Clinical and Cost Effectiveness of Inhaler Devices used in the Routine Management of Chronic Asthma in Older Children

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ABOUT 'HOME UNIT'

Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield, with support from the NHS Executive Trent. Members of staff in the Sheffield Unit, based in the School of Health and Related Research (ScHARR), have been engaged in reviewing the effectiveness and cost-effectiveness of health care interventions in support of the National Institute of Clinical Excellence.

In order to share expertise on this work, we have set up a wider collaboration, InterTASC, with units in other regions. These are the Wessex Institute for Health Research and Development, Southampton University, The University of Birmingham Department of Public Health and Epidemiology, The Centre for Reviews and Dissemination, University of York.

CONTRIBUTIONS OF AUTHORS

Dr Jean Peters led the review of clinical effectiveness and undertook the review of background information.

Dr Matt Stevenson undertook the economic analysis.

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Dr Jennifer Lim undertook the selection of studies and data extraction for the review of clinical effectiveness.

Ms Sarah Smith undertook the review of ease of use, patient/carer preference and compliance.

CONFLICTS OF INTEREST

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None of the authors have any financial interests in the companies producing or marketing asthma Inhalers.

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SUMMARY

Description of proposed service

This review examines the clinical and cost effectiveness of hand held inhalers to deliver medication for the routine management of chronic asthma in children aged between five and fifteen years.

Epidemiology and background

Asthma is a common disease of the airways, with a prevalence of treated asthma in five to fifteen year olds of around 12% and actual prevalence in the community as high as 23%. Treatment for the condition is predominantly by inhalation of medication. There are three main types of inhaler device, pressurised metered dose, breath actuated, and dry powder, with the option of attachment of a spacer to the first two devices under some prescribed circumstances. Two recent reviews have examined the clinical and cost effectiveness evidence on inhaler devices but one was for children aged under five and in the second the comparison made was between pressurised metered dose inhalers and other types only.

Number and quality of studies, and direction of evidence

Fourteen randomised controlled studies were identified that looked at the clinical effectiveness of inhaler devices for delivering β_2-agonists and a further seven delivering corticosteroids and one delivering cromoglycate. Overall, there were no differences in clinical efficacy between inhaler device with the exception that a pressurised metered dose inhaler with a spacer appeared to be more effective than one without. Seven randomised controlled trials examined the impact on clinical effectiveness of using a non CFC propellant in place of a CFC one in metered dose inhalers, both pressurised and breath activated, although only one study considered the latter type. No differences were found between inhalers containing either propellant. A further 30 studies of varying quality, from ten randomised controlled trials to non-controlled studies, were identified that looked at impact of use by, and preference for, inhaler type, and adherence in children. Differences between the studies and limitations in comparative data between different inhaler device types, make it difficult to draw any firm conclusions from this evidence.

Summary of benefits

There are no obvious benefits for one inhaler device type over another for use in children aged five to fifteen.

Costs and cost/QALY

Two approaches have been taken, a cost-minimisation approach and a QALY threshold approach. In the QALY threshold approach, additional QALYs that each device must produce compared with a cheaper device to achieve an acceptable cost per QALY have been calculated. Using the cheapest and

most expensive devices for delivering 200 ug of beclamathasone per day and a threshold of five thousand pounds the largest QALY needed was 0.008088. With such small QALY increase no intervention can be categorically rejected as not cost effective.

Notes on generalisability of findings

The majority of studies were carried out with children with mild to moderate asthma and therefore the findings may not be generalisable to those at the more severe end of the spectrum of the disease. The findings may not be generalisable to all inhaler devices delivering all β_2-agonists as there were few studies that used the long acting β_2-agonists.

Need for further research

Many of the previous studies are likely to have been under-powered. Further clinical trials with a robust methodology, sufficient power and qualitative components are needed to demonstrate any differences in clinical resource use and patients' asthma symptoms. Further studies should also include the behavioural aspects of patients towards their medication and its delivery mechanisms. It is acknowledged that sufficient power may prove impractical due to the large numbers of patient required.

LIST OF ABBREVIATIONS

ACORN	A classification of restricted neighbourhood
AMP	Adenosine 3',5' monosphate
AUC	area under the curve
BDP	Beclamethasone dipropionate
BTS	British Thoracic Society
CFC	chlorofluorocarbon (pMDI propellant)
DPI	dry powder inhaler
DTB	Drug and Therapeutics Bulletin
EIB	Exercise induced bronchoconstriction
FEF_{25-75}	maximum expiratory flow over 25% to 75% of expiration
FEV_1	maximum volume of air expired in first second of expiration (from maximum capacity)
FEV_{25-75}	maximum expiratory volume over mid expiration
FVC	forced vital capacity
HFA	hydrofluoroalkane (pMDI propellant, replacement for CFC)
ITT	intention to treat analysis
l/min	litres per minute
LYG	life years gained
MDI	metered dose inhaler
PEF	peak expiratory flow
PIF	peak inspiratory flow
PEFR	peak expiratory flow rate
PIFR	peak inspiratory flow rate
PP	per protocol analysis
pMDI	pressurised metered dose inhaler
QALY	quality adjusted life year

DEFINITION OF TERMS

Chronic asthma – experience of the disease at all times except when experiencing an acute episode.

1. AIM OF THE REVIEW

This review examines the clinical and cost effectiveness of manual pressurised metered dose inhalers, breath actuated metered dose inhalers, and breath actuated dry powder inhalers, with and without spacers as appropriate, to deliver medication for the routine management of chronic asthma in children aged between five and fifteen.

2. BACKGROUND

2.1 DESCRIPTION OF UNDERLYING HEALTH PROBLEM

2.1.1 Definition of the condition

Asthma is a common chronic inflammatory reversible disease of the airways associated with recurrent day to day symptoms and acute exacerbations. It affects the lower airways manifesting as airway obstruction with mucosal inflammation as a major contributor. The resultant narrowing (bronchoconstriction) of the airways leads to a reduction in the flow of gases between the air and lung alveoli resulting in symptoms of wheeziness and breathlessness. The condition can be triggered by a variety of environmental factors such as infection, allergy, airborne chemicals and also exercise. The degree of severity seen in the disease is broad and the condition is the cause of considerable morbidity and a rare cause of death.

Chronic asthma

Childhood asthma morbidity can be divided into:

- Infrequent episodic asthma – this constitutes up to 75% of the childhood asthmatic population and is associated with episodes occurring less than once every 4-6 weeks, minor wheezing after heavy exertion, no interval symptoms, and normal lung function between episodes. Prophylactic therapy is not usually needed for such patients.

- Frequent episodic asthma – this constitutes about 20% of the asthma population and is associated with somewhat more frequent attacks and wheezing on moderate exercise, which can be prevented by pre-dosing with β_2-agonists. Symptoms occur less frequently than once a week, and there is normal or near normal lung function between episodes. Prophylactic treatment is usually necessary.

- Persistent asthma - this affects roughly 5% of children with asthma and is associated with frequent acute episodes, wheezing on minor exertion, and interval symptoms requiring β_2-agonist drugs more than three times per week because of either night wakening or chest tightness in the morning. There is nearly always evidence of airflow limitation between episodes. Prophylactic treatment is essential.[1]

Acute asthma

At any of these three levels of chronic morbidity a child may also suffer acute episodes of asthma. Acute episodes range from mild in which there will be cough, audible wheezing, but peak expiratory flow (PEF) or FEV_1 will be above 75% of predicted values, and patients can speak in normal sentences between breaths, through to severe in which there will be severe distress, cyanosis, only one to three words possible between breaths and the patient will be chair or bed bound.[1]

The ability to use an inhaler correctly can be affected during episodes of acute wheeze[2] and in some acute episodes there will be problems with PEF and FEV_1. However, in children with chronic asthma not experiencing an acute episode, actual lung function should not restrict effective use of breath actuated inhaler devices.

2.1.2 Epidemiology

Incidence and Pathology

The prevalence of doctor-diagnosed asthma in England in children is around 10-23%. In eight to nine year olds in Sheffield, it was found to be 10%[3] and in 11 to 16 year olds in Nottingham, 13%.[4] A national survey across Great Britain of 12 to 14 year olds identified a prevalence of 21% in 1998[5] which endorses the findings of the Health Survey for England of 1995 to 1997.[6] This survey reported a prevalence of doctor[7]-diagnosed asthma of around 18% in girls aged 5 to 15 years and 24% in boys aged 5 to 12 years, dropping to 22% in those aged 15. However not all people who have asthma are currently being treated. Table 1 shows the number of those treated for asthma per 1,000 population for England and Wales, subdivided by age and sex.[8]

TABLE 1 PREVALENCE OF THOSE TREATED FOR ASTHMA PER 1,000 POPULATION

Age Band (years)	Male	Female
0 – 4	94.1	59.5
5 – 15	122.9	97.2
16 – 24	70.7	81.7
25 – 34	49.1	57.8
35 – 44	41.8	54.1
45 – 54	38.6	55.1
55 – 64	52.9	67.7
65 – 74	69.0	74.6
75 – 84	72.1	66.7
85+	54.6	42.4
All ages	66.2	67.7

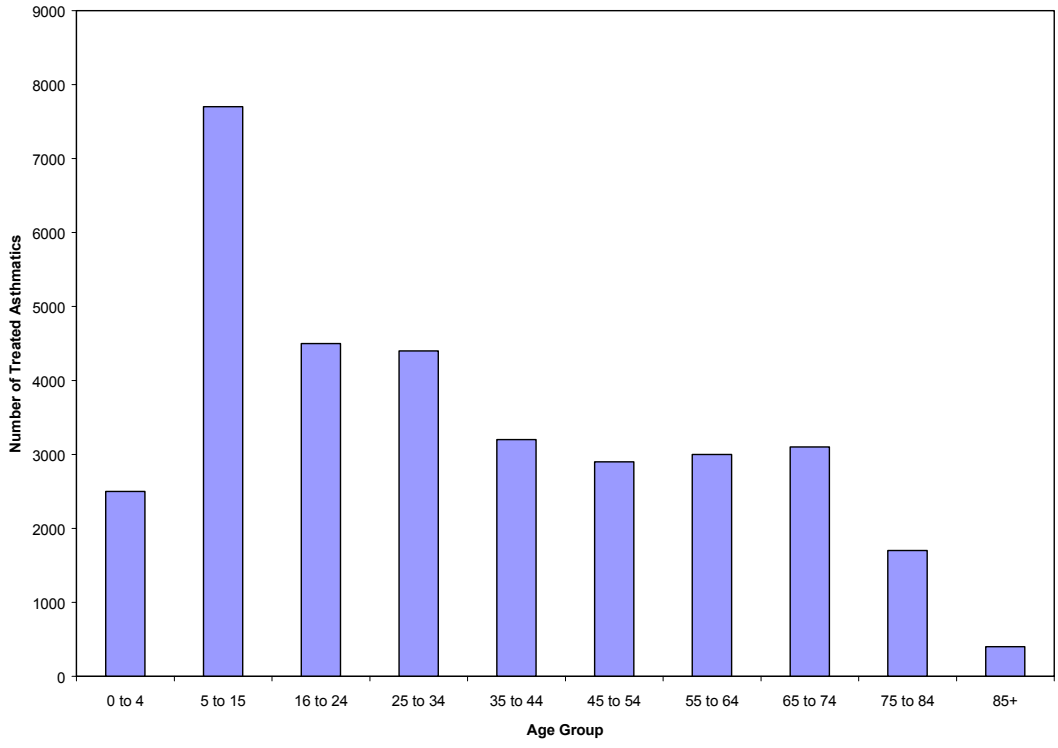
Since, in the UK, asthma treatment is strongly influenced by the guidelines of the British Thoracic Society (BTS)[9] which currently promote a step-wise management to increasingly severe asthma (see Appendix 1), the percentage of patients in each of the five BTS steps has been derived from Hoskins *et al.*[10] and is shown in Table 2.

TABLE 2 ESTIMATED PROPORTION OF PEOPLE WITH ASTHMA BY BTS STEP

	Percentage aged under 5 years	Percentage aged 5 – 15 years	Percentage aged 16 years and over
Medication below step 1	2%	11%	12%
BTS step 1	47%	20%	18%
BTS step 2	44%	44%	38%
BTS step 3	7%	19%	22%
BTS step 4	-	3%	9%
BTS step 5	-	3%	1%
Total	**100%**	**100%**	**100%**

Applying these data to a health authority of 500,000 people the numbers with asthma in each age range has been estimated. These are shown in Figure 1.

FIGURE 1 ESTIMATED NUMBER TREATED FOR ASTHMA IN A HEALTH AUTHORITY SERVING A POPULATION OF 500,000



Using the prevalence rate for patients treated with asthma and a standard population profile, in a district of 500,000 people,[11] there would be 33,500 expected asthma sufferers, distributed by age band and BTS step as shown in Table 3.

TABLE 3 EXPECTED NUMBER OF PEOPLE WITH ASTHMA, BY AGE BAND AND SEVERITY, IN A HEALTH AUTHORITY

	Aged 0 – 4 years	Aged 5 – 15 years	Aged 16+ years
Medication below step 1	57	845	2,790
BTS step 1	1,204	1,536	4,184
BTS step 2	1,147	3,379	8,834
BTS step 3	172	1,459	5,114
BTS step 4	0	230	2,092
BTS step 5	N/A	230	232
Total	**2,580**	**7,679**	**23,246**

2.1.3 Significance in terms of ill-health

Since there is no cure for asthma, once a child has a diagnosis they have a chronic persistent condition that manifests with different degrees of severity and with occasional episodes of acute symptoms. The degree of severity is assessed in terms of symptoms and reduction in lung function and the goal of treatment therefore is to achieve optimal control of the disease by preventing chronic and troublesome symptoms, maintaining near 'normal' lung function and normal activity levels, and preventing recurrent exacerbations and acute episodes, in order to maximise the quality of life for that individual and satisfaction with their care.[12] The ability to provide an early, effective treatment is also particularly important in children because it may provide longer-term advantages, both in terms of improved management of the disease and reductions in the social burden of disease caused through lost school days and reduced activity levels.[13,14,15,16]

2.2 CURRENT SERVICE PROVISION

Pharmacological therapy is aimed at reversing and preventing airway inflammation, managing acute exacerbations and relieving symptoms. Drugs used to treat respiratory airway disease can be administered systemically or topically. The advantage of the latter route is that smaller amounts of drug are required to produce a beneficial effect, with smaller drug quantities reducing the potential for adverse effects, and the drug acts more quickly. Topically delivered therapy is usually through the inhaled route with devices delivering drugs such as β_2-agonists, corticosteroids and cromoglycate-like drugs in various doses. The use of increasing doses of inhaled corticosteroids used to be the mainstay of preventive therapy. However the trend is now towards trying to minimise the dose of inhaled corticosteroids where possible, through the use of additional therapies such as β_2-agonists or oral leukotriene antagonists, because of persisting concerns of potential side effects associated with high doses of corticosteroids. Currently there is a number of different inhaler devices available that can deliver a range of drugs for the treatment of asthma in children aged five to fifteen years.

2.2.1 Evidence and guidelines to inform current service provision

A recent Cochrane systematic review examined the effectiveness of pressurised metered dose inhalers (pMDIs) with holding chambers compared with wet chamber nebulisers to deliver β_2-agonist medications for acute asthma[17] whilst a recent HTA report considered the clinical and cost effectiveness of inhaler devices for children under five with chronic asthma.[18] Finally, Brocklebank *et al*[19] have looked at pMDI devices compared with alternative inhaler delivery systems for managing asthma and chronic obstructive pulmonary disease, in patients of all ages. In their systematic review, they considered with respect to asthma

- the relationship between in-vitro measurements and in-vivo deposition measured by scintigraphy
- the relationship between in-vitro measurements and clinical effect measured by lung function
- the delivery of corticosteroids by hand-held inhalers for the treatment of stable asthma in children and adults
- the delivery of short-acting β_2-agonist bronchodilators by hand-held inhalers for the treatment of stable asthma in children and adults
- the delivery of any short-acting bronchodilators using a nebuliser compared to any hand-held inhaler (usually a pMDI) in stable asthma in children and adults
- inhaler technique with different inhaler devices.

2.2.2 Guidelines on asthma management

A number of guidelines have been developed with respect to asthma over the last few years. Of these, there are three of which clinicians and other health care professionals working with patients with asthma are most likely to be aware:

- British Thoracic Society (BTS) Guidelines for the Management of Asthma.[9]
- Scottish Intercollegiate Guideline Network (SIGN) guidelines[20] which have information on the primary care management of asthma. They are currently developing a new guideline on asthma in conjunction with the BTS. This is due to be published in summer 2002. NICE was considering the development of a guideline on asthma, but instead will await publication of this guideline and will work with SIGN and the BTS on any subsequent amendments.
- National Heart, Lung, and Blood Institute (U.S) Guidelines for the Diagnosis and Management of Asthma.[12]

The British Thoracic Society Guidelines[9] are those most commonly used in UK practice.

BTS Guidelines 1997

These were revised from guidelines published in 1993 and are not explicitly evidence-based. The guidelines recommend a five step approach to management of chronic asthma in adults and children starting with bronchodilators and introducing anti-inflammatory agents and increased doses of these if control is not maintained at the previous drug and dose regimen. For most of the recommendations school children (aged five years and over) and adults are considered to require a similar therapeutic approach (see Appendix 1).[9]

National Heart, Lung and Blood Institute, USA 1997

These guidelines were produced by an expert panel who revised and updated a 1991 set of guidelines. They also take a stepwise approach for managing asthma in children older than five years of age and adults, using four steps. However, these steps are defined in terms of symptoms, night-time symptoms and lung function rather than on level and type of medication required for control.[12]

2.2.3 Other Evidence

Drugs and Therapeutics Bulletins (DTB)

These are commissioned independent reviews produced by the Consumers' Association for Clinicians and Pharmacists. They are widely circulated to clinicians. The treatment of asthma using inhaled steroids in children was addressed in 1999[21] and in adults in 2000.[22] The choice of inhaler device for children was addressed but without any specific recommendations although inhaler devices themselves were also reviewed in 2000[23] and age-specific recommendations were then made (presented in Table 4).

TABLE 4 INHALER DEVICES: DTB AGE-SPECIFIC RECOMMENDATIONS

Age (years)	First choice	Second choice	Comments
0-2	pMDI+spacer+face mask	Nebuliser	Ensure optimum spacer use. Avoid 'open vent' nebulisers.
3-6	pMDI+spacer	Nebuliser	Very few children at this age can use a dry powder inhaler (DPI) adequately.
6-12 bronchodilators	pMDI+spacer or DPI or breath actuated pMDI		If using a DPI or breath actuated pMDI, also consider pMDI+spacer for exacerbations.
6-12 corticosteroids	pMDI+spacer	DPI or breath actuated pMDI for low dose corticosteroids only	May need to adjust dose if switching between inhalers. Advise mouth rinsing or gargling.
12+ bronchodilators	pMDI	DPI or breath actuated pMDI	Use pMDI if technique satisfactory. use large volume spacer in acute attack.
12+ corticosteroids	pMDI (+spacer for moderate or high doses)	DPI or breath actuated pMDI for low dose corticosteroids only	May need to adjust dose if switching between inhalers. Advise mouth rinsing or gargling.
All ages acute asthma	pMDI+spacer or nebuliser		Ensure optimum spacer use and appropriate dosing. Written instructions for what to do in acute asthma.

Third International Pediatric Consensus Statement on the Management of Childhood Asthma

Paediatricians with a special interest in pulmonology or allergy and clinical immunology met together in 1995 to develop clinically sound and practical guidelines for the management of childhood asthma that could be implemented in different health care systems with a reasonable chance of compliance. Their recommendations for management and treatment are based upon symptom presence and frequency in children (ages unstated). The report discusses the different inhaler devices available but makes no recommendations on specific use.[1]

However, even with the published evidence and guidelines, described above, available to inform current service provision, Brocklebank *et al.*[19] in their recent HTA systematic review on inhaler devices for asthma concluded that

> 'there appears to be a lack of consensus and guidance for the individual practitioner faced with a wide range of possible inhaler devices. The current guidelines are either vague, absent and where present, possibly contradictory'.

2.3 DESCRIPTION OF THE INTERVENTION

For use in a population of children aged five to fifteen with chronic asthma, this review considers three different inhaler device types: pressurised metered dose aerosol inhalers, breath-actuated metered-dose aerosol inhalers, and breath actuated dry powder inhalers. In addition it looks at the combined devices of spacers or extension tubes used with either pressurised metered dose or breath-actuated aerosol inhalers, and finally considers metered dose inhalers pressurised with either chlorofluorocarbon (CFC) or hydrofluoroalkane (HFA) propellants.

For the purpose of the review, the three different inhaler device types have been compared between types and also within type. In the tables in the following section information is provided on all the inhaler devices currently marketed in the UK[24] grouped by drug delivered (type and generics). Furthermore, for the purpose of the review, all comparisons reviewed have been limited to those in which the same generic drug is delivered at an equivalent dose level by all the inhaler types included in the comparison. Even within these constraints, there is some evidence that two chemically equivalent inhalers, salbutamol pMDIs, can result in statistically significant differences in therapeutic efficacy.[25]

Pressurised metered dose aerosol inhalers (pMDI)

A list of pMDI devices currently available is given in Table 5.

TABLE 5 PMDIs BY DRUG TYPE, FOR CHILDREN AGED 5-15 YEARS FOR ROUTINE MANAGEMENT OF CHRONIC ASTHMA

Drug type	Generic drug	Device brand name	Manufacturer	Users
Adrenoceptors -short acting β_2 agonists	Salbutamol	**Maxivent (cfc)**	APS	Children over 2 years
		Asmasal Spacehaler	*Medeva*	Children over 2 years
		Asmaven (cfc)	Berk	Children over 2 years
		Salamol (non cfc)	Baker Norton	Children over 2 years
		Aerolin Autohaler (cfc)	3M	Children over 2 years
		Airomir (non cfc)	3M	Children over 2 years
		Salbulin (non cfc)	3M	Children over 2 years
		Salamol Easi-Breathe (cfc)	Baker Norton	Children over 2 years
		Ventolin Evohaler (non cfc)	GlaxoSmithKline	Children over 2 years
	Terbutaline sulphate	Bricanyl (cfc)	AstraZeneca	Adults and children, no ages given
		Bricanyl (with spacer) (cfc)	AstraZeneca	Adults and children, no ages given
	Fenoterol hydrobromide	*Berotec 100*	*Boehringer Ingelheim*	
		Berotec 200	Boehringer Ingelheim	
	Reproterol hydrochloride	Bronchodil (cfc)	ASTA Medica	Adults and children aged 6 and over
Adrenoceptors -long acting β_2 agonists	Salmeterol	Serevent (cfc)	GlaxoSmithKline	Adults and children 4 and over
Other adrenoceptors	*Orciprenaline sulphate*	*Alupent*	*Boehringer Ingelheim*	(only tablets and syrup available in BNF 2001)
Antimuscarinic bronchodilators	Ipratropium bromide	Atrovent Aerosol (cfc)	Boehringer Ingelheim	Adults and children 1 month upwards
		Atrovent Forte (cfc)	Boehringer Ingelheim	
	Oxitropium bromide	Oxivent (cfc)	Boehrringer Ingelheim	Not recommended for children, no age given
Combined therapy	Ipratropium and salbutamol	Combivent (cfc)	Boehringer Ingelheim	Not for children under 12
	Ipratropium and fenoterol	Duovent (cfc)	Boehringer Ingelheim	Children over 6
Corticosteroids	Beclomethasone diproprionate	Beclazone (50, 100, 200) (cfc)	Baker Norton	Adults and children, no ages given
		Beclazone (250) (cfc)	Baker Norton	Not recommended for children (no ages given)
		Filair (50, 100, 200) (cfc)	Generics and 3M	Adults and children, no ages given
		Filair Forte (250) (cfc)	Generics and 3M	Not recommended for children (no ages given)
		Becotide (50, 100, 200) (cfc)	GlaxoSmithKline	Adults and children, no ages given
		Becloforte (250)	GlaxoSmithKline	Not recommended for

		(cfc)		children (no ages given)
		Becloforte Integra (with spacer)	GlaxoSmithKline	Not recommended for children (no ages given)
		Qvar (50, 100) (non cfc)	3M	Not recommended for children (no ages given)
	Budesonide	Pulmicort LS (cfc)	AstraZeneca	Adults and children, no ages given
		Pulmicort Aerosol	AstraZeneca	Adults and children, no ages given
		Pulmicort Aerosol (with spacer)	**AstraZeneca**	Adults and children, no ages given
	Fluticasone propionate	Flixotide aerosol (cfc)	GlaxoSmithKline	Children aged 4 upwards
		Flixotide Evohaler (50) (non cfc)	GlaxoSmithKline	Children aged 4 upwards
		Flixotide Evohaler (125, 250) (non cfc)	GlaxoSmithKline	Not indicated for children (ages unknown)
Compound preparations	Beclomethasone and salbutamol	Ventide (cfc)	GlaxoSmithKline	Adults and children, no ages given
	Fluticasone and salmeterol	**Seretide Evohaler (50, 125, 250) (non cfc)**	**GlaxoSmithKline**	Children over 12 and adults
Cromoglycate therapy	**Sodium cromoglycate**	**Cromogen**	**Baker Norton**	Adults and children, no ages given
		Cromogen Easi-Breathe (cfc)	**Baker Norton**	Adults and children, no ages given
		Intal (cfc)	Rhone-Poulenc Rorer	Adults and children, no ages given
		Intal with Syncroner (integral open-tube spacer) (cfc and hfa)	**Rhone-Poulenc Rorer (**Adventis Pharma Ltd submission)	Adults and children, no ages given
		Intal with Fisonair (large volume spacer) (cfc and hfa)	**Rhone-Poulenc Rorer (**Adventis Pharma Ltd submission)	Adults and children, no ages given
	Nedocromil sodium	Tilade (cfc)	Pantheon	Children over 6 and adults
		Tilade Syncroner (with spacer)	Pantheon	Children over 6 and adults
Compound preparations	Sodium cromglycate and salbutamol	**Aerocrom aerosol (cfc)**	**Castlemead**	Not recommended for children, no ages given
		Aerocrom Syncroner (cfc)	Castlemead	Not recommended for children, no ages given

Items in normal script were found in the recent Brocklebank *et al* systematic review[19] and the British National Formulary;[24] those in *italic* script were present in the review only;[19] and those in **bold** appear in the British National Formulary[24] but not the review.[19]
GlaxoSmithKline includes Allen and Hanburys.

In 1995 the majority of all prescriptions in England for inhaler medication containing short-acting β_2-agonists (83%) or inhaled steroids (78%) used a pMDI delivery mechanism.[26] Although for children, aged 5-12 in the West Midlands, bronchodilator prescriptions for pMDIs accounted for only 57%, with

the other 43% for DPIs.[27] The pMDI was initially introduced in 1956. It comprises a small portable plastic case in which is located an aerosol cannister containing up to 200 metered doses of the drug, propellants, traditionally CFCs, to aerolise the drug for inhalation, and lubricants. The inhaler is prepared by shaking to resuspend the drug particles and, for optimal use, the user takes a slow, deep inhalation to full capacity, actuating the device fractionally after the inhalation, and breath holds for ten seconds.

A number of common local side-effects, such as mild throat irritation, cough, mouth dryness and paradoxical bronchospasm, have been reported, associated with the CFC propellant and the lubricants.[28] However, following the decision taken at Montreal in 1987[29] CFC propellants are now being phased out and replaced with CFC free alternatives.

A number of problems have been identified that limit the effective use of pMDIs.

1. pMDIs generate many particles that are too large to reach the lower airway and are associated with significant oropharyngeal deposition.

2. The cold freon effect. With a standard metered dose inhaler (MDI), when the propellant hits the back of the oropharynx it causes the patient either to stop breathing completely or at least to breathe through the nose rather than the mouth. This is known to occur in 10 per cent of patients.[30]

3. Effective delivery of a dose with a pMDI requires co-ordination between actuation and dose inhalation. A number of users have problems in co-ordinating their inhalation with their action to release the drug from the pMDI and this can result in excessive deposition of the drug in the oropharynx.[28] Deposition of corticosteroids in the oropharynx is associated with local side effects such as oral candiasis.[28] and hoarseness due to muscle weakness. The two complications are known to be relatively rare in children, although they are more common in adults.

Spacer systems were developed to overcome these problems whilst breath actuated devices were designed to overcome the third problem specifically and a second problem which arises with the use of spacers, namely that of having to carry the spacer around with the inhaler for use during the day.

Spacers and tube extenders

Large volume spacer devices were introduced in the late 1980s to address some of the identified problems associated with pMDIs. Currently spacer devices are available as large, medium or small volume or as tube extenders.

Some spacers are integral to the pMDI and form a single unit whereas others have a flexible opening designed to accommodate all or most pMDIs available or only those of the same manufacturer. They all work on the same principle and with the same intended endpoint and outcome. Spacers address some of the problems that occur with pMDI use. However there is a number of factors

that can reduce the effectiveness of the pMDI spacer combination. A list of space devices not integral to specific inhalers is given in Table 6.

TABLE 6 SPACER DEVICES AVAILABLE AS UNITS FOR ATTACHMENT TO INHALER DEVICES

Name and manufacturer	Type	Use with
Able spacer (Clement Clarke)	Small volume device	Any pressurised aerosol inhalers
AeroChamber (3M)	Medium volume device, adult, child and infant models 145ml, rigid plastic tube. Compatible with all shapes of pMDI	Airomir, Salbulin, Qvar
Babyhaler A&H	Paediatric device	Becotide and Ventolin inhalers
E-Z Spacer, Vitalograph	Large volume, collapsible	Any pressurised aerosol inhalers
Haleraid, Glaxo Wellcome		Use with standard inhalers to increase pressure on inhaler
Nebuhaler, AstraZeneca	Large volume device, 750ml plastic pear-shaped cone	Bricanyl, Pulmicort
Volumatic, GlaxoSmithKline	Large volume device, 750mL resevoir	Compatible with all GlaxoSmithKline corticosteroid and bronchodilator MDIs

Electrostatic charge

Plastic spacers cause a rapid loss of delivery to the lungs of drug aerosol particles due to their deposition, through electrostatic charge, on the walls of the spacer. Elimination of the charge results in an increase in the aerosol half life thus reducing the criteria for good and swift co-ordination between actuation of the inhaler and inhalation, a key problem for younger children.

It has been proposed that the electrostatic charge on plastic spacers may be reduced in a number of ways, such as, coating the inside surface with anti-static paint, washing the spacer in detergent but not drying it with a cloth, building up the anti-static layer through repeated used of the pMDI, or neutralising the electrostatic charge with benzalkonium chloride.[31] However consideration would also need to be given to the stability and effectiveness of any coating used, the toxicity of chemicals employed in the coating and any interaction between drug delivered through the spacer and the coating.[31] The effectiveness of drug delivery through metal spacers, which are non electrostatic, has been compared with that through plastic. Currently metal spacers are not available in the UK, although the Nebuchamber, a stainless steel spacer device is being launched in the UK soon (Astra Zeneca submission).

Breath-actuated aerosol inhalers

Further development of pMDIs resulted in MDIs that combined the actions of actuation and inhalation thus eliminating the need for hand-lung co-ordination. The drug is released from the inhaler device when the user inhales through the mouthpiece in contrast to the user having to release the drug by pressing a button on the top of the device, with a finger and having to synchronise their inhalation with this action. With the pressurised component retained, little additional force is needed to trigger the device. Whilst some recommend that a spacer is also used with this inhaler type, to minimise the risk of oropharyngeal deposition, particularly with corticosteroid delivery, in practice spacers are rarely used with breath actuated devices. The propellant used in breath-actuated inhalers was originally CFC, but this is now being replaced by alternatives. There is one breath-actuated CFC free inhaler device currently licensed for use in the UK whilst a second, Easi-Breathe (Beclazone) is awaiting its UK licence (Norton Healthcare).

There are currently two breath actuated aerosol devices licensed for use in the UK, the Autohaler and Easi-Breathe. Details of the drugs delivered by each are given in Table 7.

Autohaler

The Autohaler contains a manually-operated lever, which when lifted, primes the inhaler through a spring-loaded mechanism, allowing the aerosol to be dispensed. The drug is released when the user breathes through the mouthpiece at a rate of 30 l/min or higher. The Autohaler is used to deliver a number of different bronchodilators: salbutamol, ipratropium bromide and oxitropium bromide, and one anti-inflammatory corticosteroid, beclomethasone dipropionate.

Easi-Breathe

This breath-actuated device consists of an aluminium cannister with a breath-operated mechanism, an actuator and a dust cap. The device is primed when the user opens the hinged cap and actuated in response to inhalation. It can be used to deliver salbutamol, a brochodilator and two anti-inflammatory drugs, the corticosteroid beclomethasone, and sodium cromoglycate.

TABLE 7 BREATH ACTUATED METERED DOSE INHALERS, BY DRUG TYPE, FOR CHILDREN AGED 5 – 15 YEARS FOR ROUTINE MANAGEMENT OF CHRONIC ASTHMA

Drug type	Generic drug	Device brand name	Manufacturer	Users
Short acting β agonists	Salbutamol	Aerolin Autohaler (cfc)	3M	Children over two
		Airomir Autohaler (non cfc)	**3M**	Children over two
		Salamol Easi-Breathe (cfc)	**Baker Norton**	Children over two
		Ventolin	**GlaxoSmithKline**	

		Easibreathe		
Antimuscarinic bronchodilators	Ipratropium bromide	Atrovent Autohaler (cfc)	Boehringer Ingelheim	Adults and children 1 month upwards
	Oxitropium bromide	Oxivent Autohaler	Boehringer Ingelheim	Not recommended for children, no ages given
Combined therapy	Ipratropium and fenoterol	Duovent (cfc) Autohaler	Boehringer Ingelheim	Children over 6
Corticosteroids	Beclomethasone	Aerobec (Autohaler 50, 100) (cfc)	3M	Adults and children, ages unknown
		AeroBec Forte Autohaler(250) (cfc)	3M	Not indicated for children, ages unknown
		Becotide Easibreathe (cfc)	**GlaxoSmithKline**	Adults and children, ages unknown
		Becloforte Easibreathe (cfc)	**GlaxoSmithKline**	Not indicated for children, ages unknown
		Qvar Autohaler (50, 100)	**GlaxoSmithKline**	Not recommended for children, no ages given
Cromoglycate therapy	Sodium cromoglycate	Cromogen Easi-Breathe	Baker Norton	Adults and children, ages not unknown

Items in normal script were found in the recent Brocklebank *et al* systematic review[19] and the British National Formulary;[24] those in *italic* script were present in the review only;[19] and those in **bold** appear in the British National Formulary[24] but not the review.[19]
GlaxoSmitKline includes Allen and Hanburys.

Chlorofluorocarbons (CFCs)

CFCs have long been used as propellants in pMDIs as they are non-inflammable and chemically inert. However, the free chlorine radicals produced by breakdown of CFCs in the stratosphere have been associated with the catalytic conversion of ozone to molecular oxygen with implications for depletion of the ozone layer, although medical aerosols use only 0.5% of worldwide consumption. The Montreal protocol,[29] signed by 27 nations in 1987, proposed a reduction in CFC production by 50% by 1999. This has subsequently been amended to achieve elimination of CFCs by 2000. Potential costs to the NHS of this transition of bronchodilators and corticosteroids from CFC to non-CFC versions have been estimated to be as high as £270m.[32] Metered dose inhaler manufacturers and pharmaceutical companies have been working over the past few years to produce non-CFC propellant metered dose inhalers. Alternative propellants now available include the hydrofluoroalkanes (HFAs).

There is some evidence that use of HFA propellants has led to improved lung deposition, and a reduction in dose may become possible when moving a child with stable asthma from a CFC to an HFA propelled inhaler.[33]

Dry powder inhalers (DPIs)

DPI devices contain the drug in the form of a dry powder. The devices lack propellants and other potentially harmful additives but the micronised drug in most DPI devices is mixed with a coarse carrier substance, usually lactose, which has been shown to cause airway irritation in some asthmatic patients.[34] DPIs work on the principle of mechanical inhalation driven by the user's own

inspiratory efforts, i.e. they are breath-activated by the user. The energy imparted to the system by the user is used to disperse the drug particles. The dispersion is aided through the use of a carrier in many of the devices, together with a variety of physical forces, dependent upon the device, such as turbulence and/ or a grill. Different DPIs require different minimum flow rates. However, with all current DPIs patients should inhale as forcefully as possible as it is the inspiratory effort rather than the resistance that is crucial to the effectiveness of the drug dispersal. In an acute asthma episode the level of inspiratory effort achieved may be insufficient but for children with a chronic stable condition, the minimum flow rate required should be achievable.

The mechanism in a DPI eliminates the requirement for synchronisation between actuation and inhalation, as required in pMDIs. Therefore, by design, the problems of co-ordination associated with pMDIs, although to some extent eliminated with the additional use of a spacer device, are not present in DPIs. In general DPIs and pMDIs are equally portable although the inclusion of a spacer device with the pMDI reduces the portablity of this as a delivery system.

A list of dry powder inhalers currently available is given in Table 8.

TABLE 8 DRY POWDER INHALERS BY DRUG TYPE FOR CHILDREN AGED 5-15 YEARS FOR ROUTINE MANAGEMENT OF CHRONIC ASTHMA

Drug type	Generic drug	Device brand name	Manufacturer	Users
Short acting β agonists	Salbutamol	Asmasal Clickhaler	Medeva	Children over two years
		Ventodisks Diskhaler	GlaxoSmithKline	
		Ventolin Accuhaler	GlaxoSmithKline	
		Ventolin Rotohaler	GlaxoSmithKline	
	Terbutaline sulphate	Bricanyl Turbohaler	AstraZeneca	
Long acting β agonists	Formoterol fumarate/ Eformoterol fumarate	Foradil	Novartis	Adults and children over 5
		Oxis Turbohaler	AstraZeneca	Adults and children over 12
	Salmeterol	Serevent Accuhaler	GlaxoSmithKline	Adults and children 4 and over
		Serevent Diskhaler	GlaxoSmithKline	Adults and children 4 and over
Antimuscarinic bronchodilators	Iprotropium bromide	Atrovent Aerocaps (with Atrovent Aerohaler)	Boehringer Ingelheim	Adults and children 1 month upwards
Cortcosteroids	Beclomethasone	Asmabec Clickhaler (50, 100)	Medeva	Adults and children, no ages given
		Asmabec Spacehaler 250	**Medeva**	
		Asmabec Clickhaler (250)	Medeva	Not recommended for children
		Becodisks Diskhaler	GlaxoSmithKline	Adults and children, ages not given
		Becotide Rotacaps (100, 200, 400) (with Rotahaler)	GlaxoSmithKline	Adults and children, ages not given
		Becloforte (400) (with Diskhaler)	GlaxoSmithKline	Not recommended for children, ages unknown
	Budesonide	Pulmicort Turbohaler	AstraZeneca	Adults and children, ages not given
	Fluticasone propionate	Flixotide Accuhaler	GlaxoSmithKline	Children 4-16 years (50-100mg only) and adults
		Flixotide Diskhaler	GlaxoSmithKline	Children 4 years upwards
Compound preparations	Beclomethasone and salbutamol	Ventide Rotacaps (with Rotahaler) including Paediatric Rotocaps	GlaxoSmithKline	Adult and paediatric, no ages given
	Fluticasone	Seretide (100)	GlaxoSmithKline	Children aged over 4 and

	and salmeterol	Accuhaler		adults
		Seretide (250 and 500) Accuhaler	GlaxoSmithKline	Children aged over 12 and adults
Cromoglycate therapies	Sodium cromoglycate	Intal Spincaps (with Spinhaler)	Rhone-Poulenc Rorer (Adventis Pharma Ltd submission)	Adults and children, no ages given
		Intal Syncroner	*Rhone-Poulenc Rorer*	

Items in normal script were found in the recent Brocklebank *et al* systematic review[19] and the British National Formulary;[24] those in *italic* script were present in the review only;[19] and those in **bold** appear in the British National Formulary[24] but not the review.[19]

Rotohaler and Spinhaler

Two DPIs, the Rotohaler and Spinhaler were introduced over ten years ago. Both are unit-dose DPIs with each unit dose of the drug blended with a carrier substance, lactose, and contained in a gelatin capsule. The drug is delivered when the gelatin capsule is pierced. Users have to carry a supply of capsules and load each one as required, which may be a difficult feat in someone experiencing an acute asthma attack or with limited dexterity, as in younger children. The Rotohaler, and its later derivative, the Diskhaler, which contains eight doses of individual plastic and foil bubble blister packs of the drug, and the Spinhaler operate under two different principles. The Rotohaler and Diskhaler operate on the cyclone principle whereas Spinhaler capsules are attached to a turbine that rotates upon inhalation.[34] Some powder is deposited on various parts of the inhaler and regular cleaning is advised with a brush or scraper. One problem with the older DPIs that use gelatin capsules is that the gelatin can soften in high heat and humidity making it harder to pierce.

