03 0.43	<0.001[b]; <0.001[c]; <0.001[d] <0.001[b]; <0.001[c]; 0.003[d]
Use of systemic corticosteroids (courses per patient) Children (4-11 yrs) Adults (12-80 yrs)	 0.05 0.19	 0.30 0.42	 0.38 0.25	NR
Mortality	NR	NR	NR	
QoL	NR	NR	NR	
1or more adverse events – n (%): 1or more serious adverse events - n (%)	496 (54%) 46 (5%)	475 (52%) 62 (7%)	528 (57%) 48 (5%)	0.58[b]; 0.99 [c] ; 0.03 [d]
Pharyngitis – n (%)	88 (10%)	88 (10%)	86 (9%)	0.93 [b]; 0.99 [c]; 0.87 [d]
Respiratory infection – n (%)	158 (17%)	144 (16%)	182 (20%)	0.49 [b]; 0.15 [c]; 0.03 [d]
Rhinitis –n (%)	80 (9%)	72 (8%)	76 (8%)	0.61 [b]; 0.80 [c]; 0.86 [d]

RESULTS

Outcomes	**Group A (*n*=925)**	**Group B (*n*=909)**	**Group C (*n*=926)**	***p*-value**
Bronchitis –n (%)	51 (6%)	61 (7%)	76 (8%)	0.29 [b]; 0.02 [c]; 0.25 [d]
Sinusitis –n (%)	43 (5%)	39 (4%)	33 (4%)	0.74 [b]; 0.29 [c]; 0.47 [d]
Headache –n (%)	31 (3%)	35 (4%)	42 (5%)	0.62 [b]; 0.19 [c]; 0.49 [d]
Tremor – n (%)	20 (2%)	18 (2%)	19 (2%)	0.87 [b]; 0.99 [c]; 0.99 [d]
Palpitation –n (%)	10 (1%)	11 (1%)	3 (<0.5%)	0.83 [b]; 0.09 [c]; 0.03 [d]
Tachycardia –n (%)	5 (0.5%)	4 (<0.5%)	3 (<0.5%)	0.99 [b]; 0.73 [c]; 0.72 [d]
Candidiasis	9 (1%)	6 (1%)	10 (1%)	0.61 [b]; 0.82 [c]; 0.45 [d]
Dysphonia	11 (1%)	13 (1%)	12 (1%)	0.69 [b]; 0.84 [c]; 0.84 [d]
Discontinuation due to respiratory events	7 (1%)	15 (2%)	14 (2%)	0.80 [b]; 0.13 [c]; 0.85 [d]
Other:- asthma control days (%)[f]	45	44	37	0.64[b]; <0.001[c]; <0.001[d]

a least squares mean from two-way ANOVA
b Group A *v*. Group B
c Group A *v*. Group C
d Group B *v* Group C
e p values based on the instantaneous risk of experiencing at least one severe exacerbation (Cox proportional hazard model).
f defined as a day with no symptoms (day or night), no awakenings caused by asthma, and no as-needed medication use

Comments

- Time to first medically managed severe exacerbation was significantly longer in the BUD/form maintenance + relief group (Group A) compared with the BUD/form + SABA (Group B) and BUD + SABA groups (Group C); HR = 0.50 (95% CI: 0.40, 0.64) and 0.55 (95% CI: 0.43, 0.70) respectively.
- The RR of severe exacerbation requiring medical management was reduced by 53% for BUD/form maintenance + relief compared with BUD/form + SABA; HR=0.47 (95% CI: 0.39, 0.57) and by 46% compared with BUD + SABA; HR=0.54 (95% CI: 0.44, 0.66) The effect of using BUD/form for maintenance + relief remained constant over time.
- Symptom measures improved in all groups compared in baseline in requirement for reliever medication treatment and night-time awakenings
- No clinically important differences in electrocardiogram, haematology, clinical chemistry, or urinalysis were observed between the treatment groups or over time.
- Children in both the BUD/form groups grew significantly more than those in the BUD + SABA group.

