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

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On behalf of: The National Institute for Clinical Excellence

Produced by: School of Health and Related Research (ScHARR), University of Sheffield

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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.

Ms Catherine Beverly undertook the literature searches.

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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Ms Jan Gray, Asthma nurse in general practice, Rotherham

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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 β₂-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 $\beta_2$-agonists as there were few studies that used the long acting $\beta_2$-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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACORN</td>
<td>A classification of restricted neighbourhood</td>
</tr>
<tr>
<td>AMP</td>
<td>Adenosine 3',5' monophosphate</td>
</tr>
<tr>
<td>AUC</td>
<td>area under the curve</td>
</tr>
<tr>
<td>BDP</td>
<td>Beclamethasone dipropionate</td>
</tr>
<tr>
<td>BTS</td>
<td>British Thoracic Society</td>
</tr>
<tr>
<td>CFC</td>
<td>chlorofluorocarbon (pMDI propellant)</td>
</tr>
<tr>
<td>DPI</td>
<td>dry powder inhaler</td>
</tr>
<tr>
<td>DTB</td>
<td>Drug and Therapeutics Bulletin</td>
</tr>
<tr>
<td>EIB</td>
<td>Exercise induced bronchoconstriction</td>
</tr>
<tr>
<td>FEF&lt;sub&gt;25-75&lt;/sub&gt;</td>
<td>maximum expiratory flow over 25% to 75% of expiration</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>maximum volume of air expired in first second of expiration (from maximum capacity)</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;25-75&lt;/sub&gt;</td>
<td>maximum expiratory volume over mid expiration</td>
</tr>
<tr>
<td>FVC</td>
<td>forced vital capacity</td>
</tr>
<tr>
<td>HFA</td>
<td>hydrofluoroalkane (pMDI propellant, replacement for CFC)</td>
</tr>
<tr>
<td>ITT</td>
<td>intention to treat analysis</td>
</tr>
<tr>
<td>l/min</td>
<td>litres per minute</td>
</tr>
<tr>
<td>LYG</td>
<td>life years gained</td>
</tr>
<tr>
<td>MDI</td>
<td>metered dose inhaler</td>
</tr>
<tr>
<td>PEF</td>
<td>peak expiratory flow</td>
</tr>
<tr>
<td>PIF</td>
<td>peak inspiratory flow</td>
</tr>
<tr>
<td>PEFR</td>
<td>peak expiratory flow rate</td>
</tr>
<tr>
<td>PIFR</td>
<td>peak inspiratory flow rate</td>
</tr>
<tr>
<td>PP</td>
<td>per protocol analysis</td>
</tr>
<tr>
<td>pMDI</td>
<td>pressurised metered dose inhaler</td>
</tr>
<tr>
<td>QALY</td>
<td>quality adjusted life year</td>
</tr>
</tbody>
</table>

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 $\beta_2$-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 $\beta_2$-agonist drugs more than three times per week because of either night waking 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>
<thead>
<tr>
<th>Age Band (years)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 4</td>
<td>94.1</td>
<td>59.5</td>
</tr>
<tr>
<td>5 – 15</td>
<td>122.9</td>
<td>97.2</td>
</tr>
<tr>
<td>16 – 24</td>
<td>70.7</td>
<td>81.7</td>
</tr>
<tr>
<td>25 – 34</td>
<td>49.1</td>
<td>57.8</td>
</tr>
<tr>
<td>35 – 44</td>
<td>41.8</td>
<td>54.1</td>
</tr>
<tr>
<td>45 – 54</td>
<td>38.6</td>
<td>55.1</td>
</tr>
<tr>
<td>55 – 64</td>
<td>52.9</td>
<td>67.7</td>
</tr>
<tr>
<td>65 – 74</td>
<td>69.0</td>
<td>74.6</td>
</tr>
<tr>
<td>75 – 84</td>
<td>72.1</td>
<td>66.7</td>
</tr>
<tr>
<td>85+</td>
<td>54.6</td>
<td>42.4</td>
</tr>
<tr>
<td>All ages</td>
<td>66.2</td>
<td>67.7</td>
</tr>
</tbody>
</table>

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 \textit{et al.}\(^10\) and is shown in Table 2.
TABLE 2  ESTIMATED PROPORTION OF PEOPLE WITH ASTHMA BY BTS STEP

<table>
<thead>
<tr>
<th>Medication below step 1</th>
<th>Percentage aged under 5 years</th>
<th>Percentage aged 5 – 15 years</th>
<th>Percentage aged 16 years and over</th>
</tr>
</thead>
<tbody>
<tr>
<td>BST step 1</td>
<td>2%</td>
<td>11%</td>
<td>12%</td>
</tr>
<tr>
<td>BST step 2</td>
<td>47%</td>
<td>20%</td>
<td>18%</td>
</tr>
<tr>
<td>BST step 3</td>
<td>44%</td>
<td>44%</td>
<td>38%</td>
</tr>
<tr>
<td>BST step 4</td>
<td>-</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>BST step 5</td>
<td>-</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

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,\(^1\) there would be 33,500 expected asthma sufferers, distributed by age band and BTS step as shown in Table 3.


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

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.\(^\text{12}\) 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.\(^\text{13,14,15,16}\)

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 $\beta_2$-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 $\beta_2$-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 $\beta_2$-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 \textit{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 $\beta_2$-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 199921 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 200023 and age-specific recommendations were then made (presented in Table 4).
### TABLE 4 INHALER DEVICES: DTB AGE-SPECIFIC RECOMMENDATIONS

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

### 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’. ¹
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 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.

**Pressurised metered dose aerosol inhalers (pMDI)**

A list of pMDI devices currently available is given in Table 5.
<table>
<thead>
<tr>
<th>Drug type</th>
<th>Generic drug</th>
<th>Device brand name</th>
<th>Manufacturer</th>
<th>Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenoceptors -short acting β&lt;sub&gt;2&lt;/sub&gt; agonists</td>
<td>Salbutamol</td>
<td>Maxivent (cfc)</td>
<td>APS</td>
<td>Children over 2 years</td>
</tr>
<tr>
<td></td>
<td>Asmasal</td>
<td>Spacehaler</td>
<td>Medeva</td>
<td>Children over 2 years</td>
</tr>
<tr>
<td></td>
<td>Asmaven (cfc)</td>
<td>Berk</td>
<td>Children over 2 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salamol (non cfc)</td>
<td>Baker Norton</td>
<td>Children over 2 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aerolin Autohaler (cfc)</td>
<td>3M</td>
<td>Children over 2 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Airomir (non cfc)</td>
<td>3M</td>
<td>Children over 2 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salbulin (non cfc)</td>
<td>3M</td>
<td>Children over 2 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salamol Easy-Breathe (cfc)</td>
<td>Baker Norton</td>
<td>Children over 2 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ventolin Evohaler (non cfc)</td>
<td>GlaxoSmithKline</td>
<td>Children over 2 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Terbutaline sulphate</td>
<td>Bricanyl (cfc)</td>
<td>AstraZeneca</td>
<td>Adults and children, no ages given</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(with spacer) (cfc)</td>
<td>AstraZeneca</td>
<td>Adults and children, no ages given</td>
</tr>
<tr>
<td></td>
<td>Fenoterol hydrobromide</td>
<td>Berotec 100</td>
<td>Boehringer Ingelheim</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Berotec 200</td>
<td>Boehringer Ingelheim</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reproterol hydrochloride</td>
<td>Bronchodil (cfc)</td>
<td>ASTA Medica</td>
<td>Adults and children aged 6 and over</td>
</tr>
<tr>
<td>Adrenoceptors -long acting β&lt;sub&gt;2&lt;/sub&gt; agonists</td>
<td>Salmeterol</td>
<td>Serevent (cfc)</td>
<td>GlaxoSmithKline</td>
<td>Adults and children 4 and over</td>
</tr>
<tr>
<td>Other adrenoceptors</td>
<td>Orciprenaline sulphate</td>
<td>Alupent</td>
<td>Boehringer Ingelheim</td>
<td>(only tablets and syrup available in BNF 2001)</td>
</tr>
<tr>
<td>Antimuscarinic bronchodilators</td>
<td>Ipratropium bromide</td>
<td>Atrovent Aerosol (cfc)</td>
<td>Boehringer Ingelheim</td>
<td>Adults and children 1 month upwards</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atrovent Forte (cfc)</td>
<td>Boehringer Ingelheim</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxtropium bromide</td>
<td>Oxivent (cfc)</td>
<td>Boehringer Ingelheim</td>
<td>Not recommended for children, no age given</td>
</tr>
<tr>
<td>Combined therapy</td>
<td>Ipratropium and salbutamol</td>
<td>Combitvent (cfc)</td>
<td>Boehringer Ingelheim</td>
<td>Not for children under 12</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Beclomethasone dipropionate</td>
<td>Beclazone (50, 100, 200) (cfc)</td>
<td>Baker Norton</td>
<td>Adults and children, no ages given</td>
</tr>
<tr>
<td></td>
<td>Beclazone (250) (cfc)</td>
<td>Baker Norton</td>
<td>Not recommended for children (no ages given)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Filair (50, 100, 200) (cfc)</td>
<td>Generics and 3M</td>
<td>Adults and children, no ages given</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Filair Forte (250) (cfc)</td>
<td>Generics and 3M</td>
<td>Not recommended for children (no ages given)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Becolide (50, 100, 200) (cfc)</td>
<td>GlaxoSmithKline</td>
<td>Adults and children, no ages given</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Becloforte (250)</td>
<td>GlaxoSmithKline</td>
<td>Not recommended for</td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td>Manufacturer</td>
<td>Notes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-----------------------</td>
<td>--------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Becloforte Integra (with spacer)</td>
<td>GlaxoSmithKline</td>
<td>Not recommended for children (no ages given)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qvar (50, 100) (non cfc)</td>
<td>3M</td>
<td>Not recommended for children (no ages given)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide</td>
<td>Pulmicort LS (cfc)</td>
<td>AstraZeneca</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulmicort Aerosol</td>
<td>AstraZeneca</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulmicort Aerosol</td>
<td>AstraZeneca</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluticasone propionate</td>
<td>Flixotide aerosol (cfc)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flixotide Evohaler (50) (non cfc)</td>
<td>GlaxoSmithKline</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flixotide Evohaler (125, 250) (non cfc)</td>
<td>GlaxoSmithKline</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Compound preparations</td>
<td>Beclomethasone and salbutamol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seretide Evohaler (50, 125, 250) (non cfc)</td>
<td>GlaxoSmithKline</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sodium cromoglycate</td>
<td>Cromogen</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intal (cfc)</td>
<td>Rhone-Poulenc Rorer</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intal with Syncroner (integral open-tube spacer) (cfc and hfa)</td>
<td>Rhone-Poulenc Rorer (Adventis Pharma Ltd submission)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nedocromil sodium</td>
<td>Tilade (cfc)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sodium cromglicate and salbutamol</td>
<td>Aerocrom aerosol (cfc)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

In 1995 the majority of all prescriptions in England for inhaler medication containing short-acting β2-agonists (83%) or inhaled steroids (78%) used a pMDI delivery mechanism. Although for children, aged 5-12 in the West Midlands, bronchodilator prescriptions for pMDIs accounted for only 57%, with
the other 43% for DPIs. The pMDI was initially introduced in 1956. It comprises a small portable plastic case in which is located an aerosol canister 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. However, following the decision taken at Montreal in 1987 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.

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. Deposition of corticosteroids in the oropharynx is associated with local side effects such as oral candidiasis 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

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

**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. 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. 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 bronchodilator 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 | |
### 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, 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. 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.

### 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. DPIs work on the principle of mechanical inhalation driven by the user’s own

---

<table>
<thead>
<tr>
<th>Bronchodilators</th>
<th>Easibreathe</th>
<th>Boehringer Ingelheim</th>
<th>Adults and children 1 month upwards</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimuscarinic</td>
<td>Ipratropium</td>
<td>Boehringer</td>
<td></td>
</tr>
<tr>
<td>bronchodilators</td>
<td>bromide</td>
<td>Ingelheim</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxitropium</td>
<td>Boehringer</td>
<td>Not recommended for children, no ages given</td>
</tr>
<tr>
<td></td>
<td>bromide</td>
<td>Ingelheim</td>
<td></td>
</tr>
<tr>
<td>Combined therapy</td>
<td>Ipratropium</td>
<td>Boehringer</td>
<td>Children over 6</td>
</tr>
<tr>
<td></td>
<td>and fenoterol</td>
<td>Ingelheim</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Beclomethasone</td>
<td>3M</td>
<td>Adults and children, ages unknown</td>
</tr>
<tr>
<td></td>
<td>Aerobec (Autohaler 50, 100) (cfc)</td>
<td>3M</td>
<td>Not indicated for children, ages unknown</td>
</tr>
<tr>
<td></td>
<td>Becotide Easibreathe (cfc)</td>
<td>GlaxoSmithKline</td>
<td>Adults and children, ages unknown</td>
</tr>
<tr>
<td></td>
<td>Becloforte Easibreathe (cfc)</td>
<td>GlaxoSmithKline</td>
<td>Not indicated for children, ages unknown</td>
</tr>
<tr>
<td></td>
<td>Quvar Autohaler (50, 100)</td>
<td>GlaxoSmithKline</td>
<td>Not recommended for children, no ages given</td>
</tr>
<tr>
<td>Cromoglycet</td>
<td>Sodium cromoglycate</td>
<td>Baker Norton</td>
<td>Adults and children, ages not unknown</td>
</tr>
<tr>
<td>therapy</td>
<td>Easibreathe</td>
<td>Boehringer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Easibreathe</td>
<td>Ingelheim</td>
<td></td>
</tr>
</tbody>
</table>

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

GlaxoSmithKline includes Allen and Hanburys.
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 portability of this as a delivery system.