Rotohalers and Diskhalers deliver either salbutamol (a short-acting β-agonist, a bronchodilator) or beclomethasone dipropionate (an anti-inflammatory corticosteroid). In addition the Diskhaler can deliver salmeterol (a long-acting β-agonist, a bronchodilator). The Spinhaler delivers sodium cromoglycate, a non-steroidal anti-inflammatory drug.

More recently other multi-dose DPIs incorporating new design approaches have been introduced.

Diskus/ Accuhaler

The Diskus is another multidose DPI. It is a disk-shaped plastic device approximately 9cm in diameter and 3cm wide. A built-in dosage counter counts down the number of doses left from a 60 dose pack. Each unit dose is packed in a foil blister and contains a mixture of dry powdered drug and lactose. All 60 doses are provided sequentially on a long coiled strip within the device. Movement of a small lever coupled with an audible and palpable click advances the strip and indicates that the dose is loaded and the inhaler ready for use. In the priming, the next blister foil is aligned for use and its lid is dislodged from the base foil and collected on a contracting wheel. As the user inhales, which can be from any orientation, air is drawn in through the device

and aerolises the blister contents releasing the drug through the mouthpiece. The empty strip is stored in a further storage area. When not in use, the mouthpiece is protected by an integral cover.[34]

The Diskus delivers ventolin and sameterol (short and long-acting β-agonists respectively, both bronchodilators), fluticasone propionate (an anti-inflammatory corticosteroid) and a combined prescription of salmeterol and fluticasone propionate.

The Diskhaler and Accuhaler are both unit dose devices whilst the Turbohaler and Clickhaler are both resevoir devices.

Turbohaler

The Turbohaler is a multidose DPI that contains 200 metered doses of the drug. Unlike other DPIs and pMDIs it does not contain any propellants, additives or lubricants. The inhaler device assembly consists of moulded plastics with a steel spring. There are two compartments, one in which the dry powder is stored and a dosing unit through which the dry powder is delivered. Priming is necessary before the first dose and is accomplished by holding the unit upright (mouthpiece on top) and turning the brown grip fully to the right then fully to the left until it clicks, and repeating to load the first dose. For each successive dose the inhaler need not be primed, but it must be held upright during this process to ensure that an accurate dose is delivered. A dose of powder is shaved off from a drug reservoir with each twist of the end of the unit. Then as the user inhales through the mouthpiece, the drug is forced through small conical holes of the dosing unit into the inhalation chamber. A spiral insert fitted inside the mouthpiece generates high air-flow resistance and de-aggregates the powder to create an aerosol of small particles. The spiral insert also increases resistance to minimise the generation of very high inspiratory flow rates so reducing the likelihood of drug particles impinging upon the posterior oropharyngeal wall. During inhalation the Turbohaler may be held upright or horizontally while the user inhales through the mouthpiece deeply and forcefully. The device should not be shaken after the dose is loaded and should not be used with a spacer. The child should not exhale into the inhaler. A red mark appears in the indicator window to indicate when a limited number of doses remain. The inhaler contains a desiccant that may sound, when shaken, as though some drug is present even when all doses have been used.[35]

The Turbohaler requires a minimum flow of 30l/min and 60l/min ideally. This is a more powerful flow than that required with the Rotohaler and Diskhaler because of in-built areas of resistance in the Turbohaler structure.

The Turbohaler is used to deliver terbutaline sulphate and formoterol furate (short-acting and long acting β-agonists respectively, both bronchodilators), and budesonide (an anti-inflammatory corticosteroid).

Clickhaler

The Clickhaler is similar to a pMDI in appearance. It contains 100 or 200 actuations, depending upon drug and dose, has a dose counter and locks when empty. Children aged seven to sixteen years with mild to moderate stable asthma have been shown to generate peak flow rates of 60l/min or more when using this device.[36]

The Clickhaler delivers salbutamol (a short-acting β-agonist bronchodilator) or beclomethasone (an anti-inflammatory corticosteroid).

At least two other DPIs are under development.

[Yamanouchi provided confidential information which was included in the version of the report that was sent to the Appraisals Committee, but this information has been removed from this current document]

Pulvinal (Trinity Pharmaceuticals)

Pulvinal is a new DPI soon to be launched in the UK. It is a multidose DPI comprising a rotating mouthpiece with a dose-lock button to prevent unintentional priming, and a drug chamber, containing the drug and a lactose carrier and a metering and distribution system. The DPI delivers the anti-inflammatory corticosteroid, beclomethasone dipropionate.

Drugs

A person's asthmatic condition can be managed using a number of therapeutic approaches. For the purpose of this review a specific list of drugs has been considered that are available for delivery in one or more types of inhaler device described above. The drugs included are bronchodilators (short and long acting β_2-agonists, other adrenoceptors, antimuscarine bronchodilators) and anti-inflammatory drugs (corticosteroids, cromoglyates) that are licensed for use in five to fifteen year old children.

Bronchodilators (relievers)

The principle action of the β_2-agonists is to relax the airway smooth muscle by stimulating the β_2-receptors, which increases cyclic AMP and produce functional antagonism to bronchoconstriction. They are used as an adjunct to anti-inflammatory therapy for providing short or long term control of symptoms, especially nocturnal symptoms and to prevent exercise-induced bronchospasm. Short-acting β_2-agonists cause a prompt increase in airflow, peaking at 30 minutes, and then fading rapidly. Whereas long-acting inhaled β_2-agonists have a longer duration of bronchodilation of at least 12 hours after a single dose. Whilst with fometerol the onset of action is similar to that seen in short-acting β_2-agonists, with salmeterol onset of action is slower.

Anti-inflammatory agents (preventers)

Corticosteroids are the most potent anti-inflammatory agents currently used to treat asthma. Three inhaled corticosteroid compounds are currently licensed for use within the UK: fluticasone propionate, budesonide and beclomethasone dipropionate (BDP), although not all are available through all three of the inhaler delivery devices under review: pressurised metered dose, breath actuated metered dose, dry powder.

Differences in the relative potency and efficacy of each compound have been reviewed.[37] There is substantial evidence to suggest that significant differences in potency exist between the different corticosteroid compounds although these can be overcome by giving equipotent doses. Whilst different laboratories report different relative potencies, the rank order of BDP<budesonide<fluticasone propionate is consistent across laboratories.[37] With respect to efficacy, the review concluded that current evidence does not support an efficacy difference among inhaled corticosteroids.[37]

Sodium cromoglycate and nedocril sodium also provide effective non-steroidal anti-inflammatory treatment in some children.[38]

Combined therapies and compound drug preparations are also considered in this review if they are currently delivered through one of the inhaler devices described above and are licensed for use in five to fifteen year old children.

Drug delivery

This is currently believed to be best achieved by delivering both symptom relieving and preventative anti-flammatory medication as directly as possible to the lungs. However the effectiveness of such drugs requires that the drug not only reaches its target areas but is evenly dispersed across them. The process of delivering drugs to the relevant sites is influenced by a number of factors associated with the drug, the delivery mechanism, and the patient.

In terms of the actual physical mode of delivery of asthma drugs there is a number of counterbalancing factors that need to be considered in the achievement of the goal of optimal drug delivery and symptom control. For example, aerosol delivery provides a non-uniform drug deposition across the lungs whilst with systematic therapy the distribution is much more uniform. However the speed of onset of β_2-agonists through aerosol delivery is much more rapid than when the same drug is deliver systemically. Similarly, for inhaled corticosteroids, the improvement seen in therapeutic index in the last few years has been as a result of using inhaled rather than systematic delivery of corticosteroid therapy.

In terms of patient–related issues, there is also a number of factors to be considered:

- **Competence** Incompetent inhaler technique in children, due either to poor training in using a device or a mis-suited device, can reduce significantly the proportion of the dose of drug molecule that is actually inhaled, or delivered, and also the amount of drug deposition to the lung. This can mean that much higher metered doses of the drug will be needed to achieve the same clinical effect, therefore impacting on the cost-effectiveness of the drug/delivery system, or it can simply result in poor clinical management of the disease. Younger children, in particular, have difficulties in achieving the co-ordination of actuation and inhalation. Poor inhalation can also lead to increased side effects from drugs, particularly in the case of corticosteroids with oral mucosa-related problems. Again this can lead to additional treatment-related costs. But, in his review of inhaler use in children with asthma, Pedersen concluded that most children older than five years of age can be taught the effective use of an inhaler. He also concluded that, once the correct technique had been learnt, it was rarely forgotten if the inhaler was used regularly.[2]

- **Adherence** Poor adherence to medication, due either to physical or cognitive difficulties experienced with a specific delivery device, can strongly impair the effectiveness of treatment and result in poorly managed asthma. Some children can find certain devices much too difficult to handle physically. Such problems of poor adherence due to device-related difficulties, can lead to higher healthcare costs in the longer term. A number of devices are now being launched that record date and time of actuation and this may have an impact on patient adherence.[39]

- **Contrivance** Not using the device effectively or appropriately, such as using a pMDI without the spacer, even when knowing how to do so, can result in poor drug delivery and less than optimum benefit from treatment.

Therefore, as well as selecting the most appropriate medication for children with asthma, in terms of the actual clinical properties of the drug itself, it is also vital that the selected delivery device system is that most appropriate to the child's own life-style and physical/ cognitive/ emotional needs.[23]

Thus the dose reaching the lungs of a person with asthma has little to do with the prescribed dose and is influenced by factors described above such as choice of device, inhaler technique, and adherence.[38] This relationship is further compromised in that variations occur in deposition of the drug in the lungs of the patient with different types of inhalers, with or without spacers. The drug–delivery system is an unique combination. A review of *in-vitro* evidence concluded that data from one MDI spacer combination should not be extrapolated to other combinations. In one study, deliveries of BDP by MDI in combination with a spacer, from three different manufacturers, ranged from 21% to 33%.[37] Some figures on variation in drug deposition by different inhalers, shown in Table 9, was produced in another study.[40]

TABLE 9 PATTERN OF DRUG DEPOSITION WITH DIFFERENT INHALERS

Percentage of total drug dose			
Site of deposition	DPI	MDI	MDI with large volume spacer
Lung	10-15	10-15	20
Oro-pharynx	80	80	15
Device	5	5	65
Patient	95	95	35

Whilst less *in vivo* evidence is available, what exists also supports variations in pulmonary delivery by inhaler device although the evidence by drug and device is not all in the same direction in all studies.[37] The dose prescription therefore needs to relate to the expected lung dose for a specific device-drug combination rather than the factory-dispensed dose.

One review of drug delivery concluded that studies in children show that the percentage of the drug deposited in the lungs is smaller than in adults although the values are not a reflection of the smaller lungs and body weight of the children.[41] Everard, in his review of asthma drug delivery systems, identified three issues that should be addressed when considering these systems in children: the suitability of the device for the age of the user; a liking or toleration of the device by the user; and a device-drug combination that minimises the systemic effects for a given clinical benefit.[38] With β_2-agonists, because of their wide therapeutic index, the first two factors and issues of cost are important whereas for inhaled steroids the third issue becomes more important.[38]

Scope of the review

The study question for this current review is to appraise 'the clinical and cost effectiveness of the use of inhalers in the routine management of chronic asthma in children aged 5 – 15 years'.

Inhaler devices for the purpose of this question are defined as pressurised metered dose aerosol inhalers, breath-actuated metered dose aerosol inhalers, and dry powder inhalers with the former two considered with or without the use of a spacer and using CFC or non-CFC propellants.

There is also requirement to examine the relationship between '*in-vivo*' and '*in-vitro*' evidence in terms of the relationship between in-vitro measurements and

- lung deposition measured by scintigraphy
- clinical effect measured by lung function.

3. EFFECTIVENESS

3.1 METHODS FOR REVIEWING EFFECTIVENESS

3.1.1 Search strategy

The search aimed to identify all papers relating to childhood asthma inhalers and outcomes previously addressed in the systematic review by Brocklebank *et al*.[19] and published subsequent to publication of that review. The search also aimed to identify all papers that addressed childhood asthma inhalers (e.g. comparisons between different powder devices) or outcomes (e.g. patient preference/compliance, quality of life, unwanted effects, etc.) not covered in Brocklebank *et al'*s review.[19] An update of the Brocklebank *et al.*[19] search on *in vitro* studies was also undertaken. All literature searches were conducted between April-July 2001.

Sources searched

Fifteen electronic bibliographic databases were searched, covering biomedical, science, social science, health economic and grey literature (including current research). A list of databases is provided in Appendix 2.

In addition, the reference lists of the Brocklebank *et al.*[19] review and other relevant articles were checked. Various health services research related resources were consulted via the Internet. These included health economics and HTA organisations, guideline producing agencies, generic research and trials registers, and specialist asthma sites. A list of these additional sources is given in Appendix 3.

Search terms

A combination of free-text and thesaurus terms were used. Asthma search terms were combined with generic terms regarding asthma inhalers (e.g. administration, inhalation; aerosols, powders, meter(ed) dose(s), mdi(s), pmdi(s), etc.), and limited to children. Searches were also conducted on named inhalers and spacers (e.g. Maxivent, Spacehaler, Accuhaler, etc.). Copies of the search strategies used in the major databases are included in Appendix 4.

Search restrictions

Where possible (e.g. in the smaller databases), searches were not restricted by publication type or study design. However, methodological filters aimed at identifying guidelines, systematic reviews, clinical trials, economic evaluations, unwanted effects, compliance and quality of life studies, were used in Medline (refer to Appendix 4 for details of the filters used). Searches for reviews, guidelines and clinical trials, were limited to 1998 onwards, as earlier studies had already been identified by the Brocklebank *et al*.[19] review. No language restrictions were used.

3.1.2 Inclusion and exclusion criteria

Inclusion criteria

Subjects: human patients aged between five and fifteen years with chronic asthma or experiencing a mild to moderate exacerbation (increased symptoms and reduced lung function requiring usual treatment delivery but at an increased frequency and/or dosage, not requiring emergency treatment or addition of oral steroids). For searches for 'in vitro' evidence, the inclusion criteria omit 'subjects'.

Intervention: use of any one inhaler device to deliver bronchodilators (short and long acting $beta_2$ agonists, other adrenoceptor agonists, antimuscarinic bronchodilators), corticosteroids (beclometasone diproprionate, budesonide and fluticasone proprionate), cromoglycate, nedocromil, or combination therapy, for the routine management of chronic asthma. This includes any inhaler devices delivering drugs not licensed for the UK but included within the categories defined above (but such drug/ device combinations will be specifically identified in the review).

Inhaler devices to include:

- pressurised metered dose aerosols, using either CFC or HFA propellant, with or without a spacer (all sizes)
- breath actuated metered dose aerosols, using either CFC or HFA propellant
- breath actuated dry powder devices

Comparators: Alternative inhaler devices from the list above, ***but delivering the same form of medication, by generic drug, not by drug type, and at the equivalent dose level.***

Exclusion criteria

Interventions: Any interventions on drug efficacy in isolation from device used to deliver it.

Language: Any papers not available in the English language (as a rapid review, this review is subject to a very short time scale that precludes time for translation).

Time: No date limits will be imposed.

Studies available only as abstracts will also be excluded.

3.1.3 Data extraction strategy

All abstracts, and titles for those articles for which abstracts were not available, were double read and consensus reached on which papers should be acquired for further consideration of the evidence based upon the full text of the article. All papers were read and appraised by two reviewers who extracted relevant information from the paper for this review directly onto an extraction/ evidence table. One reviewer worked with the clinical effectiveness literature and the second with the compliance/preference literature. Quality assurance was monitored by the double extraction of the first three, and a random selection of subsequent papers, by a third reviewer and comparison of the material extracted for content and accuracy.

3.1.4 Quality assessment strategy

Included papers were assessed according to the accepted hierarchy of evidence, whereby meta-analyses of randomised controlled trials are taken to be the most authoritative forms of evidence, with uncontrolled observational studies the least authoritative.

- Any randomised controlled trials were assessed with respect to randomisation procedures, blinding, handling of withdrawals and dropouts, using Jadad's scoring system.[42]

- Non randomised studies using quantitative data, such as case-control, cohort, case series and case reports have been assessed with respect to validity using guidelines from the Centre for Health Evidence based upon the Users Guides to Evidence-Based Medicine.[43]

- Qualitative evidence has been assessed using the CASP checklist for qualitative research.[44]

In most instances, use of data from non-randomised studies has only been considered in cases where there has been insufficient evidence from good quality randomised controlled trials. This is the case for issues of ease of use, preference, compliance, and resource use. Qualitative evidence has specifically been included for issues on preference.

- The quality of the economic literature has been assessed according to the 'Guidelines for authors and peer reviewers of economic submissions' to the BMJ.[45]

3.2 RESULTS

3.2.1 QUANTITY AND QUALITY OF RESEACH AVAILABLE

3.2.1.1 Number of references

Seven thousand two hundred and thirty four references were identified in total, from all the searches carried out, of which 1731 were unique. Twelve potentially useful foreign language papers were excluded on the basis of language. Table 10 provides a breakdown of the references ordered and used in this review.

TABLE 10 REFERENCE STATISTICS

Topic	Number identified*	Number ordered/ contacted	Number used		
			Reviews	RCTs	Non-RCTs
In vitro/ in vivo update	31	2	0	0	0
Clinical effectiveness, reviews, guidelines	375	17	2	0	0
Clinical effectiveness trials	5531	287)	0	28	0
Patient preference, ease of use	183	287)	0	10	20
Non-specific searches	605	287)			
Cost effectiveness	369	16	0	0	0
Current research	140	4	0	0	0
* includes duplicates Totals		326	2	38	20

3.2.1.2 Exclusions

Details of all studies excluded and reasons for their exclusion are given in the table in Appendix 5.

3.2.1.3 Research registers

Three potentially useful research studies were identified from searches of the research registers, all of which were due for completion by 2000. The lead researchers were contacted in each case for further details. However, one has since retired, a second sent a further contact name and a third has not replied. Given the anticipated completion dates for the research, it is hoped that any published results from these studies should have been identified in our literature searches if they were relevant.

3.2.2 CLINICAL EFFECTIVENESS

3.2.2.1 Review question

The study question for this current review is to appraise 'the clinical and cost effectiveness of the use of inhalers in the routine management of chronic asthma in children aged 5 – 15 years'.

For the clinical effectiveness, this review updates the available information on the in vitro questions addressed by Brocklebank *et al.* in their recent review.[19]

- Is there any relationship between in-vitro measurements and lung deposition measured by scintigraphy?
- Is there any relationship between in-vitro measurements and clinical effect measured by lung function?

Plus

- comparing between three hand-held inhaler device types delivering either bronchodilatory drugs, corticosteroids, or cromoglycate compounds, for the routine treatment of chronic asthma in children aged between 5 and 15 years of age. (building on findings from Brocklebank *et al.*[19] where available).

The three inhaler device types are pressurised metered dose aerosol inhalers, breath-actuated metered dose aerosol inhalers, dry powder inhalers, with the former two considered with or without the use of a spacer and using a CFC or non-CFC propellant.

3.2.2.2 In-vitro evidence

Information to answer this was taken from the recent Brocklebank *et al* review[19] and updated with any new published evidence. Brocklebank *et al.*[19] found three studies that met their review criteria and from these they concluded that

> 'one can assume that in-vitro assessments of inhaler performance are important in inhaler development, quality control and for production purpose. However, there are currently insufficient data to verify the ability of in-vitro assessments to predict inhaler performance in-vivo. ….As can be seen from the studies discussed above, the correlation between in vitro and in vivo measurements are specific to the inhaler and drug combination. Therefore data from one inhaler and drug combination should not be used to predict in vivo behaviour in another. In addition the extrapolation of in vitro techniques to the in vivo situation requires an appropriate experimental system, such as an impactor using an anatomical human throat replica as an inlet.[19]

Our search update identified no further studies published in the past two years.

3.2.2.3 Delivery of drugs for children with chronic asthma

Whilst the recent systematic review of inhaler devices for asthma and chronic obstructive pulmonary disease[19] will be used to inform this review, it did not address all of the issues defined for this review. Two of the five key areas addressed in the Brocklebank *et al.* review[19] are of relevance to this review:

- the delivery of corticosteroids by hand held inhalers for the treatment of stable asthma in children and

- the delivery of bronchodilators in the same manner and to the same patient group.

In both of the above areas, studies were considered if they compared a standard pMDI inhaler, with or without a spacer device versus one of the other types of inhaler device (DPI, CFC-free or breath actuated).

The scope of this review is broader than that of Brocklebank *et al*.[19] in terms of

- inhaler device comparisons in that we have included comparisons between and within each of the three inhaler types

- the range of drugs to be considered that can be delivered by these inhaler devices. In addition to corticosteroids, this review includes other anti-inflammatory drugs, the cromoglycates. For bronchodilators our specification is also broader. Brocklebank *et al.*[19] included the β_2-agonists, and of these, the short acting ones only. This review includes inhaler devices delivering long-acting β_2-agonists, other bronchodilators and the antimuscarinic drugs as well as short-acting β_2-agonists.

A summary of the comparisons made and number of papers identified within each comparision is provided in Table 11.

TABLE 11 EVIDENCE FOR SYSTEMATIC REVIEW

Comparision		Number of studies	
Inhalers	**Drug**	**Brocklebank *et al.*[19]**	**This review**
pMDI with/ without spacer vs pMDI with/ without spacer, same propellants	β_2-agonists	Not included	7
pMDI with/ without spacer vs breath actuated MDI	β_2-agonists	0	0
pMDI with/ without spacer vs DPI	β_2-agonists	9	4
DPI vs DPI	β_2-agonists	Not included	3
pMDI with/ without spacer vs pMDI with/ without spacer, same propellants	Corticosteroids	Not included	1
pMDI with/ without spacer vs breath actuated MDI	Corticosteroids	0	0
pMDI with/ without spacer vs DPI	Corticosteroids	3	2
DPI vs DPI	Corticosteroids	Not included	2
pMDI with/ without spacer vs breath actuated MDI	Cromoglycates	Not included	2
pMDI with/ without spacer vs pMDI with/ without spacer, different propellants	β_2-agonists	1	4
pMDI with/ without spacer vs pMDI with/ without spacer, different propellants	Corticosteroids	0	1
Breath-actuated vs breath-actuated, different propellants	Corticosteroids	0	1
pMDI with/ without spacer vs pMDI with/ without spacer, different propellants	Cromoglycates	0	1

Only one study[46] was found relating to any inhaler device comparisons with the same propellant delivering cromoglycates and only one[46] on comparisons of other inhaler types with breath-actuated inhaler devices, with the same study addressing both of these areas.

In presentation of the findings from the Brocklebank *et al* systematic review[19] we have chosen, with permission from the authors, to present their relevant extraction tables of evidence. The reason for this is that because very little evidence was found, the authors presented information as narrative with conclusions, rather than combined in a meta-analysis with an overall measure of clinical effectiveness for each inhaler device type. This form of presentation of our evidence alongside that of Brocklebank *et al*. enables the reader to compare all the evidence for comparisons of each set of inhaler devices rather

than adding small additional pieces of evidence to previous summaries. Indeed, we found little additional evidence for those comparisons for inhaler types that Brocklebank *et al.* had already addressed. We did however identify a number of papers that examined some other comparisons, such as those between different DPIs, a comparison that had not been addressed in the previous review. We have also taken the decision not to do any meta-analyses, given the the limited amount of evidence available within each comparison group.

A) Delivery of β_2-agonist bronchodilators by hand held inhaler devices using the same propellants

Nine studies were found in total by Brocklebank *et al.,*[19] comparing inhaler devices using the same propellant and delivering brochodilating drugs. This review identified an additional 14 studies that fulfilled the inclusion criteria. Details of all studies are given in Appendices 6 – 8.

A1) Comparisons of pMDIs with/ without a spacer vs. other pMDIs with/ without a spacer (Appendix 6)

This comparison was not included in the Brocklebank *et al* review.[19]

Seven papers were identified.[47,48,49,50,51,52] In Kerac *et al.*,[47] a randomised trial compared an MDI against two other MDI spacer combinations (Volumatic, plastic bottle) all delivering salbutamol, and a MDI placebo, in 48 children and adults. However, with an age range of 10-75 years, few of the patients are likely to be within the 5-15 year age eligibility criteria for this review. Significant differences in peak expiratory flow rate (PEFR) ($p<0.5$) were found between both MDI spacer combinations and the MDI placebo, thirty minutes after inhalation but there were no significant differences between the two spacerless MDI (salbutamol and placebo). A second study[48] using salbutamol compared an MDI with an MDI spacer combination (Volumatic) in ten children aged 8 to 14, but found no difference between inhaler devices over a 30 minute period after inhalation. In Lee and Evans,[52] a cross-over study, their four treatment arms were comparisons of albuterol delivered by a pMDI compared with three other MDI spacer combinations to 20 children aged 8-15 years. The authors reported no differences either overall or for 14 children who had a correct inhaler technique, in increase in FEV_1 following treatment between any of the delivery systems. However, for the six children identified as having an incorrect pMDI technique, there was a significantly greater FEV_1 response in the three MDI-spacer combinations compared with the pMDI alone ($p<0.05$). In one further study,[50] of 16 children aged 5 to 12 years randomised to either MDI or MDI plus spacer, both delivering the bronchodilator metaproterenol sulphate, or MDI, and MDI plus spacer both delivering a placebo, no differences were found in FEV_1 or $FEV_{25-75\%}$ between the two drug-delivering inhaler combinations. The final three studies,[51,53,49] all in children, looked at an MDI compared with an MDI plus spacer delivering terbutaline sulphate. Whilst in Becker *et al.,*[49] no differences were seen in FEV_1 or $FEF_{25-75\%}$ between the two devices, in both of the other two studies,[51,53] the MDI-spacer combination was significantly better for PEFR in

the 60 minutes after inhaltion. The study participants were 18 aged between 4.9 to 13.7 years[51] and 12 aged 7 to 11 years.[53]

In summary, from the evidence of a small number of studies, with small numbers of participants, mainly carried out in children, there is no clear evidence in favour of either delivery system (a pMDI or pMDI spacer combination devilvering brochodilating drugs) to support better lung function performance.

A2) pMDIs with/ without a spacer vs DPIs (Appendix 7)

Nine studies were identified by Brocklebank *et al*.[19] In two the DPI used was a Rotohaler and salbutamol was delivered. For the other seven, the DPI was a Turbohaler and turbutaline was delivered except for one study which used salbutamol. All except one were based upon a cross-over design. The main outcomes reported were lung function variables and overall no significant differences were found in FEV_1, FEF_{25-75}, FVC or PEFR between the pMDI and the DPI.

The conclusions of the reviewers[19] were that they were not able to demonstrate any difference in the clincial bronchodilator effect of short term β_2-agonists delivered by pMDI or DPI. However they also highlighted the fact that in the studies appraised 'the studies used a dosing schedule of 1:1 and, given the prescribing recommendations for salbutamol suggest 100-200ug by MDI and 200-400ug by Rotohaler, and for turbutaline 250-500ug by pMDI and 500ug by Turbohaler, the 1:1 dosing schedule would tend to favour Turbohaler over pMDI and may disadvantage the Rotohaler when compared with a pMDI. '

Four additional studies have been published within the past two years, two used a cross-over design[54,55] whilst the other two were based around parallel groups.[56,57] The Spiros DPI was used in two of the studies,[54,56] an Easyhaler in a third,[55] and a Diskus in the fourth.[57] Three studies used salbutamol or albuterol whilst the fourth[57] used a long-acting β_2-agonist, salmeterol. As with the nine earlier studies, no significant differences were found in FEV_1, in the area under the FEV curve, or in peak expiratory flow (PEF). Whilst two studies had small numbers of subjects (<32), the other two were much larger than many seen in this research area with 283 and 498 respectively.[56,57] However, the problem with all four studies as a source of evidence for this review is that the population studied ranged from seven to 79 years of age, with only a small proportion of children included in each study who were <15 years of age and no subgroup analysis by age was available.

The Spiros DPI and Easyhaler are not currently available in the UK.

A3) DPIs vs DPIs (Appendix 8)

This comparison was not part of the Brocklebank *et al.* review.[19]

Two studies were identified[58,59] that compared the Diskus DPI with the Diskhaler DPI, both delivering salbutamol. One was a three way cross-over study[58] whilst the second used parallel groups.[59] In neither study was any significant difference found between the percentage predicted FEV_1[58] or PEFR and symptoms.[59] However, in Bronsky *et al.* there were only 24 subjects (mean age 9, SD 2.1) and whilst Boulet *et al.* had 380 subjects at the end of their study, their mean age was 39 (range 12-70), making it unlikely that many of those studied are within the age range of interest for this review. A third study[60] compared the single-dose Rotohaler with the multi-dose Pulvinal, both delivering salbutamol to 13 children aged 8 to 12. No differences were found between the two devices with respect to FEV_1 or PEFR.

B) Delivery of corticosteroids by hand held inhaler devices, using the same propellants

Three studies were identified by Brocklebank *et al.*[19] and a further five in this review. Details of all the studies are given in Appendices 9 – 11.

B1) pMDIs with/ without spacer vs pMDIs with/ without spacer (Appendix 9)

This comparison was not included in the Brocklebank *et al.* review.[19]

One study was identified[61] that compared two pMDI spacer combinations delivering budesonide. Drug delivery was measured as the amount of drug deposited on a filter placed between the spacer outlet and the patient's mouth. Significantly higher ($p<0.0001$) drug dose deposits were recorded on filters attached to the metal Nebuchamber than on those attached to a Volumatic. However, there were only 16 patients aged 5-8 in this randomised cross-over trial. The metal spacer, which at 250ml is one third the size of the plastic spacer (750ml) is currently not available in the UK.

B2) pMDIs with /without spacer vs DPIs (Appendix 10)

Brocklebank *et al.*[19] found three randomised controlled trials comparing pMDIs (two with spacers) with DPIs. In two studies beclomethasone dipropionate was used and in the third budesonide. The authors' summary of one study was 'this large and well designed study does support the equivalence of pMDI+Nebuhaler versus Turbohaler at half of the pMDI dose. However it does not present any evidence for advantages over the accepted place of pMDI+large volume spacer as the device of choice in childhood asthma management'. The other two studies are basically dismissed by the authors One was in abstract form only and in the second inappropriate or unsuitable devices were used with children, such as no spacer and a Rotohaler DPI.The study was also underpowered.

This review found two further studies. In Agertoft *et al.*[62] the amount of drug deposited on a filter was compared when using either a pMDI Nebuhaler combination or a Turbohaler DPI both delivering budesonide. Drug deposition

was significantly higher from the pMDI Nebuhaler combination in children aged six to fifteen years but for younger children aged four and five years there were no differences between the two inhaler devices. Secondly, Bateman *et al.*[63] compared an HFA MDI versus DPI (Diskus) both delivering a combined therapy of fluticasone depropronate and salmeterol. The subjects were aged eleven to 70 and they found no differences in lung function and symptoms.

B3) DPIs vs DPIs (Appendix 11)

Two studies were identified [64,65] both of which compared the Diskus with the Diskhaler with fluticasone propionate as the medication. In neither study were any difference found between the two inhaler devices in either FEV_1, symptom scores, albuterol use, or night-time wakenings. Both studies had sufficient power according to the details given in each paper. In one[64] the number of subjects within the age range of relevance for this review was low, as the 229 subjects studied ranged from 12 to 76 years of age. However, in the second study,[65] the 437 children recruited were aged four to eleven years.

C) Delivery of cromoglycates by hand-held inhaler devices using the same propellants (Appendix 12)

One study was identified[46] that compared a pMDI with a breath-actuated inhaler device (autohaler) in children aged 4 to 18 (with one person aged 39!). The drug used was sodium cromoglycate. No differences were found between the devices for a number of lung function parameters. However, the study was underpowered with 181 people recruited, 166 completing the eight- week follow-up compared with the 150 people per group required in the authors' power calculation.

D) Delivery of bronchodilators or anti-inflammatory drugs by hand held inhaler devices using different propellants

The Montreal Protocol of 1987[29] proposed to phase out CFC propellants over the next few years. The United Kingdom government committed to the removal of CFCs from all medicinal products by 1999. Because of this, manufacturers have been working on the development of pMDIs using alternative propellants to deliver bronchodilating and anti-inflammatory drugs for asthma management. There have been problems but the first non-CFC short-acting β_2-agonist inhaler became available in 1998 and further products have now been launched. There is some evidence that the pMDIs with HFA give better drug deposition and that drug doses may be reduced compared with those given through pMDI CFC inhalers.[66] In this review our brief was not to examine the evidence of effectiveness for different drug doses and therefore we have looked only at studies that compared inhaler devices that have delivered the same drug in equivalent doses in the comparators. In this section the same approach has applied.

Given the time scale for, and difficulties in, development of non-CFC inhalers and the difficulties, Brocklebank *et al.*[19] identified only one study examining

this issue whilst a further seven have been published in the past two years. Details of all these studies are to be found in Appendices 13-16.

D1) Delivery of β_2-agonist bronchodilators by pMDI using different propellants (Appendix 13)

Brocklebank *et al.*[19] identified one study in their review, which looked at lung function in children with asthma using either a CFC or non-CFC inhaler delivering a short-acting β_2-agonist. No differences in FEV_1 were found.

A further four studies[67,68,69,70] have been identified all of which compared pMDI-CFC propelled albuterol with pMDI-HFA propelled equivalent dose of albuterol. In one study[70] the subjects recruited were over twelve years of age and, with an average age around thirty, few of the 313 would be within the age range for this review. However, in the other three studies the subjects were aged four to eleven[67,68], and six to eleven.[69] No significant differences were found between the CFC and HFA subjects with respect to mean percentage predicted FEV_1, mean percentage predicted PEF.[67,68] Colice *et al.*[69] examining the impact of the two pMDI devices in children with exercise induced asthma also found no significant differences in the percentage change in FEV_1 post exercise between the two groups.

A similar pattern of evidence was also seen in the study on older patients,[70] with no changes in pulmonary function, morning or night-time PEFR values, symptom scores, night-time awakenings, use of back-up short acting β2-agonists, when subjects switched from inhalers containing CFC to those containing HFA propellants.

D2) Delivery of corticosteroids by pMDI using different propellants (Appendix 14)

One study has examined the impact on lung function of CFC versus non CFC pMDIs delivering either a corticosteroid, triamcinolone acetonide via a pMDI spacer[71] The subjects in the Pearlman *et al.* study[71] were aged six to thirteen. Pearlman *et al.*, examining the effect of three different dose regimens (150μg, 300μg, 600μg/day) each delivered by both CFC and HFA propelled pMDI, found no differences in morning and evening PEFR, FEV_1, symptom scores, night time wakening, or albuterol use[71].

D3) Delivery of corticosteroid therapy by breath actuated inhalers using different propellants (Appendix 15)

Of all the evidence found only one study used breath actuated inhaler devices. Farmer *et al.*[72] looked at differences between two breath actuated inhalers delivering beclomethasone dipropionate to children aged seven to twelve years, one of which used CFC and the second HFA propellants. The study may have been slightly underpowered based on their 90% power subject number calculation in that 105 patients were required for each arm of the study and only 199 participated completely. No significant differences were reported for PEF, FEV_1, symptom scores, and relief medication use.

D4) Delivery of cromoglycate therapy by pMDIs using different propellants (Appendix 16)

Only one study from all the evidence found compared inhaler devices delivering sodium cromoglycate,[73] in this case using pMDIs and CFC compared with HFA propellants. The authors found no differences in either symptom scores, use of albuterol, PEFam, PEFpm in their 280 subjects aged 12 to 79. Patients rated the effectiveness of their treatment similarly in the two treatment groups (73% for CFC, 77% for HFA, p=0.99). However clinicians rated the CFC inhaler more effective (63%) for patients than the HFA one (56%) (p=-0.04).

3.2.2.4 Discussion

The evidence on the clinical effectiveness of different inhaler devices delivering a range of bronchodilating and anti-inflammatory medication in vivo is patchy. In terms of devices, whilst pMDI and DPI have been compared both against each other and within type, only two studieshave looked at breath actuated inhalers[46,72] and one of these was not a comparison of device types but of propellants used.[72] Similarly in terms of drugs, whilst short-acting β_2-agonists and corticosteroids are well represented in the evidence, only two studies[46,73] considered the difference between inhalers delivering sodium cromoglycate, and for one of these it was a comparison of propellants.[73] Few studies have addressed the question of long acting β_2 –agonists alone[57] or as a combined therapy.[63]

In general, from the evidence available, the impact of different inhaler devices, delivering asthma medication, on lung function and symptoms in children aged 5 to 15 with chronic asthma treated in a randomised control trial situation suggests that there are no obvious benefits to asthma symptom control using one specific inhaler type over another, or even one inhaler device over another within type. With the exception that there is some very limited evidence to support the use of spacers with pMDI[47,51,53] and a suggestion that those made of metal may be more effective than those currently available in the UK that are made of plastic.[61] There are however also cost implications with this latter option.

Being unable to identify any significant differences when they may actually exist may be due to studies being under powered (Type 2 error). In most instances no power calculation was reported and subject numbers were usually low (<50 per treatment arm). Where power calculations were reported, sample sizes were in the order of 70+ with one exception.[74] It would be illogical if, with most of the studies looking at the same primary outcomes, FEV_{1max}, PEF, PEFR, presumably with similar levels of effect, in similar populations of children with a similar condition (mild to moderate asthma) that they did not all require similar subject numbers to be sufficiently powered.

In a systematic review of studies CFC-MDIs compared with nonCFC MDIs delivering short acting β_2-agonists, Hughes *et al.*[75] pointed out the many of the

trials reviewed were under powered. A second point made related to the ability of studies to demonstrate equivalence. This issue is relevant for this review also.