METHODOLOGICAL COMMENTS

- **Allocation to treatment groups:** block randomisation by computer-generated list with treatment stratified by age group in an 8:1 ratio (adults: children).
- **Blinding:** double-blind with respect to treatment group; unclear whether the outcome assessors were blinded.
- **Comparability of treatment groups:** the groups are reported to be comparable with regard to demographic and baseline disease characteristics. There appeared to be no baseline imbalance in patient characteristic across the treatment groups.
- **Method of data analysis:** the primary efficacy analyses of time to first severe asthma exacerbation was described using Kaplan-Meier plots and a log-rank test, with analysis of instantaneous risk described using a Cox proportional hazards model. Total number of severe exacerbations were compared using a Poisson regression model, with adjustments for over-dispersion. Secondary efficacy endpoints were evaluated by

METHODOLOGICAL COMMENTS

analysis of co-variance, with the baseline value as covariate and the mean daily data over the 12-month treatment period as the treatment mean. All hypothesis testing was two-sided, with p values of less than 5% considered significant.

- **Sample size/power calculation:** designed to have 80% power to detect a 23% reduction in exacerbation rate in any of the treatment groups.
- **Attrition/drop-out:** all patients who received at least 1 dose of study medication were included in the ITT analysis (for both efficacy and safety). The attrition rate was 15%, with 4% of randomised patients failing to meet the criterion for as-needed medication during the run-in period. Reasons for discontinuations were adverse events 2% (n=67); eligibility criteria not fulfilled 4% (n=111); lost to follow-up 2% (n=47) and other (not specified) 7% (n=187). The total n analysed for primary endpoint and safety was 2753, with LOCF for missing data. LOCF was not undertaken for three patients in Group A, one in Group B and one in Group C

GENERAL COMMENTS

- **Generalisability:** relatively inclusive eligibility criteria; not applicable to ICS-naïve populations or patients with mild asthma.
- **Outcome measures:** appropriately defined and objective
- **Inter-centre variability:** not reported; unclear whether randomisation was stratified by centre and whether centre was analysed as a covariate in the ANOVA model.
- **Conflict of interests:** study support and one author's had received previous funding from AstraZeneca.

QUALITY CRITERIA FOR ASSESSMENT OF EXPERIMENTAL STUDIES	
1. Was the assignment to the treatment groups really random?	adequate
2. Was the treatment allocation concealed?	unknown
3. Were the groups similar at baseline in terms of prognostic factors?	reported
4. Were outcome assessors blinded to the treatment allocation?	unknown
5. Was the care provider blinded?	unknown
6. Was the patient blinded?	unknown
7. Were the point estimates and measure of variability presented for the primary outcome measure?	adequate
8. Did the analyses include an intention to treat analysis?	partial
9. Were withdrawals and dropouts completely described?	partial

From: NHS Centre for Reviews and Dissemination – Undertaking Systematic Reviews of Research on Effectiveness: Guidance for those Carrying Out or Commissioning Reviews (Report 4) http://www.york.ac.uk/inst/crd/report4.htm