A list of dry powder inhalers currently available is given in Table 8.
<table>
<thead>
<tr>
<th>Drug type</th>
<th>Generic drug</th>
<th>Device brand name</th>
<th>Manufacturer</th>
<th>Users</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short acting β agonists</strong></td>
<td>Salbutamol</td>
<td>Asmasal Clickhaler</td>
<td>Medeva</td>
<td>Children over two years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GlaxoSmithKline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ventodisks Diskhaler</td>
<td></td>
<td>GlaxoSmithKline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ventolin Accuhaler</td>
<td></td>
<td>GlaxoSmithKline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ventolin Rotohaler</td>
<td></td>
<td>GlaxoSmithKline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Terbutaline sulphate</td>
<td>Bricanyl Turbohaler</td>
<td>AstraZeneca</td>
<td></td>
</tr>
<tr>
<td><strong>Long acting β agonists</strong></td>
<td>Formoterol fumarate/Eformoterol fumarate</td>
<td>Foradil</td>
<td>Novartis</td>
<td>Adults and children over 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxis Turbohaler</td>
<td>AstraZeneca</td>
<td>Adults and children over 12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salmeterol</td>
<td>Serevent Accuhaler</td>
<td>GlaxoSmithKline</td>
<td>Adults and children 4 and over</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serevent Diskhaler</td>
<td>GlaxoSmithKline</td>
<td>Adults and children 4 and over</td>
</tr>
<tr>
<td><strong>Antimuscarinic bronchodilators</strong></td>
<td>Iprotropium bromide</td>
<td>Atrovent Aerocaps (with Atrovent Aerohaler)</td>
<td>Boehringer Ingelheim</td>
<td>Adults and children 1 month upwards</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td>Beclomethasone</td>
<td>Asmabec Clickhaler (50, 100)</td>
<td>Medeva</td>
<td>Adults and children, no ages given</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asmabec Spacehaler 250</td>
<td>Medeva</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asmabec Clickhaler (250)</td>
<td>Medeva</td>
<td>Not recommended for children</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Becodisks Diskhaler</td>
<td>GlaxoSmithKline</td>
<td>Adults and children, ages not given</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Becotide Rotacaps (100, 200, 400) (with Rotahaler)</td>
<td>GlaxoSmithKline</td>
<td>Adults and children, ages not given</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Becloforte (400) (with Diskhaler)</td>
<td>GlaxoSmithKline</td>
<td>Not recommended for children, ages unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Budesonide</td>
<td>Pulmicort Turbohaler</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluticasone propionate</td>
<td>Flixotide Accuhaler</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td><strong>Compound preparations</strong></td>
<td>Beclomethasone and salbutamol</td>
<td>Ventide Rotacaps (with Rotahaler) including Paediatric Rotacaps</td>
<td>GlaxoSmithKline</td>
<td>Adult and paediatric, no ages given</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluticasone Seretide (100)</td>
<td>GlaxoSmithKline</td>
<td>Children aged over 4 and</td>
</tr>
</tbody>
</table>
and salmeterol

<table>
<thead>
<tr>
<th>and salmeterol</th>
<th>Accuhaler</th>
<th>adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seretide (250 and 500) Accuhaler</td>
<td>GlaxoSmithKline</td>
<td>Children aged over 12 and adults</td>
</tr>
<tr>
<td>Cromoglycate therapies</td>
<td>Sodium cromoglycate</td>
<td>Rhone-Poulenc Rorer (Adventis Pharma Ltd submission)</td>
</tr>
<tr>
<td>Intal Syncroner</td>
<td>Rhone-Poulenc Rorer</td>
<td></td>
</tr>
</tbody>
</table>

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

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. 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 \( \beta \)-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 reservoir 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 \( \beta \)-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 \(\beta\)-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 β2-agonists, other adrenoceptors, antimuscarine bronchodilators) and anti-inflammatory drugs (corticosteroids, cromoglylates) that are licensed for use in five to fifteen year old children.

Bronchodilators (relievers)

The principle action of the β2-agonists is to relax the airway smooth muscle by stimulating the β2-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 β2-agonists cause a prompt increase in airflow, peaking at 30 minutes, and then fading rapidly. Whereas long-acting inhaled β2-agonists have a longer duration of bronchodilation of at least 12 hours after a single dose. Whilst with fomterol the onset of action is similar to that seen in short-acting β2-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. 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. With respect to efficacy, the review concluded that current evidence does not support an efficacy difference among inhaled corticosteroids.

Sodium cromoglycate and nedocri sodium also provide effective non-steroidal anti-inflammatory treatment in some children.

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-inflammatory 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 $\beta_2$-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.

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. 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%. Some figures on variation in drug deposition by different inhalers, shown in Table 9, was produced in another study.

### TABLE 9 PATTERN OF DRUG DEPOSITION WITH DIFFERENT INHALERS

<table>
<thead>
<tr>
<th>Percentage of total drug dose</th>
<th>DPI</th>
<th>MDI</th>
<th>MDI with large volume spacer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of deposition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>10-15</td>
<td>10-15</td>
<td>20</td>
</tr>
<tr>
<td>Oro-pharynx</td>
<td>80</td>
<td>80</td>
<td>15</td>
</tr>
<tr>
<td>Device</td>
<td>5</td>
<td>5</td>
<td>65</td>
</tr>
<tr>
<td>Patient</td>
<td>95</td>
<td>95</td>
<td>35</td>
</tr>
</tbody>
</table>

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. 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. 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. With β₂-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.

### 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.\textsuperscript{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.\textsuperscript{19} An update of the Brocklebank et al.\textsuperscript{19} search on \textit{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.\textsuperscript{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.\textsuperscript{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 dipropionate, budesonide and fluticasone propionate), 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 RESEARCH 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

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

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. review19 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.’

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 \textit{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 \textit{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 \textit{et al.}\(^{19}\) included the \(\beta_2\)-agonists, and of these, the short acting ones only. This review includes inhaler devices delivering long-acting \(\beta_2\)-agonists, other bronchodilators and the antimuscarinic drugs as well as short-acting \(\beta_2\)-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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Drug</th>
<th>Number of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>pMDI with/ without spacer vs pMDI with/ without spacer, same propellants</td>
<td>β₂-agonists</td>
<td>Not included</td>
</tr>
<tr>
<td>pMDI with/ without spacer vs breath actuated MDI</td>
<td>β₂-agonists</td>
<td>0</td>
</tr>
<tr>
<td>pMDI with/ without spacer vs DPI</td>
<td>β₂-agonists</td>
<td>9</td>
</tr>
<tr>
<td>DPI vs DPI</td>
<td>β₂-agonists</td>
<td>Not included</td>
</tr>
<tr>
<td>pMDI with/ without spacer vs pMDI with/ without spacer, same propellants</td>
<td>Corticosteroids</td>
<td>Not included</td>
</tr>
<tr>
<td>pMDI with/ without spacer vs breath actuated MDI</td>
<td>Corticosteroids</td>
<td>0</td>
</tr>
<tr>
<td>pMDI with/ without spacer vs DPI</td>
<td>Corticosteroids</td>
<td>3</td>
</tr>
<tr>
<td>DPI vs DPI</td>
<td>Corticosteroids</td>
<td>Not included</td>
</tr>
<tr>
<td>pMDI with/ without spacer vs breath actuated MDI</td>
<td>Cromoglycates</td>
<td>Not included</td>
</tr>
<tr>
<td>pMDI with/ without spacer vs pMDI with/ without spacer, different propellants</td>
<td>β₂-agonists</td>
<td>1</td>
</tr>
<tr>
<td>pMDI with/ without spacer vs pMDI with/ without spacer, different propellants</td>
<td>Corticosteroids</td>
<td>0</td>
</tr>
<tr>
<td>Breath-actuated vs breath-actuated, different propellants</td>
<td>Corticosteroids</td>
<td>0</td>
</tr>
<tr>
<td>pMDI with/ without spacer vs pMDI with/ without spacer, different propellants</td>
<td>Cromoglycates</td>
<td>0</td>
</tr>
</tbody>
</table>

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 limited amount of evidence available within each comparison group.

A) Delivery of $\beta_2$-agonist bronchodilators by hand held inhaler devices using the same propellants

Nine studies were found in total by Brocklebank et al. comparing inhaler devices using the same propellant and delivering bronchodilating 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.7

Seven papers were identified. In Kerac et al.47,48,49,50,52 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 study48 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 FEV$_{25-75%}$ 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 inhalation. The study participants were 18 aged between 4.9 to 13.7 years\textsuperscript{51} and 12 aged 7 to 11 years.\textsuperscript{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 delivering bronchodilating drugs) to support better lung function performance.

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

Nine studies were identified by Brocklebank 	extit{et al.}\textsuperscript{19} In two the DPI used was a Rotohaler and salbutamol was delivered. For the other seven, the DPI was a Turbohaler and turbutanline 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\textsubscript{1}, FEF\textsubscript{25-75}, FVC or PEFR between the pMDI and the DPI.

The conclusions of the reviewers\textsuperscript{19} were that they were not able to demonstrate any difference in the clinical bronchodilator effect of short term $\beta_2$-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 turbutanline 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\textsuperscript{54,55} whilst the other two were based around parallel groups\textsuperscript{56,57} The Spiros DPI was used in two of the studies,\textsuperscript{54,56} an Easyhaler in a third,\textsuperscript{55} and a Diskus in the fourth.\textsuperscript{57} Three studies used salbutamol or albuterol whilst the fourth\textsuperscript{57} used a long-acting $\beta_2$-agonist, salmeterol. As with the nine earlier studies, no significant differences were found in FEV\textsubscript{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.\textsuperscript{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 	extit{et al.} review.\textsuperscript{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\(_1\) 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.\textsuperscript{63} compared an HFA MDI versus DPI (Diskus) both delivering a combined therapy of fluticasone debonprone 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\textsuperscript{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\textsubscript{1}, symptom scores, albuterol use, or night-time wakenings. Both studies had sufficient power according to the details given in each paper. In one\textsuperscript{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,\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsubscript{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.\textsuperscript{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.\textsuperscript{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 $\beta_2$-agonist bronchodilators by pMDI using different propellants (Appendix 13)

Brocklebank et al.\(^\text{19}\) 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 $\beta_2$-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 $\beta_2$-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 (150\(\mu\)g, 300\(\mu\)g, 600\(\mu\)g/day) each delivered by both CFC and HFA propelled pMDI, found no differences in morning and evening PEFR, FEV\(_1\), symptom scores, night time waking, 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,\textsuperscript{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 studies have looked at breath actuated inhalers\textsuperscript{46,72} and one of these was not a comparison of device types but of propellants used.\textsuperscript{72} Similarly in terms of drugs, whilst short-acting $\beta_2$-agonists and corticosteroids are well represented in the evidence, only two studies\textsuperscript{46,73} considered the difference between inhalers delivering sodium cromoglycate, and for one of these it was a comparison of propellants.\textsuperscript{73} Few studies have addressed the question of long acting $\beta_2$-agonists alone\textsuperscript{57} or as a combined therapy.\textsuperscript{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\textsuperscript{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.\textsuperscript{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.\textsuperscript{74} It would be illogical if, with most of the studies looking at the same primary outcomes, FEV$_1$\textsubscript{max}, 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 $\beta_2$-agonists, Hughes \textit{et al.}\textsuperscript{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. 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). 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 and there appeared to be no obvious differences in these by inhaler type irrespective of drug delivered with one exception.

The cost of replacing CFC with HFA inhalers was predicted to be high 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 β₂-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 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) amounted to randomised controlled trials of which six (plus the extension study) were blinded.

[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 In two studies the age ranges were 4 to 18 years46 and 4.8 to 15.1 years.84 Subject numbers for all studies, with the exception of four, ranged between 1360 and 463.59 For the four exceptions, subject numbers were considerably higher at 1133101, 117398, 205694 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 technique89,95,96,102,59,101 and improvement in lung function and symptoms95,100,83 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 technique98,99 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.,\textsuperscript{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.\textsuperscript{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).\textsuperscript{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).\textsuperscript{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\textsuperscript{88,81,92} although correlation between self-reported and estimated actual use is often poor or non-existent.\textsuperscript{90,91} Some discordance was also seen between parent/child and parent/physician reports of asthma medication use.\textsuperscript{97} Factors such as age\textsuperscript{82,96} socio-economic status,\textsuperscript{92} and ethnicity\textsuperscript{92,94} were also found to interplay with measured adherence, with adherence appearing to decline with progress into adolescence.\textsuperscript{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.\textsuperscript{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).\textsuperscript{96}

Most of the evidence found related to comparisons of different DPI devices. In Sharma et al.,\textsuperscript{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. 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. 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. Patient preference was significantly in favour of the Diskus over the Turbohaler in Ng et al. However in Van der Palen et al. 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 and in Boulet et al. 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.

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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\textsuperscript{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\textsuperscript{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 2001112 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

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 or MIMS June 2001.
**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\textsuperscript{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\textsuperscript{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

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

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\textsuperscript{109} and supplementary requested information\textsuperscript{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.\textsuperscript{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 subdivided 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\textsuperscript{118} presented by the sponsor\textsuperscript{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\textsuperscript{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

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\textsuperscript{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\textsuperscript{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 hydrobromide  
Comparators for economic analyses: None

Product 3  
Name: Autohaler  
Device type: Breath actuated inhaler  
Drug delivered: Ipratropium bromide, ipratropium bromide + fenoterol hydrobromide  
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.\textsuperscript{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.\textsuperscript{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\(^2\)\(^1\) 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\textsuperscript{112} and MIMS May 2001.\textsuperscript{124} These have been multiplied by the appropriate daily doses and are comparable with the prices in the submissions.\textsuperscript{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. Therefore, 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 orophangeal or 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.

\[(\text{Device Cost A} - \text{Device Cost B}) / \text{Cost per QALY threshold selected}.\]

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\textsuperscript{125,126,127} has been calculated.