In nearly half of the studies identified the sample populations lay entirely within the age range of interest for this review.[48,52,50,49,51,53,76,77,78,79,60,58,61,80,69,71,72] However, 22 studies covered a much greater age range distribution with the ageband of interest lying in one tail of the distribution and it is possible that any variation in response through age differences may be masked because of this wider age distribution. Subgroup analysis by ageband was not available for any of the studies that looked at adolescents and adults and indeed the studies may not have had sufficient power for such analyses. Exclusion of all studies from the review in which the age range was not totally within the review criteria would not only have reduced the amount of evidence considerably.

It is also possible that the populations studied in the evidence identified do not represent the population profile for childhood asthma. Fifty percent of the studies recruited subjects specifically with mild to moderate asthma and a number of studies specifically excluded those with more severe disease. Yet children with moderate to severe disease would also be taking inhaled medication, albeit at a higher dose (Step 4 of the BTS guidelines).[9] It is not necessarily appropriate to assume that children with more severe asthma would have shown similar lung function responses with different inhaler types to those seen in this evidence.

In terms of therapeutic benefit associated with the different inhaler devices those studies that reported adverse effects reported few or none[52,50,51,55,54,56,59,60,57] and there appeared to be no obvious differences in these by inhaler type irrespective of drug delivered with one exception.[63]

The cost of replacing CFC with HFA inhalers was predicted to be high[32] but in 2001, with most of these costs being non-recurring, and the number of HFA devices in the market place increasing, any major potential impact of this transfer on clinical effectiveness should be declining.

One way of biasing trial results would be to have dissimilar treatment arms. One example could be that in one treatment arm a patient would be required to take a dose more times per day than in another although the final dose is equivalent. This could encourage possible non-compliance in those having to take a drug more frequently and patient preference for the lower dose number regimen independent of the research question. In the studies considered in this review treatments in each treatment arm were taken at similar frequencies although there were some instances in which one puff was required compared with two in a second treatment arm.

3.2.2.5 Summary

To summarise, the clinical evidence suggests that for children aged between 5 and 15 with chronic asthma, for routine maintenance.

- there is no difference in benefit between pMDI using either CFC or HFA propellants or DPI, or between two DPIs, delivering either short-acting β_2-agonists or corticosteroids
- there is some evidence of benefit from using a pMDI spacer combination rather than a pMDI alone, and specifically a metal spacer
- there is no evidence on the clinical advantage or disadvantage of breath-actuated inhalers compared with either pMDI or DPI.

3.2.2.6 Recommendations

Further properly designed equivalence trials, adequately powered might produce some non-equivalent evidence. However subject numbers required would be very large. It would seem more useful to explore patient issues surrounding inhaler use.

Given the lack of evidence on clinical effectiveness it is opportune to revisit the three issues raised by Everard[38] when considering asthma drug delivery systems in children: suitability for age of user, liking or tolerance of device by user, a device-drug combination that minimises the systemic effects for a given clinical benefit. This review has demonstrated that there appear to be no differences between device drug combinations for given clinical benefit with minimal systemic effect. Therefore the other two issues become more important. In the next section the review considers the evidence on factors relating to patient adherence to inhaled asthma medication associated with different inhaler device in children aged five to fifteen and their carers. Adherence will be affected by the suitability of the device and the users' liking of it.

3.2.3 Ease of use, patient/carer preference and compliance for inhaler devices

3.2.3.1 Review question

This section of the review looks at the impact of ease of use, preference for, and adherence to, different inhaler types on their clinical effectiveness in children aged five to fifteen.

3.2.3.2 Quantity and quality of the evidence

The quantity and particularly the quality of the evidence to inform this section of the review are poor. Of the 30 papers included in the review (data summarised in Appendix 17), ten studies (plus an extension study) [81,82,83,84,49,59,85,46,60,86,87] amounted to randomised controlled trials of which six (plus the extension study) were blinded.[81,82,83,84,49,59,85]

[Yamanouchi provided confidential information which was included in the version of the report that was sent to the Appraisals Committee, but this information has been removed from this current document]

However, the intervention compared in one of these randomised controlled trials was on training and the primary outcome was ability to use after training rather than ease of use or compliance with use.[83] The remainder included large and small open, non-controlled studies considering various perceived adherence factors in addition to the choice and ease of use of the inhaler device or ability to use after a training programme. Sixteen of the studies did not involve comparisons between two or more inhaler device types.[88,89,90,91,81,92,93,94,95,96,97,98,99,100,83,101] Six studies that looked at instruction giving have been included because of their impact upon use, although not directly upon ease of use.[89,102,103,104,100,83] In 13 of the studies selected lung function and symptom variables were the primary outcome measures used along with patient compliance and use in some studies but not all.[88,93,95,104,100,46,84,60,49,59,86,87,101] In the other 17 studies the primary outcomes related to adherence factors only.

With respect to the ages of the participants, in eight studies the age range studied was within the 5 to 15 year ageband of relevance to this review.[88,91,92,94,95,97,60,49] Subjects older than 15 were included in 15 studies[90,81,82,96,102,103,104,98,99,100,105,59,86,85,101] and younger than five in a further 5.[89,93,83,87,106] In two studies the age ranges were 4 to 18 years[46] and 4.8 to 15.1 years.[84] Subject numbers for all studies, with the exception of four, ranged between 13[60] and 463.[59] For the four exceptions, subject numbers were considerably higher at 1133[101], 1173[98], 2056[94] and 4529.[96] Seventeen studies have less than 100 subjects.

The majority of studies are observational, with small subject numbers, with participants older than 15 years, and they do not directly address the issues of interest, namely the impact of ease of use, preference for, and adherence to, different inhaler device types on clinical effectiveness in the management of routine asthma in children aged between 5 and 15.

3.2.3.3 Use

The most general finding was that adequate, individual (verbal) instruction was the key to correct inhaler technique[89,95,96,102,59,101] and improvement in lung function and symptoms[95,100,83] regardless of the choice of inhaler device.[102,89] Choice of inhaler device did not appear to represent a barrier to effective use in children over the age of five years with the proviso that adequate (verbal) instruction and supervision was provided. Deciding upon an inhaler device in combination with lung function testing appeared to produce better outcomes in terms of efficiency of use.[104]

A range of problems have been identified with poor technique[98,99] not necessarily specific to the inhaler device.[49,86] Age may have an impact on ability to use, with younger children (4 to 6 years of age) having a less efficient technique than those somewhat older (7 to 16)[104] although in a second study, improvements in ability to use after a training intervention were independent of age.[102]

In terms of ease of use, in Ng *et al.,*[105] 22 of 31 male adolescents rated the DPI (Diskus) as easiest to use, compared with three in favour of the DPI (Turbohaler) (p=0.002) and six for the breath-actuated autohaler (p=0.03). The subjects (n=463), in a comparison study of two other DPIs, rated the Diskus (85%) and Diskhaler (45%) as very easy to use.[59] A further study reported the investigator's assessment of their 13 patients. Ease of use was recorded as excellent in 10 and good in three using the DPI (Pulvinal) compared with 3 excellent, 8 good, and 2 fair when using the DPI (Rotohaler).[60] One specific factor that impacts upon ease of use is the ability to load the device correctly and significant differences were found between the percentage of errors made when loading the DPI Turbohaler compared with the DPI Diskus (p=0.045).[86]

[Yamanouchi provided confidential information which was included in the version of the report that was sent to the Appraisals Committee, but this information has been removed from this current document]

3.2.3.4 Adherence

When examining adherence, measuring it in some way was consistently a far more accurate reflection of adherence than self-reporting methods. Self-reported adherence by patients to drug-dose schedules has been overestimated by as much as 100% compared with records of actual use[88,81,92] although correlation between self-reported and estimated actual use is often poor or non-existent.[90,91] Some discordance was also seen between parent/child and parent/physician reports of asthma medication use.[97]

Factors such as age[82,96] socio-economic status,[92] and ethnicity[92,94] were also found to interplay with measured adherence, with adherence appearing to decline with progress into adolescence.[82,107] It is suggested that even greater attention needs to be paid to adherence factors in this patient group. Finally, there was little correlation between symptom scores and measures of adherence. This is probably confounded by the inclusion of children with mild to moderate asthma only in most study designs, the relatively short duration of study periods and the small numbers of patients involved.

3.2.3.5 Preference

Patient preference where expressed, tended to favour dry powder devices over metered dose inhalers but comparative outcome data was sparse. In a comparison of a pMDI with a DPI (Rotohaler) the younger children in a study of 4 to 15 year olds preferred the Rotohaler but this was not one of the listed outcomes of the study and no numbers were reported.[84] The DPI Diskhaler was also preferred over the pMDI by the majority of the children in the Kesten *et al.* study (p<0.001).[96]

Most of the evidence found related to comparisons of different DPI devices. In Sharma *et al.,*[106] the DPI Diskus scored more highly than the DPI Turbohaler in terms of a list of features including attractiveness, dose indicator, shape,

ease of use and ease of carrying but not size. Overall, design was the key factor guiding preference among 10 to 14 year olds and ease of use among those aged 4 to 9.[106] The DPI Diskus was rated more favourably than the DPI Turbohaler in another study on similar features, that is, dose indicator, ease of correct use.[108] In this parallel group study, more children in the Diskus group (85%) compared with the Turbohaler group (58%) said that they would be happy to receive the same device again, while 8% and 25% in the same to groups would not.[108] Patient preference was significantly in favour of the Diskus over the Turbohaler in Ng *et al.*[105] However in Van der Palen *et al.*[86] the reverse finding was seen with more people preferring the Turbohaler (25) to the Diskus (17) (eight had no preference). These differences were not significantly different and the participants were an older group (15 to 74 years of age) but significant differences were found in favour of the Turbohaler with respect to ease of carrying, size, inconspicuousness and dose counter ($p<0.001$). Some variation in preference relating to the features listed earlier was also seen between Diskus and Diskhaler DPIs[85] and in Boulet *et al.*[59] 73% preferred the Diskus, 15% the Diskhaler whilst 12% expressed no preference. Another DPI comparison between Pulvinal and Rotohaler found 11 of 13 prefer Pulvinal, one preferring the Rotohaler and 2 with no preference.[60]

[Yamanouchi provided confidential information which was included in the version of the report that was sent to the Appraisals Committee, but this information has been removed from this current document]

The pMDI inhaler has also been compared with the breath actuated autohaler, and in this study 90 of 181 children and adolescents found the autohaler more acceptable that the pMDI, 24 opted for the reverse opinion and 43 found both devices equally acceptable ($p<0.001$).

3.2.3.6 Summary

Overall the evidence on patient preference, ease of use and adherence is limited in quantity, with respect to covering all the different inhaler devices and appropriate outcomes, and that available is of a less than robust quality.

3.2.3.7 Recommendations

Well-designed qualitative studies, or qualitative data collected during a randomised controlled trial, would provide a greater understanding of the factors that underlie children's relationships with their inhaler devices for their asthma. Given apparent equivalence in clinical effectiveness between inhaler types and the importance of patient factors, such studies would contribute greatly to our understanding and therefore management of children and adolescents with chronic asthma.

4. ECONOMIC ANALYSIS

4.1 METHODS FOR ECONOMIC ANALYSIS

Economic analysis was undertaken in the form of a review of existing cost-effective evidence, including evidence submitted to NICE by companies producing asthma inhalers, followed by further economic modelling undertaken by the review team.

4.2 REVIEW OF THE ECONOMIC SUBMISSIONS AND PUBLISHED LITERATURE

No published studies analysing the cost-effectiveness of different inhaler types with the same drug in the required population were found. The reason for exclusion, in the majority of the papers requested and reviewed were either that different drugs were being used in addition to different devices, or that the study population did not match the 5-15 age range specified in the review inclusion criteria.

Sponsors of inhaler devices were invited by NICE to submit evidence on the effectiveness of their devices. The following is an appraisal of economic evidence submitted to NICE by companies producing inhaler devices.

Each submission was documented given the following categories:

Sponsor name
Number of sponsor products in the submission.

For each product the following categories were used where applicable:

Product name
Product device type
Drug delivered
Comparator device(s) for economic analyses

Economic analyses were appraised according to the following categories:

Analytical approach taken
Time horizon considered
Discounting rates used where applicable
Source of drug and device costs
Assumptions made for the economic analyses of each product
Conclusion reached for each product
Budgetary impact model presented where applicable

Each submission was assessed on the appropriateness and accuracy of the economic analyses presented.

4.2.1 Overview of economic analyses in submissions

Eight of the ten submissions adopted a standard cost-minimisation approach, citing that no significant clinical difference between devices has been proven. Therefore the cheapest option, with which the patient is both compliant and proficient in using, should be chosen.

The submission by Norton Healthcare[109] has used a cost-consequence approach, using a retrospective observational database to look at resource usage between patients that had changed to their product (Easi-Breathe) and patients that had changed to pMDIs. The resultant data showed that there were significantly fewer GP consultations on Easi-Breathe and that the overall direct NHS costs were less. It was hypothesised that there would also be allied quality adjusted life-year (QALY) increases due to Easi-Breathe treatment, however these weren't quantified to provide a cost-effectiveness ratio.

The submission by GlaxoSmithKline[110] argued that although no evidence was found proving that the inhaler devices were significantly different, this did not mean that the inhalers were necessarily equivalent, as the published trials may not have had enough power to detect small differences.

The review team concurs that there is no statistically significant evidence of equivalence. However, if a pragmatic consensus of clinicians was that the devices were equivalent, then a cost-minimisation approach should be taken.

4.2.2 Review of the economic analysis presented in Submission 1[111].

Company name: 3M
Number of products detailed in the submission: 2

Product 1
Name: Autohaler
Device type: Breath actuated pMDI
Drug delivered: Salbutamol (HFA and CFC), Beclamethasone (HFA and CFC)
Comparator for economic analyses: pMDIs and DPIs

Product 2
Name: AeroChamber
Device type: Medium volume spacer device
Compatible with: All pMDI
Comparator for economic analyses: other spacers

Analytical approach taken: Cost minimisation
Time Horizon 1 year
Discounting: None-taken
Drug and Device costs taken from BNF March 2001[112] or MIMS June 2001.[113]

Product 1 (Autohaler)

Assumptions made:

All devices have the same clinical efficacy and an equal adherence rate.

Submission conclusion:

That pMDIs are the cheapest device, based on requisition cost, but were patients unable to adhere to pMDI technique then Autohaler devices were the next cheapest option.

Budgetary impact model presented:

A typical health authority district of 500,000 people is used as the population base. Were all patients prescribed pMDIs then the estimated inhaler cost would be £919,000. This figure would be £1,477,000 if all patients used Diskhalers (a comparatively expensive DPI treatment). These are used as references for the expected cost of £1,065,000 were all patients to be prescribed Autohalers. Scaling these figures to the population of England and Wales, the figures are £96m, £154m and £112m respectively.

Reviewer comment:

The cost methodology used is potentially flawed in that it allows for non-integer doses to be taken per day. For example the cost of the drug is calculated to per ug, and then multiplied up to calculate the daily cost. This presents a problem, when the daily requirement is 400ug per day and a puff contains 250mg. Clearly 2 puffs would be needed, not 1.6 as has been calculated.

However this does not influence the main conclusion that the Qvar Autohaler is the cheapest non-pMDI device. It is noted however that the Qvar Autohaler is not recommended for children under 12, and that the Aerobic Autohaler is more expensive than a number of competitor devices.

The impact of the equivalence assumptions made, with regards to the QALY improvement necessary for the device to be cost-effective has been explored in the model presented by the review team.

Product 2 (AeroChamber)

Assumptions made:

All spacers have the same clinical efficacy and an equal adherence rate.

Submission conclusion:

Based on the manufacturer's recommended lifespan for each spacer the cheapest option is the AeroChamber, at a cost saving of £1.22 per patient per year compared with the next cheapest device.

Budgetary impact model presented:

An estimate of 125,000 spacers prescribed per year was made. If this figure were correct then the savings compared with the next cheapest spacer would be estimated at £153,000, although it is not explicitly stated whether this figure applies to the UK or England and Wales.

Reviewer comment:

The mathematics behind the calculations appear robust.

The impact of the equivalence assumptions made, with regards to the QALY improvement necessary for the device to be cost-effective has been explored in the model presented by the review team.

4.2.3 Review of the economic analysis presented in Submission 2[114]

Company name: Aventis
Number of products detailed in the submission: 3

Product 1
Name: Fisonair
Device type: Large volume spacer
Compatible with: Intal pMDI (Sodium Cromoglycate)
Comparator for economic analyses: Intal pMDI.

Product 2
Name: Syncroner
Device type: pMDI with an integral open tube spacer.
Drug delivered: Intal (Sodium Cromoglycate) or Tilade (Nedocromil Sodium)
Comparator for economic analyses: Intal pMDI or Tilade pMDI

Product 3
Name: Spinhaler
Device type: Dry powder inhaler
Drug delivered: Intal (Sodium Cromoglycate)
Comparator for economic analyses: Intal pMDI

Analytical approach taken: Cost minimisation
Time Horizon 1 year
Discounting: None-taken
Source for drug and device costs. Not stated although equal to those in the BNF March 2001[112] or MIMS June 2001.[113]

Product 1 (Fisonair)

Submission conclusion:

The additional cost of using a Fisonair device is £5.94 per annum. Were a GP consultation avoided, at a minimum cost of £15, then the device would be cost-saving.

Budgetary impact model presented:

None.

Reviewer comment:

The mathematics regarding 1 GP consultation, or indeed 1 GP consultation per 2 patients, becoming cost-saving are correct. However no evidence has been presented that GP consultations are reduced by use of a Fisonair.

The impact of the equivalence assumptions made, with regards to the QALY improvement necessary for the device to be cost-effective has been explored in the model presented by the review team.

Product 2 (Syncroner)

Assumptions made:

The Syncroner has the same clinical efficacy and an equal adherence rate as the comparative (ie Intal or Tilade) pMDI.

Submission conclusion:

Assuming a daily regimen equal to the normal maximum dose, the Intal Syncroner is £0.19 per patient cheaper per 28 days therapy. This is approximately £1.14 per patient per year.

The costs of Tilade Syncroner and Tilade Inhaler are very similar, a difference of £0.01 per patient per 28 days, in favour of the Syncroner.

It is concluded that the Syncroner is cost-saving compared to the comparative pMDIs.

Budgetary impact model presented:

None.

Reviewer comment:

The cost difference between Intal pMDI and Intal Syncroner appears to be £0.21 per patient per 28 days, which would result in an approximate £1.26 saving per patient per year.

It is agreed that the Syncroner is cost-saving given the assumptions made.

The impact of the equivalence assumptions made, with regards to the QALY improvement necessary for the device to be cost-effective has been explored in the model presented by the review team.

Product 3 (Spinhaler)

Assumptions made:

The Spinhaler has the same clinical efficacy and an equal adherence rate as the Intal pMDI.

Submission conclusion:

That the cost of the Spinhaler and Intal spincaps is calculated to be £28.30 less per year than the cost of Intal pMDIs.

Budgetary impact model presented:

None.

Reviewer comment:

It is agreed that the Spinhaler is cost-saving given the assumptions made.

The impact of the equivalence assumptions made, with regards to the QALY improvement necessary for the device to be cost-effective has been explored in the model presented by the review team.

4.2.4 Review of the economic analysis presented in Submission 4[115]

(no Submission 3).

Company name: Celltech
Number of products detailed in the submission: 1

Product 1
Name: Clickhaler
Device type: DPI
Drug delivered: Salbutamol or beclamethasone
Comparator for economic analyses: other DPIs

Analytical approach taken: Cost minimisation
Time Horizon 1 year
Discounting: None-taken
Source for drug and device costs: MIMS March 2000[116].

Product 1 (Clickhaler)

Assumptions made:

All devices have the same clinical efficacy and an equal adherence rate.
Only HFA devices would be considered.

Submission conclusion:

That the Clickhaler is the cheapest DPI device.

Budgetary impact model presented:

Changing all DPI users to a Clickhaler could have saved the NHS up to £14m in 1999. Up to a further £39m could have been saved were all patients on Beclamethasone, fluticasone or budesonide switched to a Clickhaler delivering beclamethasone.

Reviewer comment:

The focus on HFA only devices means that some types, such as Easi-Breathe, with HFA licences pending, have been omitted from the analyses. The explicit budgetary impact calculations have not been given. It is noted that the cost saving from switching patients on fluticasone or budesonide has been calculated although the Clickhaler does not deliver these drugs. It is also noted that the costs of the drugs used in this submission are over a year old compared with the costs used in the other submissions and the review team model.

4.2.5 Review of the Economic Analysis presented in Submission 5[110]

Company name: GlaxoSmithKline
Number of products detailed in the submission: 6

Product 1
Name: Inhaler
Device type: pMDI (CFC)
Drug delivered: Beclamethasone, salmeterol, beclamethasone + salbutamol
Comparator for economic analyses: None

Product 2
Name: Evohaler
Device type: pMDI (HFA)
Drug delivered: Salbutamol, fluticasone, fluticasone + salmeterol
Comparator for economic analyses: None

Product 3
Name: Diskhaler
Device type: DPI
Drug delivered: Beclamethasone, salmeterol, salbutamol, fluticasone
Comparator for economic analyses: None

Product 4
Name: Accuhaler
Device type: DPI
Drug delivered: Salbutamol, fluticasone, salmeterol, fluticasone + salmeterol
Comparator for economic analyses: None

Product 5
Name: Rotahaler
Device type: DPI
Drug delivered: Beclamethasone, beclamethasone + salbutamol
Comparator for economic analyses: None

Product 6
Name: Volumatic
Device type: Large volume spacer
Compatible with: all GlaxoSmithKline pMDIs
Comparator for economic analyses: None

Analytical approach taken: Budgetary impact model only
Time Horizon: 1 year
Discounting: None-taken
Source for drug and device costs: BNF March 2001[112] or MIMS June 2001.[113]

GlaxoSmithKline has not undertaken any economic analysis other than a budgetary impact model citing that there are no trials that have proved

equivalence between different inhaler devices. As such it is claimed that cost-effectiveness or cost minimisation analyses are inappropriate.

Budgetary impact model presented:

If all patients using a pMDI also used a spacer the total cost of asthma treatment would increase by £0.33m per annum.

If 20% of all of those patients on GlaxoSmithKline pMDIs were prescribed Accuhalers (DPIs) there would be an increase in total costs of £0.43m per annum.

If 100% of all of those patients on GlaxoSmithKline pMDIs were prescribed Accuhalers (DPIs) there would be an increase in total costs of £1.3m per annum.

The submission rates these increases as not imposing a large extra burden on the NHS resources in England and Wales.

Reviewer comment:

There is no conclusive evidence that inhalers types are equivalent. The model produced by the review team allows some interpretation of the QALY gains that would be needed for a more expensive inhaler to be cost-effective with a cheaper inhaler. However if a pragmatic consensus was that the devices were equivalent then a cost-minimisation approach should be taken.

4.2.6 Review of the economic analysis presented in Submission 6[109] and supplementary requested information[117]

Company name: Norton Healthcare
Number of products detailed in the submission: 1

Product 1
Name: Easi-Breathe
Device type: Breath actuated inhaler
Drug delivered: Salbutamol or Beclamethasone
Comparator for economic analyses: pMDIs

Analytical approach taken: Cost consequence
Time Horizon: 5 years
Discounting: None-taken
Source for drug and device costs: MIMS June 2001.[113]

Product 1 (Easi-Breathe)

Assumptions made:

That the retrospective observational data seen in the Asthma Resource Use Study was representative of the true difference between the resources consumed when comparing pMDI and Easi-Breathe.

Submission conclusion:

Total costs are reduced by £17.46 per patient per annum when using Easi-Breathe compared with a pMDI, constituted of reduced GP consultations for asthma related illnesses. In supplementary analysis the difference in total costs between pMDI users and Easi-Breathe users was reported as £17.94 with a p-value of 0.014.

A sensitivity analysis drawing random observations from the 95% confidence intervals for inhaled steroids, B2-agonists, oral steroids, antibiotics, GP consultations gave results that showed that Easi-Breathe was cheaper on 99.11% occasions compared to pMDI.

Budgetary impact model presented:

Were all beclamethasone or salbutamol pMDI patients switched to Easi-Breathe, an extra device cost of £2.17m per annum would be expected for an estimated 674,000 users. It is postulated that these patients would accrue a saving of £13.94m per annum, resulting in a net saving of £11.77m per annum. An analysis phasing in Easi-Breathe by 20% of pMDI use over the forthcoming 5 years is also presented.

Reviewer comment: Divided into two sections; study design and the data presented.

Asthma Resource Use Study design.

The Asthma Resource Use Study was a retrospective observational analysis of the resource use of two cohorts of asthma sufferers over a 12-month period, using the Doctors Independent Network database (DIN-Link). DIN-Link is a large longitudinal database from 100 practices, equating to approximately 360 geographically representative GPs and 900,000 patients.
These cohorts were divided into a group where all asthma medication (beclamethasone and salbutamol) was given via a pMDI and a group where such medication was delivered by Easi-Breathe. Each group was then sub-divided into whether the patient was an existing medication user, or whether the patient was a new sufferer. It appears that only the results for existing patients were presented in the submission.
It is shown that the baseline dose of beclamethasone was higher for the group on Easi-Breathe than pMDI. The sponsors report that this suggests that Easi-Breathe users may have had more severe symptoms, or that they were

switched to Easi-Breathe in order that control of the asthma was achieved. This is plausible although not categorically conclusive. It could be that those GPs with a keener interest in asthma were more likely to use Easi-Breathe and more likely to have previously controlled their patients' asthma with the use of higher doses. Alternatively the demographics and social status for the patients using Easi-Breathe may be more conducive to better adherence rates, which may lead to less resource usage than those less adherent using pMDIs. The extent of this bias was examined using the ACORN (A Classification Of Residential Neighbourhoods) socio-economic groups developed by CACI Limited[118] presented by the sponsor[117]. There are six groups with the bottom group described as; older people, less prosperous areas, council estate residents, better-off homes, council estate residents, high unemployment, council estate residents, greatest hardship, people in multi-ethnic, low income areas. In the study 38% of the pMDI cohort of patients with socio-economic data were in this group. This figure was only 12% for those in the Easi-Breathe group. This is countered by the higher proportions in the higher socio-economic groups, but may be a factor were deprivation (i.e. class F) to influence device usage, whilst classes A-E could use a device correctly. Anecdotal evidence (M. Everard Personal Communication) and evidence from the current review contained in section 3.2.2.4 suggests that this may be a factor.

After further analysis[117] it was seen that patients who had not changed either pMDI device or Easi-breathe device were not counted in the analysis. This may introduce bias if the act of switching pMDI device, or changing to a pMDI device is related to lack of control of asthma.

Patients that did not switch pMDI device may be happy and suffering fewer attacks than those that change device. Whilst this may also be true for Easi-breathe users, if both cohorts had similar resource usage then pMDIs would be cheaper due to the lower acquisition costs.

As such, the conclusions drawn in the submission regarding cost-offsets are relevant only to those patients who changed to a pMDI device and those who changed to Easi-breathe. No conclusions can be drawn comparing resource use between patients who remained on the same pMDI and those who remained on Easi-Breathe.

Data presented.

If only those cost vectors which were individually significant (B2-agonist prescriptions, antibiotic prescriptions and GP consultations) are summated, the cost saving is reduced to £10.58 per patient per annum. This would reduce the total projected cost-savings were all beclamethasone or salbutamol pMDI patients switched to Easi-Breathe, to £6.28m per annum.
The sensitivity analysis presented needed further explanation. There is no discussion on the distribution assumed between the 95% confidence intervals of each vector (e.g., normal, uniform) or on the correlation between vectors. It is probable that those in the upper distribution for antibiotics would also be in the upper distribution for GP consultations. The assumption of no correlation

between vectors is likely to constrain the higher differences, as in the above example; patients would have to fall randomly into both an upper distribution of GP consultations and antibiotic use.

There appears to be a discrepancy between the cost savings given £17.46 and those from the addition of the individual vectors in Table 30 in the report (£15.86) that is not accounted for by the excluded outpatient attendance figures. The reason for this discrepancy is not given. Similarly there seems to be an error in the number of GP consultations prevented. Results shown in Table 10 show an average of 2.504 GP consultations, but also shows an average of 2.179 consultations for lower respiratory tract infections and 0.965 consultations for upper respiratory tract infections. These summated equal 3.144 consultations, which is greater than the total number reported.

If the Asthma Resource Use Study results are valid, then Easi-Breathe produces cost-savings. Analyses with and without such savings are presented in the review team's model. It is stressed however that the cost-offset comparing seen could only be taken as valid under the conditions of the study (i.e. patients who switch to a pMDI or switch to Easi-breathe) pMDI during the year, and assuming that there was no bias in socio-economic status of the cohorts.

No conclusion can be drawn from the evidence presented in the submission for new sufferers of asthma, or for patients who do not switch to a pMDI or who remain on the same pMDI.

4.2.7

[Yamanouchi provided confidential information which was included in the version of the report that was sent to the Appraisals Committee, but this information has been removed from this current document]

4.2.8 Review of the economic analysis presented in Submission 8[120]

Company name: AstraZeneca
Number of products detailed in the submission: 1

Product 1
Name: Turbohaler
Device type: DPI
Drug delivered: Budesonide, terbutaline, eformoterol, budesonide + eformoterol

Analytical approach taken: No quantified analysis
Time Horizon: None
Discounting: None-taken
Source for drug and device costs. MIMS June 2001[113].

Product 1 (Turbohaler)

Submission conclusion:

Turbohaler significantly reduces hospitalisation compared to pMDI.

Budesonide Turbohaler reduces hospitalisation and increases symptom free days.

Eformoterol Turbohaler increases symptom free days.

That compliance is a key driver and that patient preference should be a key factor in determining the device selected.

Budgetary impact model presented:

None quantitative. A relationship between poor compliance and associated increased costs is hypothesised, with the claim that were more patients to be compliant on Turbohaler then direct costs may be reduced.

Reviewer comment:

The efficacy results presented unfortunately do not meet the scope of the review, either through participants being older than the required age range or because different drugs and different devices were being compared.

The model presented by the review team investigates the increase in QALYs needed in order for more expensive devices to become cost-effective. Estimations of increased QALYs due to better compliance together with the review team model allows a more informed decision to be made on device selection.

4.2.9 Review of the Economic Analysis presented in Submission 10[121]

(No Submission 9)

Company name: Trinity Pharmaceuticals
Number of products detailed in the submission: 3

Product 1
Name: Pulvinal
Device type: DPI
Drug delivered: Beclamethasone and salbutamol
Device currently not available.
Comparators for economic analyses: other DPIs

Product 2
Name: Inhaler
Device type: pMDI
Drug delivered: Ipratropium bromide, ipratropium bromide + fenoterol hyprobromide
Comparators for economic analyses: None

Product 3
Name: Autohaler
Device type: Breath actuated inhaler
Drug delivered: Ipratropium bromide, Ipratropium bromide + fenoterol hyprobromide
Comparators for economic analyses: None

Product 1

Analytical approach taken: Cost minimisation
Time Horizon 1 year
Discounting: None-taken
Source for drug and device costs. MIMS January 2001.[122]

Products 2 and 3

Analytical approach taken: None taken
Time Horizon: None
Discounting: None-taken
Source for drug and device costs. MIMS April 2001.[123]

Product 1 (Pulvinal)

Assumptions made:

All devices have the same clinical efficacy and an equal adherence rate.

Submission conclusion:

Pulvinal will be the cheapest DPI on the market, saving between £1.90 and £121.11 per patient per annum on beclamethasone and between £4.56 and £19.96 per patient per annum on salbutamol.

Budgetary impact model presented:

None, bar individual patient figures.

Reviewer comment:

The Pulvinal device is currently not licensed in the UK, as such it is noted that the price quoted is only a projected price.

Products 2 and 3 (pMDI and Accuhaler)

Submission conclusion:

That the Drugs and Therapeutics Bulletin[21] recommendations for ages 6-12 are also applicable for the age group 5-15.

Budgetary impact model presented:

None, bar individual patient figures.

Reviewer comment:

No additional calculations have been conducted.

4.3 REVIEW GROUP MODEL

4.3.1 Methodology

Little evidence has been presented that show that the clinical outcomes are different between inhaler devices. As such the review group has undertaken a simple cost-minimisation approach, but also a QALY threshold approach.

The QALY is a more sophisticated measure of health benefit than the more traditionally used Life year gained (LYG), as it allows an indication of a patient's health in the LYG to be considered, allowing distinctions to be made between patients with full health and those that are severely disabled. In this subject area there is very little quality of life data, with none specifically provided by the sponsors. In addition this is a disease area with a low mortality rate and little evidence to suggest any treatment can improve this rate. As such, explicit cost per QALY values have not been calculated. The QALY threshold approach allows the marginal QALYs needed to be gained for a more expensive device to be purchased to be calculated.

For both methodologies all unit costs have been taken from BNF 41 March 2001[112] and MIMS May 2001.[124] These have been multiplied by the appropriate daily doses and are comparable with the prices in the submissions.[109,110,111,114,115,119,120,121] For devices that can be refilled, it has been assumed that 2 devices will be bought per annum, with refills bought for the remaining doses. For spacer devices, apart from where specifically stated in the manufacturer's guidance, it has been assumed that 2 spacers per annum are required. It is assumed that the spacers will be used without a mask. It has been further assumed that where a manufacturer of a pMDI does not manufacture a spacer, then a spacer made by a company which does not manufacture pMDIs would be added.

The cost-minimisation approach simply chooses the cheapest method of delivering the required daily dose assuming all devices are equivalent. Therefoe, only drug and device costs are considered.

The QALY threshold approach uses a relatively low default direct medical cost per QALY purchasing limit of £5,000, at which price it is assumed that the intervention would be purchased. Additional analyses have been undertaken assuming a £20,000 cost per QALY threshold, which is assumed to be the maximum price at which the intervention would be purchased. This form of analysis is preferable to that of cost-minimisation as it allows a more informed decision to be made if there is an expectation of different QALYs between devices.

For example, a clinician may believe that an individual patient would be more adherent on Device A, and that this would lead to an increase in the quality of life. If the estimation of the marginal QALYs was above the threshold values presented for Device A in Tables 1-12 in Appendix 18, then that device should be purchased at the relevant cost per QALY threshold. Alternative source of

increased QALYs may occur by reducing the deposit of drug in the orophangealor by suffering fewer asthma symptoms.

If conversely, the clinician believes that, for an individual patient, all devices are equivalent in terms of the QALYs accrued, then all marginal QALYs are zero, and the cheapest device should be selected. In this instance, this approach replicates the results of a cost-minimisation analysis. Examples are given in the tables in Appendix 18.

The scope of the project was the cost-effectiveness of the devices themselves, not the drug prescribed. As such the analysis has focussed on which device should be given if the clinician has decided that a certain drug is required. Thus there is a separate table for each drug considered.

Each table has assumed that the costs incurred by the NHS are independent of device type. That is, there will be no change in the amount of asthma medication prescribed, outpatient visits or GP consultations required dependent on device. On clinical advice the high strength beclamethasones (250 ug and above) and equivalent strengths for budesonide and fluticasone have not been costed due to their unsuitability for children.

The exception is for Easi-Breathe products that deliver beclamethasone and salbutamol, where the Norton Healthcare submission has provided some evidence that resources are saved. As such, beclamethasone Easi-Breathe devices have been modelled twice, once at its acquisition cost and once at a cost set to be a conservative £10 per patient per annum below the cheapest pMDI. The value of £10 is the approximate summation of differences for only those vectors with a statistically significantly different value and includes the reduction in costs due to reduced GP consultations. It has been assumed that the cost offsets seen in the submission were due to the beclamethasone device solely, and not the salbutamol device. It is stressed that the cost-offset attributed to the Easi-Breathe device is only valid in comparisons with patients who change to a new pMDI device and assuming that there was no bias introduced by the socio-economic status of those patients studied.

4.3.2 Results

Sample results are presented in Tables 1 – 12 in Appendix 18 with an example detailed in this section. In each table the devices have been ranked in ascending cost order. This allows the cost minimisation analysis to consist solely of selecting the first device on the list. Where this is an Easi-Breathe beclamethasone device, the second device could be selected if the cost-offset was not to be believed.

Although not presented the results for turbutaline sulphate, reproterol hyperchloride, nedocromil sodium, beclamethasone + salbutamol, fluticasone + salmeterol, ipratropium + salbutamol, ipratropium and fenoterol, salmeterol, eformoterol fumerate, ipratropium bromide are similar to those presented in Tables 1-5 in Appendix 18.

The results presented are for relatively low dosage levels. Tables 5 and 6, assumes a high dosage of beclamethasone is given.

An example of using the tables to determine the device for cost-minimisation

Table 3 in Appendix 18 assumes that a daily dose of 200 ug of Beclamethasone (100 ug for Qvar as per manufacturer's dosage levels) is required. A cost minimisation approach assumes equal efficacy and would thus select Beclazone Easi-breathe 100 at £18.62 per annum (device cost of £28.62 minus £10 cost offsets), if the £10 cost offset were to be believed. If this cost offset was not validated then Beclazone 200 would be selected as the cheapest device at £28.62 per annum.

An example of using the tables to determine the incremental QALY thresholds between devices

It is assumed that a daily dose of 200 ug of beclamethasone (100 ug for Qvar as per manufacturer's dosage levels) is required. (Table 2 in Appendix 18).

The QALY threshold approach allows some indication of the incremental QALYs that more expensive devices would need to achieve to be cost-effective at the £5,000 cost per QALY level.

As an example, Filair 200 would cost £28.73 per annum to provide the dose, assuming one daily puff of 200 ug Filair. With the addition of an AeroChamber the cost is £33.01 per annum, an incremental cost of £4.28. In order for the AeroChamber device to have a cost per QALY of £5,000, 0.00086 extra QALYs per annum would be required. (This is equivalent to less than 8 hours of perfect health per annum).

The value of 0.00086 can be found in the Filair 200 row and moving rightwards until the Filair 200 + Aerochamber column is found.

Thus, were it believed that the additional AeroChamber produced more QALYs than this figure, it would be deemed cost-effective at the £5,000 level, whereas conversely if it were believed that fewer QALYs would be produced then the device would not be cost-effective at this level.

Although beyond the initial scope of the project, different dosages of the drugs (e.g. Filair 100ug and 200ug) to achieve the same daily dose have been included in order that some indication is given of the QALYs needed to be obtained by giving two smaller strength doses rather than a single large dose as is sometimes clinical practice.

Calculating QALY threshold results

QALY threshold results for those drugs that are not presented can be calculated by the following formula, assuming that no costs offsets are considered.

(Device Cost A - Device Cost B) / Cost per QALY threshold selected.

Therefore if Device A cost £60 per annum and Device B cost £65 per annum, the QALY threshold value at £5,000 cost per QALY would be (65-60)/ 5000 = 0.001.

Further research

The trial size needed to detect a QALY difference of 0.008088 at a 95% significance level and 80% power, assuming a general population QALY standard deviation of 0.1[125,126,127] has been calculated.

.

The approximate number needed is calculated with the following formula[128]

16 / [(Effect size needed to detect / population standard deviation)]^2

Substituting in the numbers from our example

16 / [0.008088 / 0.1] ^ 2

which equals just under 2,500 in each arm.

As the detection level approaches 0.0025 and 0.0001, the number of patients required would rise to 25,600 and 160,000 respectively in each arm.

Such trials are likely to prove impractical, especially given the large numbers of potential combinations that exist.