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
Ref ID: 218 **Author:** Van den Berg *et al* **Year:** 2000 **Country:** 9 countries **Study design:** Randomized, double-blind, double-dummy, parallel-group design **Number of centres:** 35 **Funding:** Glaxo Wellcome Research and Development	**Group A:** *n* = 125 Drug(s): FP/S Dose: 100/50µg b.i.d. Delivery: combination inhaler (dry power inhaler) Duration: 12 wks **Group B:** *n* = 132 Drug(s): FP + S Dose: 100 +50µg b.i.d. Delivery: concurrent separate inhaler (dry power inhaler) Duration: 12 wks **Run-in period:** Duration: 2 wks ICS: continued to take their regular inhaled corticosteroid Relief: salbutamol inhaler as required **Additional treatment allowed:** Relief: salbutamol as required for symptomatic relief Other: any other concurrent medication provided the dose remained constant.	**Number randomised:** 257 **Sample attrition/dropout:** 10 (4%) with 5 (2%) in each group **Sample crossovers:** Not reported **Inclusion criteria:** ▪ Aged 4 -11yrs ▪ Reversible airways obstruction ▪ Remained symptomatic on ICS treatment alone (BDP BUD, or flunisolide at dose of 400-500 µg/day, or FP at a dose of 200-250µg/day for at least 4 wks before the start of the study run-in period) ▪ A symptom score (day-time & night-time) of ≥1 on at least 4 of the last 7 consecutive days of the run-in period ▪ A mean PEFR (am) over the 7 days that was 50-85% of the PEFR measured 15min after inhaled salbutamol (400µg) ▪ PEFR≥50% of predicted normal **Exclusion criteria:** ▪ Had changed asthma medication or had taken salmeterol or any other long-acting $ß_{2\text{-agonists}}$ or oral $ß_{2\text{-agonists}}$ in the 4 wks before the start of the run-in period ▪ Had a lower respiratory tract infection ▪ Had taken oral, depot, or parenteral corticosteroids during the 4 wks before the run-in period ▪ Had received ≥2 courses of oral, depot, or parenteral corticosteroids within 12 wks of the run-in period ▪ Had suffered an acute exacerbation of reversible airways obstruction requiring hospitalization ▪ Unable to use a mini-Wright peak flow meter ▪ Had known hypersensitivity to inhaled corticosteroids, $ß_{2\text{-agonists}}$, or lactose ▪ Had received any investigational drug within the previous month ▪ Females who had reached menarche	**Primary measure:** ▪ Mean PEFR (am & pm) **Secondary measures:** ▪ FEV_1 ▪ Adverse events **Method of assessing outcomes:** ▪ Clinic assessment at beginning of the run-in and treatment periods, at 2, 4, 8, and 12 wks during treatment, and 2 wks after study treatment ended ▪ FEV_1*: when possible at each clinic visit; highest of three readings on each occasion ▪ Daily measurement on a diary card: ▫ PEFR (am)*: highest of three readings on each occasion; measured with a mini-Wright peak flow meter and recorded ▫ Day & night-time symptom scores ▫ Any use of salbutamol rescue medication ▪ Compliance with treatment: calculated from the number of doses used divided by the expected use. ** Measured before taking study medication or rescue salbutamol.* **Length of follow-up:** 14 wk

STUDY	TREATMENT	PARTICIPANTS	OUTCOMES
		Baseline characteristics: ▪ Mean age (range) = 7.6 (4 – 11) yrs ▫ 4 -5 yrs = 27 ▫ 6-7 yrs = 34 ▫ 8-11 yrs = 67.5 ▪ Sex (m/f) = 151/106 ▪ Mean duration of asthma ▫ <1 yrs = 10.5 ▫ 1-5 yrs = 72.5 ▫ >5 yrs = 45.5 ▪ Mean history of atopy, n = 84 ▪ Mean clinic PEFR, L/min ▫ % predicted = 243 ▫ Reversibility, % =10 ▪ Concurrent asthma medication (Ketotifen), n = 1	

RESULTS

Outcomes	Group A (*n*=)	Group B (*n*=)	*p*-value
FEV_1 [a], L : adjusted mean change from baseline at week 12	0.21	0.13	P = 0.052
PEFR, L/min: adjusted mean change from baseline at week 12 Am [b] Pm [c]	 33 29	 28 25	 P = 0.103 P = 0.164
Symptom-free days [d]			
Nocturnal awakenings			
Acute exacerbations			
Use of systemic corticosteroids			
Use of reliever medication [f]			
Mortality			
QoL			
Adverse events [g] – n (%): patients	13 (10)	6 (5)	
PEFR (am) predicted, %: adjusted mean change from baseline at week 12	15	13	P = 0.361
Patients had a median symptom score of zero, n (%): mean change from baseline at endpoint Daytime Night-time	 76 (61) 97 (78)	 78 (59) 100 (76)	 P = 0.904 P = 0.799

[a] The difference between the two treatment was not significant at week 12 (-0.08 L, 95% CI – 0.14 to – 0.01, P = 0.05) or at any other time points

[b] The adjusted change in mean morning PEFR between the two treatment groups at other time intervals was similar to that for weeks 1-12, expect at week 2 there was a significant difference in favour of combination therapy (- 9 L/min, 95% CI -15 to -3, P = 0.017)

[c] The adjusted change in evening PEFR for most other periods were similar to that for weeks 1-12, expect at week 2 there was a significant difference in favour of combination therapy (- 8 L/min, 95% CI -13 to -2, P = 0.027)

[d] There was no significant difference between the two groups in median percentages of symptom-free days and

RESULTS			
Outcomes	**Group A (*n*=)**	**Group B (*n*=)**	***p*-value**
nights during the 12 wks [f] There was no significant difference between the two groups in rescue-free days and nights during the 12 wks [g] Considered by investigator to be drug-related (*detailed adverse events reported in the table 3 in the paper*).			