The approximate number needed is calculated with the following formula\textsuperscript{128}

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

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 perfect 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,\textsuperscript{129} and suffering a vertebral fracture has a QALY loss of 0.092.\textsuperscript{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.\textsuperscript{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 equivalently 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 $200\mu g$ 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 provided data that a device produces direct medical cost offsets compared with an alternative device for the defined population.

None of the submissions provided quantitative 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 beclometasone 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 symptoms/relief are adequate for some patients and may be needed more than once daily move to step 2.

**Before altering a treatment step ensure that the patient is having the treatment and inhaler technique. Address any fears.**

### Step 2:

**Regular inhaled anti-inflammatory agents**

- Inhaled short acting β agonists as required plus beclometasone or budesonide 100–400 μg twice daily or fluticasone 50–200 μg twice daily. Alternatively, use cromoglycate or nedocromil aerosol or nedocromil in a susceptible patient, or if control is not achieved start inhaled steroids.

**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 beclometasone or budesonide > 800 μg daily or fluticasone > 500 μg daily should be referred to a paediatrician with an interest in asthma.

### Step 3:

**High dose inhaled steroids or long acting inhaled steroids plus long acting inhaled β agonist bronchodilators**

- Inhaled short acting β agonists as required plus beclometasone or budesonide increased to 800–2000 μg daily or fluticasone 400–1000 μg daily via a large volume spacer or nebuliser. Alternatively, use cromoglycate or nedocromil in a susceptible patient, or if control is not achieved start inhaled steroids.

**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 beclometasone or budesonide > 800 μg daily or fluticasone > 500 μg daily should be referred to a paediatrician with an interest in asthma.

### Step 4:

**Addition of regular steroid tablets**

- Inhaled short acting β agonists as required with inhaled beclometasone or fluticasone 800–2000 μg daily or fluticasone 400–1000 μg daily via a large volume spacer or nebuliser plus a sequential therapeutic trial of one or more of:
  - Inhaled long acting β agonists
  - Sustained release β agonists
  - Inhaled tiotropium or olodaterol (long acting β agonist)
  - High dose inhaled bronchodilators
  - Cromoglycate or nedocromil.

**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 beclometasone or budesonide > 800 μg daily or fluticasone > 500 μg daily should be referred to a paediatrician with an interest in asthma.

### Step 5:

**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 oral steroids it may take place over 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 (daily or 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

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*Image credit: Modified from an original by Dr. David Georgiou, Consultant Paediatrician, Royal London Hospital.*

*In association with the Clinical Practitioners in Asthma Group, the British Association for Respiratory Medicine, the British Association for Paediatric Respiratory Medicine and the Royal College of Paediatrics and Child Health.*

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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. SchHARR 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  asthmas.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  asthmas*

CDSR and CCTR
(The Cochrane Library 2001 Issue 2)
#1  asthmas*:me
#2  asthmas*
#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 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
#15  child*:me
#16  #3 and #14
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 nebulaler 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 #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 'inhahalational-drug-administration' / all subheadings
#5 'inhahalation-' / all subheadings
#4 explode 'inhaaler-' / 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$.tw
3 or/1-2
4 administration, inhalation/
5 "nebulizers and vaporizers"/
6 exp aerosols/
7 is.fs
8 aerosols.rw
9 powders.rw
nebulizer.tw
nebulizer.tw
or/4-11
3 and 12
meter$ dose$.tw
 mdi or mdis).tw
 pmdi$.tw
 powder inhal$.tw
 inhal$. suspens$.tw
 or/14-18
 3 and 19
 maxivent.af
 spacehaler.af
 asmaven.af
 salamol.af
 autohaler.af
 airomir.af
 salbulin.af
 easibreathe.af
 easi-breathe.af
 evohaler.af
 ventolin.af
 bricanyl.af
 berotec.af
 bronchodil.af
 serevent.af
 alupent.af
 atrovent.af
 oxivent.af
 combivent.af
 douvent.af
 beclazone.af
 flair.af
 becotide.af
 becloforte.af
 qvar.af
 pulmicort.af
 flixotide.af
 ventide.af
 seretide.af
 cromogen.af
 intal.af
 tilade.af
 aerocom.af
 aerobec.af
 asmasal.af
 clickhaler.af
 ventodisk$.af
 diskhaler.af
 rotohaler.af
turbohaler.af
foradil.af
aerocap$.af
asmabec.af
rotacap$.af
accuhaler.af
steri-nab.af
ipratropium.af
respointin.af
or/21-69
3 and 69
integra.af
fisonair.af
nebuhaler.af
aeroscopic.af
syncroner.af
nebuchamber.af
volumatic.af
rotahaler.af
spinhaler.af
turbhaler.af
diskus.af
sidestream.af
ventstream.af
lc plus.af
lc star.af
halo lite.af
eaerobec.af
aerolizer.af
pari baby.af
or/71-89
3 and 90
spacer$.tw
holding chamber$.tw
aerochamber.tw
babyhaler.af
haleraid.af
nebuhaler.af
or/92-97
3 and 98
13 or 20 or 70 or 91 or 99
exp child/
child$.tw
infant$.tw
adolescent$.tw
teenager$.tw
paediat$.tw
pediat$.tw
or/101-107
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$ compliant$.tw
3 patient$ 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
paediatric asthma quality of life questionnaire.tw
child asthma short form.tw
children$ health survey for asthma.tw
about my asthma.tw
or/1-19
## APPENDIX 5 Excluded studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
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<tbody>
<tr>
<td>Baumgarten et al. 2000</td>
<td>patients aged &gt; 15 years old</td>
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<tr>
<td>Bourne et al. 1996</td>
<td>not available from the British Library</td>
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<tr>
<td>Williams &amp; Richards 1997</td>
<td>comparing different drug and doses (400µg budesonide vs 200µg fluticasone propionate)</td>
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<tr>
<td>Cavagni et al. 1993</td>
<td>spacer device (Jet disposable - Chiesi Farmaceutici S.p.A., Parma, Italy) not in criteria</td>
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<tr>
<td>Cunningham &amp; Crain 1994</td>
<td>on patients with episodic Emergency Department visit for an acute asthma attack</td>
</tr>
<tr>
<td>Spector 2000</td>
<td>review article on oral therapy</td>
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<tr>
<td>Price &amp; Kemp 1999</td>
<td>on oral tablet therapy</td>
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<tr>
<td>Liam &amp; Lim 1998</td>
<td>include children with acute asthma</td>
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<tr>
<td>Ruggins et al. 1993</td>
<td>on patients with acute asthma</td>
</tr>
<tr>
<td>Milanowski et al. 1999</td>
<td>adult patients, comparing different drug doses</td>
</tr>
<tr>
<td>Brand et al. 2001</td>
<td>patients aged &lt; 5 years old</td>
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<tr>
<td>Salat et al. 2000</td>
<td>patients aged &gt; 15 years old</td>
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<tr>
<td>Tonnel et al. 2000</td>
<td>patients aged &gt; 15 years old</td>
</tr>
<tr>
<td>Ayres et al. 2000</td>
<td>patients aged &gt; 15 years old</td>
</tr>
<tr>
<td>Perruchoud et al. 2000</td>
<td>patients aged &gt; 15 years old</td>
</tr>
<tr>
<td>Demedts et al. 1999</td>
<td>patients mostly &gt; 15 years old</td>
</tr>
<tr>
<td>Magnussen 2000</td>
<td>patients aged &gt; 15 years old</td>
</tr>
<tr>
<td>Quezada et al. 1999</td>
<td>comparing effects of different drugs</td>
</tr>
<tr>
<td>Beerendonk et al 1998</td>
<td>patients aged &gt; 15 years old</td>
</tr>
<tr>
<td>Dahl et al 1997</td>
<td>patients aged &gt; 15 years old</td>
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<tr>
<td>Mawhinney et al. 1991</td>
<td>patients aged &gt; 15 years old</td>
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<tr>
<td>Conroy et al. 2000</td>
<td>on drugs</td>
</tr>
<tr>
<td>Chang et al 2000</td>
<td>on asthma management</td>
</tr>
<tr>
<td>Geoffroy et al. 1999</td>
<td>patients aged &gt; 15 years old</td>
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<tr>
<td>Jacobson et al. 1999</td>
<td>patients aged &gt; 15 years old</td>
</tr>
<tr>
<td>Samaranyakaye &amp; Perera 1998</td>
<td>acute asthma</td>
</tr>
<tr>
<td>Berg &amp; Dunbar-Jacob 1998</td>
<td>patients aged &gt; 15 years old</td>
</tr>
<tr>
<td>Zar et al. 1999</td>
<td>acute asthma</td>
</tr>
<tr>
<td>Thompson et al. 1998</td>
<td>patients aged &gt; 15 years old</td>
</tr>
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<td>Seale &amp; Harrison 1998</td>
<td>patients aged &gt; 15 years old</td>
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<td>Argenti et al. 2000</td>
<td>patients aged &gt; 15 years old</td>
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<td>Zar et al. 1999</td>
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<tr>
<td>Quittner et al. 2000</td>
<td>patients with cystic fibrosis</td>
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<tr>
<td>Shappiro et al. 1998</td>
<td>different drug doses</td>
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<tr>
<td>Chan &amp; DeBruyne 2000</td>
<td>study's population was parents</td>
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<tr>
<td>Giannini et al. 2000</td>
<td>patients aged &gt; 15 years old</td>
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<td>Santanello et al. 1999</td>
<td>patients aged &gt; 15 years old</td>
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<tr>
<td>Jones et al. 1992</td>
<td>on asthma morbidity in primary care</td>
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<tr>
<td>Lipworth et al. 1998</td>
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<td>Bousquet J et al. 2000</td>
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<tr>
<td>Wildhaber JH et al. 1996</td>
<td>&lt; 4 years old</td>
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<tr>
<td>Warren &amp; Zuberbuhler, 1998</td>
<td>&lt; 5 yrs old</td>
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<td>Schlaeppi M et al., 1996</td>
<td>&gt;=16 yrs old</td>
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<td>Clark &amp; Lipworth</td>
<td>healthy volunteers</td>
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<td>Thorsson et al., 1994</td>
<td>&gt; 15 yrs old</td>
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<tr>
<td>Wildhaber et al., 2000</td>
<td>&gt;= 18 years old</td>
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<tr>
<td>****Nielsen et al. 1998</td>
<td>not comparing devices</td>
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<tr>
<td>Newman et al., 1989</td>
<td>Patients aged 21-76 yrs old</td>
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<tr>
<td>Smith et al., 1998</td>
<td>comparing different drugs</td>
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<tr>
<td>Mitchell &amp; Nigel, 1997</td>
<td>In-vitro testing of 3 spacers - not in our criteria</td>
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<td>Barry &amp; O’Callaghan, 1996</td>
<td>In-vitro drug delivery fr. 7 spacers - not in our criteria</td>
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<td>Pierart et al, 1999</td>
<td>In-vitro, subjects are health adult volunteers</td>
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<td>Barry et al, 1999</td>
<td>In-vitro, spacer devices - not in our criteria</td>
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<tr>
<td>Barry &amp; O’Callaghan, 1997</td>
<td>In-vitro, drug delivery and spacer - not in our criteria</td>
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<td>Berg et al, 1998</td>
<td>In-vitro, spacer and pMDI - not in our criteria</td>
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<td>Wildhaber et al, 1996</td>
<td>In-vitro, spacer device - not in our criteria</td>
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<td>In-vitro, spacers - not in our criteria</td>
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<td>Chuffart et al., 2001</td>
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<td>$$$$ Pedersen, 1983</td>
<td>Acute asthma</td>
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<td>Oliver et al., ?? (Ref. 2436)</td>
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<td>Solé et al, 1993 (2484)</td>
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<td>Nankani et al, 1990 (2516)</td>
<td>drug not inhaler device intervention</td>
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<td>Petrie et al, 1990 (2381)</td>
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<td>Xuan et al, 1989 (2511)</td>
<td>drug not device</td>
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<td>Ståhl et al, 1996 (2507)</td>
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<td>Ahrens et al, 1995 (2361)</td>
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<td>Chapman, 1995 (2499)</td>
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<td>Löfdahl et al, 1994 (2509)</td>
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<td>Pedersen &amp; Hansen, 1995 (2512)</td>
<td>drug intervention</td>
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<td>Corris et al, 1992 (2505)</td>
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<td>Repper et al, 1994 (2515)</td>
<td>drug intervention</td>
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<td>Juntunen-Backman et al, 1996 (2445)</td>
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<tr>
<td>Burgess et al, 1993 (2420)</td>
<td>abstract only</td>
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<tr>
<td>Barry &amp; O’Callaghan, 1994 (2444)</td>
<td>in vitro, but wrong research question</td>
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<td>Fuller, 1986 (2424)</td>
<td>adults</td>
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<td>Böllert et al, 1997 (2419)</td>
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<td>O’Reilly et al, 1986 (2437)</td>
<td>adults</td>
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<tr>
<td>Dubus &amp; Dolvich, 2000 (2400)</td>
<td>in vitro, wrong research question</td>
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<td>Mahadewsingh et al, 1996 (2433)</td>
<td>adults</td>
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<tr>
<td>Stenius-Aarniala et al, 1993</td>
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<tr>
<td>Finlay &amp; Zuberbuhler, 1999</td>
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<td>Turpeinen et al, 1999 (2416)</td>
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<td>pedersen &amp; Mortensen, 1990 (2412)</td>
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<td>Terzano &amp; Mannino, 1996 (2441)</td>
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<td>Vidgenre et al, 1988 (2397)</td>
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<td>Benedictus et al, 1994 (2485)</td>
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<td>Agertoft &amp; Pedersen, 1994 (2407)</td>
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<td>Gorman et al, 1990 (2411)</td>
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<td>Zainudin et al, 1990 (2486)</td>
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<td>Engel et al, 1990 (2487)</td>
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<td>Gunawardena et al, 1997 (2426)</td>
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<td>Deenstra et al, 1988 (2423)</td>
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<td>Laurikainen et al, 1997 (2432)</td>
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<td>Nelson &amp; Loffert, 1994 (2435)</td>
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<td>Haahtela et al, 1994 (2427)</td>
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<td>Lipworth &amp; Clark, 1997 (2396)</td>
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<td>Lipworth &amp; Clark, (2492)</td>
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<td>Pedersen, 1992 (2474)</td>
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<td>Kassirer, 1994 (2497)</td>
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<td>Nantel et al, 1996 (2475)</td>
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<td>Hidinger &amp; Dorow, 1984 (2429)</td>
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<td>Oliver et al, (2436)</td>
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<td>Pedersen, 1983 (2438)</td>
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<td>Gurwitz et al, 1983 (2483)</td>
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<td>Dawson et al, 1985 132</td>
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<td>Weinstein, 2000 133</td>
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<td>Haughney, 1995 135</td>
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<td>Gillies, 1997 136</td>
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<td>Ahonen et al, 2000 137</td>
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### Papers in foreign language – not extracted