Conclusions

It is seen in Table 3 in Appendix 18 the largest QALY needed at the 200 ug of Beclamethasone dose per day is 0.00809, assuming no Easi-Breathe cost offsets. (This equates to an additional 71 hours of perfecrt health per annum). It is clear that with the small QALY increase required that no intervention can be categorically dismissed as not being cost-effective. This is further compounded when the fact that a cost per QALY threshold of £5,000 has been taken. Using a threshold of £20,000 the largest incremental QALY shown is 0.002022 (Table 5 in Appendix 18), assuming no Easi-Breathe cost offset, and many QALY increments required less than 0.001. (This latter figure is equivalent to less than 9 hours of perfect helath per annum).

It is noted that the maximum incremental QALY needed for the other drugs analysed is comparable with the results for low dose beclamethasone. (Tables 7-12 in Appendix 18)

To put such QALY increments into perspective, suffering a wrist fracture in a year has a QALY loss of 0.01,[129] and suffering a vertebral fracture has a QALY loss of 0.092.[130]

It is stressed that these tables assume clinical equivalence. Were a device to prevent a hospitalisation compared with another device when both delivered the same medication, due for example to a patient's reluctance to use a device, the cost-effectiveness would be significantly reduced. The cost of an average hospitalisation for a patient over 5 years was calculated to be £857 per patient per stay at 1996 prices.[131] which is far in excess of the marginal costs presented. However, no submission with the exception of that of Norton Healthcare has made any claim on a reduction in resources used by different device type.

The tables presented in this analysis allow health providers to estimate, taking into consideration patient preferences, the device that is most likely to be cost-effective for an individual patient. In cases where the patient and clinician believe that the devices produce equivalent QALYs then the cheapest device should be selected, but in cases where there are estimations of different QALYs, the most appropriate device can be selected.

5. IMPLICATIONS FOR OTHER PARTIES

No implications for other parties were identified.

6. FACTORS RELEVANT TO NHS

With respect to CFC and HFA propellants although we are in the transition phase at present with dual availability of both CFC and CFC-free versions of the same product, for a number of products, this phase is coming to an end as the second pMDI non CFC corticosteroid is launched. From the evidence available there appear to be no differences between the old CFC and new HFA devices delivering equivally therapeutic doses of either reliever or anti-inflammatory asthma medication. The enforced change, whilst costly is also providing an opportunity for the NHS to review its prescribing practices. The evidence from this review should help to inform that debate.

7. DISCUSSION

Overall there is no evidence to suggest, on the grounds of relative clinical efficacy, that any one hand-held inhaler device is either better or worse than any other when used by children in the routine management of their chronic asthma. There is some evidence to support additional benefit of using a spacer with a pMDI rather than the pMDI on its own. Limited evidence, predominantly from observational studies, suggests that patient preference tends to favour one DPI over another, but good comparative data was sparse. Overall it would appear that choice of inhaler device does not represent a barrier to effective use in children over five years of age, if adequate instruction and supervision are provided.

In terms of cost effectiveness, the largest QALY needed at a dose of 200μg of beclomethasone dipropionate per day was calculated to be 0.00809, assuming no cost offsets from a breath-actuated device (Easi-Breathe). Thus with such a small QALY increase required no intervention can be categorically dismissed as not being cost-effective.

Further studies, using double blind randomised studies with adequate power are needed and subjects representing the full profile of the disease, from the mild to moderate to those at the severe end of the disease spectrum. Such studies also need a qualitative component to try and understand the factors that underlie children's relationships with their condition and their management thereof. The third dimension to any future studies is to ensure that they are sufficiently powered to examine health resource differences and asthma symptoms between devices.

8. CONCLUSIONS

Only one submission[109] provided data that a device produces direct medical cost offsets compared with an alternative device for the defined population.

None of the submissions provided quantitive data on any quality of life benefits associated with a specific device compared with another.

The yearly costs of each device and drug type were calculated. Assuming a cost per QALY threshold levels of £5,000 or £20,000 it was seen that the marginal QALYs needed to be deemed cost-effective were very small.

As such no device type could be categorically rated as not cost-effective. Tables 1-12 in Appendix 18 provide indications of the marginal QALYs needed when comparing between devices.

If a clinician and patient decide that a device would improve a patient's quality of life by more than the marginal QALY then the more expensive device should be selected. However, if the clinician and patient concur that the patient's quality of life is not affected by device-type then the cheapest device should be selected.

9. APPENDICES

APPENDIX 1

Chart 1

Management of chronic asthma in adults and schoolchildren

- Avoidance of provoking factors where possible
- Patient's involvement and education
- Selection of best inhaler device
- Treatment stepped up as necessary to achieve good control
- Treatment stepped down if control of asthma good

Notes

- **Patients should start treatment at the step most appropriate to the initial severity. A rescue course of prednisolone may be needed at any time and at any step. The aim is to achieve early control of the condition and then to reduce treatment.**
- **Until growth is complete any child requiring beclomethasone or budesonide > 800 µg daily or fluticasone > 500 µg daily should be referred to a paediatrician with an interest in asthma.**

Prescribe a peak flow meter and monitor response to treatment

Step 1:

Occasional use of relief bronchodilators

Inhaled short acting β agonists "as required" for symptom relief are acceptable. If they are needed more than once daily move to step 2. Before altering a treatment step ensure that the patient is having the treatment and has a good inhaler technique. Address any fears.

Step 2:

Regular inhaled anti-inflammatory agents

Inhaled short acting β agonists as required
plus
beclomethasone or budesonide 100–400 µg twice daily or fluticasone 50–200 µg twice daily. Alternatively, use cromoglycate or nedocromil sodium, but if control is not achieved start inhaled steroids

Step 3:

High dose inhaled steroids or low dose inhaled steroids plus long acting inhaled β agonist bronchodilator

Inhaled short acting β agonists as required
plus either
beclomethasone or budesonide increased to 800–2000 µg daily or fluticasone 400–1000 µg daily via a large volume spacer
or
beclomethasone or budesonide 100–400 µg twice daily or fluticasone 50–200 µg twice daily plus salmeterol 50 µg twice daily. In a very small number of patients who experience side effects with high dose inhaled steroids, either the long acting inhaled β agonist option is used *or* a sustained release theophylline may be added to step 2 medication. Cromoglycate or nedocromil may also be tried.

Step 4:

High dose inhaled steroids and regular bronchodilators

Inhaled short acting β agonists as required with inhaled beclomethasone or budesonide 800–2000 µg daily or fluticasone 400–1000 µg daily via a large volume spacer
plus
a sequential therapeutic trial of one or more of

- inhaled long acting β agonists
- sustained release theophylline
- inhaled ipratropium or oxitropium
- long acting β agonist tablets
- high dose inhaled bronchodilators
- cromoglycate or nedocromil.

Step 5:

Addition of regular steroid tablets

Inhaled short acting β agonists as required with inhaled beclomethasone or budesonide 800–2000 µg daily or fluticasone 400–1000 µg daily via a large volume spacer and one or more of the long acting bronchodilators
plus
regular prednisolone tablets in a single daily dose

Stepping down:

Review treatment every three to six months. If control is achieved a stepwise reduction in treatment may be possible. In patients whose treatment was recently started at step 4 or 5 or included steroid tablets for gaining control of asthma this reduction may take place after a short interval. In other patients with chronic asthma a three to six month period of stability should be shown before slow stepwise reduction is undertaken.

Outcome of steps 1–3: control of asthma

- Minimal (ideally no) chronic symptoms, including nocturnal symptoms
- Minimal (infrequent) exacerbations
- Minimal need for relieving bronchodilators
- No limitations on activities including exercise
- Circadian variation in peak expiratory flow (PEF) < 20%
- PEF ≥ 80% of predicted or best
- Minimal (or no) adverse effects from medicine

Outcome of steps 4–5: best possible results

- Least possible symptoms
- Least possible need for relieving bronchodilators
- Least possible limitation of activity
- Least possible variation in PEF
- Best PEF
- Least adverse effects from medicine

NATIONAL ASTHMA CAMPAIGN conquering asthma

BRITISH THORACIC SOCIETY

Working for Healthier Lungs

in association with the General Practitioner in Asthma Group, the British Association of Accident and Emergency Medicine, the British Paediatric Respiratory Society and the Royal College of Paediatrics and Child Health

Adapted from poster designed by Business Design Group

APPENDIX 2 Electronic bibliographic databases searched

1. Best Evidence
2. Biological Abstracts
3. CCTR (Cochrane Controlled Trials Register)
4. CDSR (Cochrane Database of Systematic Reviews)
5. Embase
6. HEED (Health Economic Evaluations Database)
7. HMIC (Health Information Management Consortium - comprising DH-Data, the King's Fund Database, and Helmis)
8. Medline
9. NHS DARE (Database of Assessments of Reviews of Effectiveness)
10. NHS EED (Economic Evaluations Database)
11. NHS HTA (Health Technology Assessment)
12. PsycINFO
13. PubMed (last 90 days)
14. Science Citation Index
15. Social Sciences Citation Index

APPENDIX 3 Other sources searched

1. ABPI (Association of the British Pharmaceutical Industry)
2. AHRQ (Agency for Healthcare Research and Quality)
3. Alberta Clinical Guidelines Programme
4. American Thoracic Society
5. ARIF (Aggressive Research Intelligence Facility)
6. Bandolier
7. British Thoracic Society
8. CCOHTA (Canadian Co-ordinating Centre for Health Technology Assessment)
9. CCT (Current Controlled Trials)
10. CenterWatch Trials Register
11. Centre for Clinical Effectiveness, Monash University
12. Centre for Health Economics, University of York
13. ClinicalTrials.gov, NIH Clinical Trials Database
14. CRiB (Current Research in Britain)
15. eMC(Electronic Medicines Compendium)
16. EMEA (European Agency for the Evaluation of Medicinal Products)
17. eGuidelines
18. HSTAT (Health Services/Technology Assessment Text, US National Library of Medicine)
19. INAHTA (International Network of Agencies for Health Technology Assessment) Clearinghouse
20. MCA (Medicines Control Agency)
21. MRC (Medical Research Council) Funded Projects Database
22. National Guideline Clearinghouse
23. National Heart, Lung and Blood Institute
24. National Research Register
25. NCCHTA (National Co-ordinating Centre for Health Technology Assessment)
26. NHS CRD (Centre for Reviews and Dissemination), University of York
27. NHS R&D Programmes
28. NIH (National Institutes of Health) Consensus Development Programme
29. North of England Guidelines, University of Newcastle
30. OMNI (Organising Medical Networked Information)
31. ReFeR (Research Findings Register)
32. SBU (Swedish Council for Health Technology Assessment)
33. ScHARR Library Catalogue
34. SIGN (Scottish Intercollegiate Guidelines Network)
35. SumSearch
36. Trent Working Group on Acute Purchasing
37. TRIP (Turning Research into Practice) Database
38. Health Evidence Bulletins, Wales
39. Wessex DEC (Development and Evaluation Committee) Reports
40. West Midlands DES (Development and Evaluation Services) Reports

APPENDIX 4 Search strategies used

Best Evidence

(Ovid Biomed 1991-present)

1 asthma$.mp. [mp=title, abstract, full text, keywords, caption text]
2 inhal$.mp. [mp=title, abstract, full text, keywords, caption text]
3 aerosol$.mp. [mp=title, abstract, full text, keywords, caption text]
4 meter$ dose$.mp. [mp=title, abstract, full text, keywords, caption text]
5 mdi.mp. [mp=title, abstract, full text, keywords, caption text]
6 mdis.mp. [mp=title, abstract, full text, keywords, caption text]
7 pmdi$.mp. [mp=title, abstract, full text, keywords, caption text]
8 spacer$.mp. [mp=title, abstract, full text, keywords, caption text]
9 or/2-8
10 1 and 9
11 child$.mp. [mp=title, abstract, full text, keywords, caption text]
12 infant$.mp. [mp=title, abstract, full text, keywords, caption text]
13 adolescent$.mp. [mp=title, abstract, full text, keywords, caption text]
14 teenager$.mp. [mp=title, abstract, full text, keywords, caption text]
15 paediat$.mp. [mp=title, abstract, full text, keywords, caption text]
16 pediat$.mp. [mp=title, abstract, full text, keywords, caption text]
17 or/11-16
18 10 and 17

Biological Abstracts

(SilverPlatter WebSPIRS-present)

#5 #1 and #2 and #3 and #4
#4 trial*
#3 (child* or infant* or adolescent* or teenager* or paediat* or pediat*)
#2 (inhal* or haler* or aerosol* or meter* dose* or mdi or mdis or pmdi* or or spacer*)
#1 asthma*

CDSR and CCTR

(The Cochrane Library 2001 Issue 2)

#1 asthma*:me
#2 asthma*
#3 #1 or #2
#4 administration-inhalation*:me
#5 nebulizers-and vaporizers*:me
#6 aerosols*:me
#7 aerosol*
#8 inhaler*
#9 nebuliz*
#10 nebulis*
#11 meter* near dose*
#12 mdi or mdis
#13 pmdi*
#14 #4 or #5 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
#15 child*:me
#16 #3 and #14

#17 #16 and #15

Cinahl
(Ovid Biomed 1982-present)
1 exp asthma/
2 asthma$.tw
3 or/1-2
4 “nebulizers and vaporizers”/
5 aerosols/
6 inhal$.tw
7 aerosol$.tw
8 powder$.tw
9 meter$ dose$.tw
10 (mdi or mdis).tw
11 pmdi$.tw
12 spacer$.tw
13 or/4-12
14 3 and 13
15 exp child/
16 child$.tw
17 infant$.tw
18 adolescent$.tw
19 teenager$.tw
20 paediat$.tw
21 pediat$.tw
22 14 and 21

Citation Indexes (Science and Social Sciences)
(Web of Science 1981-present)
Topic=asthma* and (inhal* or aerosol* or meter* dose* or mdi or mdis or pmdi* or spacer*) and (child* or infant* or teenager* or adolescent* or paediat* or pediat*) and trial*; DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI; Timespan=All Years (sorted by latest date)

CRD Databases (NHS DARE, EED, HTA)
(CRD Web site - complete databases)
asthma*/All fields AND (inhal* or aerosol* or meter* dose* or mdi or mdis or pmdi* or spacer*)/All fields AND (child* or infant* or teenager* or adolescent* or paediat* or pediat*)/All fields

Embase
(SilverPlatter WebSPIRS 1980-present)
#37 #23 or #30 or #34 or #36
#36 #22 and #25
#35 spacer* or holding chamber* or aerochamber or babyhaler or haleraid or nebuhaler
#34 #22 and #33
#33 #31 or #32

#32 integra or fisonair or nebuhaler or aeroscopic or syncroner or nebuchamber or volumatic or rotahaler or spinhaler or turbuhaler or diskus or sidestream or ventstream or lc plus or lc star or halo lite or aerobec or aerolizer or pari baby
#31 maxivent or spacehaler or asmaven or salamol or autohaler or airomir or salbulin or easibreathe or easi-breathe or evohaler or ventolin or bricanyl or berotec or bronchodil or serevent or alupent or atrovent or oxivent or combivent or duovent or beclazone or filair or becotide or becloforte or qvar or pulmicort or flixotide or ventide or seretide or cromogen or intal or tilade or aerocom or aerobec or asmal or clickhaler or ventodisk* or diskhaler or rotohaler or turbohaler or foradil or aerocap* or asmabec or rotacap* or accuhaler or steri-nab or ipratropium or respontin
#30 #22 and #29
#29 #24 or #25 or #26 or #27 or #28
#28 inhal* suspen*
#27 powder inhal*
#26 pmdi* in ti, ab
#25 (mdi or mdis) in ti, ab
#24 meter* dose*
#23 #22 and #13
#22 #3 and #21
#21 #14 or #15 or #16 or #17 or #18 or #19 or #20
#20 pediat*
#19 paediat*
#18 teenager*
#17 adolescent*
#16 infant*
#15 child*
#14 explode 'child-' / all subheadings
#13 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
#12 nebulis*
#11 nebuliz*
#10 powder*
#9 aerosol*
#8 explode 'nebulizer-' / all subheadings
#7 'aerosol-' / all subheadings
#6 'inhalational-drug-administration' / all subheadings
#5 'inhalation-' / all subheadings
#4 explode 'inhaler-' / all subheadings
#3 #1 or #2
#2 asthma* in ti, ab
#1 explode 'asthma-' / all subheadings

HEED
(OHE HEED CD-ROM - complete database)

Search terms:
- asthma*
- inhal* or haler* or aerosol* or meter* dose* or mdi or mdis or pmdi* or spacer*
- child* or infant* or adolescent* or teenager* or paediat* or pediat*

Fields searched:
- Abstract
- All data
- Article title
- Book title
- Keywords
- Technology Assessed

HMIC
(SilverPlatter WinSPIRS 1983-present)
#1 asthma*
#2 inhal*
#3 haler*
#4 aerosol*
#5 meter* dose*
#6 mdi or mdis
#7 pmdi*
#8 spacer*
#9 #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 1 and #9
#11 child*
#12 infant*
#13 adolescent*
#14 teenager*
#15 paediat*
#16 pediat*
#17 #11 or #12 or #13 or #14 or #15 or #16
#18 #9 and #17

Medline
(Ovid Biomed 1966-present)
1 exp asthma/
2 asthma$.tw
3 or/1-2
4 administration, inhalation/
5 “nebulizers and vaporizers”/
6 exp aerosols/
7 is.fs
8 aerosols.rw
9 powders.rw

10 nebuliz$.tw
11 nebulis$.tw
12 or/4-11
13 3 and 12
14 meter$ dose$.tw
15 (mdi or mdis).tw
16 pmdi$.tw
17 powder inhal$.tw
18 inhal$ suspens$.tw
19 or/14-18
20 3 and 19
21 maxivent.af
22 spacehaler.af
23 asmaven.af
24 salamol.af
25 autohaler.af
26 airomir.af
27 salbulin.af
28 easibreathe.af
29 easi-breathe.af
30 evohaler.af
31 ventolin.af
32 bricanyl.af
33 berotec.af
34 bronchodil.af
35 serevent.af
36 alupent.af
37 atrovent.af
38 oxivent.af
39 combivent.af
40 douvent.af
41 beclazone.af
42 filair.af
43 becotide.af
44 becloforte.af
45 qvar.af
46 pulmicort.af
47 flixotide.af
48 ventide.af
49 seretide.af
50 cromogen.af
51 intal.af
52 tilade.af
53 aerocom.af
54 aerobec.af
55 asmasal.af
56 clickhaler.af
57 ventodisk$.af
58 diskhaler.af
59 rotohaler.af

60 turbohaler.af
61 foradil.af
62 aerocap$.af
63 asmabec.af
64 rotacap$.af
65 accuhaler.af
66 steri-nab.af
67 ipratropium.af
68 respontin.af
69 or/21-69
70 3 and 69
71 integra.af
72 fisonair.af
73 nebuhaler.af
74 aeroscopic.af
75 syncroner.af
76 nebuchamber.af
77 volumatic.af
78 rotahaler.af
79 spinhaler.af
80 turbuhaler.af
81 diskus.af
82 sidestream.af
83 ventstream.af
84 lc plus.af
85 lc star.af
86 halo lite.af
87 aerobec.af
88 aerolizer.af
89 pari baby.af
90 or/71-89
91 3 and 90
92 spacer$.tw
93 holding chamber$.tw
94 aerochamber.tw
95 babyhaler.af
96 haleraid.af
97 nebuhaler.af
98 or/92-97
99 3 and 98
100 13 or 20 or 70 or 91 or 99
101 exp child/
102 child$.tw
103 infant$.tw
104 adolescent$.tw
105 teenager$.tw
106 paediat$.tw
107 pediat$.tw
108 or/101-107
109 100 and 108

PsycINFO
(SilverPlatter WebSPIRS 1967-present)
#19 #18 and #17
#18 #3 and #11
#17 #12 or #13 or #14 or #15 or #16
#16 paediat* or pediat*
#15 teenager*
#14 adolescent*
#13 infant*
#12 child*
#11 #4 or #5 or #6 or #7 or #8 or #9 or #10
#10 spacer*
#9 powder*
#8 pmdi*
#7 mdi or mdis
#6 meter* dose*
#5 inhal*
#4 aerosol*
#3 #1 or #2
#2 asthma*
#1 'asthma-' in de

PubMed
(last 90 days from 18/05/01)
#26 Search #16 AND #24 Limits: 90 days
#25 Search #16 AND #24
#24 Search #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
#23 Search pediat* [tw]
#22 Search paediat* [tw]
#21 Search teenager* [tw]
#20 Search adolescent* [tw]
#19 Search infant* [tw]
#18 Search child* [tw]
#17 Search child [mh]
#16 Search #3 AND #15
#15 Search #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
#14 Search spacer* [tw]
#13 Search pmdi* [tw]
#12 Search mdis [tw]
#11 Search mdi [tw]
#10 Search meter* dose* [tw]
#9 Search powder* [tw]
#8 Search inhaler* [tw]
#7 Search aerosol* [tw]
#6 Search aerosols [mh]
#5 Search "nebulizers and vaporizers" [mh]
#4 Search administration, inhalation [mh]

#3 Search #1 and #2
#2 Search asthma* [tw]
#1 Search asthma [mh]

In vitro search strategies (2000-present)

Embase
(SilverPlatter WebSPIRS 2000-present)
#1 #11 and (PY=2000-2001)
#2 #3 and #10
#3 #4 or #5 or #6 or #7 or #8 or #9
#4 random* near5 trial*
#5 'randomized-controlled-trial' / all subheadings
#6 single blind procedure / all subheadings
#7 double blind procedure / all subheadings
#8 crossover procedure / all subheadings
#9 randomization / all subheadings
#10 #1 and #2
#11 asthma*
#12 'in vitro'

Medline
(Ovid Biomed 2000-present)
1 in vitro.af
2 exp asthma/
3 asthma$.tw
4 or/2-3
5 clinical trial.pt
6 5 and 6
7 limit 7 to yr=2000-2001

Methodological search filters used in Ovid Medline

Guidelines

1 guideline.pt
2 practice guideline.pt
3 exp guidelines/
4 health planning guidelines/
5 or/1-4

Systematic reviews

1 meta-analysis/
2 exp review literature/
3 (meta-analy$ or meta analy$ or metaanaly$).tw
4 meta analysis.pt
5 review academic.pt
6 review literature.pt
7 letter.pt
8 review of reported cases.pt
9 historical article.pt
10 review multicase.pt
11 or/1-6
12 or/7-10
13 11 not 12

Randomized controlled trials

1 randomized controlled trial.pt
2 controlled clinical trial.pt
3 randomized controlled trials/
4 random allocation/
5 double blind method/
6 or/1-5
7 clinical trial.pt
8 exp clinical trials/
9 ((clin$ adj25 trial$)).ti, ab
10 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti, ab
11 placebos/
12 placebos.ti, ab
13 random.ti, ab
14 research design/
15 or/7-14
16 comparative study/
17 exp evaluation studies/
18 follow up studies/
19 (control$ or prospectiv$ or volunteer$)).ti, ab
20 prospective studies/
21 or/16-20
22 6 or 15 or 21

Economic evaluations

1 economics/
2 exp “costs and cost analysis”/
3 economic value of life/
4 exp economics, hospital/
5 exp economics, medical/
6 economics, nursing/
7 economics, pharmaceutical/
8 exp models, economic/
9 exp “fees and charges”/
10 exp budgets/
11 ec.fs
12 (cost or costs or costed or costly or costing$).tw
13 (economic$ or pharmacoeconomic$ or price$ or pricing).tw
14 or/1-13

Unwanted effects

1 ae.fs
2 ct.fs
3 co.fs
4 ((side or adverse or unintended or unwanted) adj2 (effect$ or event$)).tw
5 harm$.tw
6 complication$.tw
7 contraindication$.tw
8 or/1-7

Patient preference/compliance

1 exp patient acceptance of health care/
2 patient$ complian$.tw
3 patient$ preference$.tw
4 or/1-3

Quality of life (asthma)

1 exp quality of life/
2 quality of life.tw
3 life quality.tw
4 qaly$.tw
5 quality adjusted life year$.tw
6 (sf36 or sf 36 or short form 36).tw
7 (eq5d or eq 5d or euroqol).tw
8 asthma self-efficacy scale.tw
9 juniper.tw
10 asthma quality of life questionnaire.tw
11 aqlq.tw
12 living with asthma questionnaire.tw
13 asthma bother profile.tw
14 asthma symptom checklist.tw
15 childhood asthma questionnaire.tw

16 paediatric asthma quality of life questionnaire.tw
17 child asthma short form.tw
18 children$ health survey for asthma.tw
19 about my asthma.tw
20 or/1-19

APPENDIX 5 Excluded studies

Study	Reason for exclusion
Baumgarten et al. 2000	patients aged > 15 years old
Bourne et al. 1996	not available from the British Library
Williams & Richards 1997	comparing different drug and doses (400μg budesonide vs 200μg fluticasone propionate)
Cavagni et al. 1993	spacer device (Jet disposable - Chiesi Farmaceutici S.p.A., Parma, Italy) not in criteria
Cunnningham & Crain 1994	on patients with episodic Emergency Department visit for an acute asthma attack
Spector2000	review article on oral therapy
Price & Kemp 1999	on oral tablet therapy
Liam & Lim 1998	include children with acute asthma
Ruggins et al. 1993	on patients with acute asthma
Milanowski et al. 1999	adult patients, comparing different drug doses
Brand et al. 2001	patients aged < 5 years old
Salat et al. 2000	patients aged > 15 years old
Tonnel et al. 2000	patients aged > 15 years old
Ayres et al. 2000	patients aged > 15 years old
Perruchoud et al. 2000	patients aged > 15 years old
Demedts et al. 1999	patients mostly > 15 years old
Magnussen 2000	patients aged > 15 years old
Quezada et al. 1999	comparing effects of different drugs
Beerendonk et al 1998	patients aged > 15 years old
Dahl et al 1997	patients aged > 15 years old
Mawhinney et al. 1991	patients aged > 15 years old
Conroy et al. 2000	on drugs
Chang et al 2000	on asthma management
Geoffroy et al. 1999	patients aged > 15 years old
Jacobson et al. 1999	patients aged > 15 years old
Samaranayake & Perera 1998	acute asthma
Berg & Dunbar-Jacob 1998	patients aged > 15 years old
Zar et al. 1999	acute asthma
Thompson et al. 1998	patients aged > 15 years old
Seale & Harrison 1998	patients aged > 15 years old
Argenti et al. 2000	patients aged > 15 years old
Zar et al. 1999	acute asthma
Quittner et al. 2000	patients with cystic fibrosis
Shappiro et al. 1998	different drug doses
Chan & DeBruyne 2000	study's population was parents
Giannini et al. 2000	patients aged > 15 years old
Santanello et al. 1999	patients aged > 15 years old
Jones et al. 1992	on asthma morbidity in primary care
Lipworth et al. 1998	on drugs

Bousquet J et al. 2000	on drugs
Wildhaber JH et al. 1996	< 4 years old
Warren & Zuberbuhler, 1998	< 5 yrs old
Schlaeppi M et al., 1996	>=16 yrs old
Clark & Lipworth	healthy volunteers
Thorsson et al., 1994	> 15 yrs old
Wildhaber et al., 2000	>= 18 years old
****Nielsen et al. 1998	not comparing devices
Newman et al., 1989	Patients aged 21-76 yrs old
Smith et al, 1998	comparing different drugs
Mitchell & Nigel, 1997	In-vitro testing of 3 spacers - not in our criteria
Barry & O'Callaghan, 1996	In-vitro drug delivery fr. 7 spacers - not in our criteria
Pierart et al, 1999	In-vitro, subjects are health adult volunteers
Barry et al, 1999	In-vitro, spacer devices - not in our criteria
Barry & O'Callaghan, 1997	In-vitro, drug delivery and spacer - not in our criteria
Berg et al, 1998	In-vitro, spacer and pMDI - not in our criteria
Wildhaber et al, 1996	In-vitro, spacer device - not in our criteria
Everard et al., 1992	In-vitro, spacers - not in our criteria
Chuffart et al., 2001	in-vitro, spacers - not in our criteria
$$$$ Pedersen, 1983	Acute asthma
Oliver et al., ?? (Ref. 2436)	non-RCT, cross-over study
Gurwitz et al, 1983	non-rct, acute and chronic asthma
Solé et al, 1993 (2484)	acute asthma
Nankani et al, 1990 (2516)	drug not inhaler device intervention
Petrie et al, 1990 (2381)	adults only
Xuan et al, 1989 (2511)	drug not device
Ståhl et al, 1996 (2507)	drug not device
Ahrens et al, 1995 (2361)	in vitro, wrong research question
Chapman, 1995 (2499)	review
Löfdahl et al, 1994 (2509)	abstract only
Pedersen & Hansen, 1995 (2512)	drug intervention
Corris et al, 1992 (2505)	drug intervention
Repper et al, 1994 (2515)	drug intervention
Juntunen-Backman et al, 1996 (2445)	abstract only
Burgess et al, 1993 (2420)	abstract only
Barry & O'Callaghan, 1994 (2444)	in vitro, but wrong research question
Fuller, 1986 (2424)	adults
Böllert et al, 1997 (2419)	adults
O'Reilly et al, 1986 (2437)	adults
Dubus & Dolvich, 2000 (2400)	in vitro, wrong research question
Mahadewsingh et al, 1996 (2433)	adults
Stenius-Aarniala et al, 1993	adults

(2440)	
Finlay & Zuberbuhler, 1999 (2403)	subjects < 5 years
Turpeinen et al, 1999 (2416)	subjects < 5 years
pedersen & Mortensen, 1990 (2412)	non-asthmatic children
Terzano & Mannino, 1996 (2441)	in vitro, wrong research question
Vidgren et al, 1988 (2397)	healthy volunteers
Benedictus et al, 1994 (2485)	drug intervention
Agertoft & Pedersen, 1994 (2407)	subjects < 5 years
Gorman et al, 1990 (2411)	drug intervention
Newman et al, 1991 (2479)	adults
Zainudin et al, 1990 (2486)	adults
Engel et al, 1990 (2487)	subjects > 15 years
Gunawardena et al, 1997 (2426)	adults
Deenstra et al, 1988 (2423)	adults
Laurikainen et al, 1997 (2432)	adults
Nelson & Loffert, 1994 (2435)	adults
Haahtela et al, 1994 (2427)	adults
Lipworth & Clark, 1997 (2396)	healthy volunteers
Lipworth & Clark, (2492)	abstract only
Pedersen, 1992 (2474)	abstract only
Kassirer, 1994 (2497)	editorial
Nantel et al, 1996 (2475)	device unknown, no drug delivered
Hidinger & Dorow, 1984 (2429)	adults
Oliver et al, (2436)	non randomised
Pedersen, 1983 (2438)	acute asthma
Gurwitz et al, 1983 (2483)	acute asthma
Dawson et al, 1985 [132]	different drug doses
Hirsch et al, 1997 [78]	acute asthma
Weinstein, 2000 [133]	discussion article
Agertoft&Pedersen, 1998 [134]	inhaler technique training intervention
Haughney, 1995 [135]	discussion article
Gillies, 1997 [136]	discussion article
Ahonen et al, 2000 [137]	some included papers in abstract form only

Papers in foreign language – not extracted

Study
Carrion Valero et al., 2000
Aguilar Miranda & Mallol Villablanca 2000
Sanchez-Jimenez et al., 1998
Chinet, 2000
Rufin et al., 2000
Garde Garde & Pomares, 1999
Zureik & Delacourt, 1999
Alvarez et al, 2001
Dubus, 2001
Dubus et al, 1997
Aceves et al, 1995
Cordero et al, 1987

APPENDIX 6 pMDIs with or without spacer vs pMDIs with or without spacer, with the same propellants, delivering bronchodilating drugs (Randomised controlled trials, physiological and clinical outcomes)

Authors, year	Treatment inhaler type, drug and dose Study design	Location, setting, inclusion/exclusion power calculation, type of analysis	Patients, number, age mean± SD (range), male/female, ethnicity	Follow-up Outcomes	Results	Comments
Kerac *et al.*, 1998[47]	**T1:** MDI **T2:** MDI+spacer (Volumatic, Glaxo Inc.) **T3:** MDI+plastic 1-litre soft-drink bottle spacer **T4: MDI** **Drug:** Salbutamol (2 puffs) T1, T2 & T3). Placebo T4 **Design:** Randomised, double-blind, placebo-controlled Jadad's score = 3	1 site, Calcutta, India. **In:** chronic stable asthmatic outpatients **Out:** none **Power calculation** no **Per protocol analysis** assumed	**At beginning:** 48 **At end:** 48 **Age:** 43.8 ±3.5 (10 - 75) **M/F:** 25/23	**Run-in: S**albutamol 4 mg + deriphyllin 100 mg taken orally 3 times/day was withheld overnight. Morning baseline PEFR <80% of predicted for age and height. **FU:** Patients attended on 4 occasions, each 2 weeks apart. All devices used on each occasion but only one contained active drug. **Primary:** PEFR measured 15 and 30 min after MDI administration	Mean±SE baseline PEFR, 156.9±8.4. No significant differences among the 4 groups (p> 0.1). Significant % improvement in PEFR over baseline in T" and T3 compared with T4, 30 min after inhalation, and in T2 vs T4 at 15 min after inhalation (both p<0.05). No differences between T1 and T4.	Mostly adult patients. Plastic bottle spacer is as effective as commercial spacer.
Green & Price, 1991 [48]	**T1:** MDI+spacer (Volumatic) & placebo via MDI **T2:** MDI & placebo via MDI+spacer **T3:** placebo via both devices **Drug:** Salbutamol, 200 µg **Design:** randomised, single-blind (patient), placebo-controlled Jadad's score = 1	1 site, London, U.K. **In:** asymptomatic at the time of study, proficient in FEV, manoevres Power calculation: no Per protocol analysis assumed	**At beginning:** 10 **At end:** 10 **Age:** 11(8-14) **M/F: nil**	**Run-in:** stop medication 24h before study **FU:** 3 occasions – 2 to 7 days apart and within 14 days. **Primary:** baseline FEV_1(BO), FEV_1 after 15 min (B15), FEV_1 after a further 15 min (B30)	No significant difference in baseline FEV_1 for the study days (P>0.05). From B0 to B15, standardisesd FEV_1 rose significantly in T1 (mean+8.1%, 95%CI±4.2%, p=0.0005) and T2 (mean+5.9% CI±1.8%, p=0.0005)vs. T3 (mean+0.25%, 95% CI±2.5%, paired *t*-test).	No significant difference in bronchodilation between MDI+ spacer and MDI. Retrospective power calculation, 75 subjects needed.
Lee & Evans, 1987[52]	**T1:** MDI **T2:** MDI+ spacer (InspirEase) **T3:** MDI+spacer (Aerochamber)	1 center, New York **In:** stable asthma, correct inhalation technique from a MDI, receiving beta-agonist aerosol	**At beginning:** 23 **At end:** 20	**Run-in:** taught proper use of 3 inhalation aids (InspirEase,	14 children have correct inhalation technique while 6 have errors. Incorrect technique - 1 with MDI, 3 with InspirEase, 2 with InspirEase & Aerochamber, 0 for Aerosol Bag.	No additional benefits from T2,T3 & T4 for those with MDI

	T4: MDI+spacer (Aerosol Bag) **Drug:** Albuterol, 2 puffs, 180 μg All operations were assisted by the examiner to ensure correct use of aids. **Design:** randomised, double-blind, cross over, placebo Jadad's score = 3	from MDI. **Power calculation:** no **Per protocol analysis** assumed	**Age**: 12.5(8-15) **M/F: nil**	Aerochamber, Aerosol Bag) in laboratory. **FU:** 3 subsequent days **Primary:** pulmonary function (FEV_1), correct MDI technique	Overall and for 14 children with correct technique, no significant differences in FEV_1 % increase from baseline over 3 hours, following inhalation, in all treatment groups. For 6 children with incorrect MDI technique significant difference ($p<0.05$) in FEV1% increase from baseline, over 3 hours after inhalation between T2, T3 and T4 compared with T1. Also at 15 and 30 minutes only, T2 and T4 > T3 ($p<0.05$)., Side effects similar in all treatments.	correct technique but benefit of spacer with incorrect MDI technique. Aerochamber requires slightly greater skill in its use than InspirEase & Aerosol Bag. The latter two aids allow re-breathing of aerosol while Aerochamber doesn't. All aids require some skill in using - teaching is important for effective use.
Rachelefsky *et al*., 1986	**T1:** MDI placebo **T2:** MDI **T3:** MDI+spacer placebo **T4:** MDI+spacer (Aerochamber, Monagham Medical Corporation) **Drug:** Brochodilator Metaprterenol sulphate, 130 μg, 2 puffs **Design:** randomised, double-blind, placebo-controlled Jadad's score = 2	1 site, USA. **In:** moderate asthma, fulfilled the American Thoracic Society criteria for reversible airway disease **Power calculation:** no **Per protocol analysis** assumed	**At beginning:** 16 **At end:** 16 **Age:** 9±2 SD (5-12) **M/F: nil**	**Run-in:** instruction given on proper closed-mouth technique at each visit, including 3-minute videotape viewing. All bronchodilators were stopped 12h before and long-acting theophylline 24h before time of study. **FU:** 4 separate days. **Primary:** FEV1, FVC, midmaximal expiratory volume (FEF25-75%) before, 5, 14, 30 min & hourly for 6 hours after drug administration. **Secondary:** side effects	No significant difference between T2 &T4 for FEV_1 and $FEF_{25-75\%}$. Both T2 & T4 signifianctly different from placebo (T1, T3). ***FEV_1 increases from baseline over a 6-hr period (%inc±SD)*** / ***$FEF_{25-75\%}$ % increases % from baseline*** **Time** **T2** **T4** **T2** **T4** 15 min 26±12* 18±12* 56±16* 44±45* **30 min** 25±10* 20±14* 56±17* 47±54* **1h** 32±12* 20±18* 74±29* 53±63* **2h** 27±9* 23±23* 62±29* 49±74* **3h** 17±7 15±22 37±35* 36±51* **4h** 14±13 6±15 34±29* 29±38* **5h** 9±13 4±21 21±33 9±21 **6h** 3±10 1±19 3±21 6±36 No obvious side-effect was noted.	The pMDI tube spacer (aerochamber) is as effective as the standard MDI device in administering metaproterenol to asthmatic children who ideally have been taught to use both correctly.
Becler *et al.*	**T1: MDI**+spacer (tube 80ml.	1 hospital, Canada	**At**	**Run-in:** stop oral	**Pulmonary functions values** (mean±SEM for % predicted normal for	Both

1985[49]	10x3.2cm) & placebo via MDI **T2:** MDI & placebo via MDI+spacer **T3:** placebo via both devices **Drug:** Terbutaline, 250µg/actuation, given in a total doese of 500µg. Placebo was the cfc propellant-surfactant mixture used in the active inhaler **Design:** randomised, double-bline, placebo-controlled Jadad's score = 2	**In:** had a history of asthma, documented reversibility of obstruction to airflow previously (increase FEV_1>20% after a bronchodilator aerosol), $FEF_{25-75\%}$ <70% predicated normal.- **Out:** severe acute asthma on study day **Power calculation:** no **Per protocol analysis** assumed	**beginning:** 34 T1: 12 T2: 12 T3: 10 **At end:** 34 **Age:** **T1:** 11.7±0.8 **T2:** 10.2±0.6 **T3:** 10.5±0.6 **M/F: nil**	medication for 12 h or inhaled bronchodilator aerosol for 6 h before study. Demonstration & supervision given by investigator **FU:** 3 occasions – 2-7 days apart and withn 14 days. **Primary:** pulmonary functions	age, sex & height for FEV1/FVC which is an absolute value). T3 placebo results omitted from this table. **Test** **Pre-treatment** **0.5** **1.0** **1.5** **2.0** **Hours post-treatment** **FEV_1 T1** 78.3±6.1" 93.3±6.6 92.7±6.4 90.8±6.7 89.7±6.2 T2 87.0±6.8 103.3±8.3* 101.8±8.3* 101.3±8.1* 100.4±8.3* **FEV_1/FVC** **T1 66.8**±3.4 77.2±3.8 77.3±4.1 76.0±4.0 74.5±3.9 T2 69.5±2.2 78.4±3.1 78.6±3.1 77.8±3.3 75.4±2.8 FEF_{25-75} T1 38.3±5.5 57.8±8.4 62.1±9.1 60.9±10.4 58.7±9.7 T2 40.6±4.8 63.8±8.1 63.5±8.4 64.4±8.1 63.3±8.1 $Vmax_{25}$ T1 60.4±7.4 83.1±9.3 82.5±9.0 85.8±10.2 86.3±8.1 T2 70.8±7.6 92.2±9.3 83.0±9.0 85.8±10.2 79.4±10.2 T3 67.6±7.7 66.3±11.4 64.9±10.3 64.9±12.0 61.6±9.6 $Vmax_{50}$ **T1 41.7**±5.0 60.2±8.4 64.2±8.4 63.4±9.0 61.2±10.1 T2 48.7±5.0 71.0±7.7* 68.1±7.8 71.2±8.4 71.5±8.6 $Vmax_{75}$ **T1 26.0**±4.9 41.5±7.6 47.2±8.0 44.0±9.8 43.1±9.0 T2 24.4±4.9 42.3±6.7 43.1±7.6 50.3±9.9 40.8±7.1	MDI+spacer and pMDI were equally effective in improving pulmonary function from the baseline state.
Hidinger & Kjellman, 1984[51]	**T1**: pMDI **T2:** pMDI+spacer (750ml collapsible spacer) **Drug:** Terbutaline sulphate, 1 puff, 0.24mg **Design**: Randomised, open, cross-over. **Jadad's score = 1**	1 paediatric out-patient department, Sweden In: bronchial asthma. All children were regular users of β_2-receptor agonists. All children had used pMDI prior to study. Out: not stated Power calculation: no Pre-protocol analysis	**At** beginning 18 (4.9-13.7) **M/F:** 12/6	**Run in:** β_2-agonists withehld ≤ 10h prior to experient, theophyllines also excluded for > 24h. Tea/coffee not allowed in the morning of study. **FU**: 2 days, 2-14 days apart **Primary:** PEFR at 0, 5,20 & 60 min after inhalation of the aerosol.	5 min after inhalation there was a significant increase over basal values in PEFR for T1 &T2 (P<0.001) & the response persisted throughout the oberservation period (60 min). Mean PEFR for T2 was significantly > vs. T1,5,20 & 60 min after taking the aerosol (p<0.05). The mean maximum value (mean max_{5-60}) for T2 was significantly > vs. T1 (p<0.01). *PEFR (mean±SD),l/min* **Min after inhalation** **T1** **T2** **Pdiff** **0** **182±69.4** **194±71.5** **Not sig** **5** **216±64.0** **232±68.7** **<0.05** **20** **217±68.4** **234±69.5** **<0.05** **60** **219±65.2** **235±62.5** **<0.05** **Mean $_{Max50-60}$** **$_{227}$±65.5** **243±64.9** **<0.01** **There were no differences in effects related to age.**	The use of such a spacer attached to the usual actuatior improved the efficacy when subjects inhaled 1 puff of terbutaline sulphate.
Ellul-Micallef, 1980[53]	**T1:** pMDI **T2:** pMDI+spacer (750ml collapsible spacer**)** **Drug:** Terbutaline sulphate, 1 puff, 0.25 mg **Design:** randomised, corss-over **jadad's score = 1**	1 site, Sweden In: moderate bronchila asthma Out: not stated Power calculation: no Pre-protocol analysis	**At beginning:** 12 **Age:** 7-11 **M/F:** 8/4	**Run in**: on 1srt & 2nd visits, patients familiarised themelseved with a peak flow meter. **FU:** 4 separate occasions at approximately weekely intervals. **Primary:** PEFR at 0, 5, 20, & 60 min after inhalation of the aerosol.	**PEFR was 181±6 l/mm (mean±SEM) for T1 vs. T2 206±6 l/mm. The values obtained when the spacer was attached were significantly > when measured at 20 min (p<0.001) anbd 60 min (p<0.01) after therapy but not at 5 minutes.**	Adding the spacer to a pMDI resulted in significnatly better pulmonary function.