METHODOLOGICAL COMMENTS

- **Allocation to treatment groups:** stated as randomised trial, but no details reported.
- **Blinding:** double-blind with respect to the interventions.
- **Comparability of treatment groups:** reported as the two treatment groups were similar with respect to demographic characteristics, history of asthma, and baseline lung function.
- **Method of data analysis:** treatment groups were defined as equivalent if the 90%CI for the difference between mean PEFR (am) during combination and concurrent therapy was within ± 15 L/min. All tests were carried out at the two-sided 5% level of significance. PEFR and FEV1 values were analysed using analysis of covariance, adjusting for baseline, age, gender, and country. Centres were grouped by country to avoid the effects of too few patients in any one centre. Symptom scores and use of rescue medication were analysed using the Van Elteren extension to the Wilcoxon rank sum test.
- **Sample size/power calculation:** not reported
- **Attrition/drop-out:** 10 (4%) patients withdrew with 5 (4%) from each treatment group; 2 (2%) patients withdrew from each group due to adverse events. Analyses were performed on an intent-to-treat basis.

GENERAL COMMENTS

- **Generalisability:** relatively inclusive eligibility criteria; not applicable to ICS-naïve population.
- **Outcome measures:** appropriate and objective
- **Inter-centre variability:** not reported; no stratification of randomisation by centre described
- **Conflict of interests:** supported by Glaxo Wellcome Research and Development and one author from it

QUALITY CRITERIA FOR ASSESSMENT OF EXPERIMENTAL STUDIES	
1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Unknown
5. Was the care provider blinded?	Unknown
6. Was the patient blinded?	Adequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analyses include an intention to treat analysis?	Adequate
9. Were withdrawals and dropouts completely described?	Adequate

From: NHS Centre for Reviews and Dissemination – Undertaking Systematic Reviews of Research on Effectiveness: Guidance for those Carrying Out or Commissioning Reviews (Report 4) http://www.york.ac.uk/inst/crd/report4.htm

APPENDIX 5 : Systematic review of clinical effectiveness: List of studies from updated literature search to be included in any future update of the assessment report

RCTs

Pohunek P, Kuna P, Jorup C, De BK. Budesonide/formoterol improves lung function compared with budesonide alone in children with asthma. *Pediatric Allergy & Immunology* 2006;17:458-65.

Systematic reviews

Pedersen S. Clinical safety of inhaled corticosteroids for asthma in children: An update of long-term trials. *Drug Safety* 2006;29:599-612.

APPENDIX 6 : Systematic review of clinical effectiveness: Conference abstracts identified in the clinical effectiveness review

Geppe NA, Karpushkina AV, Kolossova NG, Yarovaya EB. the effects of fluticasone propionate /salmeterole 50/100ug bid in children with asthma versus beclometasone propionate 200ug BD fluticasone propionate 100ug bid dry powder inhalers [Abstract]. *European Respiratory Journal* 2004;24:378s.

GlaxoSmithKline. A multicentre, randomised, double-blind, double-dummy, parallel group comparison of three treatments: 1) salmeterol/fluticasone propionate (SFC) (50/100mcg strength) bd via DISKUS/ACCUHALER inhaler, 2) fluticasone propionate 200mcg bd via DISKUS/ACCUHALER inhaler, 3) fluticasone propionate 100mcg bd via DISKUS/ACCUHALER inhaler in children aged 4-11 years with asthma. *www clinicalstudyresults org* 2004.

Mokina NA, Geppe NA. The experience of study of comparative efficiency of steroid fluticasone and becla metasone at children [Abstract]. *European Respiratory Journal* 2004;24:165s.