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<tr>
<td>Carrion Valero et al., 2000</td>
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<td>Aguilar Miranda &amp; Mallol Villablanca 2000</td>
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<td>Sanchez-Jimenez et al., 1998</td>
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<td>Chinet, 2000</td>
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<td>Rufin et al., 2000</td>
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<td>Garde Garde &amp; Pomares, 1999</td>
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<td>Zureik &amp; Delacourt, 1999</td>
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<td>Alvarez et al, 2001</td>
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<td>Dubus, 2001</td>
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<td>Aceves et al, 1995</td>
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<td>Cordero et al, 1987</td>
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**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)

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Treatment inhaler type, drug and dose</th>
<th>Study design</th>
<th>Location, setting, inclusion/exclusion</th>
<th>Patients, number, age mean± SD (range), male/female, ethnicity</th>
<th>Follow-up Outcomes</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kerac et al., 1998</td>
<td>T1: MDI</td>
<td>T2: MDI+spacer (Volumatic, Glaxo Inc.)</td>
<td>1 site, Calcutta, India. In: chronic stable asthmatic outpatients</td>
<td>At beginning: 48 at end: 48 Age: 43.8±3.5 (10-75) M/F: 25/23</td>
<td>Run-in: Salbutamol 4 mg + deriphyllin 100 mg taken orally 3 times/day was withheld overnight. Morning baseline PEFR &lt;80% of predicted for age and height.</td>
<td>Mean±SE baseline PEFR, 156.9±8.4. No significant differences among the 4 groups (p&gt;0.1). Significant % improvement in PEFR over baseline in T1 and T3 compared with T4, 30 min after inhalation, and in T2 vs T4 at 15 min after inhalation (both p&lt;0.05). No differences between T1 and T4.</td>
<td>Mostly adult patients. Plastic bottle spacer is as effective as commercial spacer.</td>
</tr>
<tr>
<td>Green &amp; Price, 1991</td>
<td>T1: MDI+spacer (Volumatic) &amp; placebo via MDI</td>
<td>T2: MDI &amp; placebo via MDI+spacer</td>
<td>1 site, London, U.K. In: asymptomatic at the time of study, proficient in FEV1 manoeuvres</td>
<td>At beginning: 10 At end: 10 Age: 11(8-14) M/F: nil</td>
<td>Run-in: stop medication 24h before study FU: 3 occasions – 2 to 7 days apart and within 14 days. Primary: baseline FEV1, BO, FEV1 after 15 min (B15), FEV1 after a further 15 min (B30)</td>
<td>No significant difference in baseline FEV1 for the study days (p&gt;0.05). From B0 to B15, standardised FEV1 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+0.2%, 95% CI:2.2%, paired t-test).</td>
<td>No significant difference in bronchodilation between MDI+ spacer and MDI. Retrospective power calculation, 75 subjects needed.</td>
</tr>
<tr>
<td>Lee &amp; Evans, 1987</td>
<td>T1: MDI</td>
<td>T2: MDI+ spacer (InspirEase)</td>
<td>1 center, New York In: stable asthma, correct inhalation technique from a MDI, receiving beta-agonist aerosol</td>
<td>At beginning: 23 At end: 20</td>
<td>Run-in: taught proper use of 3 inhalation aids (InspirEase)</td>
<td>14 children have correct inhalation technique while 6 have errors. Incorrect technique - 1 with MDI, 3 with InspirEase, 2 with InspirEase &amp; Aerochamber, 0 for Aerosol Bag.</td>
<td>No additional benefits from T2, T3 &amp; T4 for those with MDI.</td>
</tr>
<tr>
<td>Group</td>
<td>Design</td>
<td>Drug</td>
<td>Power calculation</td>
<td>Per protocol analysis</td>
<td>Age</td>
<td>Overall and for 14 children with correct technique, no significant differences in FEV₁ % increase from baseline over 3 hours, following inhalation, in all treatment groups.</td>
<td>Jadad’s score = 3</td>
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<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>T1</td>
<td>randomised, double-blind</td>
<td>MDI placebo</td>
<td>no</td>
<td>assumed</td>
<td>12.5(8-15)</td>
<td>Aerochamber, Aerosol Bag in laboratory.</td>
<td>From MDI.</td>
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<tr>
<td>T2</td>
<td>double-blind, cross over, placebo</td>
<td>MDI</td>
<td></td>
<td></td>
<td></td>
<td>FU: 3 subsequent days</td>
<td></td>
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<tr>
<td>T3</td>
<td>double-blind, placebo</td>
<td>MDI+spacer placebo</td>
<td></td>
<td></td>
<td></td>
<td>Primary: pulmonary function (FEV₁), correct MDI technique</td>
<td></td>
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<tr>
<td>T4</td>
<td>double-blind, Aerosol Bag</td>
<td>MDI+spacer (Aerochamber, Monagham Medical Corporation)</td>
<td></td>
<td></td>
<td></td>
<td>All operations were assisted by the examiner to ensure correct use of aids.</td>
<td></td>
</tr>
</tbody>
</table>

Power calculation:
- No
- Per protocol analysis: assumed

**Design:** randomised, double-blind, cross over, placebo

**Jadad’s score:** = 3

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| T1    | MDI placebo | 1 site, USA. | 16 | 16 | At beginning: | At end: | No significant difference between T2 & T4 for FEV₁ and FEF₂₅-₇₅%.
Both T2 & T4 significantly different from placebo (T1, T3).

| T2    | MDI | At 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. |
|-------|-----|---------------------------------------------------------------|------|-----|-----------------------------------------------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| T3    | MDI+spacer placebo | 1 hospital, Canada | Run-in: stop oral | Pulmonary functions values (mean±SEM for % predicted normal for Both) |
| T4    | MDI+spacer (Aerochamber, Monagham Medical Corporation) | | | |

**Drug:**
- Albuterol, 2 puffs, 180 µg
- Brochodilator Metaproterenol sulphate, 130 µg, 2 puffs
- Metaproterenol sulphate, 130 µg, 2 puffs

**Design:**
- randomised, double-blind, placebo-controlled

**Jadad’s score:** = 2

---

**Side effects similar in all treatments.**

*REFERENCES*

Rachelefsky et al., 1986

Becler et al.
**1985**

T1: pMDI
T2: pMDI + spacer (750ml collapsible spacer)

**Drug:** Terbutaline sulphate, 1 puff, 0.24mg

**Design:** Randomised, double-blind, placebo-controlled

Jadad’s score = 1

**In:** had a history of asthma, documented reversibility of obstruction to airflow previously (increase FEV₁ > 20% after a bronchodilator aerosol), FEV₁ < 70% predicted normal.

**Out:** severe acute asthma on study day

**Power calculation:** no

**Protocol analysis assumed**

**At beginning:**

- T1: 34
- 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 within 14 days.

**Primary:** pulmonary functions

<table>
<thead>
<tr>
<th>Test Pre-treatment</th>
<th>Hours post-treatment</th>
<th>T1 78.3 ± 6.1</th>
<th>T2 87.3 ± 6.8</th>
<th>T3 101.8 ± 8.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>0.5</td>
<td>93.3 ± 6.6</td>
<td>103.3 ± 8.3</td>
<td>101.3 ± 6.1</td>
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<tr>
<td>FEF&lt;sub&gt;25-75&lt;/sub&gt;</td>
<td>1.0</td>
<td>92.7 ± 4.4</td>
<td>90.8 ± 6.7</td>
<td>100.4 ± 8.3</td>
</tr>
<tr>
<td>FEF&lt;sub&gt;50&lt;/sub&gt;</td>
<td>1.5</td>
<td>90.8 ± 6.7</td>
<td>89.7 ± 6.2</td>
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<tr>
<td>FEF&lt;sub&gt;75&lt;/sub&gt;</td>
<td>2.0</td>
<td>89.7 ± 6.2</td>
<td></td>
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</tbody>
</table>

**Hidinger & Kjellman, 1984**

T1: pMDI
T2: pMDI + spacer (750ml collapsible spacer)

**Drug:** Terbutaline sulphate, 1 puff, 0.24mg

**Design:** Randomised, double-blind, placebo-controlled

Jadad’s score = 1

**In:** bronchial asthma. All children had used pMDI prior to study.

**Out:** not stated

**Power calculation:** no

**Protocol analysis assumed**

**At beginning:**

- T1: 18 (4.9 - 13.7)
- M/F: 12/6

**Run in:** β<sub>2</sub>-agonists withheld ≤ 10h prior to experiment, 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.

- PEFR was 181 ± 61 l/min for T1 vs. T2 206 ± 64 l/min. The values obtained when the spacer was attached were significantly > when measured at 20 min (p < 0.001) and 60 min (p < 0.01) after therapy but not at 5 minutes.

**Kirton & Kjellman, 1984**

T1: pMDI
T2: pMDI + spacer (750ml collapsible spacer)

**Drug:** Terbutaline sulphate, 1 puff, 0.25 mg

**Design:** Randomised, cross-over

Jadad’s score = 1

**In:** moderate bronchial asthma

**Out:** not stated

**Power calculation:** no

**Protocol analysis assumed**

**At beginning:**

- T1: 24 ± 4.9
- M/F: 42/34.9

**Run in:** on 1st & 2nd visits, patients familiarised themselves with a peak flow meter.

**FU:** 4 separate occasions at approximately weekly intervals.

**Primary:** PEFR at 0, 5, 20 & 60 min after inhalation of the aerosol.

- PEFR was 181 ± 61 l/mm (mean±SEM) for T1 vs. T2 206 ± 64 l/mm. The values obtained when the spacer was attached were significantly > when measured at 20 min (p < 0.001) and 60 min (p < 0.01) after therapy but not at 5 minutes.

**Ellul-Micallef, 1980**

T1: pMDI
T2: pMDI + spacer (750ml collapsible spacer)

**Drug:** Terbutaline sulphate, 1 puff, 0.25 mg

**Design:** Randomised, cross-over

Jadad’s score = 1

**In:** had a history of asthma, documented reversibility of obstruction to airflow previously (increase FEV₁ > 20% after a bronchodilator aerosol), FEV₁ < 70% predicted normal.