APPENDIX 7 pMDIs with or without spacer vs dry powder devices, delivering bronchodilating drugs (randonised controlled trials, physiological and clinical outcomes)

Evidence reported by Brocklebank *et al*[19]

Study Author, Year	Methodology	Details	Results	Comments
Kemp 1989[138] Asthma Research Centre, USA *Citation*: J Allergy Clin. Immunol 83(3); 697-702	*Design*: 2 separate studies reported (a) randomised double-blind double-dummy crossover study using 2 doses: 100 & 200ug on separate days & (b) a parallel run study using 200ug qid for 12 weeks. Used computer coded treatment. *Device*: Rotahaler vs pMDI alone *Drug*: salbutamol *Dose*: (a) 90-100 & 180-200ug and study (b) 180-200ug *Duration*: (a) 360min & (b) 12 weeks	*Participants:* (a) 30 children, mean age 9.4yrs. Lung function measured from 5 to 360min post-dose. *Study quality*: Cochrane-A ……. *Participants:* (b) 204 (164F) children, age range 4-11, mean age 8.2yrs. Lung function measured from 5 to 480min post-dose. *Study quality*: Cochrane-A	Study A: *No significant differences in:* FEV_1, HR or BP Study B: *No significant differences in:* FEV_1, FEF_{25-75}, FVC, PEFR, dropout rate or symptom scores. *Significant difference in:* Number of acute exacerbations (requiring intervention): 26 (25%) in the pMDI group vs 13 (13%) Rotahaler group (p<0.05).	Analyses of baseline mean FEV_1 (using unpaired two-tailed t-test) showed that the pMDI group had significantly lower FEV_1 when compared to the RH group. This may explain the higher rate of acute exacerbations seen in the pMDI group.
Bronsky, 1995[76] Medical Research Centre, Utah Supported by Glaxo Research *Citation*: J of Asthma 32(3) 207-214.	*Design*: randomised double-blind double-dummy crossover study using Latin-square treatment schedule. Exercise challenge used. *Device*: Rotahaler vs pMDI alone *Drug*: salbutamol *Dose*: pMDI-180ug vs RH-200ug *Duration*: 51 min	*Participants:* 44 children, age range 4-11, mean age 8yrs, Pulmonary function test performed up to 51 min after taking the drug and running on a treadmill for 6min at pre-determined target rates (85% of HR_{max}). Study also reported 15 min post dose FEV_1 (i.e. pre-exercise). *Study quality*: Cochrane-B	*No significant differences in:* pre and post exercise FEV_1 after drug administration.	Study used exercise challenge to show that the two devices are equally effective against E1A.
Ahlstöm 1989[139] Sweden Medical Hospital *Citation*: Allergy 44, 515- 518	*Design*: open randomised crossover study. *Device*: Turbuhaler vs MDI + Nebuhaler *Drug*: terbutaline *Dose*: 0.5mg qid (both devices) *Duration*: 14 days	*Participants*: 21 children (7F), age range 2-5yrs, mean age 3.9yrs. PEFR measured 15 min after drug administration. *Study quality:* Cochrane-B	*No significant differences in:* day or night symptom scores, day or night side effects or additional use of beta-2 medication. Significant difference in: morning PEFR favouring Turbuhaler over pMDI + Nebuhaler (p=0.046)	PEFR result to be treated with caution as evening baseline PEFR was significantly (p=0.03) higher in the Turbuhaler group.

Fuglsang, 1989[77] AstraZeneca, Sweden *Citation*: Pediatric Pulmonology 7; 112-115	*Design*: single-blinded double-dummy, crossover study, used computer generated schedule. *Device*: Turbuhaler vs pMDI alone *Drug*: terbutaline *Dose*: 2.0mg (both devices) *Duration*: cumulative dosing study, giving a total dose of 2.0mg within 80 min	*Participants*: 13 children (3F), age range 7-15 years, mean age 10.5yrs. Pulmonary function testing done 15 min post-dose. *Study quality:* Cochrane-B	*No significant differences in:* FEV_1, $FEF_{25-75\%}$, PEFR or FVC. *Significant differences in:* Heart rate (HR) when using pMDI but not with Turbuhaler. More children complained of tremor in the pMDI (7) group than in the Turbuhaler group (0)	

Study Author, Year	Methodology	Details	Results	Comments
Hultquist 1989[140] AstraZeneca, Sweden *Citation*: Allergy, 44, 467-470	*Design*: randomised double-blind double-dummy crossover study. *Device*: Turbuhaler vs pMDI alone *Drug*: terbutaline *Dose*: 0.5mg + prn (both devices) *Duration*: 2 weeks	*Participants*: 57 children, age range 6-18 years, mean age 11, PEFR was measured 10 min post-dose. *Study quality:* Cochrane-B	*No significant differences in:* PEFR (morning & evening) and symptom scores. *Significant differences in:* Preference for device where more children preferred the Turbuhaler (49%) than the pMDI (23%).	
Laberge 1994[141] Depart of Ped Quebec, Canada *Citation*: J Pediatr 124: 815-817	*Design*: randomised double-blind double-dummy crossover study, used random numbers. *Device*: Turbuhaler vs pMDI + Nebuhaler *Drug*: terbutaline *Dose*: cumulative dosing study, giving a total dose of 2.0mg within 80 min than followed by 5mg of nebulised salbutamol.	*Participants*: 10 children, age range 3-6 years, mean age 4.6yrs. Lung function measured 15 min after each dose of medication. *Study quality:* Cochrane-A	*No significant differences in:* HR, BP, tremor or airways resistance	
Svenonius 1994[142] Astra Draco AB, Lund Sweden *Citation*: Allergy 49, 408-412	*Design*: randomised double-blind double-dummy crossover study. Exercise challenge used. *Device*: Turbuhaler vs pMDI alone *Drug*: terbutaline *Dose*: 1mg (both devices) *Duration*: 15 min	*Participants:* 12 children (2F), age range 9-17, mean age 13.8. Lung function measured before exercise than given the drug and measured again up to 15 min post-dose to observe reversibility of E1A. *Study quality*: Cochrane-B	*No significant differences in:* FEV_1 and VTG.	
Hirsch 1997[78] German Medical Hospital *Citation*: Resp Med. 91: 341 – 346	*Design*: randomised double-blind double-dummy parallel study, used drawing lots. *Device*: Turbuhaler vs pMDI alone *Drug*: terbutaline *Dose*: 0.5mg (both devices) *Duration*: 10 min	*Participants*: 118 children, age range 8-15, mean age 11.3 Pulmonary function testing done in 10 min post-dose. *Study quality:* Cochrane-A	*No significant differences in:* Change from baseline FEV_1 and FVC *Significant differences in:* Vmax50% favouring pMDI	
Razzouk 1999[79] AstraZeneca, Sweden *Citation*: Int J Pharma 180, 169-175	*Design*: randomised double-blind double-dummy crossover study. *Device*: Turbuhaler vs pMDI alone *Drug*: salbutamol *Dose*: 100ug (both devices) *Duration*: 240 min	*Participants*: 40 children (9F), age range 6-12, mean age 9. Pulmonary function testing performed from 15-240 min post-dose. *Study quality:* Cochrane-B	*No significant differences in:* Geometric means of FEV_1 and FEV_{1max}. Study also used Turbuhaler 50ug vs Turbuhaler 100ug & pMDI 100ug, showing no significant differences.	

Additional evidence from the current review

Authors, year	Treatment inhaler type, drug and dose Study design	Location, setting, inclusion/exclusion power calculation, type of analysis	Patients, number, age mean± SD (range), male/female, ethnicity	Follow-up Outcomes	Results	Comments
Koskela *et al*., 2000[55]	**T1:** DPI (Easyhaler®) (Buventol Easyhaler®, Orion Pharma, Finland) **T2:** pMDI+spacer (Volumatic®, Glaxo Wellcome, UK) **T3:** Easyhaler® **T4:** pMDI +spacer **Drug:** Salbutamol 100μg **T1, T2** Placebo, **T3, T4** **Design:** Randomised, crossover, double-blind, double-dummy. Jadad's score = 2	1 hospital, Finland. **In:** mild to moderate asthma, 7 to 65 yrs old, no smoking during 6 mths to study, 4 wks to study FEV_1 or PEF ≥15% **Power calculation: Yes,** 90%, P= 0.05 **Analysis** ITT and per protocol	**At beginning:** 22 **Age**: 19(7-65) No. patients < 16 yrs : 12 **M/F:** 10/12 **At end:** 21	**Run-in:** Abstained from controlled-release theophylline preparation ≥48 h, from oral and inhaled long-acting sympathomimetics ≥6h, no caffeine-containing drinks 4hr before lung function tests. Correct inhalation technique taught **FU:** 2 study days - interval ≥24 hrs. **Primary:** FEV_{1max} **Secondary:** area under FEV_1 curve (FEV_1AUC) before study, and at 15, 30 & 60min, FEV_{1max} as % of predicted value at baseline (during the first study day), FVC_{max}, PEF_{max}	No significant differences in primary or secondary efficacy variables between T1 and T2. **Mean (SD) ITT analysis** **T1 T2** **Baseline 60 min Baseline 60 min** FEV_1max 2.44(0.9) 2.69(0.93) 2.43(0.9) 2.67(0.97) FEV_1 predicted% 80.9(10.9) 89.5(10.7) 80(12.3) 88(11.7) AUC FEV_1 - 10.2(9.1) - 10.1(9.0) FVC 3.26(1.17) 3.35(1.19) 3.25(1.17) 3.31(1.18) No correlation with age, or PIFR and relative treatment effect of the 2 devices. Even a PIFR as low as 23 l/min via Easyhaler is sufficient to obtain a similar treatment effect to normal inhalation from a pMDI plus spacer. No adverse effects.	A reasonanably low inspiratory flow rate (30l/min) via Easyhaler® produces an equivalent improvement in lung function to a correctly used pMDI plus spacer.
Ahrens *et al*., 1999[54]	**T1 & T2: DPI (**Spiros) **T3 & T4:** MDI **Drug:** **T1&T2** albuterol sulfate (108μg=90μg of albuterol base/actuation). T1 1, T2 3 actuations T3&T4 Ventolin (90μg albuterol base/actuation). T3 1, T4 3 actuations **Design**: Randomised, double-blind,	**USA** **In:** mild to moderate asthma, ≥12 years age, FEV_1 ≥65% & PC_{20} ≤ 4mg/ml, PC_{20} (20% decrease in FEV_1) to increase 8-fold after 2 actuations of Ventolin. At subsequent visits, FEV_1≥65% & PC_{20} to be within 2-fold of sceening value, non-smokers. **Out**: used ≥ an average of 1 β-agonist inhaler/mth, respiratory tract infection in 30 days, oral corticosteroid ≤3 mths of screening, history of life-	**At beginning:** 31 **At end:** 24 **Age:** 26.2 (12-46) **M/F:** 15/9	**FU:** 4 study days **Primary: PC_{20} measured by** methacholine challenge **Secondary:** adverse events	No significant differences in PC_{20} FEV_1 dose response curves between all treatments Adverse events profiles were similar for the two inhalers.	4 of 24 ≤15 years (3=13 yrs and 1=12 yrs). In this patient group, the dose delivered by Spiros DPI is comparable to that delivered by Ventolin MDI. Each actuation of Spiros = 1.12 actuations of

	cross-over, double-dummy Jadad's score = 3	screening, history of life-threatening asthma, other significant illness. clinically significant respiratory disorders, current/ex smokers, history of life-threatening asthma exacerbation, seasonal allergic asthma, use of other named medication within specific timeframe of visit 1 - inhaled corticosteroid, oral or parenteral steroid. theophylline, ipratropium bromide, oral or nebulised $\beta_2$agonists, salmeterol, nedocromil sodium. **Power calculation** no **Per protocol analysis for efficacy** **ITT for safety analysis**				Ventolin in the delivery of albuterol(90% confidence level 0.68 - 1.94).

Authors, year	Treatment inhaler type, drug and dose Study design	Location, setting, inclusion/exclusion power calculation, type of analysis	Patients, number, age mean± SD (range), male/female, ethnicity	Follow-up Outcomes	Results	Comments	
Nelson, *et al.* 1999[56]	**T1:** DPI (Spiros) + pMDI placebo **T2:** pMDI + DPI (Spiros) placebo **T3:** DPI (Spiros) and MDI **Drug:** Albuterol sulphate, T1 (108μg/actuation = 90μg/actuation) Albuterol T2 (90μg/actuation) 2 actuations qid for each inhaler T3 lactose placebo **Design**: Randomised, double-blind, double-dummy, placebo-controlled 3-way-parallel group, phase III Jadad's score = 3	20 centers, USA **In:** non-smokers, mild to moderate asthma, ≥12 years age, min 1 year of asthma documentation, healthy (medical history, physical examination, a 12-lead ECG, clinical laboratory test), no hospital admission within 4 weeks prior to study, FEV_1 40% to 80% normal predicted, washout, $FEV_1 \geq 12\%$ 30 min following 2 inhalations from albuterol MDI. **Out**: administration of oral steroid **No power calculation** **Per protocol analysis** assumed	**At beginning:** 283 **T1**: 97 **T2:** 92 **T3:** 94 **Age:** **T1:** 34.2 (13.4) **T2:** 34.6(15.4) **T3:** 32.4(14.2) **M/F:** **T1:** 37/60 **T2:** 47/45 **T3:** 42/52 **At end:** 240 **T1:** 81 **T2:** 80 (79 in AUCBL analysis) **T3**: 77 (76 in AUCBL analysis)	**Run-in:** 7-14 days, instruction & training to use and record PEF on diary card. training with Spiros inhalation system and MDI **FU:** 12 wks **Primary:** FEV_{1max}, $AUCFEV_1$ above baseline. **Secondary: rescue** albuterol use, episodes of exacerbation, daily PEF, nocturnal asthma symptom scores from self recorded dairy cards.	The Spiros and MDI groups were comparable in all FEV_1 parameters and superior over the placebo group (p=0.0001). With exception of treatment wk 0 for the max % change in FEV_1, the duration of effect and the AUCBL, no statistically significant differences betweenT1 and T2 for any FEV_1 parameters. (Wk 0, mean change) **T1 T2** Baseline FEV_1(%) 37.71 31.29 AUCBL (L/min) 141.50 181.73 Duration of effect(min) 192.0 162.7 (Wk 12, mean change, p=0.0001) **T1 T2** Baseline FEV_1(%) 30 29 AUCBL (L/min) 126.29 126.85 Duration of effect(min) 150 144 Statistically significant differences for morning and evening PEF values among all groups but they were small and not considered to be clinically important. No statistically differences among groups on asthma exacerbation, daily use of rescue albuterol or asthma symptom scores.	In this patient group, no difference in clinical benefit for Spiros DPI and albuterol MDI with same medication and same dose. 5 withdrawals for treatment-related adverse effects (T1 3, T2 1, T3 1). The incidence pattern is consistent with the pattern of expected in a generally healthy asthmatic population over a period of time. Asthma exacerbation due to change in medication : T1 6, T2 4, T3 7)	11

Authors, year	Treatment inhaler type, drug and dose Study design	Location, setting, inclusion/exclusion power calculation, type of analysis	Patients, number, age mean± SD (range), male/female, ethnicity	Follow-up Outcomes	Results	Comments
Wolfe *et al.* 2000[57]	**T1:** DPI (Diskus) + MDI placebo **T2:** MDI + DPI (Diskus) placebo **T3:** DPI (Diskus) and MDI **Drug:** Salmeterol T1 50 μg, twice daily T2 42 μg, twice daily T3 placebo **Design**: Randomised, multicentre, double-blind, double-dummy, placebo-controlled parallel group. Jadad's score = 3	27 centres, USA **In: Screening :** ≥12 years age, ≥ 6 mths history of mild to moderate asthma that required pharmacotherapy, baseline FEV_1 50 - 85% predicted normal value after abstaining from asthma medications, ≥15% reversibility of airway obstruction within 30 min following 2 actuations of albuterool aerosol (180 μg). On treatment day 1, about 2 wks after screening visit, reproducible lung function within 15% of the best screening visit pre-albuterol FEV_1 and within 50 - 85% of the predicted normal value. Patients with stable regimen of inhaled or intranasal corticosteroids, cromolyn or nedocromil started at least 1 mth before screening and regimen constant throughout the study. **Out**: upper or lower respiratory tract or middle ear infections within 6 wks of study entry, evidence og pulmonary abnormalities unrelated to asthma, > a 10-pack year history of smoking, smoked within 1 yr prior to study entry, exposed to secondary tobacco smoke (≥ 4 hr/day), and presented clinically significant concurrent disease. **Power calculation** Yes, 90% power, p<0.05 Intention to treat analysis	**At beginning:** 498 (mean age 33, 12 -79 yrs) **T1**: 165 **T2:** 166 **T3:** 167 **At end:** 395 **T1**: 134 **T2:** 139 **T3:** 122 **Age:** **T1:** 33 (12-74) **T2:** 35 (12-79) **T3:** 34 (12-74) **M/F:** **T1:** 79/86 **T2:** 78/88 **T3:** 78/89 **Ethnic: White/Black/ Hispanic/other** **T1:** 131/18/15/1 **T2:** 135/12/18/1 **T3:** 128/19/19/1	**Baseline period:** 2 wks. All patients received both a Diskus and a MDI device. Instruction given on use. Supplement aerosol MDI given to all patients. **FU:** 12 wks **Primary:** 12-hr serial measurements at day 1, weeks 4 & 12, of FEV_1, PEF, self-rated asthma symptom scores, nighttime awakenings and supplemental albuterol use **Secondary:** adverse events.	No significant differences between T1 and T2 in improvement in pulmonary function. Compared with T3 placebo, significant decreases demonstrated in T1 & T2 in albuterol use, nighttime awakenings and increases in %days with no asthma symptom for the entire study period. (Mean change %) **T1** **T2** **T3** FEV_1 23 22 9 PEF am(L/min) 17 - 31 22 -30 7 - 17 Albuterol use -2.1±0.2 -1.9±0.2 -0.7±0.2 Night without awakenings 12±2 16±2 4±2 Symptom scores -0.4±0.1 -0.4±0.1 -0.2±0.1 No significant differences in adverse event related to study drug among the groups. (T1 11[7%], T2 9[5%], T3 6[4%])	In this patient group, no difference in clinical benefit for Diskus vs. MDI with same dose and drug. No differences between gender, ethnicity, or patients with inhaled corticosteroid vs. those without.

APPENDIX 8 DPIs vs DPIs delivering bronchodilating drugs (randomised controlled trials, physiological and clinical outcomes)

Authors, year	Treatment inhaler type, drug and dose Study design	Location, setting, inclusion/exclusion power calculation, type of analysis	Patients, number, age mean± SD (range), male/ female, ethnicity	Follow-up Outcomes	Results	Comments
Dal Col *et al.,* 1995[60]	**T1:** DPI (Pulvinal, multidose) **T2:** DPI (Rotahaler, single dose) **T3:** placebo via Pulvinal **T4:** placebo via Rotohaler **Drug:** Salbutamol powder, single dose, 200μg **Design:** Randomised, cross-over Jadad's score = 1	1 site, USA In: stable asthma, at screening visit- FEV_1 & PEFR > 75% predicted normal, history of exercise-induced asthma & reversible airway obstruction. On day 1 of study, with no treatment, patients had to have ≥ 15% max fall in FEV_1 vs. baseline values to continue trial. Out: in case of possible exposure to sensitising agents during the course of study, acute attacks of asthma in the 2 mths prioir to study, presence of concomitant disease, or of cardiac, heptic, renal or endocrine disorders, use of oral steroids during the previsou 2 mths, & impossibility to discontinue concomitant treatments 24h before testing. Power calculation: no Pre-protocol analysis.	**At beginning** 13 **Age:** 10.9 (8-12) **M/F:** 9/4	**Run in:** standard exercise performed at the same time on each of trial days – lasted 6 min on a treadmill with a 10° slope. Use of sodium cromoglycate, nedrocomil sodium, bronchodilators & antihistamines were stopped for ≥24h before each test, inhaled steroid use permitted but dose to remain constant throughout study. Instructions rto use inhalers with drawings to illustrate the correct inhaltion technique. FU: 4 consecutive days, 15 min before standardised exercise test. Primary: FEV1 & PEFR before and between treatment & exercise challenge test, and after exercise challenge test, east of use and correct handling technique.	No significant difference between T1 and T2 ($p>0.05$) The investigtor's opinion on ease of use for T1 was excellent for 10 patients and good for the other 3 patients. The opinion for T2 was excellent for 3 patients, good for 8 and fair for 2 patients. No patient reported a verdict of 'poor', for ease of uyse for either T1 or T2. 11 patients preferred T1 while 1 patient preferred T2, 2 patients had no preference. No adverse events reported throughout study.	

Bronsky *et al*. 1999[58]	**T1: DPI (**Diskus) **T2: DPI (**Diskhaler) **T3:** DPI (Diskhaler) **Drug:** T1&T2 Salmeterol 50μg T3 placebo **Design**: Randomised, double-blind, double-dummy, placebo-controlled, single-dose, three-way crossover Diskus - a multidose DPI, 60 individual 50μg doses of salmeterol xinafoate Diskhaler - a 4-dose blister pack powder delivery system, require reloading Jadad's score = 3	2 sites (17 countries) **In:** mild to moderate, presence of exercise-induced-asthma (EIA), ages 4 to 11 yrs, FEV_1 ≥70% predicted, asthma triggers other than exercise (cold, air, allergens & tobacco smoke). **Out:** received any short-acting β_2-agonists ≤ 8h of screening visit, oral short-acting β_2-agonists ≤ 12h, oral extended-release β_2-agonists or inhaled long-acting β_2-agonists ≤ 24h, or required β_2-agonists other than study drug & supplemental albuterol during trial. Upper/lower respiratory tract/middle ear infections ≤ 6wks of study entry, clinically significant concurrent disease, abnormalities in complete blood count, renal & hepatic profiles, abnormal 12-lead ECG, pulmonary abnormalities unrelated to asthma or secondary exposure to tobacco ≤ 8h/day. **Power calculation** no **Intent-to-treat analysis**	**At beginning & end :** 24 **Age:** Mean (SD) 9(2.1) **Sex (M/F) :** 14/10 **Ethnicity (White/Black):** 22/2	**FU:** 3 treatment visits & a post-treatment follow-up visit. 2 - 14 days apart. **Primary:** Serial FEV_1 at 1, 6, & 12hrs after study drug administration. **Secondary:** adverse events.	No significant differences found between T1 and T2 in mean % predicted FEV_1 after Exercise induced bronchostriction (EIB) at 1, 6 & 12 hrs. Also, there is no difference in the magnitude of bronchoprotection provided by salmeterol from the two devices. mean % predicted FEV_1 **T1** **T2** **T3** baseline 85.2 85.2 83.2 (1hr pre-exercise) EIB(after drug administration) at: 1 hr 1.4± 2.6 0.0± 3.0 10.5± 2.6 (P=0.002 vs.T3) (P<0.001 vs.T3) 6 hrs 5.4± 1.4 5.7± 1.3 11.1±2.0 (P=0.03 vs.T3) (P=0.07 vs.T3) 12 hrs 5.6± 2.1 4.0± 1.3 12.1± 3.2 (<0.02 vs.T3) (P=0.01 vs.T3) 3 adverse events but not study drug related.	Salmeterol powder delivered via Diskus and Diskhaler give equivalent and long-lasting bronchoprotection against EIB in children.

Authors, year	Treatment inhaler type, drug and dose Study design	Location, setting, inclusion/exclusion power calculation, type of analysis	Patients, number, age mean± SD (range), male/female, ethnicity	Follow-up Outcomes	Results	Comments
Boulet *et al*., 1995[59]	**T1:** Diskus & placebo via Diskhaler **T2:** Diskhaler & placebo via Diskus **Drug:** Salmeterol, 50 μg b.i.d. **Design:** randomised, double-blind, double-dummy, parallel-group, multicenter. Jadad's score = 3	16 sites, USA In: ≥ 12 yrs old, FEV_1 between 60% - 90% predicted normal, receiving adequate anti-inflammatory & inhaled β_2- agonist. The last 7 days of baseline period, mean am PEFR 60%-80% 15 min after inhalation of 800μg albuterol. No methylxanthines, anti-cholinergics, oral/parental corticosteroids/ other routine β_2-agonist during study. **Power calculation:** 99%, 150/group **Per protocol analysis:** assumed	**At beginning:** 463 **At end:** 380 **T1:** 190 **T2:** 190 **Age**: **T1:** 39(12-70) **T2:** 39(12-69) **M/F:** **T1:** 77/113 **T2:** 78/112	**Run-in:** 2-wk, instruction leaflet and taught by physician on the use of study devices given. **FU:** 4 wks - questionnaires completed on 4 visits (screening visit, after run-in period, the 6-wk and 12-wk of study) **Primary:** self-filled daily record of am & pm PEFR, am & pm asthma symptom scores, & use of albuterol; clinic-recorded pulmonary function tests and adverse effects	Increase in mean morning PEFR during treatment, T1=T2. No significant differences observed for pm PEFR, am & pm symptoms and albuterol backup use. Results on ease of use reported in Appendix xx No unexpected adverse events.	Majority patients >15 years old. Diskus and Diskhaler , both with salmeterol, produce similar clinical effects.

APPENDIX 9 pMDIs with or without spacer vs pMDIs with or without spacer, both with same propellants, delivering anti-inflamatory drugs: corticosteroids (randomised controlled trials, physiological and clinical outcomes)

Authors, year	Treatment inhaler type, drug and dose Study design	Location, setting, inclusion/exclusion power calculation, type of analysis	Patients, number, age mean± SD (range), male/female, ethnicity	Follow-up Outcomes	Results	Comments
Janssens *et al*. 1999[61]	**T1:** pMDI+spacer (Nebuchamber®) (Astra), metal 250ml no facemask **T2:** pMDI+spacer (Volumatic®) (Glaxo Wellcome) polycarbonate 750ml + plastic connector (Astra) to fit pMDI Drug Budesonide 200μg b.i.d. (Pulmicort®) Filter between mouth and spacer **Design:** Randomised crossover Jadad's score = 2	One hospital, Australia **In:** Stable asthma - no exacerbation requiring oral corticosteroids or change in medication in ≥1 mth, aged 1-8 years, no other lung function related disorder. **No power calculation** **Per protocol analysis** assumed	**At beginning:** Not stated **At end:** 16 **Age**: 83 mth (65-104) **M/F:** 12/4 All used pMDI/spacer >6mth: Breath-a-Tech® (Scott Dibben) (3), Volumatic (12), Turbuhaler® (Astra) (1)	**Run-in:** 1 wk instruction and practice with spacer and pMDI **FU:** 2 wks - 1 wk with each spacer plus new filters for every use **Primary:** Filter dose (budesonide deposited on filter) as % of nominal dose **Secondary:** Asthma symptom scores (from diary)	Filter doses higher in T1 vs. T2 (p<0.0001). mean%±SD **T1** **T2** Dose 50.3±9.2 19.4±7.2 Children with higher filter doses for T1 also had higher filter doses for T2 (r=0.79, p=0.0003). No correlation between filter dose and sample number for T1 or T2. Within-subject variation (CV) smaller for T1 than T2 (p=0.003) but children with higher variation in T1 also had higher variation in T2 (r=0.7, p=0.028). No change with age. mean%±SD **T1** **T2** CV 23.1±9.1 34.0±6.5 No difference in mean asthma scores for T1 vs. T2 (0.4% not co-operative). Some mistakes in use, no analysis by treatment	Subjects split into 2 age groups, 1-4, 5-8 years, results for second group only included in this table. Within subject variation considerable and not spacer or age dependent, but actual doses delivered to mouth higher in metal spacer.

APPENDIX 10 pMDIs with or without spacer versus DPIs, delivering anti-inflammatory drugs: corticosteroids (randomised controlled trials, physiological and clinical outcomes)

Evidence from the Brocklebank *et al* review[19]

Author, year		Details	Results	Comments
Adler 1997 Efficacy and safety of beclomethasone dipropionte (BDP) delivered via a novel dry powder inhaler (Clickhaler) in paediatric patients with asthma	*Design*: Parallel, double blind, double dummy RCT *Device*: pMDI+ Volumatic vs Clickhaler *Drug*: Beclomethasone *Dose*: upto 400ug/day *Duration*: 4 weeks	Participants: 144 asthmatic children, mean age 10.9, range 6–17 years *Quality*: Cochrane B	*No significant differences in:* Change in morning PEFR. Other outcomes are unspecified and reported as non-significant without details.	Published in abstract form only.
Agertoft 1993 [80] Importance of inhaler device on the effect of budesonide (Also published as Ugeskr Laeger 1994: 156: 4134 – 4137)	*Design*: Parallel, open RCT *Device*: pMDI+ Nebuhaler vs Turbuhaler *Drug*: Budesonide *Dose*: pMDI+Nebuhaler – run-in dose Turbuhaler – half of run-in dose *Duration*: 9 weeks	*Participants*: 126 asthma patients, 87M, 39F mean age range 9.2, range 4-15 241 children were screened by halving their steroid dosage. The 126 that deteriorated asthma control went forward to randomisation. *Quality*: Cochrane B	*No significant differences in:* Clinic: Change from baseline of: FEV_1, FVC, $FEF_{25-75\%}$ (mid expiratory flow) and %falls in FEV_1, FVC, $FEF_{25-75\%}$ and PEFR in response to exercise 24hr urinary cortisol. Home diary cards: PEFR (am and pm), day and night symptom score. *Statistical difference in:* relief medication use, puffs/week.	This study supports equivalence of pMDI+ Nebuhaler versus Turbuhaler at half the pMDI dose. This should not be taken to mean that the device is twice as effective. There was no difference in 24 hour urinary cortisol between the groups implying a similar delivered dose of medication. Relief medication usage is statistically different between groups but the effect is small (less than 1 extra puff/week). Ranked ahead of Edmunds 1979 due to much greater study size.
Edmunds 1979 [84] A clinical comparison of beclomethasone dipropionate delivered by pressurised aerosol and as a powder from a Rotahaler. Implies Rotahaler supplied by Allen and Hanbury's Research Division. *Citation*: Archives of Disease of Childhood 1979, 54: 233-235	*Design*: Cross-over RCT, double-blinded, double-dummy *Device*: pMDI versus Rotahaler *Drug*: Beclomethasone *Dose*: 2puffs qds v 1 capsule qds (presumed each 200ug qds) *Duration*: 2 X 1 month	*Participants*: 14 asthma patients, 7M, 7F mean age 9.7 years, range 4.8-15.1 *Quality*: Cochrane A	*No significant differences in:* PEFR (am and pm), symptom free days and relief salbutamol use. *Significant difference in:* mean symptom scores in favour of pMDI (p=0.04) 8 patients preferred aerosol, 2 preferred Rotahaler	Poorly presented study with no statistical results given (author states 'no significance') Rotahaler (Rotacaps) is an unusual device to use now and would normally be considered to need twice the pMDI dosage. This study is presumed to be 1:1 dosing.

Additional evidence from the current review

Authors, year	Treatment inhaler type, drug and dose Study design	Location, setting, inclusion/exclusion power calculation, type of analysis	Patients, number, age mean± SD (range), male/female, ethnicity	Follow-up Outcomes	Results	Comments
Agertoft *et al* 1999 [62]	**T1:** DPI (Turbuhaler) (AstraZeneca, Lund, Sweden, **T2:** pMDI+spacer (Nebuhaler,750ml, Astra Zeneca), **Drug:** Budesonide 200μg **Design:** Randomised, crossover, controlled Filter betwenn inhaler systema and lips to collect drug inhaled Jadad's score = 2	One out-patient clinic, Denmark **In:** asthma - requiring continuous treatment with inhaled corticosteroids. aged 3-15 years. No diseases that might influence the ability to inhale normally. **No power calculation** **Per protocol analysis** assumed	**At beginning:** Not stated **At end:** 198 **Age**: 9 (3-15) **M/F:** 132/66 No. of children in each of the 13 age groups ranged from 15 to 24 children.	**Run-in:** demonstration of correct use of pMDI Nebuhaler and Turbuhaler given by nurse. Each child given one try. All children received continuous inhaled therapy with pMDI Nebuhaler for several mths before start. All children > 5 yrs had experience in using Turbuhaler for rescue terbutaline or daily budesonide treatment. **FU:** not stated **Primary:** Mean filter doses **Secondary:** PIF, fine particle fractions usine in-vitro test.	A statistically significant correlation between dose and age was seen for T1 (*r*-=0.51, p=0.001) and T2 (*r* = 0.16, p=0.03). Filter dose via T1= T2 for children aged 4 and 5 yrs old. In children > 5 yrs, T1 delivered a significantly higher dose than T2 (p<0.03 to p=0.001). Children with higher filter doses for T1 also had higher filter doses for T2 (r=0.79, p=0.0003). Within-subject variation (CV) for T1 = T2 for older children who had experience in using both devices. The estimated inhaled dose of particles size with a mass medium aerodynamic diameter (MMAD) of ≤ 5μm is higher in T1 than T2 for older children.	Results for children aged 3-4 yrs not included. No explanation as to why older children had a significantly higher dose delivered with Turbuhaler than pMDI Nebuhaler.
Bateman *et al* 2001 [63]	**T1:** HFA Diskus™ placebo, 1 inhalation, twice/day **T2:** Diskus ™ **T3:** MDI CFC placebo Diskus™, **Drug:** Salmeterol/ fluticasone propionate **Design**: Randomised, multi-centre, double-blind, double-dummy, parallel-group Jadad's score = 3	69 centers, 10 countries **In:** ≥12 years age, mild to moderate asthmatic, of reversible airway obstruction, smoking history of <10 pack-years, used ICS (beclomethasone dipropionate, budesonide/ flunisolide 400-500μg/day or FP 200-250μg/day) ≥4 wks before entering study. During run-in period - last 7 days, mean am PEF, 50-85% after inhaling salbutamol (400μg), symptomatic i.e. cumm. total symptom score >8	**At beginning:** 724 but 497 randomised . **T1:** 165 **T2:** 167 **T3**: 165 **Age:** **T1:** 40.7(11-78) **T2:** 38.6(11-	**Run-in period:** 2 wks, continued with usual ICS therapy & symptomatic relief with salbutamol (Ventolin™). At end, discontinued current ICS therapy. **FU:** 12 wks treatment + 2 wks follow-up **Primary:** mean am	No significant differences between T1 & T2. Improvements were similar in all variables - lung function (am and pm PEF), clinic FEV_1, symptom scores, use of rescue salbutamol,adverse events. **T1** **T2** During the 12-wk period, morning PEF increase, L/min 42 43 Adjusted mean am PEF increase from baseline, L/min 43 46 Mean pm PEF, L/min 38 35 Clinic FEV_1, increase from baseline at wk-12, % 17 15 Clinic FEV_1, adjusted mean change	Likely that majority of patients > 15 yrs age Only included data comparing MDI (T1) & Diskus (T2). Patients are allowed the use of spacer

		& be taking salbutamol ≤800μg/day, FEV_1 >50% predicted normal. **Out**: had received a long-acting/oral β_2-agonist ≤2 wks of run-in period, changed asthma medication, had a lower respiratory tract infection ≤4 wks of run-in period, acute asthma exacerbation requiring hospitalisation ≤12 wks of study entry, prior treatment with oral, depot/parental ICS/combination therapy(containing β_2-agonist &/ICS). **Power calculation** at 90% power **Per protocol and Intent-to-treat analysis**	79) **T3:** 39.5(12-76) **M/F:** **T1:** 73/92 **T2:** 79/88 **T3:** 67/98 **At end:** 430 **T1:** 145 **T2:** 145 **T3**: 140 **Pre-protocol pop :** 383 **T1:** 128 **T2:** 131 **T3**: 124	PEF over wks 1-12, **Secondary:** pm PEF, am & pm symptom scores, back-up salbutamol use, clinic FEV_1.	from baseline wks 1-12 No. symptom-free am, wks 1-12, medium proportions, % No. symptom-free pm, wks 1-12, medium proportions,% No. back-up salbutamol-free am, wks 1-12, medium proportions, % No. back-up salbutamol-free pm, wks 1-12, medium proportions,% Adverse event, no. of patients(%) 95(57%)	10 55 71 73 90	10 52 78 75 93 82(50%)	(T1 24, T2 22, T3 26) In this patient group, comparable clinical efficacy for HFA MDI vs. Diskus with same medication and same dose. Drug-related adverse event highest in T2 (18)vs.T1(13)

APPENDIX 11 DPIs vs DPIs delivering anti-inflammatory drugs: corticosteroids (randomised controlled trials, physiological and clinical outcomes)

Authors, year	Treatment inhaler type, drug and dose Study design	Location, setting, inclusion/exclusion power calculation, type of analysis	Patients, number, age mean± SD (range), male/female, ethnicity	Follow-up Outcomes	Results	Comments
Peden *et al* 1998[65]	**T1:** DPI (Diskus), **T2: DPI (**Diskus), **T3: DPI (**Diskhaler), **T4:** DPI (Diskhaler), **T5:** Placebo **Drug:** Fluticasone propionate T1&T3 50 μg BID, twice daily T2&T4 100 μg BID, twice daily Patients had to withhold theophylline treatment, if any, for 24 to 36 hours before clinic visits and albuterol use for ≥6 hours before clinic visits. **Design:** Randomised, double-blind, double-dummy, parallel-group, placebo-controlled Jadad's score = 3	34 centers, U.S.A. **In:** children aged 4 –11 years, chronic asthma, symptoms requiring maintenance treatment > 3 mths immediately before study, PEF ≤85% (aged 4 - 5 yrs, FEV_1 50% - 85% (aged 6 - 11 yrs), ≥15% reversibility in FEV_1 within 30 min after 2 puffs of albuterol or documentation of this reversibility within 6 mths before study. **Out:** life-threatening asthma or other severe concurrent disease, exposed to or had chicken pox ≤3 wks before study, a lower respiratory tract infection ≤ the previous 2 wks, used oral or parental corticosteroids ≤1 mth before study, used methotrexate or gold salts or any other prescriptions or over -the-counter medication, participated in previous clinical trial with Diskus or Diskhaler devices. FEV_1 values < FEV_1 stability limit and PEF values < PEF stability limit at each clinic visit and during the 7 days preceeding each visit, ≤ 2 or fewer days of ≤ 12 puffs of albuterol aerosol per day or ≤6 albuterol powder per day, >2 nighttime awakenings resulting from asthma and requiring albuterol, and 2 or fewer days during a morning or evening PEF above PEF stability limit.	**At beginning:** not stated **At end:** 437 **At end:** **T1**: 90 **T2:** 87 **T3:** 91 **T4:** 83 **T5:** 86 **T1:** 11 **T2:** 14 **T3:** 13 **T4:** 12 **T5:** 7 **Age** **4-5 yr: 57** **6-11 yrs :** **T1:** 79 **T2:** 73 **T3:** 78 **T4:** 71 **T5:** 79 **M/F(%):** **T1:** 59/41 **T2:** 68/32 **T3:** 55/45 **T4:** 60/40 **T5:** 71/29	**Run-in:** 2-wk single-blind, placebo Instruction for proper use of device given. **Baseline:** Parents/caregivers to complete a device satisfaction questionnaire rating the importance of convenience to carry, ease of holding and operating, ease of loading and cleaning (Diskhaler only), and ease of reading remaining doses. **FU:** 12 wks **Primary:** FEV_1, PEF, am&pm, PEF, asthma symptoms, nighttime awakenings requiring albuterol, albuterol use. **Secondary:** Patient compliance	No significant differences between T1, T2, T3, T4 for FEV1 mean (%) change from baseline and % predicted, and PEF. No statistically significant differences in albuterol use, nighttime awakenings and asthma symptom scores. (mean % change ±SEM, p≤0.05, 50μg BID) **diskus (n=90) diskhaler (n=91) Placebo (n=86)** FEV_1 15.77±1.97 17.89±2.28 6.96±2.45 PEF 26±3 30±3 14±4 Albuterol use (puff/day) -0.75±0.23 -1.02±0.18 0.08±0.23 Nighttime awakenings/night -0.03±0.01 -0.04±0.01 0.07±0.04 Symptom scores [Symptom score :0=none, 1=mild, 2=moderate, 3=severe] -0.36±0.07 -0.41±0.07 -0.02±0.09 (mean % change ±SEM, p≤0.05, 100μg BID) **diskus (n=90) diskhaler (n=91) Placebo (n=86)** FEV_1 17.93±2.44 18.61±3.08 6.96±2.45 PEF: 27±3 33±4 14±4 Albuterol use (puff/day) -1.04±0.20 -0.90±0.23 0.08±0.23 Nighttime awakenings/night -0.06±0.02 -0.06±0.02 0.07±0.04 Symptom scores -0.41±0.07 -0.36±0.07 -0.02±0.09	Both the diskus and diskhaler were comparable in efficacy. Details on results of device satisfaction from parents/caregivers not included in paper.

		During the last 7 days run-in, ≥3 days ≥12 puffs/day albuterol, ≥6 doses/day of albuterol powder, ≥3 mornings of PEF decrease >20% of the previous evening's PEF, & ≥3 nighttime awakenings requiring albuterol. Non-compliance : ≤70% of placebo, & didn't complete dairy cards. **Power calculation** 80% power **ITT analysis**				
Galant *et al* 1999[64]	**T1: DPI (**Diskus) & Diskhaler placebo **T2: DPI (**Diskhaler) & Diskus placebo **T3:** Diskus&Diskhaler placebo **Drug:** Fluticasone propionate 500μg **Design**: Randomised, double-blind, double-dummy, parallel-group, placebo-controlled. Jadad's score = 4	16 sites, USA **In:** mild-moderate asthma, children ≥12 yrs old**,** stratified by baseline theraphy of inhaled corticosteroid for at least 3 mths immediately to study, or β_2-agonist therapy alone, a forced FEV_1 = 50 -80%, ≥ 15% reversibility FEV_1 (30 min after upto 4 puffs of albuterol at screening) or ≥ 15% variability in FEV_1 within 6 mths prior to study. **Out**: pregnant or lactating, severe chronic disease, used methotrexate or gold salts, nedoromil or sodium cromolyn, oral or parental corticosteroid within 4wks prior to study, or any prescription or over-the -counter medication that minght affect the course of asthma or its treatment. Lack of efficacy after run-in period (FEV_1 values >FEV_1 stability limit, ≤3 days where PEF<PEF stability limit during 7 days preceding a study visit, ≤2 days of ≥12 puffs albuterol /day, or ≤2 nighttime awakennings requiring albuterol and exacerbation requiring hospitalisation and drug excluded by study protocol). **Power calculation** power 80% **Intention-to-treat analysis**	**At beginning** 229 **At end:** 213 **T1:** 64 **T2:** 79 **T3:** 70 **Age:** **T1:** 32(12-62) **T2:** 34(12-76) **T3:** 32(13-73) **M/F (%)** **T1:** 56/44 **T2:** 54/46 **T3:** 54/46 **Subjects 12-17 yrs:** **T1:** 10 **T2:** 7 **T3:** 13	**Baseline:** 3 mths therapy with inhaled corticosteroid or β_2-agonists alone **Run in**: 2 wks, single-blind, assessing compliance and familiarisation of devices **FU:** 12 wks **Primary: am** predose FEV_1, probability remain in study, subject-rated asthma symptom for wheeze, cough & breath shortness, subject-measured morning & evening PEF, albuterol use and nighttime awakening requiring albuterol, adverse events **Secondary:** systemic exposure to fluticasone propionate, drug compliance	No significant differences between Diskus and Diskhaler groups for FEV_1, symptom scores, use of albuterol, lung function($p \geq 0.05$) except for am PEF($p \leq 0.05$). (mean change ±SEM, $p \leq 0.05$ except Diskus) **Diskus** / **Diskhaler** / **Placebo** FEV_1 am predose, L: 0.52±0.06 (n=59) / 0.40±0.06 (n=73) / 0.05±0.07 (n=63) FEV_1: 22.37±2.38 (n=59) / 16.61±2.24 (n=73) / 3.01±3.03 (n=63) Am PEF: 12±2(n=58) / 7±1(n=71) / -3±1(n=62) Pm PEF: 6 ±1(n=59) / 5±1(n=71) / -1±1(n=60) Albuterol use: -1.54±0.36 (n=59) / -1.41±0.32 (n=58) / 0.76±0.31 (n=71) Nighttime awakenings: -0.03±0.02 (n=60) / 0.00±0.04 (n=58) / 0.10±0.05 (n=72) Total symptom scores: -0.20±0.05 (n=59) / -0.10±0.05 (n=72) / 0.04±0.05 (n=61) [Total symptom score : 0 to 3 (0=none, 1=mild, 2=moderate, 3=severe) & =] No significant differences in probability to remain in study over time between device groups. Potentially drug-related adverse events was 14%, 16% and 23% for placebo, Diskus and Diskhaler respectively. Compliance rate for Diskus and Diskhaler =94% scheduled doses.	Both Diskus and Diskhaler produced comparable benefits with same medication and same dose. No age details of withdrawn subjects. Withdrawal from study: 5% (T1 & T2), 34% (T3)

Appendix 12 MDI with/ without spacer vs breath-actuated devices delivering anti-inflammatory drugs: sodium cromoglycate (randomised controlled trials, physiollogical and clinical outcomes

	Treatment inhaler type, drug and dose Study design	Setting & Location Inclusion/Exclusion Power calculation, type of analysis	Patients, number, age mean ± SD (range) years Male:Female ethnicity	Follow-up Outcomes	Results	Comments
Arshad *et al.* 1993[46]	T1: Breath-actuated (Autohaler) T2: MDI Drug: sodium cromoglycate, 2 puffs (10mg), 4 times /day Design: Randomised, open, crossover, controlled. jadad's score = 1	multicentre, UK **In:** stable aasthma, airways reversibility of ≥ 15% to an inhaled bronchodilator, currently treated with sodium cromoglycate, duration 10 wks – 15 yrs (mean 6.5 yrs), ability to use the MDI. **Out:** not stated **Power calculation** 150/group, at power 90% **Pre-protocol analysis**	At beginning 181 At end 166 T1: 90 T2: 91 Age: 10.4 (4-18) (except 1 patient aged 39 yrs old) m/f: 181/0	Run In: All medications for treatment of asthma permitted, but a[art from inhaled bronchodilators, dose to remain the same throught study period FU: 8 wks (4week treatment period before crossover), 3 clinical visits. **Primary:** spirometry pre & post β-2 inhaler, daily diary cards with 4 names symptoms symptom scores, bronchodilator use and PEFR twice a day, overall assessment of the severity of asthma over the previous 4 weeks by the clinician, treatment efficacy assessed by patient & clinician, self-assessed acceptibility of device, unusual events. **Secondary:** ease of use, co-ordination of actuation with inhalation and the control of asthma in the 2 treatment periods.	No statistically significant differences for pulmonary function tests (PEFR, FEV_1, FEV_1 reversibility & FVC) between T1 & T2. The morning PEFR and the differential (morning-evening PEFR) were significantly higher ($p<0.05$) for the second device operiod (whichever inhaler was used after crossover). No significant differences vetween devoices could be detected. No significant differences between devices or period for the mean numbers of puffs of inhaled bronchodilator used during the night and day. In the clinician's opinion, overall severity of asthma did not differ for the 2 devices, notr was there ant difference in thge number an distribution of unusual events. Both patients' and clinicians' opinions of sodium cromoglycate effectiveness were significantly better for Autohaler vs. MDI ($p<0.01$). 56 patients found devices & 35 found MDI better. 90 patients found autohaler to be > acceptable than MDI, 24 found MDI more acceptable ($P<0.001$) & 43 found both devices equally acceptable.	No significant differences found between sutohaler and MDI in clinical efficacy.

Appendix 13 pMDIs with/ without spacer vs pMDIs with/ without spacer, with different propellants, delivering the same bronchodilating drugs. (Randomised controlled trials, physiological and clinical outcomes)

Evidence from Brocklebank *et al* [19]

Study Author, Year	Methodology	Details	Results	Comments
Custovic 1995 Depart of Paediatrics Manchester UK Also has Glaxo involvement *Citation*: J Pharm Med 5, 161 – 168	*Design*: randomised double blind double-dummy crossover study, computer generated schedule. Histamine challenge used. *Device*: HFA-pMDI alone vs CFC-pMDI alone *Drug*: salbutamol *Dose*: 200ug (both devices) *Duration*: 30 min	*Participants*: 25 children, age range 6-14 years, mean age 10yrs. Pulmonary function test performed 30min post-dose, than histamine challenge performed and FEV_1 measured until FEV_1 decreased by 20% (PD_{20}). *Study quality:* Cochrane-A	*No significant differences in:* FEV_1 or protection against histamine-induced bronchoconstriction as measured by PD_{20}.	

Additional evidence from the current review

Authors, year	Treatment inhaler type, drug and dose Study design	Location, setting, inclusion/exclusion power calculation, type of analysis	Patients, number, age mean± SD (range), male/female, ethnicity	Follow-up Outcomes	Results	Comments
Shapiro *et al* 2000(a) [67]	**T1:** HFA pMDI **T2:** CFC pMDI **T3:** placebo, HFA propellant only **Drug:** Albuterol, 2 puffs, 4-6 hrs [1 puff Ventolin HFA (108μg albuterol sulfate) = 1 puff Ventolin CFC (90μg albuterol base)] **Design**: Randomised, double-blind, placebo-controlled Jadad's score = 3	11 sites (USA and Puerto Rico) **In:** ages 4 to 11 yrs, asthma requiring physician-prescribed chronic pharmcotherapy ≥6mths, no significant pulmonary disease/serious chronic disease, PEF or FEV_1 = 50-80% predicted, FEV_1 reversibility ≥15% **Out:** signs of unstable asthma during run-in, life-threatening asthma, not allowed medications with potential impact on the analyses of cardiovascular end points. **Power calculation** 80%, a difference of 10% in % of predicted FEV_1, p ≤0.5	**At beginning:** 135 **T1:** 46 **T2:** 46 **T3:** 43 **At end:** 118 **Age:** Mean **T1:** 9.0 **T2:** 8.5 **T3:** 9.0 **Sex (M %) :** **T1:** 54 **T2:** 72 **T3:** 53	**Run-in:** 1-2 wks, instruction of proper use of MDI & peak flow meter **FU:** 2 wks **Primary:** Mean % predicted PEF during 6-hr serial tests (day1 & wk2), Mean % predicted FEV_1 for patients aged 6 - 11 yrs and 4 - 5 yrs **Secondary:** daily self am & pm PEF,	T1 and T2 produced comparable bronchodilation as assessed by the mean increase in percentage predicted PEF, better than placebo. No significant differences between T1 and T2 in mean increases. Serial FEV_1 similar to those calculated for PEF. Improvement in all diary card variables - no significant differences found between the two active treatment groups. *6-hr serial PEF (%) :* **T1** (Day1 n=46, Wk2 n=41) **T2** (Day1 n=46, Wk2 n=41) **T3** (Day1 n=43, Wk2 n=36) Baseline PEF, predicted: 71.5±2.4, 78.5±3.1, 71.0±2.2, 76.7±2.8, 69.7±2.1, 72.3±2.8 Changes in PEF, predicted: 13.9±1.4, 10.8±1.4, 12.6±1.4, 10.8±1.4, 6.3±1.7, 4.5±0.9 *Mean change from baseline in diary card variables :* **T1 (n=46) T2 (n=46) T3 (n=41)** am PEF,L/min 17±4* 9±4 2±3	Ventolin HFA produces brochodilation that is clinically comparable to the effects of inhaled ventolin CFC.

		Per protocol analysis assumed		guardian/self-rated asthma symptoms, % nocturnal awakenings requiring albuterol, asthma exacerbation frequency.	pm PEF, L/min 15±3* 11±4 3±3 Albuterol use (mean puff/day) -1.8±0.4* -2.0±0.4* -0.8±0.4 Day with no albuterol,% 36.4±6.1* 39.5±5.6* 11.5±6.2 Nighttime without awakenings (%) 1±4 4±2 5±4 Asthma symptom scores -0.3±0.1* -0.1±0.1 0.1±0.1 [* p<0.03 vs T3]	
Colice *et al* 1999 [69]	**T1:** HFA **T2:** CFC **T3:** CFC **T4:** placebo HFA **Drug:** Albuterol, 2 puffs **Design**: Randomised, single-blind, placebo-controlled, four-period crossover Jadad's score = 3	1 site, USA **In:** 6 - 11 yrs, stable asthma(no episode of emergency care within 4 wks of pre study visit) requiring short-acting β_2-agonists for control of symptoms, chronic asthma (≥6 mths), presence of EIB within 30 min following a standardised exercise, withhold medication and methylxanthine-containing foods and beverages for ≥ 6 hr, FEV_1 ≥ 70% predicted, demonstrated proper technique in using a press & breathe MDI, not obese, no lower/upper respiratory tract infections, not using salmeterol(48 hr), theophylline products (48hr), cromolyn sodium/ndocromil sodium (1 wk), oral/injectable steroids (8 wks)/astemizole (3 mths) prior to prestudy visit. No use of these medication throughout study. **Out:** failure to confirm EIB by pre study exercise challenge, withdrawal of consent and baseline FEV_1 < 70% predicted. **Power calculation** no **Per protocol analysis** assumed	**At beginning:** 16 **At end:** 15 **Age:** Mean 9.4(6 - 11) **Sex (M/F) :** 11/5	**FU:** 4 treatment visits 3 - 7 days apart. **Primary:** smallest % change from predose FEV_1 post-exercise. **Secondary:** % and absolute change from predose FEV1 post-exercise .	No significant differences among active treatment results were found. **T1 T2 T3 T4** Smallest % change in FEV_1 post-exercise 1.9± 16.4 -0.3±11.4 -0.7±13.5 -25.5±16.0 [T1, T2 & T3 vs T4 all p<0.001] Number(%) of patients protected from EIB 14(93) 15(100) 14(93) 5(33)	Albuterol HFA has similar bronchodilator efficacy and safety profile as CFC albuterol.

Shapiro *et al*. 2000(b) [68]	**T1:** HFA albuterol, 2 puffs **T2:** CFC albuterol, 2 puffs Drug: Albuterol **Design**: Open-label, parallel group, randomised Jadad's score =	multicenter, USA **In:** stable asthma. 4 - 11 yrs using short-acting inhaled $\beta_2$agonists for 6 mths, FEV_1 ≥50% predicted after witholding short-acting inhaled $\beta_2$agonists for 6hr. increase in FEV_1≥12% within30min after 2 puffs CFC albuterol **Out**: other pulmonary disease, clinically significant concomitant nonpulmonary disease, upper respiratory tract infection within 4 wks of screening, lower respiratory tract infection within 2wks of screening or a known idiosyncratic reaction to sympathomimetic drug, theophylline use (within 3 days), oral $\beta_2$agonists (within 1 wk), inhaled corticosteroid (within 4 wks), momoamine oxidase inbitors, tricyclic antidepressants, and $\beta_2$antagonist (within 6 wks and astemizole (within 80 days) prior to study entry.ipratropium bromide, oral or nebulised $\beta_2$agonists, salmeterol, nedocromil sodium. **Power calculation** requiring 30/group, at 90% power **Per protocol analysis** assumed	**At beginning:** 63 **T1**: 33 **T2:** 30 **Age:** **T1:** 4-7 yr (9children) & 8-11 yr (24 children) **T2:** 4-7 yr (6 children) & 8-11 yr (24 children)	**Run-in:** ≥7 days **FU:** 4 wks **Primary:** actual & % change from predose in FEV_1 at study day1 and wk4., AUC for bronchodilato ion effect **Secondary:** symptom scores, PEF am and pm, nocturnal awakenings scores, average albuterol use	No significant differences between T1 & T2 for FEV_1 at day1 and wk4, am and pm PEF. No significant differences between T1 & T2 for individual asthma symptom scores, nighttime asthma sleep disturbance scores and rescue study drug use over 4-week study period.	In this patient group, no difference in clinical benefit for CFC vs. HFA with same medication and dose.
Lumry *et al* 2001[70]	**T1:** MDI CFC (Glaxo Wellcome), **T2:** HFA **T3:** placebo (HFA propellant alone, 4 times/day)	25 out-patient centers, USA **In:** mild to moderate bronchial asthma, ≥12 years age, a 6-mth history of asthma, a medication-	**At beginning:** 313 **T1:** 108 **T2:** 101 **T3**: 104	**Baseline period:** 3 wks, Ventolin CFC via MDI, 180	Pulmonary function, am and pm PEFR values, back-up Ventolin use, symptom scores and nocturnal awakenings all remained unchanged relative to baseline levels when switched from T1 to T2. **Mean(SE) Ventolin CFC,T3 Ventolin HFA,T2**	Likely that majority of patients > 15 yrs age In this patient

	Drug: Albuterol 180 μg/4 times/day **Design**: Randomised, multi-center, double-blind, parallel-group	free forced FEV1 50%-80% normal predicted, ≥15% FEV_1 increase in 30 min of Ventolin inhalation (2 puffs, 180μg) **Out**: requiring asthma medication other than Ventolin during study or having significant other concurrent illnesses. **Power calculation** requiring 80/group, at 80% power, p=0.05 **Per protocol analysis** assumed	**Age:** **T1:** 32 ±14.8 **T2:** 30.6±12.2 **T3:** 29.7±13.8 **M/F:** **T1:** 56/44 **T2:** 55/45 **T3:** 50/50 **Ethnicity % (Caucasian/ Black/other) :** **T1:** 79/13/8 **T2:** 75/13/12 **T3:** 81/12/7 **At end:** 276 **T1:** 99 **T2:** 91 **T3**: 86	μg/4 times/day **FU:** 12 wks **Primary:** serial pulmonary function testing. **Secondary:** mean change am & pm PEF, back-up Ventolin use, asthma symptoms, nocturnal awakenings.	**Run-in period / Wk 1-3 / WK1-12** Morning PEFR, L/min 351(8.9) / 353(10.2) / 356(10) Evening PEFR, L/min 388(9.2) / 384(9.7) / 390(9.8) Back-up Ventolin use (puffs/day) 1.1(0.2) / 1.3(0.2) / 1.2(0.2) % of days with no back-up Ventolin 62.9(3.7) / 58.4(4.0) / 60.5(3.8) Asthma symptom score 2.0(0.1) / 2.0(0.1) / 2.0(0.1) % of days with no asthma symptom 28.9(3.7) / 29.0(3.8) / 30.0(3.8) Night with no awakenings 82.4(2.8) / 82.5(2.8) / 81.7(2.9) Mean FEV_1 responses (L) after 1st dose of double-blind treatment (day 1), T1 and T2 not significantly different (p>0.291). **Serial pulmonary function results : day 1** **T1 (n=100) / T2 (n=91) / T3 (n=95)** %patients≥15% improvement 82 / 77 / 19 Median onset of effect, hrs 0.06 / 0.07 / 6.0 Mean duration of effect, hr(SE) 3.26(0.24) / 3.07(0.25) / 0.57(0.17) % max effect(SE) 30.1(1.83) / 28.4(1.34) / 14.4(1.05) Median time max effect, hrs 1.0 / 1.0 / 3.0 Mean AUC(bl), L-hrs(SE) 0.84(0.16) / 2.48(0.19) / 2.65(0.18) No significant difference between T1 and T2 for all serial pulmonary function but difference with placebo (p<0.01).	group, comparable clinical efficacy for CFC vs. HFA propellant in an MDI with same medication and same dose. Ventolin CFC & Ventolin HFA have similar adverse event profile. Treatment related adverse event highest in T3(9%), vs. T1(2%), T2(4%).

Appendix 14 pMDIs with/ without spacer vs pMDI wiith/ without spacer, with diffferent propellants, delivering corticosteroids or combined therapy (Randomised controlled trials, physiological and clinical outcomes)

Authors, year	Treatment inhaler type, drug and dose Study design	Location, setting, inclusion/exclusion power calculation, type of analysis	Patients, number, age mean± SD (range), male/female, ethnicity	Follow-up Outcomes	Results	Comments
Bateman *et al* 2001 [63]	**T1:** HFA MDI + Diskus™ placebo, 1 inhalation, twice/day **T2:** Diskus ™ + HFAMDI placebo **T3:** CFCMDI Fpmly) + Diskus placebo **Drug:** Salmeterol/ fluticasone propionate **Design**: Randomised, multi-centre, double-blind, double-dummy, parallel-group Jadad's score = 3	69 centers, 10 countries **In:** ≥12 years age, mild to moderate asthmatic, of reversible airway obstruction, smoking history of <10 pack-years, used ICS (beclomethasone dipropionate, budesonide/ flunisolide 400-500μg/day or FP 200-250μg/day) ≥4 wks before entering study. During run-in period - last 7 days, mean am PEF, 50-85% after inhaling salbutamol (400μg), symptomatic i.e. cumm. total symptom score >8 & be taking salbutamol ≤800μg/day, FEV_1 >50% predicted normal. **Out**: had received a long-acting/oral β_2-agonist ≤2 wks of run-in period, changed asthma medication, had a lower respiratory tract infection ≤4 wks of run-in period, acute asthma exacerbation requiring hospitalisation ≤12 wks of study entry, prior treatment with oral, depot/parental ICS/combination therapy(containing β_2-agonist &/ICS). **Power calculation** at 90% power	**At beginning:** 724 but 497 randomised. **T1:** 165 **T2:** 167 **T3**: 165 **Age:** **T1:** 40.7(11-78) **T2:** 38.6(11-79) **T3:** 39.5(12-76) **M/F:** **T1:** 73/92 **T2:** 79/88 **T3:** 67/98 **At end:** 430 **T1:** 145 **T2:** 145 **T3**: 140 **Pre-protocol pop :** 383 **T1:** 128 **T2:** 131 **T3**: 124	**Run-in period:** 2 wks, continued with usual ICS therapy & symptomatic relief with salbutamol (Ventolin™). At end, discontinued current ICS therapy. **FU:** 12 wks treatment + 2 wks follow-up **Primary:** mean am PEF over wks 1-12, **Secondary:** pm PEF, am & pm symptom scores, back-up salbutamol use, clinic FEV_1.	No significant differences between T1 & T2. Improvements were similar in all variables - lung function (am and pm PEF), clinic FEV_1, symptom scores, use of rescue salbutamol,adverse events. **T1** **T2** During the 12-wk period, morning PEF increase, L/min 42 43 Adjusted mean am PEF increase from baseline, L/min 43 46 Mean pm PEF, L/min 38 35 Clinic FEV_1, increase from baseline at wk-12, % 17 15 Clinic FEV_1, adjusted mean change from baseline wks 1-12 10 10 No. symptom-free am, wks 1-12, medium proportions, % 55 52 No. symptom-free pm, wks 1-12, medium proportions,% 71 78 No. back-up salbutamol-free am, wks 1-12, medium proportions, % 73 75 No. back-up salbutamol-free pm, wks 1-12, medium proportions,% 90 93 Adverse event, no. of patients(%) 82(50%) 95(57%)	Likely that majority of patients > 15 yrs age Only included data comparing MDI (T1) & Diskus (T2). Patients are allowed the use of spacer (T1 24, T2 22, T3 26) In this patient group, comparable clinical efficacy for HFA MDI vs. Diskus with same medication and same dose. Drug-related adverse event highest in T2 (18)vs.T1(13)

		Per protocol and Intent-to-treat analysis				

Pearlman *et al* 1999[71]	**T1:** CFC (75 μg/puff),150μg/day, 1 puff twice daily **T2:** CFC (75 μg/puff), 300μg/day, 2 puffs twice daily **T3:** CFC (75 μg/puff), 600μg/day, 4 puffs twice daily **T4:** HFA (75 μg/puff),150μg/day, 1 puff twice daily **T5:** HFA (75 μg/puff),300μg/day, 2 puffs twice daily **T6:** HFA (75 μg/puff),600μg/day, 4 puffs twice daily **Drug:** Triamcinolone acetonide Abuilt-in spacer-mouthpiece was used for both the HFA and CFC formulations. **Design**: Randomised, double-blind Jadad's score = 3	43 centers, USA **In:** 6 - 13 yrs, 1 yr history of perennial asthma requiring daily medication and inhaled β_2-agonists for at least previous mth, FEV_1 = 50% - 100% of predicted **Out:** life-threatening asthma, anoxic seizures, significant hypercapnia, recent hospitalisation for asthma, systemic corticosteroid use once within previous mth or >2 courses during previous year, any significant clinical/laboratory abnormalities/clinical conditions. **Power calculation** no **Intent-to-treat analysis**	**At beginning:** 473 **T1:** 75 **T2:** 82 **T3:** 82 **T4:** 76 **T5:** 83 **T6:** 75 **Age:** **T1:** 10.2(6-13) **T2:** 9.6(6.1-13) **T3:** 9.9(6-26.1) **T4:** 9.9(6.1-13) **T5:** 9.7(5.9-13) **T6:** 9.6(6.1-12.5) **Sex (M/F) :** **T1:** 48/27 **T2:** 62/20 **T3:** 56/26 **T4:** 51/25 **T5:** 50/33 **T6:** 53/22 **At end:** 374	**Baseline period:** 3 to 28 day, instructions given on the use of portable meter to measure am and pm PEFR **FU:** 12-week treatment period. **Primary:** mean % change from baseline to endpoint. **Secondary:** mean % change in $FEF_{25\%-75\%}$ from baseline to endpoint, changes in am and pm PEFR, nocturnal awakenings, patient efficacy ratings & asthma symptom scores .	Comparison between HFA and CFC formulations within dose levels showed that the 2-formulations were therapeutically equivalent at all 3 doses for albuterol use, am and pm PEFR and nocturnal awakenings. Although there are differences in FEV_1 and 24-hr symptom scores between formulations, they were not significant. No significant differences for comparisons across dose levels for albuterol use (rescue medication), 24-hr symptom scores/nocturnal awakenings. Significant improvements in FEV_1 for all doses of both formulations found. **(mean ±SE)** **FEV_1 Baseline(L) %Change** TAA CFC T1 1.59±0.05 13.53±3.24 T2 1.44±0.05 19.40±2.67 T3 1.45±0.04 22.62±2.67 TAA HFA T4 1.48±0.04 12.17±3.24 T5 1.47±0.04 21.39±3.10 T6 1.43±0.05 22.02±3.26 **PEFR (mL/min) (mean ±SE) am pm %change $FEF_{25\%=75\%}$** TAA CFC T1 19.0±4.5 15.2±4.2 23.2±10.8 T2 23.0±4.3 15.8±4.2 42.8±10.3 T3 30.2±4.3 25.6±4.1 42.3±10.3 TAA HFA T4 24.2±4.3 20.2±4.3 29.9±8.7 T5 20.5±4.0 18.8±4.1 33.0±8.3 T6 27.4±4.3 24.3±4.3 53.6±8.7 Albuterol use decrease across dose levels for both HFA and CFC but overall treatment effect was significant with HFA formulation (p=0.001), not in the CFC formulation (p=0.270). Significant improvements (p<0.05) from baseline observed for am and pm asthma symptom scores, 24-hr symptom scores and no. of nocturnal awakenings in the HFA groups. The CFC groups demonstrated significant changes (p<0.05) from baseline only for am and pm asthma symptoms and 24-hr symptom scores. **Asthma symptoms(mean ±SE)** **am symtpom score / pm symptom score / 24-hr symptom score / nocturnal awakenings (no./d)** TAA CFC T1 -0.5±0.1 -0.4±0.1 -1.0±0.2 -0.2±0.1 T2 -0.7±0.1 -0.6±0.1 -1.3±0.2 -0.4±0.1 T3 -0.9±0.1 -0.8±0.1 -1.7±0.2. -0.4±0.1 *P* 0.044 0.044 0.045 0.105 TAA HFA T4 -0.5±0.1 -0.5±0.1 -0.9±0.2 -0.1±0.1 T5 -0.8±0.1 -0.7±0.1 -1.6±0.2 -0.2±0.1	Therapeutic equivalent found at all 3 dose levels between HFA and CFC propellants delivery with TAA

Appendix 15 Breath actuated inhalers with different propellants, delivering corticostroids (Randomised controlled trials, physiological and clinical outcomes)

Authors, year	Treatment inhaler type, drug and dose Study design	Location, setting, inclusion/exclusion power calculation, type of analysis	Patients, number, age mean± SD (range), male/female, ethnicity	Follow-up Outcomes	Results	Comments
Farmer *et al* 1999[72]	**T1:** HFA **T2:** CFC **Drug:** Beclomethasone dipropionate (BDP), 100μg **Design**: Randomised, multi-centre, double-blind, parallel group Jadad's score = 4	44 general practice and hospital sites, UK, South Africa, Czech Republic, Yugoslavia and Hungary **In:** 7 - 12 yrs, $FEV_1 \geq 60\%$ predicted for height and gender, FEV_1 reversibility ≥10% after inhaling 200μg salbutamol via pMDI, documented FEV_1 reversibility ≥10% in previous 12 mths, currently use an inhaled bronchodilato β-agonist/sodium cromoglycate or constant dose of nedocromil sodium. **Out:** currently use inhaled/oral corticosteroids, unstable asthma, significant medical/phychological conditions. **Power calculation** 90%, 105patients/group **Per protocol analysis** assumed	**At beginning:** 229 **At end:** 199 **Age:** Mean **T1:** 10.0(7-12.9) **T2:** 9.8(6.6-12.8) **Sex (M/F) :** **T1:** 71/45 **T2:** 75/38	**Run-in:** 2-week placebo, 1 puff/twice/day from a CFC placebo Easibreathe™ inhaler. At end of run-in, required the use of relief bronchodilator (≥2 puffs on at least 3 out of the last 7 days of the run-in period. **FU:** 4 treatment visits - 1, 4, 8 and 12 weeks . **Primary:** Lung function (PEF& FEV_1), self-recorded symptom scores and relief medication use	Equivalent results for all lung function parameters obtained for mean morning and evening PEF with the estimated treatment difference being 2.6% and 2.1% respectively. Exception was the mean daily variability in PEF which decreased from 21-16% in T1 and from 22-16% in T2. Compared to baseline, significant decreases in proportions of patients reporting am and pm symptoms and use of relief medication in both T1 & T2. **Mean (SD) T1 T2 Estimate (95% CI) - HFA/CFC(%)** am PEF (l/min) Baseline 299(56) 294(62) Endpoint 340(61) 328(54) Endpoint[1] 338 330 102.6(99.1,106.2) pm PEF (l/min) Baseline 302(57) 297(61) Endpoint 340(61) 329(51) Endpoint[1] 338 331 102.1(98.1,105.6) clinic PEF (l/min) Baseline 308(60) 305(69) Endpoint 335(59) 335(59) Endpoint[1] 337 333 101.2(97.3,105.1) clinic FEV_1 (l/min) Baseline 1.82(0.42) 1.77(0.42) Endpoint 1.98(0.45) 1.92(0.40) Endpoint[1] 1.97 1.91 103.5(99.6,107.5) daily variability PEF(%) Baseline 20.8(11.7) 22.3(11.6) Endpoint 16.1(13.6) 16.5(10.9) Endpoint[1] 16.2 16.3 99.4(78.6,116.9) [[1] least square]	HFA inhaler is therapeutically equivalent to CFC inhaler at similar dose (100 μg b.i.d. BDP)

Appendix 16 pMDIs with/ without spacer vs pMDI with/ without spacer, with different propellants, delivering cromoglycate therapy (Randomised controlled trials, physiological and clinical outcomes)

Furukawa *et al* 1999[73]	**T1:** MDI CFC **T2:** MDI HFA **T3:** placebo with HFA propellant **Drug:** Cromolyn sodium, 2mg qid Albuterol MDI used as needed in all groups. **Design**: Randomised, double-blind placebo-controlled parallel group Jadad's score = 3	29 sites, USA **In:** mild to moderate bronchial asthma, ≥12 years age, cromolyn sodium use for ≥2 mths, inhaled $\beta_2$agonists use for ≥1mth, FEV1≥60% normal predicted **Out**: other clinically significant respiratory disorders, current/ex smokers, history of life-threatening asthma exacerbation, seasonal allergic asthma, use of other named medication within specific timeframe of visit 1 - inhaled corticosteroid, oral or parental steroid. theophylline, ipratropium bromide, oral or nebulised $\beta_2$agonists, salmeterol, nedocromil sodium. **Power calculation** requiring 100/group, at 90% power **Per protocol analysis** assumed	**At beginning** **T1**: 91 **T2:** 94 **T3:** 95 **At end:** **T1:** 84 **T2:** 88 **T3**: 84 **Age:** **T1:** 30.3 (12-79) **T2:** 30 (12-62) **T3:** 26.9 (12-68) **M/F:** **T1:** 40/51 **T2:** 39/55 **T3:** 48/47	**Baseline period:** 2-4 wks **FU:** 12 wks **Primary:** symptom summary score (daytime + nighttime asthma scores) **Secondary:** lung function, albuterol use, symptom scores am and pm, PEFs, self and clinician rated effectiveness or T, treatment related events	No significant differences in symptom score decreases, use of albuterol, lung function, treatment-related eventsT1 vs T2 (p≥0.05). (mean change %) **T1** (n=84) **T2** (n=88) Symptom score -22 -27 Daytime score -25 -29 Nighttime score -18 -23 Morning PEF 1.3 5.3 Evening PEF 0.1 4.7 albuterol use -13 -27 Clinician-rated T1 as effective for 63% patients vs T2 (56%) (p=0.042), no difference for patient rated T1 (73%) and T2 (77%) (p=0.989).	Likely that majority of patients > 15 yrs age In this patient group, no difference in clinical benefit for CFC vs. HFA propellant in an MDI with same medication and same dose. Differences between clinician and patient ratings on effectiveness. 4 withdrawals for treatment-related adverse effects (T1 1, T2 2, T3 1)

APPENDIX 17 Ease of use, patient/carer preference and compliance for alternative devices (Randomised controlled trials and non-trial evidence)