**Out:** severe acute asthma on study day

**Power calculation:** no

**Protocol analysis assumed**

**At beginning:**

- T1: 34
- 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

**Drug:** Terbutaline, 250µg/actuation, given in a total dose of 500µg.

**Design:** randomised, double-bline, placebo-controlled

Jadad’s score = 2

**Drug:** Terbutaline, 250µg/actuation, given in a total dose of 500µg.

**Design:** randomised, double-bline, placebo-controlled

Jadad’s score = 2

**Placebo was the cfc propellant-surfactant mixture used in the active inhaler**

**Test Pre-treatment**

- FEV<sub>1</sub>: 78.3 ± 6.1
- T2: 87.3 ± 6.8
- T3: 101.8 ± 8.3

**Hours post-treatment**

- 0.5: 93.3 ± 6.6
- 1.0: 92.7 ± 4.4
- 1.5: 90.8 ± 6.7
- 2.0: 89.7 ± 6.2

**FEV/FVC**

- T1: 66.8 ± 3.4
- T2: 69.5 ± 2.2

**FEF<sub>25-75</sub>**

- T1: 38.3 ± 5.5
- T2: 40.6 ± 4.8

**Vmax<sub>25</sub>**

- T1: 60.4 ± 7.4
- T2: 70.8 ± 7.6

**Vmax<sub>50</sub>**

- T1: 41.7 ± 5.0
- T2: 48.7 ± 4.8

**Vmax<sub>75</sub>**

- T1: 26.0 ± 4.9
- T2: 24.4 ± 4.9

**T3 placebo results omitted from this table.**

**Adding the spacer to a pMDI resulted in significantly better pulmonary function.**

**Power calculation:** no

**Pre-protocol analysis assumed**

**At beginning:**

- 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

**Test Pre-treatment**

- FEV<sub>1</sub>: 78.3 ± 6.1
- T2: 87.3 ± 6.8

**Hours post-treatment**

- 0.5: 93.3 ± 6.6
- 1.0: 92.7 ± 4.4
- 1.5: 90.8 ± 6.7
- 2.0: 89.7 ± 6.2

**FEV/FVC**

- T1: 66.8 ± 3.4
- T2: 69.5 ± 2.2

**FEF<sub>25-75</sub>**

- T1: 38.3 ± 5.5
- T2: 40.6 ± 4.8

**Vmax<sub>25</sub>**

- T1: 60.4 ± 7.4
- T2: 70.8 ± 7.6

**Vmax<sub>50</sub>**

- T1: 41.7 ± 5.0
- T2: 48.7 ± 4.8

**Vmax<sub>75</sub>**

- T1: 26.0 ± 4.9
- T2: 24.4 ± 4.9

**T3 placebo results omitted from this table.**

**MDI+spacer and pMDI were equally effective in improving pulmonary function from the baseline state.**

**The use of such a spacer attached to the usual actuator improved the efficacy when subjects inhaled 1 puff of terbutaline sulphate.**
APPENDIX 7  pMDIs with or without spacer vs dry powder devices, delivering bronchodilating drugs (randomised controlled trials, physiological and clinical outcomes)

Evidence reported by Brocklebank et al.19

<table>
<thead>
<tr>
<th>Study Author, Year</th>
<th>Methodology</th>
<th>Details</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kemp 1989134</td>
<td>Asthma Research Centre, USA Citation: J Allergy Clin Immunol 83(3); 697-702</td>
<td>Design: 2 separate studies reported (a) randomised double-blind double-dummy crossover study using 2 doses: 100 &amp; 200ug on separate days &amp; (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 &amp; 180-200ug and study (b) 180-200ug Duration: (a) 360min &amp; (b) 12 weeks</td>
<td>Participants: (a) 30 children, mean age 9.4yrs. Lung function measured from 5 to 360min post-dose. Study quality: Cochrane-A Study A: No significant differences in: FEV\textsubscript{1}, HR or BP Study B: No significant differences in: FEV\textsubscript{1}, FEF\textsubscript{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&lt;0.05).</td>
<td>Analyses of baseline mean FEV\textsubscript{1} (using unpaired two-tailed t-test) showed that the pMDI group had significantly lower FEV\textsubscript{1} when compared to the RH group. This may explain the higher rate of acute exacerbations seen in the pMDI group.</td>
</tr>
<tr>
<td>Bronsky, 199514</td>
<td>Medical Research Centre, Utah Supported by Glaxo Research Citation: J of Asthma 32(3) 207-214.</td>
<td>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</td>
<td>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 predetermined target rates (85% of HR\textsubscript{max}). Study also reported 15 min post dose FEV\textsubscript{1} (i.e. pre-exercise). Study quality: Cochrane-B</td>
<td>No significant differences in: pre and post exercise FEV\textsubscript{1} after drug administration. Study used exercise challenge to show that the two devices are equally effective against E1A.</td>
</tr>
<tr>
<td>Ahlström 1989139</td>
<td>Sweden Medical Hospital Citation: Allergy 44, 515-518</td>
<td>Design: open randomised crossover study. Device: Turbuhaler vs MDI + Nebuhaler Drug: terbutaline Dose: 0.5mg gid (both devices) Duration: 14 days</td>
<td>Participants: 21 children (7F) age range 2-5yrs, mean age 3.9yrs. PEFR measured 15 min after drug administration. Study quality: Cochrane-B</td>
<td>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.</td>
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<tr>
<td><strong>Fuglsang, 1989</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td><strong>AstraZeneca, Sweden</strong></td>
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<td><strong>Citation:</strong> Pediatric Pulmonology 7; 112-115</td>
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<tr>
<td><strong>Design:</strong> single-blinded double-dummy, crossover study, used computer generated schedule.</td>
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<tr>
<td><strong>Device:</strong> Turbuhaler vs pMDI alone</td>
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<td><strong>Drug:</strong> terbutaline</td>
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<tr>
<td><strong>Dose:</strong> 2.0mg (both devices)</td>
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<td><strong>Duration:</strong> cumulative dosing study, giving a total dose of 2.0mg within 80 min</td>
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<td><strong>Participants:</strong> 13 children (3F), age range 7-15 years, mean age 10.5 yrs.</td>
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<td><strong>Pulmonary function testing done 15 min post-dose.</strong></td>
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<tr>
<td><strong>Study quality:</strong> Cochrane-B</td>
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<tr>
<td><strong>No significant differences in:</strong></td>
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<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, FEF&lt;sub&gt;25-75&lt;/sub&gt;, PEFR or FVC.</td>
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<tr>
<td><strong>Significant differences in:</strong></td>
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<tr>
<td>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).</td>
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<td>Study Author, Year</td>
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</table>
| Hultquist 1989<sup>140</sup>  
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 + pm (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<sup>141</sup>  
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.  
Duration: 15 min | 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<sup>142</sup>  
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 EIA.  
Study quality: Cochrane-B | No significant differences in: FEV<sub>1</sub> and VTG.  
Study also used Turbuhaler 50ug vs Turbuhaler 100ug & pMDI 100ug, showing no significant differences. | |
| Hirsch 1997<sup>143</sup>  
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<sub>1</sub> and FVC  
Significant differences in: Vmax50% favouring pMDI | |
| Razzouk 1999<sup>144</sup>  
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<sub>1</sub> and FEV<sub>1max</sub>.  
Study also used Turbuhaler 50ug vs Turbuhaler 100ug & pMDI 100ug, showing no significant differences. | |
### Additional evidence from the current review

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Treatment inhaler type, drug and dose</th>
<th>Study design</th>
<th>Location, setting, inclusion/exclusion power calculation, type of analysis</th>
<th>Patients, number, age means SD (range), male/female, ethnicity</th>
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<tbody>
<tr>
<td>Koskela et al., 2000&lt;sup&gt;15&lt;/sup&gt;</td>
<td>T1: DPI (Easyhaler&lt;sup&gt;®&lt;/sup&gt;) (Buventol Easyhaler&lt;sup&gt;®&lt;/sup&gt;, Orion Pharma, Finland) T2: pMDI+spacer (Volumatic&lt;sup&gt;®&lt;/sup&gt;, Glaxo Wellcome, UK) T3: Easyhaler&lt;sup&gt;®&lt;/sup&gt; T4: pMDI +spacer</td>
<td>Design: Randomised, crossover, double-blind, double-dummy. Jadad’s score = 2</td>
<td>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&lt;sub&gt;1&lt;/sub&gt;, or PEF ≥15%</td>
<td>Number: 22 Age: 19(7-65) No. patients &lt; 16 yrs : 12 M/F: 10/12</td>
<td>FU: 2 study days - interval ≥24 hrs.</td>
<td>No significant differences in primary or secondary efficacy variables between T1 and T2.</td>
<td>A reasonable low inspiratory flow rate (30 l/min) via Easyhaler&lt;sup&gt;®&lt;/sup&gt; produces an equivalent improvement in lung function to a correctly used pMDI plus spacer.</td>
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<tr>
<td>Ahrens et al., 1999&lt;sup&gt;14&lt;/sup&gt;</td>
<td>T1 &amp; T2: DPI (Spiros) T3 &amp; T4: MDI</td>
<td>Drug: T1&amp;2 albuterol sulfate (108µg=90µg of albuterol base/actuation). T1 1, T2 3 actuations T3&amp;4 Ventolin (90µg albuterol base/actuation). T3 1, T4 3 actuations</td>
<td>USA In: mild to moderate asthma, ≥12 years age, FEV&lt;sub&gt;1&lt;/sub&gt; ≥65% &amp; PC&lt;sub&gt;20&lt;/sub&gt; ≤ 4mg/ml, PC&lt;sub&gt;20&lt;/sub&gt; (20% decrease in FEV&lt;sub&gt;1&lt;/sub&gt;) to increase 8-fold after 2 actuations of Ventolin. At subsequent visits, FEV&lt;sub&gt;1&lt;/sub&gt; ≥65% &amp; PC&lt;sub&gt;20&lt;/sub&gt; to be within 2-fold of screening 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</td>
<td>At beginning: 31 At end: 24 Age: 26.2 (12-46) M/F: 15/9</td>
<td>FU: 4 study days Primary: PC&lt;sub&gt;20&lt;/sub&gt; measured by methacholine challenge Secondary: adverse events</td>
<td>No significant differences in PC&lt;sub&gt;20&lt;/sub&gt; FEV&lt;sub&gt;1&lt;/sub&gt; dose response curves between all treatments. Adverse events profiles were similar for the two inhalers.</td>
<td>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</td>
</tr>
<tr>
<td>cross-over, double-dummy</td>
<td>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.</td>
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<td>Ventolin in the delivery of albuterol (90% confidence level 0.68 - 1.94).</td>
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<tr>
<td>Jadad’s score = 3</td>
<td>Power calculation no</td>
<td>Per protocol analysis for efficacy</td>
<td>ITT for safety analysis</td>
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<tr>
<td>Authors, year</td>
<td>Treatment inhaler type, drug and dose</td>
<td>Location, setting, inclusion/exclusion power calculation, type of analysis</td>
<td>Patients, number, age means SD (range), male/female, ethnicity</td>
<td>Follow-up Outcomes</td>
<td>Results</td>
<td>Comments</td>
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<tr>
<td>Nelson, et al. 1999</td>
<td>T1: DPI (Spiros) + pMDI placebo T2: pMDI + DPI (Spiros) placebo T3: DPI (Spiros) and MDI</td>
<td>Location, setting, inclusion/exclusion power calculation, type of analysis</td>
<td>Patients, number, age means SD (range), male/female, ethnicity</td>
<td>Follow-up Outcomes</td>
<td>Results</td>
<td>Comments</td>
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<td>Drug: Albuterol sulphate, T1 (108µg/actuation = 90µg/actuation) Albuterol T2 (90µg/actuation) 2 actuations qid for each inhaler T3 lactose placebo</td>
<td>Design: Randomised, double-blind, double-dummy, placebo-controlled 3-way-parallel group, phase III Jadad’s score = 3</td>
<td>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)</td>
<td>Run-in: 7-14 days, instruction &amp; training to use and record PEF on diary card, training with Spiros inhalation system and MDI FU: 12 wks Primary: FEV1max, AUCFEV1 above baseline. Secondary: rescue albuterol use, episodes of exacerbation, daily PEF, nocturnal asthma symptom scores from self recorded dairy cards.</td>
<td>The Spiros and MDI groups were comparable in all FEV1 parameters and superior over the placebo group (p=0.0001). With exception of treatment wk 0 for the max % change in FEV1, the duration of effect and the AUCBL, no statistically significant differences between T1 and T2 for any FEV1 parameters. (Wk 0, mean change) T1 T2 Baseline FEV1(%) 37.71 31.29 AUCCL (L/min) 141.50 181.73 Duration of effect(min) 192.0 162.7 (Wk 12, mean change, p=0.0001) T1 T2 Baseline FEV1(%) 30 29 AUCCL (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.</td>
<td>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)</td>
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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)
<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Treatment inhaler type, drug and dose</th>
<th>Location, setting, inclusion/exclusion power calculation, type of analysis</th>
<th>Patients, number, age means: SD (range), male/female, ethnicity</th>
<th>Follow-up Outcomes</th>
<th>Results</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Wolfe et al. 2000</td>
<td>T1: DPI (Diskus) + MDI placebo  T2: MDI + DPI (Diskus) placebo  T3: DPI (Diskus) and MDI</td>
<td>Location: 27 centres, USA  In: Screening: ≥12 years age, ≥6 mths history of mild to moderate asthma that required pharmacotherapy, baseline FEV1, 50 - 85% predicted normal value after abstaining from asthma medications, ≥15% reversibility of airway obstruction within 30 min following 2 actuations of albuterol aerosol (180 µg).</td>
<td>At beginning: 498 (mean age 33, 12 - 79 yrs)  T1: 165  T2: 166  T3: 167</td>
<td>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</td>
<td>No significant differences between T1 and T2 in improvement in pulmonary function. Compared with T3 placebo, significant decreases demonstrated in T1 &amp; T2 in albuterol use, nighttime awakenings and increases in %days with no asthma symptom for the entire study period. (Mean change %)  T1 23  T2 22  T3 20  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 Symptom score  -0.3 ± 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%])</td>
<td>No significant differences between gender, ethnicity, or patients with inhaled corticosteroid vs. those without.</td>
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<tr>
<td>Drug: Salmeterol  T1 50 µg, twice daily  T2 42 µg, twice daily  T3 placebo</td>
<td>Design: Randomised, multicentre, double-blind, double-dummy, placebo-controlled parallel group.  Jadad’s score = 3</td>
<td>Age:  T1: 33 (12-74)  T2: 35 (12-79)  T3: 34 (12-74)</td>
<td>At end: 395  T1: 134  T2: 139  T3: 122</td>
<td>Primary: 12-hr serial measurements at day 1, weeks 4 &amp; 12, of FEV1, PEF, self-rated asthma symptom scores, nighttime awakenings and supplemental albuterol use  Secondary: adverse events.</td>
<td>In this patient group, no difference in clinical benefit for Diskus vs. MDI with same dose and drug.</td>
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### APPENDIX 8 DPIs vs DPIs delivering bronchodilating drugs (randomised controlled trials, physiological and clinical outcomes)

<table>
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<tr>
<th>Authors, year</th>
<th>Treatment inhaler type, drug and dose</th>
<th>Location, setting, inclusion/exclusion power calculation, type of analysis</th>
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<tbody>
<tr>
<td>Dal Col et al., 1995</td>
<td>T1: DPI (Pulvinal, multidose) T2: DPI (Rotahaler, single dose) T3: placebo via Pulvinal T4: placebo via Rotahaler</td>
<td>1 site, USA In: stable asthma, at screening visit- FEV₁ &amp; PEFR &gt; 75% predicted normal, history of exercise-induced asthma &amp; reversible airway obstruction. On day 1 of study, with no treatment, patients had to have ≥ 15% max fall in FEV₁ 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 disease, or of cardiac, hepatic, renal or endocrine disorders, use of oral steroids during the previous 2 mths, &amp; impossibility to discontinue concomitant treatments 24h before testing.</td>
<td>At beginning 13 Age: 10.9 (8-12) M/F: 9/4</td>
<td>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 &amp; antihistamines were stopped for ≥24h before each test, inhaled steroid use permitted but dose to remain constant throughout study. Instructions to use inhalers with drawings to illustrate the correct inhalation technique. FU: 4 consecutive days, 15 min before standardised exercise test. Primary: FEV₁ &amp; PEFR before and between treatment &amp; exercise challenge test, and after exercise challenge test, east of use and correct handling technique.</td>
<td>No significant difference between T1 and T2 (p&gt;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.</td>
<td></td>
</tr>
<tr>
<td>T1: DPI (Diskus)</td>
<td>T2: DPI (Diskhaler)</td>
<td>T3: DPI (Diskhaler)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Drug:</strong> T1&amp;T2 Salmeterol 50µg placebo</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Design:</strong> Randomised, double-blind, double-dummy, placebo-controlled, single-dose, three-way crossover</td>
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<tr>
<td>Diskus - a multidose DPI, 60 individual 50µg doses of salmeterol xinafoate</td>
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<tr>
<td>Diskhaler - a 4-dose blister pack powder delivery system, require reloading</td>
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</tr>
<tr>
<td>Jadad's score = 3</td>
<td></td>
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</tr>
</tbody>
</table>

- 2 sites (17 countries)
- In: mild to moderate, presence of exercise-induced-asthma (EIA), ages 4 to 11 yrs, FEV1 ≥70% predicted, asthma triggers other than exercise (cold, air, allergens & tobacco smoke),
- Out: received any short-acting β2-agonists ≤8h of screening visit, oral short-acting β2-agonists ≤12h, oral extended-release β2-agonists or inhaled long-acting β2-agonists ≤24h, or required β2-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/Blac k):** 22/2

**FU:** 3 treatment visits & a post-treatment follow-up visit. 2 - 14 days apart.

**Primary:** Serial FEV1 at 1, 6, & 12hrs after study drug administration.

**Secondary:** adverse events.

**No significant differences found between T1 and T2 in mean % predicted FEV1 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.**

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline</td>
<td>83.2</td>
<td>85.2</td>
<td>85.2</td>
</tr>
</tbody>
</table>

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.**
<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Treatment inhaler type, drug and dose</th>
<th>Location, setting, inclusion/exclusion, power calculation, type of analysis</th>
<th>Patients, number, age mean ± SD (range), male/female, ethnicity</th>
<th>Follow-up Outcomes</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boulet et al., 1995</td>
<td>T1: Diskus &amp; placebo via Diskhaler T2: Diskhaler &amp; placebo via Diskus</td>
<td>Drug: Salmeterol, 50 µg b.i.d.</td>
<td>Design: randomised, double-blind, double-dummy, parallel-group, multicenter. Jadad’s score = 3</td>
<td>16 sites, USA In: ≥ 12 yrs old, FEV1 between 60%-90% predicted normal, receiving adequate anti-inflammatory &amp; inhaled β2-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 β2-agonist during study. Power calculation: 99%, 150/group</td>
<td>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</td>
<td>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 &amp; pm PEFR, am &amp; pm asthma symptom scores, &amp; use of albuterol; clinic-recorded pulmonary function tests and adverse effects</td>
</tr>
</tbody>
</table>
APPENDIX 9 pMDIs with or without spacer vs pMDIs with or without spacer, both with same propellants, delivering anti-inflammatory drugs: corticosteroids (randomised controlled trials, physiological and clinical outcomes)

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Treatment inhaler type, drug and dose</th>
<th>Location, setting, inclusion/exclusion power calculation, type of analysis</th>
<th>Patients, number, age mean; SD (range), male/female, ethnicity</th>
<th>Follow-up Outcomes</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janssens et al. 1999&lt;sup&gt;T1&lt;/sup&gt;</td>
<td>T1: pMDI+spacer (Nebuchamber® (Astra), metal 250ml no facemask T2: pMDI+spacer (Volumatic® (Glaxo Wellcome) polycarbonate 750ml + plastic connector (Astra) to fit pMDI</td>
<td>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</td>
<td>At beginning: Not stated At end: 16 Age: 83 mth (65-104) M/F: 12/4</td>
<td>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</td>
<td>Filter doses higher in T1 vs. T2 (p&lt;0.0001).</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Drug Budesonide 200µg b.i.d. (Pulmicort®) Filter between mouth and spacer</td>
<td></td>
<td></td>
<td></td>
<td>T1 T2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Design: Randomised crossover Jadad’s score = 2</td>
<td></td>
<td></td>
<td></td>
<td>Dose 50.3±9.2 19.4±7.2</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T1 T2</td>
<td>T1 T2</td>
</tr>
</tbody>
</table>
### 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\(^\text{19}\)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Details</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Adler 1997   | 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.  
Importance of inhaler device on the effect of budesonide  
(Also published as Ugeskr Laeger 1994: 156: 4134 – 4137)  
|  
| Agertoft 1993 \(^\text{20}\)  
Importance of inhaler device on the effect of budesonide  
| 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  
Duration: 9 weeks  
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 \(^\text{21}\)  
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: 2 puffs 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

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Treatment inhaler type, drug and dose Study design</th>
<th>Location, setting, inclusion/exclusion power calculation, type of analysis</th>
<th>Patients, number, age mean± SD (range), male/female, ethnicity</th>
<th>Follow-up Outcomes</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agertoft et al 1999</td>
<td>T1: DPI (Turbuhaler) (AstraZeneca, Lund, Sweden), T2: pMDI+spacer (Nebuhaler,750ml, Astra Zeneca), Drug: Budesonide 200µg</td>
<td>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</td>
<td>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.</td>
<td>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 &gt; 5 yrs had experience in using Turbuhaler for rescue terbutaline or daily budesonide treatment.</td>
<td>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 &gt; 5 yrs, T1 delivered a significantly higher dose than T2 (p&lt;0.03 to p=0.001). Children with higher filter doses for T1 also had higher filter doses for T2 (r=0.79, p=0.0005). Within-subject variation (CV) for T1 &amp; T2. 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.</td>
<td>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.</td>
</tr>
<tr>
<td>Bateman et al 2001</td>
<td>T1: HFA Diskus™ placebo, 1 inhalation, twice/day T2: Diskus™ T3: MDI CFC placebo Diskus™, Drug: Salmeterol/ fluticasone propionate</td>
<td>69 centers, 10 countries In: ≥12 years age, mild to moderate asthmatic, of reversible airway obstruction, smoking history of &lt;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 &gt;8</td>
<td>At beginning: 724 but 497 randomised T1: 165 T2: 167 T3: 165 Age: T1: 40.7(11-78) T2: 38.6(11-78)</td>
<td>FU: not stated Primary: Mean filter doses Secondary: PIF, fine particle fractions using in-vitro test.</td>
<td>No significant differences between T1 &amp; T2. Improvements were similar in all variables - lung function (am and pm PEF), clinic FEV₁ symptom scores, use of rescue salbutamol, adverse events. FU: 12 wks treatment + 2 wks follow-up Primary: mean am run-in period: 2 wks, continued with usual ICS therapy &amp; symptomatic relief with salbutamol (Ventolin™). At end, discontinued current ICS therapy.</td>
<td>Likely that majority of patients &gt; 15 yrs age. Only included data comparing MDI (T1) &amp; Diskus (T2). Patients are allowed the use of spacer</td>
</tr>
</tbody>
</table>
& be taking salbutamol ≤800µg/day, FEV₁ >50% predicted normal.

**Out:** had received a long-acting/oral β₂-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 β₂-agonist & ICS).

**Power calculation** at 90% power

**Per protocol and Intent-to-treat analysis**

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-protocol pop</td>
<td>383</td>
<td>128</td>
<td>131</td>
</tr>
<tr>
<td>T1: 145</td>
<td>145</td>
<td>140</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEF over wks 1-12, Secondary: pm PEF, am &amp; pm symptom scores, back-up salbutamol use, clinic FEV₁, from baseline wks 1-12</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>No. symptom-free am, wks 1-12, medium proportions, %</td>
<td>55</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>No. symptom-free pm, wks 1-12, medium proportions, %</td>
<td>71</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>No. back-up salbutamol-free am, wks 1-12, medium proportions, %</td>
<td>73</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>No. back-up salbutamol-free pm, wks 1-12, medium proportions, %</td>
<td>90</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Adverse event, no. of patients(%)</td>
<td>82(50%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug-related adverse event highest in T2 (16)vs.T1(13)</td>
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</tbody>
</table>

In this patient group, comparable clinical efficacy for HFA MDI vs. Diskus with same medication and same dose.
## APPENDIX 11  DPIs vs DPIs delivering anti-inflammatory drugs: corticosteroids (randomised controlled trials, physiological and clinical outcomes)

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Treatment inhaler type, drug and dose</th>
<th>Location, setting, inclusion/exclusion power calculation, type of analysis</th>
<th>Patients, number, age mean±SD (range), male/female, ethnicity</th>
<th>Follow-up Outcomes</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peden et al 1998&lt;sup&gt;35&lt;/sup&gt;</td>
<td>T1: DPI (Diskus), T2: DPI (Diskus), T3: DPI (Diskhaler), T4: DPI (Diskhaler), T5: Placebo</td>
<td>Drug: Fluticasone propionate T1&amp;T3 50 µg BID, twice daily T2&amp;T4 100 µg BID, twice daily</td>
<td>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</td>
<td>At beginning: not stated At end: 437</td>
<td>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: FEV₁, PEF, asthma symptoms, nighttime awakenings requiring albuterol, albuterol use. Secondary: Patient compliance</td>
<td>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, 50 µg BID) diskus diskhaler Placebo (n=90) (n=91) (n=86) FEV₁ 15.77±1.97 17.89±2.28 6.96±2.45 PEF 26±3 30±3 14±4 Albuterol use -0.75±0.23 -1.02±0.18 0.08±0.23 (puff/day) Nighttime −0.03±0.01 −0.04±0.01 0.07±0.04 awakenings/night Symptom −0.36±0.07 −0.41±0.07 −0.02±0.09 scores [Symptom score :0=none, 1=mild, 2=moderate, 3=severe]</td>
</tr>
</tbody>
</table>
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

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 therapy of inhaled corticosteroid for at least 3 mths immediately to study, or β2-agonist therapy alone, a forced FEV1 = 50 -80%, ≥15% reversibility FEV1, (30 min after upto 4 puffs of albuterol at screening) or ≥15% variability in FEV1 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 (FEV1 values >FEV1 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 awakenings 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

Baseline: 3 mths therapy with inhaled corticosteroid or β2 -agonists alone
Run in: 2 wks, single-blind, assessing compliance and familiarisation of devices

FU: 12 wks

Primary: am predose FEV1, 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 FEV1, symptom scores, use of albuterol, lung function(p≥0.05) except for am PEF(p≤0.05).

(mean change ±SEM, p≤0.05 except Diskus)

Diskus Diskhaler Placebo
FEV1 am 0.52±0.06 0.40±0.06 0.05±0.07 (n=59) (n=73) (n=63) predose, L
FEV1 22.37±2.38 16.61±2.24 3.01±3.03 (n=59) (n=73) (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 -1.41±0.32 0.76±0.31 (n=59) (n=58) (n=71)
Nighttime -0.03±0.02 0.00±0.04 0.10±0.05 awakenings (n=60) (n=58) (n=72)
Total symptom scores -0.20±0.05 -0.10±0.05 0.04±0.05 (n=59) (n=72) (n=61)

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, physiological and clinical outcomes)

<table>
<thead>
<tr>
<th>Treatment inhaler type, drug and dose</th>
<th>Setting &amp; Location</th>
<th>Patients, number, age mean ± SD (range) years</th>
<th>Follow-up</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Inclusion/Exclusion</td>
<td>Male:Female ethnicity</td>
<td>Outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Power calculation, type of analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>Outcomes</td>
<td>Results</td>
<td>Comments</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Power calculation</td>
<td>Pre-protocol analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients, number, age mean ± SD (range) years</td>
<td>Age: 10.4 (4-18) (except 1 patient aged 39 yrs old)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Setting &amp; Location</td>
<td>multicentre, UK</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>In:</td>
<td>stable asthma, 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.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>In:</td>
<td>stable asthma, 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.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Design:</td>
<td>Randomised, open, crossover, controlled. jadad’s score = 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1: Breath-actuated (Autohaler) T2: MDI</td>
<td>Drug:</td>
<td>sodium cromoglycate, 2 puffs (10mg), 4 times /day</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Arshad et al. 1993