Author	Treatment inhaler type, drug and dose Study design	Setting & Location Inclusion/Exclusion Power calculation, type of analysis	Patients, number, age mean ± SD (range) years Male: Female ethnicity	Follow-up Outcomes	Results	Comments
Milgrom H et al[88]	Volunteer/convenience sample for comparison of diary records, electronic monitoring and disease exacerbation in relation to adherence with inhaled corticosteroids and β agonists via pMDI	Outpatient clinic Inclusion: Children requiring both inhaled corticosteroids and β agonists via pMDI And who reliably kept clinic appointments Exclusions: Known non-compliance Use of spacers and nebulisers β agonists only as needed	N = 24 14 male 8-12 years	13 weeks Diary records compared with electronic monitoring Disease exacerbations requiring oral corticosteroids	Diary Compliance Records: 78.2% for β agonists 95.4% for corticosteroids Electronic Compliance Records: 48.0% for β agonists 32.0% for corticosteroids 8 disease exacerbations (13.7% compliance with inhaled steroid versus 68.2% compliance) (p=0.008)	Does not compare devices Small selective sample
Kamps AWA et al[89]	DPI or pMDI plus spacer Case/control Study comparing effectiveness of repeated inhalation instructions (control) versus no systematic inhalation instructions (cases)	Outpatient Clinic	N = 66 newly referred (cases) age range 1-14 years. Mean age 5 years 37 male versus N=29 in clinical trial (controls) range 5-10 years Mean age 7 years 21 male	Inhalation technique score according to criteria defined by Netherlands Asthma Foundation	Sixty cases had received inhalation instructions prior to referral: 29% using DPI correct 67% using pMDI plus spacer correct (p<0.01) Repeated comprehensive inhalation instruction in clinical trial setting or at the pharmacy resulted in: 79% using DPI correct 93% using pMDI plus spacer correct versus 39% that had received a single instruction by a general practitioner (p<0.01)	Study not designed to differentiate between devices Generalisability?
Celano et al[90]	PMDI use and pMDI/pMDI plus spacer technique	Urban hospital outpatient clinic Inclusions: 6-17 years with moderate/severe asthma Albuterol via pMDI plus at least one anti-	N=55 families 98% African-American 57% male children Age range 6-17 years Mean age 10.8 ± 2.7 years	Follow up 2-20 weeks (mean 10 weeks) Estimated MDI adherence (from canister weight)	34 sets of data for estimated adherence (range 0 to 100% (mean 44%)) Poor or no correlation between self reported and estimated use MDIC avaiulable data for 49 patients 27% scored zero and remainder demonstrated varying	Does not compare inhaler devices Several study limitations

		inflamatory agent via pMDI plus spacer Exclusions: Current immunotherapy or oral corticosteroids for significant periods over past year		Self-reported adherence MDI/MDI plus spacer technique (from MDI Checklist (MDIC)) Assessed at follow up following instruction at study entry	technique but achieved minimum criteria to ensure at least some drug delivery. Interrelation between measured adherence behaviours not significant	
Zora JA et al[91]	Maintenance β agonists (metaproterenol 2 sprays 3-5 times daily via $_p$MDI no spacer) Study of compliance assessed by canister weighings and patient records of daily inhaler use and symptom scores	Outpatient clinic Inclusions: Diagnosis of asthma confirmed by 15% reversability in the FEV_1 Maintenance β agonists	N = 17 13 male Age range 5-13 years	5 children for 2 weeks 12 children for 2 consecutive 2-week periods Compliance as assessed by canister weight	2/5 deemed compliant during 2 week study 1/12 deemed compliant during 4 week study 1/5 had diary correlating with actual use during 2 week study 0/12 had diary correlating with actual use during 4 week study Symptom scores indicated a non-significant improvement in relation more compliant use	Non-comparative Small study numbers Does not compare inhaler devices
Jonaaon G et al[81]	Turbohaler budesonide 100 or 200μg or placebo in two divided doses Group I Budesonide 200μg in the morning and placebo 100μg in the evening Group II Budesonide 100μg in the morning and placebo 100μg in the evening Group III Budesonide 100μg in the morning and budesonide 100μg in the evening Group IV Placebo 100μg in the morning and placebo 100μg in the evening Double blind randomised study of patient	Single centre Inclusions: Mild asthma (mean baseline FEV1 103% of predicted) No document power calculation Compliance level was assessed by Student's two sample t-test. ANCOVA was used to determine the degree of association with any demographic variables.	N = 163 107 male Age 7-16 years Mean age 9.9 years	2 week open run-in period followed by 12 week study period Compliance assessed by diary records and dose counts	Results are available from 161 participants Significant difference between self reported and measured compliance Morning 93% diary, 76% measured ($p<0.001$) Evening 94% diary, 77% measured ($p<0.001$) 86% had higher self-reported than measured compliance for morning medication compared to 94% for evening medication No correlation between symptom score and adherence or placebo treatment and adherence	Mild asthma Did not compare devices

	compliance assessed by diary/dose count/symptom score					
Jonasson G et al Extension Study[82]	As before	As before	N = 122 80 male 7-16 years	27 months of treatment. Measured drug adherence at six month intervals	Adherence decreased with time and with use of placebo treatment (significant level of difference after 21 months) Adherence better in the evening than in the morning a difference which became significant after three months of treatment Adherence in two different age groups (7-9 versus 10-16 years at baseline) was on all occasions higher in the younger age group but only significantly so during the first three months of treatment.	As above
Bender B et al[92]	Measuring Adherence in relation to use of pMDI Comparison between: Mother report Child report Canister weight Electronic Measurement (electronic Doser CT attached to inhaled steroid pMDI)	Single centre Inclusions: Mild/moderate asthma including at least twice-weekly asthma symptoms and requiring daily inhaled anti-inflamatory medicines. Exclusions: Severe asthma or other serious medical condiditons Non-randomised, non-controlled study	N = 27 16 male 7-12 years Mean 10.9 $\pm$ 2.5 years 6x African-American 4x Hispanic	6 moths with assessment at 2 month intervals	Mothers and children reported, on average, over 80% adherence with the prescribed inhaled steroid. Canister weight revealed, on average, adherence of 69%, significantly lower than self-report Adherence showed trend towards less I older children, children with poorer functioning families, boys, homes with a smoker or a pet and non-whites (significant difference) Favours electronic Doser as means of estimating adherence	Does not compare devices Small sample size Generalisability?
Goran A et al[93]	Use of Turbohaler terbutaline by children aged 3-6 years Open, non-controlled study	Consecutive attenders at outpatient asthma clinic	N = 59 39 male Age range 3-6 years	Efficiency of inhalation technique (scored) after instruction/demonstration and pharmacological effect of the terbutaline (sum of clinical symptom scores) in the inhaler were measured at a single visit	0%, 43%, 67% and 80% of 3,4,5 and 6 year olds respectively used the terbohaler efficiently. Statistically significant between 3yr olds and combined other age groups) 50%, 79%, 92% and 100% of 3,4,5 and 6 year olds respectively demonstrated clinical improvement of asthma symptoms after inhalation (statistically significant in all age groups - three patients not included as asymptomatic)	Does not compare devices Small sample size Selective sample Age range Generalisability?
Yeatts K et al[94]	Study of barriers to inhaler use amongst non-white (African-American) and	Population - based dample (public school system in North Carolina USA)	N = 2056 296 had used an	Sociodemographics of inhaler users	14% (2962056) reported using an inhaler in the past 12 with no differences among African-American and White children	Does not compare devices

	White Adolescents		inhaler in the past year 185 had diagnosed asthma Age 13 to 14 years 34% African-American		26% were not allowed to carry their inhaler at school Girls were more likely to be allowed to carry their inhalers at school and diagnosed asthmatic girls had a higher prevalence of wheezing the in the last year 47% compared with diagnosed asthmatic boys (26%). Smoking prevalence was higher in inhaler users (26%) compared to the study population (19%). (p=0.001) African-Americans were slightly more likely to take their inhaler medication only when needed (83%) compared with white children (75%). NB only small numbers involved.	Relevance to the UK?
Vichyanond P et al[95]	Turbohaler terbutaline 500μg three times daily Open non-comparative study of handling and efficacy (symptom scores and PEFR) following verbal and written instruction	Multi-centre outpatient clinics throughout East Asia <u>Exclusions:</u> Hypersensitivity to β agonist drugs Concommitant disease such as cardiovascular disease, renal disease or hepatic disease. <u>Inclusions:</u> Children with mild to moderate asthma, as classified according to the international consensus for the diagnosis and treatment of asthma.	N = 86 (58 had used pMDIs previously) 83 included in per protocol analysis Age range 5-14 years Mean age 8.7 years Asian children	1 week run-in 4 week study Handling assessed objectively by inverstigator and subjectively by patient/parent Efficacy from PEFR (% of predicted) and asthma symptom score (diary records and clinic assessment)	Maximum scores for inhalation were achieved by 73% of patients after combined verbal and written instructions at the start of the study and by 99% ($p<0.001$) at the end of the 4 week treatment period. Verbal instruction yielded better results for inhalation technique scores thatn written instructions at all times ($p<0.001$) 90% considered use of Turbohaler to be easy and effective in affording symptom relief. Improvements in PEFR ($p<0.01$) and reduction in asthma symptom scores ($p<0.005$ for morning scores, $p=<0.0001$ for evening scores) were observed during treatment All patients tolerated the study medication well without any serious adverse events.	Does not compare devices Generalisability?
Kesten S et al[96]	Albuterol via DPI (Diskhaler) at equivalent dose in place of usual β agonist (78% were using $_{p}$MDI alone) Non-comparative open assessment	Primary and respiratory practices <u>Inclusions:</u> Patients over 6 years of age requiring inhaled β agonist for stable reversible obstructive airways disease. Open, non-randomised study	N= 4529 2219 male Mean age 39 $\pm$ 22 years 653 between the ages of 6-12 years Age bands <13 years 13-64 years >64 years	2 weeks Patient preference over usual inhaler device Adequate demonstration of six device handling steps following initial instruction and at the end of the	54% preferred the DPI over their usual inhaler device (29%))$p<0.001$). 17% expressed no preference. The majority of paediatric patients preferred the disk delivery system to their previous inhalation device. ($p<0.001$) After instruction 98.5% demonstrated adequate technique at the initial visit At the conclusion of the trial incorrect use was noted in 10.2% of the elderly and 3.2% of all	Does not directly compare devices

		No duocumented power calculation Fisher's exact test was used for the comparisons among the three age groups. Significance level was <0.05	43 excluded on initial screening	study period.	other age groups combined. (p=<0.001) 112 patients with withdrawn due to adverse events (100 non-major, 12 major, 88 considered drug related) 3 major adverse events were considered to be drug-related	
Wilkelstein ML[97]	Convenience sample of 30 families whose children were using daily inhaled asthma medications via MDI participating in community-based research study in US	Domicilliary structured interviews relating to usage, technique and knowledge of asthma medications by both parent and child	N = 30 school age Urban, African-American 18 male Age 6-14 years	Medication concordance and discordance between parent and child and parent and physician reports of asthma medications Sociodemographic factors associated with early self-administration	93% took inhaled medication without parental supervision Early self-administration was associated with parental employment status and childhood behaviours Only 7% of children had effective MDI skills There was considerable discordance between parent/child and parent/physician reports of asthma medications	Does not compare devices Small sample size Generalisability?
Gracia-Antequera M and Morales Suarez-Varela MM[102]	DPI vs pMDI vs pMDI plus extension chamber Non-randomised intervention study After baseline assessment, intervention was instruction (structured sessions of correct use and handling of inhalers with new assessment at follow up)	Outpatient paediatric department	N = 255 142 included in per protocol analysis ie remained on same inhaler device 103 male Mean age 10.5 years 7-12 years olds made up 57% of the sample	Mean follow-up period 10.5 months	An increase in correct maneuvers was observed for al three devices: (Relative risk and 95% confidence interval of incorrect post-intervention use): DPI 0.59 (0.38-0.92) MDI 0.23 (0.10-0.56) MDI/spacer 0.54 (0.32-0.90) Multivariate analysis suggests that the improvement was observed irrespective of age or gender interval and was better when parents co-operated with nursing and medical staff.	
Kelloway Shepard J et al[103]	Autohaler Use and design of package insert instructions (PII)		N = 40 (20 x naïve 20 x previous pMDI) Adults and Children (12-17 years)		Using only PII for guidance, 5/20 (25%) of subjects failed to trigger the device. Using revised PII (based on patient feedback) 1/20 (5%) of different subjects failed to trigger the device. 85% of participants felt that the device was easier to use than an MDI	
Pederson S et al[104]	DPI (rotahaler) vs pMDI vs pMDI plus spacer	Outpatient clinic with recruitment over a 4 month period	N = 256 172 boys	Baseline assessment of FEV_1 plus	In 43% of patients, the demonstration of inhaler technique was deemed efficient.	

	Open, non-randomised study	Inclusions: Children with perennial asthma who agreed to participate with informed consent Receiving inhalation therapy on a regular basis with the inhaler regularly prescribed since treatment was started.	Age range 4-16 years (mean 9.7 years) 132 = MDI 85 = MDI/spacer 39 = Rotahaler	demonstration and details of inhaler technique and instruction. $FEV_1 \geq 15\%$ 10 mins after the demonstration then inhalation technique assessed as efficient - only evaluated in children with pre-treatment $FEV_1 \leq$ 85% of predicted on day of study	In 53% of patients, the demonstration of inhaler technique was deemed inefficient. 5% did not have reversible asthma on the day of the study No statistically significant, systematic variation with age was found when the results for all inhaler types were grouped together or considered separately. Comparison of results from those under six to all other age groups showed a significantly lower frequency of efficient technique (0% vs 47%) and a higher mean number of errors (5.9% vs 3.3) in the lower age group ($p<0.01$) for both variables. Nasal inhalation in particular was more common in younger than older children ($p<0.01$). Important =variables: Person who had taught the child how to use the inhaler Initial choice of inhaler device controlled by use of pulmonary function tests	
Arshad et al 1993 [46]	**T1**: Breath-actuated (Autohaler) **T2**: MDI **Drug**: sodium cromoglycate, 2 puffs (10mg), 4 times/day **Design**: Randomised, open, crossover, controlled. Jadad's score = 1	multicentre, UK **In**: stable asthma, airways reversibility of > 15% to an inhaled bronchodilator, currently treated with sodium cromoglycate, duration of asthma varied between 10 wks - 15 years (mean 6.5yrs), ability to use the MDI. Study participants considered goo co-ordinators for pMD technique **Out**: not stated **Power calculation** 150/group, at power 90% **Pre-protocol analysis**	**At beginning** 181 **At end**: 166 **T1**: 90 **T2**: 91 **Age**: 10.4 (4-18) (except 1 patient aged 39 years old) **M/F**: 181/0	Run in: All medications for treatment of asthma permitted, but apart from inhaled bronchodilators, dose to remain the same throughout study period. FU: 8 wks (4-week treatment period before crossover), 3 clinical visits. Primary: lung funtion, daily diary cards with 4 named symptoms sypmtom scores, bronchodilator	In the clinician's opinion, overall severity of asthma did not differ for the 2 devices, nor was there any difference in the number and distribution of unusual events. Both patients' and clinicians' opinions of sodium cromoglycate effectiveness were significantly better for Autohaler vs. MDI ($p<0.01$). 56 patients found authaler better, 67 found no difference between devices & 35 found MDI better. 90 patients found autohaler to be > acceptable than MDI, 24 found MDI more acceptable ($p<0.001$) & 43 found both devices equally acceptable.	No significant differences found between autohaler and MDI in clinical efficacy

				use. PEFR twice daily, clinican assessment of severity, treatment efficacy assessed by patient & clincian, self assessed acceptability of device, unusual events. Secondary: ease of use, co-ordination of actuation with inhalation, control of asthma in the 2 treatment periods.		
Edmunds et al., [84]	**T1**: pMDI & DPI placebo **T2** DPI (Rotahaler) & pMDI placebo **Drug:** Beclomethasone dipropionate. 2 puffs of aerosol 4 times/day; 1 capsule in the rotahaler 4 times/day. **Design**: Randomised, double-blind, crossover Jadad's score = 2	1 site, UK **In**: severe asthma. All children require treatment with beclomethasone dipropionate **Out**: not stated **Power calculation: no** **Pre-protocol analysis**	**At beginning** 14 **Age**: 9.7 (4.8-15.1) **M/F**: 7/7	**Run in**: All patients taught how to use the pMDI and rotahaler before study. **FU**: 2 months, each month, one device contained active drug & the other a placebo. **Primary**: ability to use device, sum of diary recorded symptoms, no. of sympton-free days, am & pm PEFR, & rescue salbutamol use.	Mean symptom score was significantly < with T1 vs. T2 (p=0.04). There were no significant differences between the 2 periods for any of the other recorded parameters. 'Younger' children preferred to use rotahaler (not a predefined outcome).	
Dal Col et al., 1995 [60]	**T1:** DPI (Pulvinal, multidose) **T2**: DPI (Rotahaler, single dose) **T3:** placebo via Pulvinal **T4**: Placebo via Rotahaler **Drug**: Salbutamol powder, single dose, 200µg	1 site, USA **In**: stable asthma, at screening visit - FEV_1 & PEFR > 75% predicted normal, history of exercise-induced asthma & reversible airway obstruction. On day 1 of study, with no treatment, patients had to have ≥	**At beginning** 13 **Age:** 10.9(8-12) **M/F:** 9/4	**Run in:** standard exercise same time on each trial day - 6 min on treadmill with 10° slope. Use of sodium cromoglycate, nedocromil sodium,	No significant difference between T1 and T2 (p>0.05) The investigator's opinion on ease of use for T1 was excellent for 10 patients and good for the other 3 patients. The opinion for T2 was excellent for 3 patients, good for8 and fair for 2 patients. No patient reported a verdict of 'poor'; for ease of use for either T1 or T2.	

	Design: Randomised, crossover Jadad's score = 1	15% max fall in FEV_1 vs. baseline values to continue trial. **Out**: in case of possible exposure to sensitising agents during the course of study, acute attacks of asthma in the 2 mths prior to study, presence of concomitant diseases, or of cardiac, heptic, renal or endocrine disorders, use of oral steroids during the previous 2 mths, & impossibility to discontinue concomitant treatments 24hr before testing. **Power calculation: no** **Pre-protocol analysis**		bronchodilators & antihistamines stopped $\geq$ 24h before test, inhaled steroid use permitted, dose fixed. Instruction to use inhlaers with drawings on correct technique **FU**: 4 consecutive days. **Primary**: FEV_1 & PEFR before and after treatment & exercise challenge, ease of use, correct handling technique	11 patients preferred T1 while 1 patient preferred T2, 2 patients had no preference. No adverse events reported throughout study.	
Becker et al 1985 [49]	**T1:** MDI + spacer (tube 80ml, 10x3.2 cm) & placebo via MDI **T2**: MDI & placebo via MDI + spacer **T3:** placebo via both devices **Drug:** Terbutaline, 250µg/actuation, given in a total dose of 500µg. Placebo was the cfc propellant-surfactant mixture used in the active inhaler **Design**: randomised, double-blind, placebo-controlled Jadad's score = 2	1 hospital, Canada **In**: had a history of asthma, documented reversability of obstruction to airflow previously (increase FEV_1 > 20% after a bronchodilator aerosol), $FEF_{25-75\%}$ <70% predicted normal **Out**: severe acute asthma on study day **Power calculation**: no **Per protocol analysis** assumed	**At beginning:** 34 **T1:** 12 **T2:** 12 **T3**: 10 **At end:** 34 **Age** **T1:** 11.7±0.8 **T2**: 10.2±0.6 **T3:**10.5±0.6 **M/F**: nil	**Run-in:** stop oral medication for 12h or inhaled bronchodilator aerosaol for 6h before study. Demonstration & supervision given by invesigator **FU**: 3 occasions - 2 to 7 days apart and within 14 days. **Primary**: pulmonary functions	Errors in inhaler technique 4/34 (11.7%) had no errors. Failure to / pMDI (n=34) / pMDI+spacer (n=34) Remove cap: 0 / not applicable Shake inhaler: 3 / 7 Position device correctly: 0 / 4 Extend neck slightly: 12 / 17 Close lips: 0 / 0 Exhale completely: 2 / 3 Hold breath while actuating: not applic Co-ord actuation & inspiration: early 13, late 9 / 1 Inhale slowly, deeply: 9 / 7 Hold breath (10 sec): 3 / 3 Breathe out: 3 / 2 Wait 30 sec before repeat: 1 / 1	Both MDI+spacer and pMDI were equally effective in improving pulmonary function from the baseline state
Boulet *et al*., 1995 [59]	**T1:** Diskus & placebo via Diskhaler **T2:** Diskhaler & placebo via Diskus	16 sites, USA In: ≥ 12 yrs old, FEV_1 between 60% - 90% predicted normal, receiving adequate anti-inflammatory & inhaled	**At beginning:** 463 **At end:** 380 **T1:** 190	**Run-in:** 2-wk, instruction leaflet and taught by physician on the use of study devices given.	For all ease of use, ease of monitoring remaining doses and preference, Diskus>Diskhaler (p<0.001) **Ease of use** **Diskus** **Diskhaler**	Majority patients >15 years old. Diskus is rated as easier to use and to tell remaining doses

	Drug: Salmeterol, 50 μg b.i.d. **Design:** randomised, double-blind, double-dummy, parallel-group, multicenter. Jadad's score = 3	inflammatory & inhaled β_2- agonist. The last 7 days of baseline period, mean am PEFR 60%-80% 15 min after inhalation of 800μg albuterol. No methylxanthines, anti-cholinergics, oral/parental corticosteroids/ other routine β_2- agonist during study. **Power calculation:** 90% **Per protocol analysis:** assumed	**T2:** 190 **Age**: **T1:** 39(12-70) **T2:** 39(12-69) **M/F:** **T1:** 77/113 **T2:** 78/112	**FU:** 4 wks - questionnaires completed on 4 visits (screening visit, after run-in period, the 6-wk and 12-wk of study) **Primary:** self-filled daily record of am & pm PEFR, am & pm asthma symptom scores, & use of albuterol; clinic-recorded pulmonary function tests and adverse effects	Use correctly after 1st Training, % >80 70 Use correctly at end of treatment, % 99 98 Very easy to use, % 85 45 **Easier to tell**, % 91 61 **Preference, %** 73 15 (12% with no preference) No unexpected adverse events.	than Diskhaler. Diskus is also rated as easy to learn to use than Diskhaler.
van der Palen *et al* 1999	**T1:** DPI (Turbuhaler) (Astra, Sweden) **T2:** DPI Diskus®(Accuhaler®) (Glaxo Wellcome, UK) **Drug: ?** **Design**: open, randomised, crossover Jadad's score = 1	1 site, Belgium **In:** ≥ 15 years old, naïve to Diskus®/Accuhaler® and Turbuhaler®, but currently using inhaled medication. **Out**: limited ability to understand and speak Dutch. **Power calculation** no **Per protocol analysis** not stated	**At beginning** 50 **At end:** 50 **Age:** 49(15-74)	**Baseline period:** none **FU:** Same day assessment - patients shown & asked to read inhaler-specific instruction leaflet and then use the inhaler. Inhalation technique was assessed using a purpose-designed inhaler-specific checklist. Same procedure repeated for second inhaler. Patients to scale the importance of the inhaler's features and state preference. **Primary:** ease of use and	Mean checklist scores of inhalation technique was not significant between Diskus/Accuhaler (92.7%) and Turbuhaler (92.0%) (p=0.52). From the essential checklist items, statistically difference in errors with 'loading' the device, Turbuhaler (93.5%) > Diskus/Accuhaler (97.3%) (P=0.045) % of patients performing all items correctly, Diskus/Accuhaler (25 patients, 50%) and Turbuhaler (23 patients - 46%) (P=0.75). % of patients performing all essential items correctly, 46 patients for Diskus/Accuhaler (92%) vs. 37 patients (74%) for Turbuhaler. Important/very important - 98% patients considered a clear instruction leaflet Important - >90% found ease of holding device, overall perceived ease of use, ease of use in acute exacerbation & a clear counting mechanism. Preference - 17 patients Diskus/Accuhaler vs. 25 Turbuhaler, 8 no preference. Not statistically significant between Diskus/accuhaler & Turbuhaler on preference.	Inhalation technique with both devices is equally good. Error in loading device > for Turbuhaler than Diskus/Accuhaler. (Turbuhaler requires 2 critical steps in loading while Diskus 1 correct action). More patients preferred Turbuhaler than Diskus/Accuhaler for size, ease of carrying and counting remaining dose.

				preference. Mean checklist scores of inhalation technique.	Significant differences ($p<0.001$) - Favoured Turbuhaler > Diskus/Accuhaler for ease of carrying, size, inconspicuousness & reading remaining doses	
Mahajan & Okamoto, 1997 [85]	**T1:** DPI Diskus & placebo via the Diskhaler **T2:** Diskhaler & placebo via the Diskus **T3:** placebo via the Diskus and Diskhaler **Drug:** Fluticasone propionate, 500 mg **Design:** randomised, double-blind, double-masked, placebo-controlled Jadad's score = 3	16 sites, USA In: ≥ 12 yrs old, FEV_1 between 50% - 80% predicted. **Power calculation**: no **Per protocol analysis** assumed	**At beginning:** 213 **T1:** 64 **T2:** 79 **T3:** 70 **At end:** 155 (but only 154 completed questionnaire at wk-12) **T1:** 33 **T2:** 54 **T3:** 68 **Age**: 33(12-76) **M/F: nil**	**Run-in:** 2-wk, familiarisation with placebo via Diskhaler and Diskus inhalers in single-masked manner and to assess compliance. **FU:** 12 wks - questionnaires completed on 4 visits (screening visit, after run-in period, the 6-wk and 12-wk of study) **Primary:** performance assessment based on criteria: convenient to carry, durability, ease of use, ease of loading, ease of holding and operating, ease of cleaning, and ease of telling number of dose left.	**(Performance assessment of the 7 attributes, % satisfied/very satified)** **Diskhaler Diskus** At screening, 1st exposure(n=210) 60-95 72-95 After wk-12 of use,(n=154) 57-88 76-96 Wk-12 /at time of withdrawal (n=154) 60-89 74-95 **(Global assessments, %)** **Diskhaler Diskus** *Comfortable/very comfortable:* At screening, 1st exposure(n=210) 60 72 Wk-12(n=154) 79 85 *Like/strongly like :* Wk-12(n=154) 67 85 *Satisfied/very satisfied:* Wk-12(n=154) 72 82-84 *Preference of device(n=189*) 25 61 at wk-12(13% had no preference) Statistically no significant difference between T1 and T2 for treatment effects also showed that patients were rating only devices, and not medication they received.	Diskus inhaler is preferred over the Diskhaler - possibly due to the characteristics of Diskus inhaler (convenient of not having to load Diskus with medication)

[Yamanouchi provided confidential information which was included in the version of the report that was sent to the Appraisals Committee, but this information has been removed from this current document]

APPENDIX 18 REVIEW GROUP MODEL

Table 1. QALY thresholds for 1 puff per day of Salbutamol

Cost per Qaly threshold																						
£5,000	Cost per annum	£3.14	£3.60	£3.60	£3.60	£4.20	£7.88	£7.88	£9.22	£9.70	£10.99	£11.50	£11.53	£11.54	£11.54	£12.00	£17.37	£18.32	£29.36	£30.00	£30.42	£53.21
Cost per annum	Device name(s)	Asmaven	Salamol	Airomir	Salbulin	Ventolin Evohaler	Airomir with AeroChamber	Salbulin with AeroChamber	Pulvinal	Ventolin Evohaler with Nebuhaler	Airomir Autohaler	Salomol Easi-breathe	Asmasal Clickhaler	Maxivent with Able-Spacer	Asmaven with Able-Spacer	Salamol with Able-Spacer	Ventolin Rotahaler (200)	Aerolin Autohaler	Ventolin Rotahaler (400)	Ventolin Diskhaler (200)	Ventolin Accuhaler	Ventolin Diskhaler (400)
£3.14	Maxivent	0	9.13E-05	9.13E-05	9.13E-05	0.00021	0.000947	0.000947	0.001215	0.001312	0.00157	0.001672	0.001679	0.00168	0.00168	0.001771	0.002846	0.003037	0.005245	0.005371	0.005456	0.010014
£3.14	Asmaven		9.13E-05	9.13E-05	9.13E-05	0.00021	0.000947	0.000947	0.001215	0.001312	0.00157	0.001672	0.001679	0.00168	0.00168	0.001771	0.002846	0.003037	0.005245	0.005371	0.005456	0.010014
£3.60	Salamol			0	0	0.00012	0.000856	0.000856	0.001124	0.00122	0.001478	0.00158	0.001588	0.001589	0.001589	0.00168	0.002755	0.002946	0.005154	0.00528	0.005364	0.009922
£3.60	Airomir				0	0.00012	0.000856	0.000856	0.001124	0.00122	0.001478	0.00158	0.001588	0.001589	0.001589	0.00168	0.002755	0.002946	0.005154	0.00528	0.005364	0.009922
£3.60	Salbulin					0.00012	0.000856	0.000856	0.001124	0.00122	0.001478	0.00158	0.001588	0.001589	0.001589	0.00168	0.002755	0.002946	0.005154	0.00528	0.005364	0.009922
£4.20	Ventolin Evohaler						0.000736	0.000736	0.001004	0.0011	0.001358	0.00146	0.001467	0.001468	0.001468	0.00156	0.002635	0.002825	0.005033	0.00516	0.005244	0.009802
£7.88	Airomir with AeroChamber							0	0.000268	0.000364	0.000622	0.000724	0.000732	0.000733	0.000733	0.000824	0.001899	0.00209	0.004298	0.004424	0.004508	0.009066
£7.88	Salbulin with AeroChamber								0.000268	0.000364	0.000622	0.000724	0.000732	0.000733	0.000733	0.000824	0.001899	0.00209	0.004298	0.004424	0.004508	0.009066
£9.22	Pulvinal									9.62E-05	0.000354	0.000456	0.000464	0.000465	0.000465	0.000556	0.001631	0.001821	0.004029	0.004156	0.00424	0.008798
£9.70	Ventolin Evohaler with Nebuhaler										0.000258	0.00036	0.000367	0.000368	0.000368	0.00046	0.001535	0.001725	0.003933	0.00406	0.004144	0.008702
£10.99	Airomir Autohaler											0.000102	0.00011	0.000111	0.000111	0.000202	0.001277	0.001467	0.003675	0.003802	0.003886	0.008444
£11.50	Salomol Easi-breathe												7.3E-06	8.3E-06	8.3E-06	9.96E-05	0.001175	0.001365	0.003573	0.0037	0.003784	0.008342
£11.53	Asmasal Clickhaler													1E-06	1E-06	9.22E-05	0.001167	0.001358	0.003566	0.003692	0.003777	0.008335
£11.54	Maxivent with Able-Spacer														0	9.13E-05	0.001166	0.001357	0.003565	0.003691	0.003776	0.008334
£11.54	Asmaven with Able-Spacer															9.13E-05	0.001166	0.001357	0.003565	0.003691	0.003776	0.008334
£12.00	Salamol with Able-Spacer																0.001075	0.001266	0.003474	0.0036	0.003684	0.008242
£17.37	Ventolin Rotahaler (200)																	0.000191	0.002399	0.002525	0.002609	0.007167
£18.32	Aerolin Autohaler																		0.002208	0.002334	0.002419	0.006977
£29.36	Ventolin Rotahaler (400)																			0.000126	0.000211	0.004769
£30.00	Ventolin Diskhaler (200)																				8.43E-05	0.004642
£30.42	Ventolin Accuhaler																					0.004558
£53.21	Ventolin Diskhaler (400)																					

[Yamanouchi provided confidential information which was included in the version of the report that was sent to the Appraisals Committee, but this information has been removed from this current document]

Table 2. QALY thresholds for 1 puff per day of Salbutamol

Cost per Qaly threshold																					
£20,000	Cost per annum	£3.14	£3.60	£3.60	£3.60	£4.20	£7.88	£7.88	£9.22	£9.70	£10.99	£11.50	£11.53	£11.54	£11.54	£12.00	£17.37	£18.32	£29.36	£30.00	£30.42	£53.21
Cost per annum	Device name(s)	Asmaven	Salamol	Airomir	Salbulin	Ventolin Evohaler	Airomir with AeroChamber	Salbulin with AeroChamber	Pulvinal	Ventolin Evohaler with Nebuhaler	Airomir Autohaler	Salomol Easi-breathe	Asmasal Clickhaler	Maxivent with Able-Spacer	Asmaven with Able-Spacer	Salamol with Able-Spacer	Ventolin Rotahaler (200)	Aerolin Autohaler	Ventolin Rotahaler (400)	Ventolin Diskhaler (200)	Ventolin Accuhaler	Ventolin Diskhaler (400)
£3.14	Maxivent	0	2.28E-05	2.28E-05	2.28E-05	5.3E-05	0.000237	0.000237	0.000304	0.000328	0.000392	0.000418	0.00042	0.00042	0.00042	0.000443	0.000712	0.000759	0.001311	0.001343	0.001364	0.002503
£3.14	Asmaven		2.28E-05	2.28E-05	2.28E-05	5.3E-05	0.000237	0.000237	0.000304	0.000328	0.000392	0.000418	0.00042	0.00042	0.00042	0.000443	0.000712	0.000759	0.001311	0.001343	0.001364	0.002503
£3.60	Salamol			0	0	3E-05	0.000214	0.000214	0.000281	0.000305	0.00037	0.000395	0.000397	0.000397	0.000397	0.00042	0.000689	0.000736	0.001288	0.00132	0.001341	0.002481
£3.60	Airomir				0	3E-05	0.000214	0.000214	0.000281	0.000305	0.00037	0.000395	0.000397	0.000397	0.000397	0.00042	0.000689	0.000736	0.001288	0.00132	0.001341	0.002481
£3.60	Salbulin					3E-05	0.000214	0.000214	0.000281	0.000305	0.00037	0.000395	0.000397	0.000397	0.000397	0.00042	0.000689	0.000736	0.001288	0.00132	0.001341	0.002481
£4.20	Ventolin Evohaler						0.000184	0.000184	0.000251	0.000275	0.000339	0.000365	0.000367	0.000367	0.000367	0.00039	0.000659	0.000706	0.001258	0.00129	0.001311	0.00245
£7.88	Airomir with AeroChamber							0	6.71E-05	9.11E-05	0.000156	0.000181	0.000183	0.000183	0.000183	0.000206	0.000475	0.000522	0.001074	0.001106	0.001127	0.002267
£7.88	Salbulin with AeroChamber								6.71E-05	9.11E-05	0.000156	0.000181	0.000183	0.000183	0.000183	0.000206	0.000475	0.000522	0.001074	0.001106	0.001127	0.002267
£9.22	Pulvinal									2.41E-05	8.85E-05	0.000114	0.000116	0.000116	0.000116	0.000139	0.000408	0.000455	0.001007	0.001039	0.00106	0.0022
£9.70	Ventolin Evohaler with Nebuhaler										6.45E-05	0.00009	9.18E-05	9.21E-05	9.21E-05	0.000115	0.000384	0.000431	0.000983	0.001015	0.001036	0.002175
£10.99	Airomir Autohaler											2.56E-05	2.74E-05	2.76E-05	2.76E-05	5.04E-05	0.000319	0.000367	0.000919	0.00095	0.000972	0.002111
£11.50	Salomol Easi-breathe												1.83E-06	2.07E-06	2.07E-06	2.49E-05	0.000294	0.000341	0.000893	0.000925	0.000946	0.002085
£11.53	Asmasal Clickhaler													2.5E-07	2.5E-07	2.31E-05	0.000292	0.000339	0.000891	0.000923	0.000944	0.002084
£11.54	Maxivent with Able-Spacer														0	2.28E-05	0.000292	0.000339	0.000891	0.000923	0.000944	0.002083
£11.54	Asmaven with Able-Spacer															2.28E-05	0.000292	0.000339	0.000891	0.000923	0.000944	0.002083
£12.00	Salamol with Able-Spacer																0.000269	0.000316	0.000868	0.0009	0.000921	0.002061
£17.37	Ventolin Rotahaler (200)																	4.76E-05	0.0006	0.000631	0.000652	0.001792
£18.32	Aerolin Autohaler																		0.000552	0.000584	0.000605	0.001744
£29.36	Ventolin Rotahaler (400)																			3.16E-05	5.27E-05	0.001192
£30.00	Ventolin Diskhaler (200)																				2.11E-05	0.001161
£30.42	Ventolin Accuhaler																					0.00114
£53.21	Ventolin Diskhaler (400)																					

Committee, but this information has been removed from this current document]