<table>
<thead>
<tr>
<th>T1: Breath-actuated (Autohaler)</th>
<th>T2: MDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>T1:</td>
</tr>
<tr>
<td></td>
<td>T2:</td>
</tr>
<tr>
<td>Drug: sodium cromoglycate, 2 puffs (10mg), 4 times /day</td>
<td></td>
</tr>
<tr>
<td>Design: Randomised, open, crossover, controlled. jadad’s score = 1</td>
<td></td>
</tr>
<tr>
<td>Setting &amp; Location</td>
<td>multicentre, UK</td>
</tr>
<tr>
<td>In:</td>
<td>stable asthma, 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.</td>
</tr>
<tr>
<td>Design:</td>
<td>Randomised, open, crossover, controlled. jadad’s score = 1</td>
</tr>
<tr>
<td>Power calculation</td>
<td>Pre-protocol analysis</td>
</tr>
<tr>
<td>At beginning 181</td>
<td>At end 166</td>
</tr>
<tr>
<td>T1:</td>
<td>90</td>
</tr>
<tr>
<td>T2:</td>
<td>91</td>
</tr>
<tr>
<td>Age: 10.4 (4-18) (except 1 patient aged 39 yrs old)</td>
<td></td>
</tr>
<tr>
<td>m/f: 181/0</td>
<td></td>
</tr>
</tbody>
</table>

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: 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, FEV1, FEV1 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 between devices 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, nor was there ant difference in the 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 Autohaler 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

<table>
<thead>
<tr>
<th>Study Author, Year</th>
<th>Methodology</th>
<th>Details</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Custovic 1995</td>
<td>Design: randomised double blind double-dummy crossover study, computer generated schedule. Histamine challenge used.</td>
<td>Participants: 25 children, age range 6-14 years, mean age 10yrs. Pulmonary function test performed 30min post-dose, then histamine challenge performed and FEV, measured until FEV, decreased by 20% (PD&lt;sub&gt;20&lt;/sub&gt;).</td>
<td>No significant differences in: FEV&lt;sub&gt;1&lt;/sub&gt; or protection against histamine-induced bronchoconstriction as measured by PD&lt;sub&gt;20&lt;/sub&gt;.</td>
<td></td>
</tr>
</tbody>
</table>

**Study Quality:** Cochrane-A

Additional evidence from the current review

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Treatment inhaler type, drug and dose Study design</th>
<th>Location, setting, inclusion/exclusion power calculation, type of analysis</th>
<th>Patients, number, age mean±SD (range), male/female, ethnicity</th>
<th>Follow-up Outcomes</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shapiro et al 2000(a) 67</td>
<td>T1: HFA pMDI T2: CFC pMDI T3: placebo, HFA propellant only</td>
<td>11 sites (USA and Puerto Rico) In: ages 4 to 11 yrs, asthma requiring physician-prescribed chronic pharmacotherapy ≥6mths, no significant pulmonary disease/serious chronic disease, PEF or FEV&lt;sub&gt;1&lt;/sub&gt; ≤ 50-80% predicted, FEV&lt;sub&gt;1&lt;/sub&gt; 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.</td>
<td>Age: Mean T1: 9.0 T2: 8.5 T3: 9.0</td>
<td>Run-in: 1-2 wks, instruction of proper use of MDI &amp; peak flow meter FU: 2 wks</td>
<td>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&lt;sub&gt;1&lt;/sub&gt; similar to those calculated for PEF. Improvement in all diary card variables - no significant differences found between the two active treatment groups.</td>
<td>Ventolin HFA produces bronchodilation that is clinically comparable to the effects of inhaled ventolin CFC.</td>
</tr>
</tbody>
</table>

### 6-hr serial PEF (%):

<table>
<thead>
<tr>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day1</td>
<td>Wk2</td>
<td>Day1</td>
</tr>
<tr>
<td>n=46</td>
<td>n=41</td>
<td>n=46</td>
</tr>
<tr>
<td>Baseline 71.5±2.4</td>
<td>78.5±3.1</td>
<td>71.0±2.2</td>
</tr>
<tr>
<td>PEF, predicted Changes 13.9±1.4</td>
<td>10.8±1.4</td>
<td>12.6±1.4</td>
</tr>
<tr>
<td>in PEF, predicted Mean change from baseline in diary card variables : T1 T2 T3</td>
<td>am PEF,L/min n=46 n=41 n=46 n=41 n=43 n=36</td>
<td></td>
</tr>
<tr>
<td>17±4*</td>
<td>9±4</td>
<td>2±3</td>
</tr>
<tr>
<td>T1: HFA</td>
<td>T2: CFC</td>
<td>T3: CFC</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Drug:</strong> Albuterol, 2 puffs</td>
<td><strong>Design:</strong> Randomised, single-blind, placebo-controlled, four-period crossover</td>
<td></td>
</tr>
<tr>
<td><strong>Jadad's score = 3</strong></td>
<td><strong>In:</strong> 6 - 11 yrs, stable asthma (no episode of emergency care within 4 wks of pre study visit) requiring short-acting β₂-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, FEV₁ ≥ 70% predicted, demonstrated proper technique in using a press &amp; breathe MDI, not obese, no lower/upper respiratory tract infections, not using salmeterol (48 hr), theophylline products (48 hr), cromolyn sodium/nordicromil sodium (1 wk), oral/injectable steroids (8 wks)/astemizole (3 mths) prior to prestudy visit. No use of these medication throughout study.</td>
<td></td>
</tr>
<tr>
<td><strong>Out:</strong> failure to confirm EIB by pre study exercise challenge, withdrawal of consent and baseline FEV₁ &lt; 70% predicted.</td>
<td><strong>Power calculation no Per protocol analysis assumed</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Colice et al 1999</strong></th>
<th><strong>PM PEF, L/min</strong></th>
<th><strong>Albuterol use (mean puff/day)</strong></th>
<th><strong>Day with no albuterol, %</strong></th>
<th><strong>Nighttime without awakenings (%)</strong></th>
<th><strong>Asthma symptom scores</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15±3*</td>
<td>11±4</td>
<td>3±3</td>
<td>-1.8±0.4*</td>
<td>-2.0±0.4*</td>
</tr>
<tr>
<td></td>
<td>36.4±6.1*</td>
<td>39.5±5.6*</td>
<td>11.5±6.2</td>
<td>1±4</td>
<td>4±2</td>
</tr>
<tr>
<td></td>
<td>-0.3±0.1*</td>
<td>-0.1±0.1</td>
<td>0.1±0.1</td>
<td><strong>No significant differences among active treatment results were found.</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Albuterol HFA has similar bronchodilator efficacy and safety profile as CFC albuterol.**

<table>
<thead>
<tr>
<th><strong>Primary:</strong></th>
<th><strong>Secondary:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At beginning:</strong> treatment visits 3 - 7 days apart.</td>
<td><strong>Smallest % change in FEV₁ post-exercise</strong></td>
</tr>
<tr>
<td>T1</td>
<td>T2</td>
</tr>
<tr>
<td>1.9± 16.4</td>
<td>-0.3±11.4</td>
</tr>
<tr>
<td>[T1, T2 &amp; T3 vs T4 all p&lt;0.001]</td>
<td></td>
</tr>
<tr>
<td><strong>Number(%) of patients protected from EIB</strong></td>
<td><strong>14(93) 15(100) 14(93) 5(33)</strong></td>
</tr>
<tr>
<td>Study</td>
<td>T1</td>
</tr>
<tr>
<td>-------</td>
<td>----</td>
</tr>
<tr>
<td>Shapiro et al. 2000(b)</td>
<td>HFA albuterol, 2 puffs</td>
</tr>
<tr>
<td>T1: 63 T2: 30</td>
<td>Run-in: ≥7 days</td>
</tr>
<tr>
<td>Lumry et al. 2001</td>
<td>MDI CFC (Glaxo Wellcome), T3: placebo (HFA propellant alone, 4 times/day)</td>
</tr>
</tbody>
</table>

In this patient group, no difference in clinical benefit for CFC vs. HFA with same medication and dose.
**Drug:** Albuterol 180 µg/4 times/day

**Design:** Randomised, multi-center, double-blind, parallel-group

- Free forced FEV1 50%-80% normal predicted, 15% FEV1 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

<table>
<thead>
<tr>
<th></th>
<th>Age:</th>
<th>µg/4 times/day</th>
<th>FU: 12 wks</th>
<th>Run-in period</th>
<th>WK 1-3</th>
<th>WK1-12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1: 32 ±14.8</td>
<td>T2: 30.6±12.2</td>
<td>T3: 29.7±13.8</td>
<td>Morning PEFR, L/min</td>
<td>351(8.9)</td>
<td>353(10.2)</td>
</tr>
<tr>
<td></td>
<td>T2: 30.6±12.2</td>
<td>T3: 29.7±13.8</td>
<td></td>
<td>Evening PEFR, L/min</td>
<td>388(9.2)</td>
<td>384(9.7)</td>
</tr>
<tr>
<td></td>
<td>T3: 29.7±13.8</td>
<td></td>
<td></td>
<td>Back-up Ventolin use (puffs/day)</td>
<td>1.1(0.2)</td>
<td>1.3(0.2)</td>
</tr>
<tr>
<td>M/F:</td>
<td>T1: 56/44</td>
<td>T2: 55/45</td>
<td>T3: 50/50</td>
<td>% of days with no back-up Ventolin</td>
<td>62.9(3.7)</td>
<td>58.4(4.0)</td>
</tr>
<tr>
<td>Ethnicity %</td>
<td>T1: 79/13/8</td>
<td>T2: 75/12/12</td>
<td>T3: 81/7/12</td>
<td>Asthma symptom score</td>
<td>2.0(0.1)</td>
<td>2.0(0.1)</td>
</tr>
<tr>
<td></td>
<td>T1: 79/13/8</td>
<td>T2: 75/12/12</td>
<td>T3: 81/7/12</td>
<td>% of days with no asthma symptom</td>
<td>28.9(3.7)</td>
<td>29.0(3.8)</td>
</tr>
<tr>
<td></td>
<td>T1: 79/13/8</td>
<td>T2: 75/12/12</td>
<td>T3: 81/7/12</td>
<td>Night with no awakenings</td>
<td>82.4(2.8)</td>
<td>82.5(2.8)</td>
</tr>
</tbody>
</table>

- **Mean FEV1 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

<table>
<thead>
<tr>
<th></th>
<th>T1 (n=100)</th>
<th>T2 (n=91)</th>
<th>T3 (n=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% patients ≥15% improvement</td>
<td>82</td>
<td>77</td>
<td>19</td>
</tr>
<tr>
<td>Median onset of effect, hrs</td>
<td>0.06</td>
<td>0.07</td>
<td>6.0</td>
</tr>
<tr>
<td>Mean duration of effect, hr(SE)</td>
<td>3.26(0.24)</td>
<td>3.07(0.25)</td>
<td>0.57(0.17)</td>
</tr>
<tr>
<td>% max effect(SE)</td>
<td>30.1(1.83)</td>
<td>28.4(1.34)</td>
<td>14.4(1.05)</td>
</tr>
<tr>
<td>Median time max effect, hrs</td>
<td>1.0</td>
<td>1.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Mean AUC(bl), L-hrs(SE)</td>
<td>0.84(0.16)</td>
<td>2.48(0.19)</td>
<td>2.65(0.18)</td>
</tr>
</tbody>
</table>

- No significant difference between T1 and T2 for all serial pulmonary function but difference with placebo (p=0.01).

- Concerning adverse events, Treatment related adverse event highest in T3(9%), vs. T1(2%), T2(4%).

- Significant 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 group, comparable clinical efficacy for CFC vs. HFA propellant in an MDI with same medication and same dose.
Appendix 14  pMDIs with/without spacer vs pMDI with/without spacer, with different propellants, delivering corticosteroids or combined therapy (Randomised controlled trials, physiological and clinical outcomes)

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Treatment inhaler type, drug and dose</th>
<th>Study design</th>
<th>Location, setting, inclusion/exclusion power calculation, type of analysis</th>
<th>Patients, number, age mean± SD (range), male/female, ethnicity</th>
<th>Follow-up Outcomes</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Bateman et al 2001 | T1: HFA MDI + Diskus™ placebo, 1 inhalation, twice/day  
T2: Diskus™ + HFAMDI placebo  
T3: CFCMDI Fpmy) + Diskus placebo | Randomised, multi-centre, double-blind, double-dummy, parallel-group | 69 centers, 10 countries In: ≥12 years age, mild to moderate asthma, of reversible airway obstruction, smoking history of <10 pack-years, used regular 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 >18 & be taking salbutamol ≤800μg/day, FEV1 >50% predicted normal. | Patients: 372 but 497 randomised  
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 FEV1. | No significant differences between T1 & T2. Improvements were similar in all variables - lung function (am and pm PEF), clinic FEV1, symptom scores, use of rescue salbutamol, adverse events. | Likely that majority of patients > 15 yrs age |

**Jadad’s score = 3**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th>Patients, number, age mean± SD (range), male/female, ethnicity</th>
<th>Follow-up Outcomes</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>At beginning: 724 but 497 randomised</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| T1: 165  
T2: 167  
T3: 165 | | | | | | |
| T1: 145  
T2: 145  
T3: 140 | | | | | | |

**Pre-protocol pop : 383**

| FU: 12 wks treatment + 2 wks follow-up | | | | | | |
| T1: 128  
T2: 131  
T3: 124 | | | | | | |

**Primary: mean am PEF over wks 1-12, Secondary: pm PEF, am & pm symptom scores, back-up salbutamol use, clinic FEV1.**

**Results**

<table>
<thead>
<tr>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>During the 12-wk period, morning PEF increase, L/min</td>
<td>42</td>
</tr>
<tr>
<td>Adjusted mean am PEF increase from baseline, L/min</td>
<td>43</td>
</tr>
<tr>
<td>Mean pm PEF, L/min</td>
<td>38</td>
</tr>
<tr>
<td>Clinic FEV1, increase from baseline at wk-12, %</td>
<td>17</td>
</tr>
<tr>
<td>Clinic FEV1, adjusted mean change from baseline wks 1-12</td>
<td>10</td>
</tr>
<tr>
<td>No. symptom-free am, wks 1-12, medium proportions, %</td>
<td>55</td>
</tr>
<tr>
<td>No. symptom-free pm, wks 1-12, medium proportions, %</td>
<td>71</td>
</tr>
<tr>
<td>No. back-up salbutamol-free am, wks 1-12, medium proportions, %</td>
<td>73</td>
</tr>
<tr>
<td>No. back-up salbutamol-free pm, wks 1-12, medium proportions, %</td>
<td>90</td>
</tr>
</tbody>
</table>