Table 3. QALY thresholds for 200 ug daily dose (or equivalent) of Beclamethasone

Cost per Qaly threshold																												
£5,000	**Cost per annum**	£28.62	£28.73	£28.73	£28.73	£30.08	£30.08	£30.22	£31.41	£31.41	£33.01	£33.01	£34.50	£35.69	£35.79	£37.02	£37.56	£37.67	£38.48	£38.51	£40.73	£41.29	£43.17	£47.05	£52.37	£55.21	£67.39	£69.06
Cost per annum	**Device name(s)**	Beclazone (200)	Filair (200)	Qvar (50)	Qvar Autohaler (50)	Beclazone (100)	Beclazone Easi-breathe (100)	Filair (100)	Qvar (100)	Qvar Autohaler (100)	Filair (200) + Aerochamber	Qvar (50) + Aerochamber	Filair (100) + Aerochamber	Qvar (100) + Aerochamber	Becotide (200)	Beclazone (200) + Able Spacer	Pulvinal (200)	Becotide (100)	Beclazone (100) + Able Spacer	Asmabec Clickhaler	Pulvinal (100)	Becotide (200) + Volumatic	Becotide (100) + Volumatic	Aerobic Autohaler (100)	Becotide Rotacaps (200)	Becotide Rotacaps (100)	Becodisks Diskhaler (200)	Becodisks Diskhaler (100)
£18.62	Beclazone Easi-breathe (100) '	0.002	0.00202	0.00202	0.00202	0.00229	0.00229	0.00232	0.00256	0.00256	0.00288	0.00288	0.00318	0.00341	0.00343	0.00368	0.00379	0.00381	0.00397	0.00398	0.00442	0.00453	0.00491	0.00569	0.00675	0.00732	0.00976	0.01009
£28.62	Beclazone (200)		2.2E-05	2.2E-05	2.2E-05	0.00029	0.00029	0.00032	0.00056	0.00056	0.00088	0.00088	0.00118	0.00141	0.00143	0.00168	0.00179	0.00181	0.00197	0.00198	0.00242	0.00253	0.00291	0.00369	0.00475	0.00532	0.00776	0.00809
£28.73	Filair (200)				0	0	0.00027	0.00027	0.0003	0.00054	0.00054	0.00086	0.00086	0.00116	0.00139	0.00141	0.00166	0.00177	0.00179	0.00195	0.00196	0.0024	0.00251	0.00289	0.00366	0.00473	0.0053	0.00773	0.00807
£28.73	Qvar (50) *					0	0.00027	0.00027	0.0003	0.00054	0.00054	0.00086	0.00086	0.00116	0.00139	0.00141	0.00166	0.00177	0.00179	0.00195	0.00196	0.0024	0.00251	0.00289	0.00366	0.00473	0.0053	0.00773	0.00807
£28.73	Qvar Autohaler (50) *					0.00027	0.00027	0.0003	0.00054	0.00054	0.00086	0.00086	0.00116	0.00139	0.00141	0.00166	0.00177	0.00179	0.00195	0.00196	0.0024	0.00251	0.00289	0.00366	0.00473	0.0053	0.00773	0.00807
£30.08	Beclazone (100)						0	2.9E-05	0.00027	0.00027	0.00059	0.00059	0.00089	0.00112	0.00114	0.00139	0.0015	0.00152	0.00168	0.00169	0.00213	0.00224	0.00262	0.00339	0.00446	0.00503	0.00746	0.0078
£30.08	Beclazone Easi-breathe (100)							2.9E-05	0.00027	0.00027	0.00059	0.00059	0.00089	0.00112	0.00114	0.00139	0.0015	0.00152	0.00168	0.00169	0.00213	0.00224	0.00262	0.00339	0.00446	0.00503	0.00746	0.0078
£30.22	Filair (100)								0.00024	0.00024	0.00056	0.00056	0.00086	0.00109	0.00111	0.00136	0.00147	0.00149	0.00165	0.00166	0.0021	0.00221	0.00259	0.00337	0.00443	0.005	0.00743	0.00777
£31.41	Qvar (100) *									0	0.00032	0.00032	0.00062	0.00086	0.00088	0.00112	0.00123	0.00125	0.00141	0.00142	0.00187	0.00198	0.00235	0.00313	0.00419	0.00476	0.0072	0.00753
£31.41	Qvar Autohaler (100) *										0.00032	0.00032	0.00062	0.00086	0.00088	0.00112	0.00123	0.00125	0.00141	0.00142	0.00187	0.00198	0.00235	0.00313	0.00419	0.00476	0.0072	0.00753
£33.01	Filair (200) with Aerochamber											0	0.0003	0.00054	0.00056	0.0008	0.00091	0.00093	0.00109	0.0011	0.00155	0.00166	0.00203	0.00281	0.00387	0.00444	0.00688	0.00721
£33.01	Qvar (50) with Aerochamber *												0.0003	0.00054	0.00056	0.0008	0.00091	0.00093	0.00109	0.0011	0.00155	0.00166	0.00203	0.00281	0.00387	0.00444	0.00688	0.00721
£34.50	Filair (100) with Aerochamber													0.00024	0.00026	0.0005	0.00061	0.00063	0.00079	0.0008	0.00125	0.00136	0.00173	0.00251	0.00357	0.00414	0.00658	0.00691
£35.69	Qvar (100) with Aerochamber *														2E-05	0.00027	0.00037	0.0004	0.00056	0.00056	0.00101	0.00112	0.0015	0.00227	0.00334	0.0039	0.00634	0.00667
£35.79	Becotide (200)															0.00025	0.00035	0.00038	0.00054	0.00054	0.00099	0.0011	0.00148	0.00225	0.00332	0.00388	0.00632	0.00665
£37.02	Beclazone (200) with Able Spacer																0.00011	0.00013	0.00029	0.0003	0.00074	0.00085	0.00123	0.00201	0.00307	0.00364	0.00608	0.00641
£37.56	Pulvinal (200)																	2.2E-05	0.00018	0.00019	0.00064	0.00075	0.00112	0.0019	0.00296	0.00353	0.00597	0.0063
£37.67	Becotide (100)																		0.00016	0.00017	0.00061	0.00072	0.0011	0.00188	0.00294	0.00351	0.00595	0.00628
£38.48	Beclazone (100) with Able Spacer																			6.3E-06	0.00045	0.00056	0.00094	0.00171	0.00278	0.00335	0.00578	0.00612
£38.51	Asmabec Clickhaler																				0.00045	0.00056	0.00093	0.00171	0.00277	0.00334	0.00578	0.00611
£40.73	Pulvinal (100)																					0.00011	0.00049	0.00126	0.00233	0.00289	0.00533	0.00566
£41.29	Becotide (200) with Volumatic																						0.00038	0.00115	0.00222	0.00278	0.00522	0.00555
£43.17	Becotide (100) with Volumatic																							0.00078	0.00184	0.00241	0.00485	0.00518
£47.05	Aerobic Autohaler (100)																								0.00106	0.00163	0.00407	0.0044
£52.37	Becotide Rotacaps (200)																									0.00057	0.003	0.00334
£55.21	Becotide Rotacaps (100)																										0.00244	0.00277
£67.39	Becodisks Diskhaler (200)																											0.00033
£69.06	Becodisks Diskhaler (100)																											
	* not licensed for children under 12		' assuming a £10 cost offset compared with the cheapest pMDI																									

Table 4. QALY thresholds for 200 ug daily dose (or equivalent) of Beclamethasone

Cost per Qaly threshold																												
£20,000	**Cost per annum**	£28.62	£28.73	£28.73	£28.73	£30.08	£30.08	£30.22	£31.41	£31.41	£33.01	£33.01	£34.50	£35.69	£35.79	£37.02	£37.56	£37.67	£38.48	£38.51	£40.73	£41.29	£43.17	£47.05	£52.37	£55.21	£67.39	£69.06
Cost per annum	**Device name(s)**	Beclazone (200)	Filair (200)	Qvar (50)	Qvar Autohaler (50)	Beclazone (100)	Beclazone Easi-breathe (100)	Filair (100)	Qvar (100)	Qvar Autohaler (100)	Filair (200) + Aerochamber	Qvar (50) + Aerochamber	Filair (100) + Aerochamber	Qvar (100) + Aerochamber	Becotide (200)	Beclazone (200) + Able Spacer	Pulvinal (200)	Becotide (100)	Beclazone (100) + Able Spacer	Asmabec Clickhaler	Pulvinal (100)	Becotide (200) + Volumatic	Becotide (100) + Volumatic	Aerobic Autohaler (100)	Becotide Rotacaps (200)	Becotide Rotacaps (100)	Becodisks Diskhaler (200)	Becodisks Diskhaler (100)
£18.62	Beclazone Easi-breathe (100) '	0.0005	0.00051	0.00051	0.00051	0.00057	0.00057	0.00058	0.00064	0.00064	0.00072	0.00072	0.00079	0.00085	0.00086	0.00092	0.00095	0.00095	0.00099	0.00099	0.00111	0.00113	0.00123	0.00142	0.00169	0.00183	0.00244	0.00252
£28.62	Beclazone (200)		5.5E-06	5.5E-06	5.5E-06	7.3E-05	7.3E-05	8E-05	0.00014	0.00014	0.00022	0.00022	0.00029	0.00035	0.00036	0.00042	0.00045	0.00045	0.00049	0.00049	0.00061	0.00063	0.00073	0.00092	0.00119	0.00133	0.00194	0.00202
£28.73	Filair (200)			0	0	6.8E-05	6.8E-05	7.5E-05	0.00013	0.00013	0.00021	0.00021	0.00029	0.00035	0.00035	0.00041	0.00044	0.00045	0.00049	0.00049	0.0006	0.00063	0.00072	0.00092	0.00118	0.00132	0.00193	0.00202
£28.73	Qvar (50) *				0	6.8E-05	6.8E-05	7.5E-05	0.00013	0.00013	0.00021	0.00021	0.00029	0.00035	0.00035	0.00041	0.00044	0.00045	0.00049	0.00049	0.0006	0.00063	0.00072	0.00092	0.00118	0.00132	0.00193	0.00202
£28.73	Qvar Autohaler (50) *					6.8E-05	6.8E-05	7.5E-05	0.00013	0.00013	0.00021	0.00021	0.00029	0.00035	0.00035	0.00041	0.00044	0.00045	0.00049	0.00049	0.0006	0.00063	0.00072	0.00092	0.00118	0.00132	0.00193	0.00202
£30.08	Beclazone (100)						0	7.3E-06	6.7E-05	6.7E-05	0.00015	0.00015	0.00022	0.00028	0.00029	0.00035	0.00037	0.00038	0.00042	0.00042	0.00053	0.00056	0.00065	0.00085	0.00111	0.00126	0.00187	0.00195
£30.08	Beclazone Easi-breathe (100)							7.3E-06	6.7E-05	6.7E-05	0.00015	0.00015	0.00022	0.00028	0.00029	0.00035	0.00037	0.00038	0.00042	0.00042	0.00053	0.00056	0.00065	0.00085	0.00111	0.00126	0.00187	0.00195
£30.22	Filair (100)								5.9E-05	5.9E-05	0.00014	0.00014	0.00021	0.00027	0.00028	0.00034	0.00037	0.00037	0.00041	0.00041	0.00053	0.00055	0.00065	0.00084	0.00111	0.00125	0.00186	0.00194
£31.41	Qvar (100) *									0	8E-05	8E-05	0.00015	0.00021	0.00022	0.00028	0.00031	0.00031	0.00035	0.00035	0.00047	0.00049	0.00059	0.00078	0.00105	0.00119	0.0018	0.00188
£31.41	Qvar Autohaler (100) *										8E-05	8E-05	0.00015	0.00021	0.00022	0.00028	0.00031	0.00031	0.00035	0.00035	0.00047	0.00049	0.00059	0.00078	0.00105	0.00119	0.0018	0.00188
£33.01	Filair (200) with Aerochamber											0	7.5E-05	0.00013	0.00014	0.0002	0.00023	0.00023	0.00027	0.00028	0.00039	0.00041	0.00051	0.0007	0.00097	0.00111	0.00172	0.0018
£33.01	Qvar (50) with Aerochamber *												7.5E-05	0.00013	0.00014	0.0002	0.00023	0.00023	0.00027	0.00028	0.00039	0.00041	0.00051	0.0007	0.00097	0.00111	0.00172	0.0018
£34.50	Filair (100) with Aerochamber													5.9E-05	6.4E-05	0.00013	0.00015	0.00016	0.0002	0.0002	0.00031	0.00034	0.00043	0.00063	0.00089	0.00104	0.00164	0.00173
£35.69	Qvar (100) with Aerochamber *														5E-06	6.6E-05	9.4E-05	9.9E-05	0.00014	0.00014	0.00025	0.00028	0.00037	0.00057	0.00083	0.00098	0.00159	0.00167
£35.79	Becotide (200)															6.1E-05	8.9E-05	9.4E-05	0.00013	0.00014	0.00025	0.00028	0.00037	0.00056	0.00083	0.00097	0.00158	0.00166
£37.02	Beclazone (200) with Able Spacer																2.7E-05	3.3E-05	7.3E-05	7.5E-05	0.00019	0.00021	0.00031	0.0005	0.00077	0.00091	0.00152	0.0016
£37.56	Pulvinal (200)																	5.5E-06	4.6E-05	4.7E-05	0.00016	0.00019	0.00028	0.00047	0.00074	0.00088	0.00149	0.00157
£37.67	Becotide (100)																		4E-05	4.2E-05	0.00015	0.00018	0.00028	0.00047	0.00074	0.00088	0.00149	0.00157
£38.48	Beclazone (100) with Able Spacer																			1.6E-06	0.00011	0.00014	0.00023	0.00043	0.00069	0.00084	0.00145	0.00153
£38.51	Asmabec Clickhaler																				0.00011	0.00014	0.00023	0.00043	0.00069	0.00083	0.00144	0.00153
£40.73	Pulvinal (100)																					2.8E-05	0.00012	0.00032	0.00058	0.00072	0.00133	0.00142
£41.29	Becotide (200) with Volumatic																						9.4E-05	0.00029	0.00055	0.0007	0.00131	0.00139
£43.17	Becotide (100) with Volumatic																							0.00019	0.00046	0.0006	0.00121	0.00129
£47.05	Aerobic Autohaler (100)																								0.00027	0.00041	0.00102	0.0011
£52.37	Becotide Rotacaps (200)																									0.00014	0.00075	0.00083
£55.21	Becotide Rotacaps (100)																										0.00061	0.00069
£67.39	Becodisks Diskhaler (200)																											8.3E-05
£69.06	Becodisks Diskhaler (100)																											

* not licensed for children under 12

' assuming a £5 cost offset compared with the cheapest pMDI

Table 5. QALY thresholds for 800 ug daily dose (or equivalent) of Beclamethasone

Cost per Qaly threshold																																	
£5,000	**Cost per annum**	£114.46	£114.90	£114.90	£114.90	£119.18	£119.18	£120.30	£120.30	£122.86	£125.63	£125.63	£125.63	£126.73	£128.70	£129.91	£129.91	£133.65	£143.15	£148.65	£150.23	£150.67	£154.03	£156.17	£162.94	£188.19	£199.06	£209.48	£209.66	£220.83	£266.16	£272.80
Cost per annum	**Device name(s)**	Beclazone (200)	Filair (100)	Qvar (50) *	Qvar Autohaler (50) *	Qvar (50) + AeroChamber *	Filair (100) + AeroChamber	Beclazone (100)	Beclazone Easi-breathe (100)	Beclazone (200) + Able-Spacer	Filair (200)	Qvar (100) *	Qvar Autohaler (100) *	Beclazone Easi-breathe (50)	Beclazone (100) + Able-Spacer	Qvar (100) + AeroChamber *	Filair (200) + AeroChamber	Becodisks Diskhaler (400)	Becotide (200)	Becotide (200) + Volumatic	Pulvinal (200)	Becotide (100)	Asmabec Clickhaler (100)	Becotide (100) + Volumatic	Pulvinal (100)	Aerobic Autohaler (100)	Becotide Rotacaps (400)	Becotide Rotacaps (200)	Asmabec Clickhaler (50)	Becotide Rotacaps (100)	Becodisks Diskhaler (200)	Becodisks Diskhaler (100)
£104.46	Beclazone Easi-Breathe (100) '	0.002	0.00209	0.00209	0.00209	0.00294	0.00294	0.00317	0.00317	0.00368	0.00423	0.00423	0.00423	0.00445	0.00485	0.00509	0.00509	0.00584	0.00774	0.00884	0.00915	0.00924	0.00991	0.01034	0.01169	0.01675	0.01892	0.021	0.02104	0.02327	0.03234	0.03367
£114.46	Beclazone (200)		8.8E-05	8.8E-05	8.8E-05	0.00094	0.00094	0.00117	0.00117	0.00168	0.00223	0.00223	0.00223	0.00245	0.00285	0.00309	0.00309	0.00384	0.00574	0.00684	0.00715	0.00724	0.00791	0.00834	0.00969	0.01475	0.01692	0.019	0.01904	0.02127	0.03034	0.03167
£114.90	Filair (100)			0	0	0.00086	0.00086	0.00108	0.00108	0.00159	0.00215	0.00215	0.00215	0.00237	0.00276	0.003	0.003	0.00375	0.00565	0.00675	0.00707	0.00715	0.00783	0.00825	0.00961	0.01466	0.01683	0.01892	0.01895	0.02118	0.03025	0.03158
£114.90	Qvar (50) *				0	0.00086	0.00086	0.00108	0.00108	0.00159	0.00215	0.00215	0.00215	0.00237	0.00276	0.003	0.003	0.00375	0.00565	0.00675	0.00707	0.00715	0.00783	0.00825	0.00961	0.01466	0.01683	0.01892	0.01895	0.02118	0.03025	0.03158
£114.90	Qvar Autohaler (50) *					0.00086	0.00086	0.00108	0.00108	0.00159	0.00215	0.00215	0.00215	0.00237	0.00276	0.003	0.003	0.00375	0.00565	0.00675	0.00707	0.00715	0.00783	0.00825	0.00961	0.01466	0.01683	0.01892	0.01895	0.02118	0.03025	0.03158
£119.18	Qvar (50) with AeroChamber *						0	0.00022	0.00022	0.00074	0.00129	0.00129	0.00129	0.00151	0.0019	0.00215	0.00215	0.00289	0.00479	0.00589	0.00621	0.0063	0.00697	0.0074	0.00875	0.0138	0.01597	0.01806	0.01809	0.02033	0.02939	0.03072
£119.18	Filair (100) with AeroChamber							0.00022	0.00022	0.00074	0.00129	0.00129	0.00129	0.00151	0.0019	0.00215	0.00215	0.00289	0.00479	0.00589	0.00621	0.0063	0.00697	0.0074	0.00875	0.0138	0.01597	0.01806	0.01809	0.02033	0.02939	0.03072
£120.30	Beclazone (100)								0	0.00051	0.00107	0.00107	0.00107	0.00128	0.00168	0.00192	0.00192	0.00267	0.00457	0.00567	0.00599	0.00607	0.00675	0.00717	0.00853	0.01358	0.01575	0.01784	0.01787	0.0201	0.02917	0.0305
£120.30	Beclazone Easi-Breathe (100)									0.00051	0.00107	0.00107	0.00107	0.00128	0.00168	0.00192	0.00192	0.00267	0.00457	0.00567	0.00599	0.00607	0.00675	0.00717	0.00853	0.01358	0.01575	0.01784	0.01787	0.0201	0.02917	0.0305
£122.86	Beclazone (200) with Able-Spacer										0.00055	0.00055	0.00055	0.00077	0.00117	0.00141	0.00141	0.00216	0.00406	0.00516	0.00547	0.00556	0.00623	0.00666	0.00801	0.01307	0.01524	0.01732	0.01736	0.01959	0.02866	0.02999
£125.63	Filair (200)											0	0	0.00022	0.00061	0.00086	0.00086	0.0016	0.0035	0.0046	0.00492	0.00501	0.00568	0.00611	0.00746	0.01251	0.01468	0.01677	0.0168	0.01904	0.0281	0.02943
£125.63	Qvar (100) *												0	0.00022	0.00061	0.00086	0.00086	0.0016	0.0035	0.0046	0.00492	0.00501	0.00568	0.00611	0.00746	0.01251	0.01468	0.01677	0.0168	0.01904	0.0281	0.02943
£125.63	Qvar Autohaler (100) *													0.00022	0.00061	0.00086	0.00086	0.0016	0.0035	0.0046	0.00492	0.00501	0.00568	0.00611	0.00746	0.01251	0.01468	0.01677	0.0168	0.01904	0.0281	0.02943
£126.73	Beclazone Easi-Breathe (50)														0.0004	0.00064	0.00064	0.00138	0.00329	0.00439	0.0047	0.00479	0.00546	0.00589	0.00724	0.01229	0.01447	0.01655	0.01659	0.01882	0.02789	0.02922
£128.70	Beclazone (100) with Able-Spacer															0.00024	0.00024	0.00099	0.00289	0.00399	0.00431	0.00439	0.00507	0.00549	0.00685	0.0119	0.01407	0.01616	0.01619	0.01842	0.02749	0.02882
£129.91	Qvar (100) with AeroChamber *																0	0.00075	0.00265	0.00375	0.00406	0.00415	0.00482	0.00525	0.0066	0.01166	0.01383	0.01591	0.01595	0.01818	0.02725	0.02858
£129.91	Filair (200) with AeroChamber																	0.00075	0.00265	0.00375	0.00406	0.00415	0.00482	0.00525	0.0066	0.01166	0.01383	0.01591	0.01595	0.01818	0.02725	0.02858
£133.65	Becodisks Diskhaler (400)																		0.0019	0.003	0.00332	0.0034	0.00408	0.0045	0.00586	0.01091	0.01308	0.01517	0.0152	0.01744	0.0265	0.02783
£143.15	Becotide (200)																			0.0011	0.00142	0.0015	0.00218	0.0026	0.00396	0.00901	0.01118	0.01327	0.0133	0.01553	0.0246	0.02593
£148.65	Becotide (200) with Volumatic																				0.00032	0.0004	0.00108	0.0015	0.00286	0.00791	0.01008	0.01217	0.0122	0.01443	0.0235	0.02483
£150.23	Pulvinal (200)																					8.8E-05	0.00076	0.00119	0.00254	0.00759	0.00976	0.01185	0.01188	0.01412	0.02318	0.02451
£150.67	Becotide (100)																						0.00067	0.0011	0.00245	0.0075	0.00968	0.01176	0.0118	0.01403	0.0231	0.02443
£154.03	Asmabec Clickhaler (100)																							0.00043	0.00178	0.00683	0.00901	0.01109	0.01113	0.01336	0.02243	0.02375
£156.17	Becotide (100) with Volumatic																								0.00135	0.0064	0.00858	0.01066	0.0107	0.01293	0.022	0.02333
£162.94	Pulvinal (100)																									0.00505	0.00722	0.00931	0.00934	0.01158	0.02064	0.02197
£188.19	Aerobic Autohaler (100)																										0.00217	0.00426	0.00429	0.00653	0.01559	0.01692
£199.06	Becotide Rotacaps (400)																											0.00209	0.00212	0.00435	0.01342	0.01475
£209.48	Becotide Rotacaps (200)																												3.4E-05	0.00227	0.01133	0.01266
£209.66	Asmabec Clickhaler (50)																													0.00223	0.0113	0.01263
£220.83	Becotide Rotacaps (100)																														0.00907	0.0104
£266.16	Becodisks Diskhaler (200)																															0.00133
£272.80	Becodisks Diskhaler (100)																															
	* not licensed for children under 12			' assuming a £10 cost offset compared with the cheapest pMDI																												

Table 6. QALY thresholds for 800 ug daily dose (or equivalent) of Beclamethasone

Cost per Qaly threshold																																			
£20,000	**Cost per annum**	£114.46	£114.90	£114.90	£114.90	£119.18	£119.18	£120.30	£120.30	£122.86	£125.63	£125.63	£125.63	£126.73	£128.70	£129.91	£129.91	£133.65	£143.15	£148.65	£150.23	£150.67	£154.03	£156.17	£162.94	£188.19	£199.06	£209.48	£209.66	£220.83	£266.16	£272.80			
Cost per annum	**Device name(s)**	Beclazone (200)	Filair (100)	Qvar (50) *	Qvar Autohaler (50) *	Qvar (50) + AeroChamber *	Filair (100) + AeroChamber	Beclazone (100)	Beclazone Easi-breathe (100)	Beclazone (200) + Able-Spacer	Filair (200)	Qvar (100) *	Qvar Autohaler (100) *	Beclazone Easi-breathe (50)	Beclazone (100) + Able-Spacer	Qvar (100) + AeroChamber *	Filair (200) + AeroChamber	Becodisks Diskhaler (400)	Becotide (200)	Becotide (200) + Volumatic	Pulvinal (200)	Becotide (100)	Asmabec Clickhaler (100)	Becotide (100) + Volumatic	Pulvinal (100)	Aerobic Autohaler (100)	Becotide Rotacaps (400)	Becotide Rotacaps (200)	Asmabec Clickhaler (50)	Becotide Rotacaps (100)	Becodisks Diskhaler (200)	Becodisks Diskhaler (100)			
£104.46	Beclazone Easi-Breathe (100) '	0.0005	0.00052	0.00052	0.00052	0.00074	0.00074	0.00079	0.00079	0.00092	0.00106	0.00106	0.00106	0.00111	0.00121	0.00127	0.00127	0.00146	0.00193	0.00221	0.00229	0.00231	0.00248	0.00259	0.00292	0.00419	0.00473	0.00525	0.00526	0.00582	0.00808	0.00842			
£114.46	Beclazone (200)		2.2E-05	2.2E-05	2.2E-05	0.00024	0.00024	0.00029	0.00029	0.00042	0.00056	0.00056	0.00056	0.00061	0.00071	0.00077	0.00077	0.00096	0.00143	0.00171	0.00179	0.00181	0.00198	0.00209	0.00242	0.00369	0.00423	0.00475	0.00476	0.00532	0.00758	0.00792			
£114.90	Filair (100)			0	0	0.00021	0.00021	0.00027	0.00027	0.0004	0.00054	0.00054	0.00054	0.00059	0.00069	0.00075	0.00075	0.00094	0.00141	0.00169	0.00177	0.00179	0.00196	0.00206	0.0024	0.00366	0.00421	0.00473	0.00474	0.0053	0.00756	0.0079			
£114.90	Qvar (50) *				0	0.00021	0.00021	0.00027	0.00027	0.0004	0.00054	0.00054	0.00054	0.00059	0.00069	0.00075	0.00075	0.00094	0.00141	0.00169	0.00177	0.00179	0.00196	0.00206	0.0024	0.00366	0.00421	0.00473	0.00474	0.0053	0.00756	0.0079			
£114.90	Qvar Autohaler (50) *					0.00021	0.00021	0.00027	0.00027	0.0004	0.00054	0.00054	0.00054	0.00059	0.00069	0.00075	0.00075	0.00094	0.00141	0.00169	0.00177	0.00179	0.00196	0.00206	0.0024	0.00366	0.00421	0.00473	0.00474	0.0053	0.00756	0.0079			
£119.18	Qvar (50) with AeroChamber *						0	5.6E-05	5.6E-05	0.00018	0.00032	0.00032	0.00032	0.00038	0.00048	0.00054	0.00054	0.00072	0.0012	0.00147	0.00155	0.00157	0.00174	0.00185	0.00219	0.00345	0.00399	0.00452	0.00452	0.00508	0.00735	0.00768			
£119.18	Filair (100) with AeroChamber							5.6E-05	5.6E-05	0.00018	0.00032	0.00032	0.00032	0.00038	0.00048	0.00054	0.00054	0.00072	0.0012	0.00147	0.00155	0.00157	0.00174	0.00185	0.00219	0.00345	0.00399	0.00452	0.00452	0.00508	0.00735	0.00768			
£120.30	Beclazone (100)								0	0.00013	0.00027	0.00027	0.00027	0.00032	0.00042	0.00048	0.00048	0.00067	0.00114	0.00142	0.0015	0.00152	0.00169	0.00179	0.00213	0.00339	0.00394	0.00446	0.00447	0.00503	0.00729	0.00763			
£120.30	Beclazone Easi-Breathe (100)									0.00013	0.00027	0.00027	0.00027	0.00032	0.00042	0.00048	0.00048	0.00067	0.00114	0.00142	0.0015	0.00152	0.00169	0.00179	0.00213	0.00339	0.00394	0.00446	0.00447	0.00503	0.00729	0.00763			
£122.86	Beclazone (200) with Able-Spacer										0.00014	0.00014	0.00014	0.00019	0.00029	0.00035	0.00035	0.00054	0.00101	0.00129	0.00137	0.00139	0.00156	0.00167	0.002	0.00327	0.00381	0.00433	0.00434	0.0049	0.00716	0.0075			
£125.63	Filair (200)											0	0	5.5E-05	0.00015	0.00021	0.00021	0.0004	0.00088	0.00115	0.00123	0.00125	0.00142	0.00153	0.00187	0.00313	0.00367	0.00419	0.0042	0.00476	0.00703	0.00736			
£125.63	Qvar (100) *												0	5.5E-05	0.00015	0.00021	0.00021	0.0004	0.00088	0.00115	0.00123	0.00125	0.00142	0.00153	0.00187	0.00313	0.00367	0.00419	0.0042	0.00476	0.00703	0.00736			
£125.63	Qvar Autohaler (100) *													5.5E-05	0.00015	0.00021	0.00021	0.0004	0.00088	0.00115	0.00123	0.00125	0.00142	0.00153	0.00187	0.00313	0.00367	0.00419	0.0042	0.00476	0.00703	0.00736			
£126.73	Beclazone Easi-Breathe (50)														9.9E-05	0.00016	0.00016	0.00035	0.00082	0.0011	0.00118	0.0012	0.00137	0.00147	0.00181	0.00307	0.00362	0.00414	0.00415	0.0047	0.00697	0.0073			
£128.70	Beclazone (100) with Able-Spacer															6E-05	6E-05	0.00025	0.00072	0.001	0.00108	0.0011	0.00127	0.00137	0.00171	0.00297	0.00352	0.00404	0.00405	0.00461	0.00687	0.00721			
£129.91	Qvar (100) with AeroChamber *																0	0.00019	0.00066	0.00094	0.00102	0.00104	0.00121	0.00131	0.00165	0.00291	0.00346	0.00398	0.00399	0.00455	0.00681	0.00714			
£129.91	Filair (200) with AeroChamber																	0.00019	0.00066	0.00094	0.00102	0.00104	0.00121	0.00131	0.00165	0.00291	0.00346	0.00398	0.00399	0.00455	0.00681	0.00714			
£133.65	Becodisks Diskhaler (400)																		0.00048	0.00075	0.00083	0.00085	0.00102	0.00113	0.00146	0.00273	0.00327	0.00379	0.0038	0.00436	0.00663	0.00696			
£143.15	Becotide (200)																			0.00028	0.00035	0.00038	0.00054	0.00065	0.00099	0.00225	0.0028	0.00332	0.00333	0.00388	0.00615	0.00648			
£148.65	Becotide (200) with Volumatic																				7.9E-05	0.0001	0.00027	0.00038	0.00071	0.00198	0.00252	0.00304	0.00305	0.00361	0.00588	0.00621			
£150.23	Pulvinal (200)																					2.2E-05	0.00019	0.0003	0.00064	0.0019	0.00244	0.00296	0.00297	0.00353	0.0058	0.00613			
£150.67	Becotide (100)																						0.00017	0.00028	0.00061	0.00188	0.00242	0.00294	0.00295	0.00351	0.00577	0.00611			
£154.03	Asmabec Clickhaler (100)																							0.00011	0.00045	0.00171	0.00225	0.00277	0.00278	0.00334	0.00561	0.00594			
£156.17	Becotide (100) with Volumatic																								0.00034	0.0016	0.00214	0.00267	0.00267	0.00323	0.0055	0.00583			
£162.94	Pulvinal (100)																									0.00126	0.00181	0.00233	0.00234	0.00289	0.00516	0.00549			
£188.19	Aerobic Autohaler (100)																										0.00054	0.00106	0.00107	0.00163	0.0039	0.00423			
£199.06	Becotide Rotacaps (400)																											0.00052	0.00053	0.00109	0.00336	0.00369			
£209.48	Becotide Rotacaps (200)																												8.6E-06	0.00057	0.00283	0.00317			
£209.66	Asmabec Clickhaler (50)																													0.00056	0.00283	0.00316			
£220.83	Becotide Rotacaps (100)																														0.00227	0.0026			
£266.16	Becodisks Diskhaler (200)																															0.00033			
£272.80	Becodisks Diskhaler (100)																																		
	* not licensed for children under 12			' assuming a £10 cost offset compared with the cheapest pMDI																															

Table 7. QALY thresholds for 200 ug daily dose (or equivalent) of Budesonide

Cost per Qaly threshold					
£5,000	**Cost per annum**	£34.68	£34.68	£67.53	£67.53
Cost per annum	**Device name(s)**	Pulmicort Aerosol	Pulmicort Aerosol with Nebuhaler	Pulmicort Turbohaler (100)	Pulmicort Turbohaler (200)
£24.31	Pulmicort LS	0.00207	0.002073	0.008643	0.00864
£34.68	Pulmicort Aerosol		0	0.00657	0.00657
£34.68	Pulmicort Aerosol with Nebuhaler			0.00657	0.00657
£67.53	Pulmicort Turbohaler (100)				0
£67.53	Pulmicort Turbohaler (200)				

[Yamanouchi provided confidential information which was included in the version of the report that was sent to the Appraisals Committee, but this information has been removed from this current document]

Table 8. QALY thresholds for 200 ug daily dose (or equivalent) of Budesonide

Cost per Qaly threshold					
£20,000	**Cost per annum**	£34.68	£34.68	£67.53	£67.53
Cost per annum	**Device name(s)**	Pulmicort Aerosol	Pulmicort Aerosol with Nebuhaler	Pulmicort Turbohaler (100)	Pulmicort Turbohaler (200)
£24.31	Pulmicort LS	0.00052	0.000518	0.002161	0.00216
£34.68	Pulmicort Aerosol		0	0.001643	0.00164
£34.68	Pulmicort Aerosol with Nebuhaler			0.001643	0.00164
£67.53	Pulmicort Turbohaler (100)				0
£67.53	Pulmicort Turbohaler (200)				

[Yamanouchi provided confidential information which was included in the version of the report that was sent to the Appraisals Committee, but this information has been removed from this current document]

Table 9. QALY thresholds for 100 ug daily dose (or equivalent) of Fluticasone

Cost per Qaly threshold																
£5,000	**Cost per annum**	£35.59	£44.15	£44.15	£58.40	£69.53	£69.53	£78.09	£78.09	£83.43	£83.46	£83.46	£83.46	£92.02	£92.02	£107.28
Cost per annum	**Device name(s)**	Flixotide Evohaler (50)	Flixotide (50) with Nebuhaler	Flixotide Evohaler (50) with Nebuhaler	Flixatide Accuhaler (100)	Flixotide (125)	Flixotide Evohaler (125)	Flixotide (125) with Nebuhaler	Flixotide Evohaler (125) with Nebuhaler	Flixatide Diskhaler (100)	Flixotide (25)	Flixotide Evohaler (25)	Flixatide Accuhaler (50)	Flixotide (25) with Nebuhaler	Flixotide Evohaler (25) with Nebuhaler	Flixatide Diskhaler (50)
£35.59	Flixotide (50)	0	0.001712	0.001712	0.004563	0.006789	0.006789	0.008501	0.008501	0.009568	0.009575	0.009575	0.009575	0.011287	0.011287	0.014339
£35.59	Flixotide Evohaler (50)		0.001712	0.001712	0.004563	0.006789	0.006789	0.008501	0.008501	0.009568	0.009575	0.009575	0.009575	0.011287	0.011287	0.014339
£44.15	Flixotide (50) with Nebuhaler			0	0.002851	0.005077	0.005077	0.006789	0.006789	0.007856	0.007863	0.007863	0.007863	0.009575	0.009575	0.012627
£44.15	Flixotide Evohaler (50) with Nebuhaler				0.002851	0.005077	0.005077	0.006789	0.006789	0.007856	0.007863	0.007863	0.007863	0.009575	0.009575	0.012627
£58.40	Flixatide Accuhaler (100)					0.002227	0.002227	0.003939	0.003939	0.005006	0.005013	0.005013	0.005013	0.006725	0.006725	0.009777
£69.53	Flixotide (125)						0	0.001712	0.001712	0.002779	0.002786	0.002786	0.002786	0.004498	0.004498	0.00755
£69.53	Flixotide Evohaler (125)							0.001712	0.001712	0.002779	0.002786	0.002786	0.002786	0.004498	0.004498	0.00755
£78.09	Flixotide (125) with Nebuhaler *								0	0.001067	0.001074	0.001074	0.001074	0.002786	0.002786	0.005838
£78.09	Flixotide Evohaler (125) with Nebuhaler *									0.001067	0.001074	0.001074	0.001074	0.002786	0.002786	0.005838
£83.43	Flixatide Diskhaler (100)										6.95E-06	6.95E-06	6.95E-06	0.001719	0.001719	0.004771
£83.46	Flixotide (25)											0	0	0.001712	0.001712	0.004764
£83.46	Flixotide Evohaler (25)												0	0.001712	0.001712	0.004764
£83.46	Flixatide Accuhaler (50)													0.001712	0.001712	0.004764
£92.02	Flixotide (25) with Nebuhaler														0	0.003052
£92.02	Flixotide Evohaler (25) with Nebuhaler															0.003052
£107.28	Flixatide Diskhaler (50)															
	* not indicated for children															

Table 10. QALY thresholds for 100 ug daily dose (or equivalent) of Fluticasone

Cost per Qaly threshold																
£20,000	**Cost per annum**	£35.59	£44.15	£44.15	£58.40	£69.53	£69.53	£78.09	£78.09	£83.43	£83.46	£83.46	£83.46	£92.02	£92.02	£107.28
Cost per annum	**Device name(s)**	Flixotide Evohaler (50)	Flixotide (50) with Nebuhaler	Flixotide Evohaler (50) with Nebuhaler	Flixatide Accuhaler (100)	Flixotide (125)	Flixotide Evohaler (125)	Flixotide (125) with Nebuhaler	Flixotide Evohaler (125) with Nebuhaler	Flixatide Diskhaler (100)	Flixotide (25)	Flixotide Evohaler (25)	Flixatide Accuhaler (50)	Flixotide (25) with Nebuhaler	Flixotide Evohaler (25) with Nebuhaler	Flixatide Diskhaler (50)
£35.59	Flixotide (50)	0	0.000428	0.000428	0.001141	0.001697	0.001697	0.002125	0.002125	0.002392	0.002394	0.002394	0.002394	0.002822	0.002822	0.003585
£35.59	Flixotide Evohaler (50)		0.000428	0.000428	0.001141	0.001697	0.001697	0.002125	0.002125	0.002392	0.002394	0.002394	0.002394	0.002822	0.002822	0.003585
£44.15	Flixotide (50) with Nebuhaler			0	0.000713	0.001269	0.001269	0.001697	0.001697	0.001964	0.001966	0.001966	0.001966	0.002394	0.002394	0.003157
£44.15	Flixotide Evohaler (50) with Nebuhaler				0.000713	0.001269	0.001269	0.001697	0.001697	0.001964	0.001966	0.001966	0.001966	0.002394	0.002394	0.003157
£58.40	Flixatide Accuhaler (100)					0.000557	0.000557	0.000985	0.000985	0.001251	0.001253	0.001253	0.001253	0.001681	0.001681	0.002444
£69.53	Flixotide (125)						0	0.000428	0.000428	0.000695	0.000697	0.000697	0.000697	0.001125	0.001125	0.001888
£69.53	Flixotide Evohaler (125)							0.000428	0.000428	0.000695	0.000697	0.000697	0.000697	0.001125	0.001125	0.001888
£78.09	Flixotide (125) with Nebuhaler *								0	0.000267	0.000269	0.000269	0.000269	0.000697	0.000697	0.00146
£78.09	Flixotide Evohaler (125) with Nebuhaler *									0.000267	0.000269	0.000269	0.000269	0.000697	0.000697	0.00146
£83.43	Flixatide Diskhaler (100)										1.74E-06	1.74E-06	1.74E-06	0.00043	0.00043	0.001193
£83.46	Flixotide (25)											0	0	0.000428	0.000428	0.001191
£83.46	Flixotide Evohaler (25)												0	0.000428	0.000428	0.001191
£83.46	Flixatide Accuhaler (50)													0.000428	0.000428	0.001191
£92.02	Flixotide (25) with Nebuhaler														0	0.000763
£92.02	Flixotide Evohaler (25) with Nebuhaler															0.000763
£107.28	Flixatide Diskhaler (50)															
	* not indicated for children															

Table 11. QALY thresholds for 20 mg daily dose (or equivalent) of Sodium Cromoglycate

Cost per Qaly threshold						
£5,000	**Cost per annum**	£32.71	£34.68	£34.68	£60.77	£60.77
Cost per annum	**Device name(s)**	Cromogen with Able-Spacer	Cromogen Easi-Breathe	Intal	Intal with synchroner	Intal Spincaps
£24.31	Cromogen	0.00168	0.002073	0.002073	0.007293	0.007293
£32.71	Cromogen with Able-Spacer		0.000393	0.000393	0.005613	0.005613
£34.68	Cromogen Easi-Breathe			0	0.00522	0.00522
£34.68	Intal				0.00522	0.00522
£60.77	Intal with synchroner					0
£60.77	Intal Spincaps					

Table 12. QALY thresholds for 20 mg daily dose (or equivalent) of Sodium Cromoglycate

Cost per Qaly threshold						
£20,000	**Cost per annum**	£32.71	£34.68	£34.68	£60.77	£60.77
Cost per annum	**Device name(s)**	Cromogen with Able-Spacer	Cromogen Easi-Breathe	Intal	Intal with synchroner	Intal Spincaps
£24.31	Cromogen	0.00042	0.000518	0.000518	0.001823	0.001823
£32.71	Cromogen with Able-Spacer		9.83E-05	9.83E-05	0.001403	0.001403
£34.68	Cromogen Easi-Breathe			0	0.001305	0.001305
£34.68	Intal				0.001305	0.001305
£60.77	Intal with synchroner					0
£60.77	Intal Spincaps					

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