**Adverse event, no. of patients(%)**

<table>
<thead>
<tr>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>(50%)</td>
<td>(57%)</td>
</tr>
</tbody>
</table>

**Drug-related adverse event highest in T2 (18) vs. T1 (13)**
| Per protocol and Intent-to-treat analysis |    |    |    |
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 FEV₁ baseline period: 28 day, of perennial asthma requiring daily medication. At instructions of T1: CFC (75 µg/puff), 150 µg/day, 1 puff twice daily T2: CFC (75 µg/puff), 300 µg/day, 2 puffs twice daily T3: CFC (75 µg/puff), 600 µg/day, 4 puffs twice daily T4: HFA (75 µg/puff), 150 µg/day, 1 puff twice daily T5: HFA (75 µg/puff), 300 µg/day, 2 puffs twice daily T6: HFA (75 µg/puff), 600 µg/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

Power calculation: no intent-to-treat analysis

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 in FEV₁ from baseline to endpoint. Secondary: mean % change in PEF₂₅%-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 FEV₁ 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 FEV₁ for all doses of both formulations found. (mean ±SE)

<table>
<thead>
<tr>
<th>FEV₁</th>
<th>Baseline(L)</th>
<th>%Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAA CFC</td>
<td>T1</td>
<td>1.59±0.05</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>1.44±0.05</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>1.45±0.04</td>
</tr>
<tr>
<td>TAA HFA</td>
<td>T4</td>
<td>1.48±0.04</td>
</tr>
<tr>
<td></td>
<td>T5</td>
<td>1.47±0.04</td>
</tr>
<tr>
<td></td>
<td>T6</td>
<td>1.43±0.05</td>
</tr>
</tbody>
</table>

Significant improvements in PEFR (mL/min) for am and pm %change (mean ±SE)

<table>
<thead>
<tr>
<th>PEFR (mL/min)</th>
<th>am</th>
<th>pm</th>
<th>%change</th>
</tr>
</thead>
<tbody>
<tr>
<td>(mean ±SE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAA CFC</td>
<td>T1</td>
<td>19.0±4.5</td>
<td>15.2±4.2</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>23.0±4.3</td>
<td>15.8±4.2</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>30.2±4.3</td>
<td>25.6±4.1</td>
</tr>
<tr>
<td>TAA HFA</td>
<td>T4</td>
<td>24.2±4.3</td>
<td>20.2±4.3</td>
</tr>
<tr>
<td></td>
<td>T5</td>
<td>20.5±4.0</td>
<td>18.6±4.1</td>
</tr>
<tr>
<td></td>
<td>T6</td>
<td>27.4±4.3</td>
<td>24.3±4.3</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Asthma symptoms(mean ±SE)</th>
<th>am symptom score</th>
<th>pm symptom score</th>
<th>24-hr symptom score</th>
<th>nocturnal awakenings (no./d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAA CFC</td>
<td>T1</td>
<td>-0.5±0.1</td>
<td>-0.4±0.1</td>
<td>-1.0±0.2</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>-0.7±0.1</td>
<td>-0.6±0.1</td>
<td>-1.3±0.2</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>-0.9±0.1</td>
<td>-0.8±0.1</td>
<td>-1.7±0.2</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.044</td>
<td>0.044</td>
<td>0.045</td>
</tr>
<tr>
<td>TAA HFA</td>
<td>T4</td>
<td>-0.5±0.1</td>
<td>-0.5±0.1</td>
<td>-0.9±0.2</td>
</tr>
<tr>
<td></td>
<td>T5</td>
<td>-0.8±0.1</td>
<td>-0.7±0.1</td>
<td>-1.6±0.2</td>
</tr>
</tbody>
</table>
### Appendix 15  Breath actuated inhalers with different propellants, delivering corticostroids (Randomised controlled trials, physiological and clinical outcomes)

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Treatment inhaler type, drug and dose</th>
<th>Location, setting, inclusion/exclusion power calculation, type of analysis</th>
<th>Patients, number, age mean±SD (range), male/female, ethnicity</th>
<th>Follow-up Outcomes</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farmer et al. 1999</td>
<td>T1: HFA T2: CFC</td>
<td>In: 7 - 12 yrs, FEV₁, ≥ 60% predicted for height and gender, FEV₁ reversibility ≥10% after inhaling 200µg salbutamol via pMDI, documented FEV₁ reversibility ≥10% in previous 12 mths, currently use an inhaled bronchodilator β-agonist/sodium cromoglycate or constant dose of nedocromil sodium.</td>
<td>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</td>
<td>Run-in: 2-week placebo, 1 puff/twice/day from a CFC placebo Easibreathetm inhaler. At end of run-in, required the use of relief bronchodilator or (≥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.</td>
<td>Compared to baseline, significant decreases in proportions of patients reporting am and pm symptoms and use of relief medication in both T1 &amp; T2.</td>
<td>HFA inhaler is therapeutically equivalent to CFC inhaler at similar dose (100 µg b.i.d. BDP)</td>
</tr>
</tbody>
</table>

|  | Power calculation 90%, 105patients/group Per protocol analysis assumed | | | | | |

- **Design:** Randomised, multi-centre, double-blind, parallel group
- **Jadad’s score = 4**

**Run-in:**
- Mean (SD) T1: 338(33) T2: 337(33)
- 99.4 (78.6,116.9)

**Clinic FEV₁:**
- Mean (SD) T1: 1.97(0.17) T2: 1.97(0.17)
- 103.5 (97.3,105.1)

**Daily variability:**
- Mean (SD) T1: 20.2(5.6) T2: 20.2(5.6)
- 103.5 (97.3,105.1)

**HFA vs. CFC:**
- **am PEF**
  - Baseline: 229(56) Endpoint: 340(61)
  - 99.4 (78.6,116.9)
- **pm PEF**
  - Baseline: 229(56) Endpoint: 340(61)
  - 99.4 (78.6,116.9)
- **Clinic PEF**
  - Baseline: 229(56) Endpoint: 340(61)
  - 99.4 (78.6,116.9)
- **Daily variability**
  - Baseline: 229(56) Endpoint: 340(61)
  - 99.4 (78.6,116.9)

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

<table>
<thead>
<tr>
<th>Furukawa et al 1999</th>
<th>T1: MDI CFC</th>
<th>T2: MDI HFA</th>
<th>T3: placebo with HFA propellant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug:</td>
<td>Cromolyn sodium, 2mg gid</td>
<td>Albuterol MDI used as needed in all groups.</td>
<td></td>
</tr>
<tr>
<td>In:</td>
<td>mild to moderate bronchial asthma, ≥12 years age, cromolyn sodium use for ≥2 mths, inhaled β₂-agonists use for ≥1mth, FEV1≥60% normal predicted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Design:</td>
<td>Randomised, double-blind placebo-controlled parallel group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jadad’s score = 3</td>
<td>Power calculation requiring 100/group, at 90% power</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Baseline period: 2-4 wks**

<table>
<thead>
<tr>
<th>At beginning</th>
<th>T1: 91</th>
<th>T2: 94</th>
<th>T3: 95</th>
</tr>
</thead>
<tbody>
<tr>
<td>FU: 12 wks</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Primary:** symptom summary score (daytime + nighttime asthma scores)

- **Symptom score:**
  - T1: 22
  - T2: 27
- **Daytime score:**
  - T1: -25
  - T2: -29
- **Nighttime score:**
  - T1: -18
  - T2: -23
- **Morning PEF:**
  - T1: 1.3
  - T2: 5.3
- **Evening PEF:**
  - T1: 0.1
  - T2: 4.7

**Albuterol use:**

- T1: -13
- T2: -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).

**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 events** T1 vs T2 (p≥0.05).

(At end)

<table>
<thead>
<tr>
<th>T1: 30.3 (12-79)</th>
<th>T2: 30 (12-62)</th>
<th>T3: 26.9 (12-68)</th>
</tr>
</thead>
</table>

**M/F:**

- T1: 40/51
- T2: 39/55
- T3: 48/47

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, T2, T3)

123
## APPENDIX 17 Ease of use, patient/carer preference and compliance for alternative devices (Randomised controlled trials and non-trial evidence)

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment inhaler type, drug and dose</th>
<th>Setting &amp; Location</th>
<th>Patients, number, age mean ± SD (range) years</th>
<th>Follow-up</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milgrom H et al [88]</td>
<td>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</td>
<td>Outpatient clinic</td>
<td>N = 24 14 male 8-12 years</td>
<td>13 weeks</td>
<td>Diary Compliance Records: 78.2% for β agonists 95.4% for corticosteroids</td>
<td>Does not compare devices Small selective sample</td>
</tr>
<tr>
<td>Kamps AWA et al [89]</td>
<td>DPI or pMDI plus spacer Case/control Study comparing effectiveness of repeated inhalation instructions (control) versus no systematic inhalation instructions (cases)</td>
<td>Outpatient Clinic</td>
<td>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</td>
<td>Inhalation technique score according to criteria defined by Netherlands Asthma Foundation</td>
<td>Sixty cases had received inhalation instructions prior to referral: 29% using DPI correct 67% using pMDI plus spacer correct (p&lt;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&lt;0.01)</td>
<td>Study not designed to differentiate between devices Generalisability?</td>
</tr>
<tr>
<td>Celano et al [90]</td>
<td>PMDI use and pMDI/pMDI plus spacer technique Urban hospital outpatient clinic</td>
<td>N=55 families 98% African-American 57% male children Age range 6-17 years Mean age 10.8 ± 2.7 years</td>
<td>Follow up 2-20 weeks (mean 10 weeks)</td>
<td>Estimated MDI adherence (from canister weight)</td>
<td>34 sets of data for estimated adherence (range 0 to 100% (mean 44%)) Poor or no correlation between self reported and estimated use MDIC available data for 49 patients 27% scored zero and remainder demonstrated varying</td>
<td>Does not compare inhaler devices Several study limitations</td>
</tr>
<tr>
<td>Study</td>
<td>Description</td>
<td>Inclusions</td>
<td>Exclusions</td>
<td>Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
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<td>------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Zora JA et al</td>
<td>Maintenance β agonists (metaproterenol 2 sprays 3-5 times daily via MDI no spacer)</td>
<td>Diagnosis of asthma confirmed by 15% reversibility in the FEV₁</td>
<td>Current immunotherapy or oral corticosteroids for significant periods over past year</td>
<td>Interrelation between measured adherence behaviours not significant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jonaaon G et al</td>
<td>Turbodeler budesonide 100 or 200µg or placebo in two divided doses</td>
<td>Mild asthma (mean baseline FEV₁ 103% of predicted)</td>
<td>Did not compare devices</td>
<td>No correlation between symptom score and adherence or placebo treatment and adherence</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group I</td>
<td>Budesonide 200µg in the morning and placebo 100µg in the evening</td>
<td>No document power calculation</td>
<td>Significant difference between self reported and measured compliance Morning 93% diary, 76% measured (p&lt;0.001) Evening 94% diary, 77% measured (p&lt;0.001) 86% had higher self-reported than measured compliance for morning medication compared to 94% for evening medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group II</td>
<td>Budesonide 100µg in the morning and placebo 100µg in the evening</td>
<td>Compliance level was assessed by Student's two sample t-test. ANCOVA was used to determine the degree of association with any demographic variables.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group III</td>
<td>Budesonide 100µg in the morning and budesonide 100µg in the evening</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group IV</td>
<td>Placebo 100µg in the morning and placebo 100µg in the evening</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Double blind randomised study of patient</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

inflamatory agent via pMDI plus spacer

Self-reported adherence

MDI/MDI plus spacer technique (from MDI Checklist (MDIC))

Assessed at follow up following instruction at study entry
<table>
<thead>
<tr>
<th>Study</th>
<th>Methodology</th>
<th>Population</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jonasson G et al Extension Study[82]</td>
<td>As before</td>
<td>As before</td>
<td>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.</td>
</tr>
<tr>
<td>Bender B et al[92]</td>
<td>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)</td>
<td>Single centre Inclusions: Mild/moderate asthma including at least twice-weekly asthma symptoms and requiring daily inhaled anti-inflammatory medicines. Exclusions: Severe asthma or other serious medical conditions Non-randomised, non-controlled study</td>
<td>N = 27 16 male 7-12 years Mean 10.9 ± 2.5 years 6x African-American 4x Hispanic 6 months 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 in 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</td>
</tr>
<tr>
<td>Goran A et al[93]</td>
<td>Use of Turbohaler terbutaline by children aged 3-6 years Open, non-controlled study</td>
<td>Consecutive attenders at outpatient asthma clinic</td>
<td>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)</td>
</tr>
<tr>
<td>Yeatts K et al[94]</td>
<td>Study of barriers to inhaler use amongst non-white (African-American) and (Population - based sample (public school system in North Carolina USA))</td>
<td>Population - based sample (public school system in North Carolina USA)</td>
<td>N = 2056 296 had used an Sociodemographic s of inhaler users 14% (296/2056) reported using an inhaler in the past 12 with no differences among African-American and White children</td>
</tr>
</tbody>
</table>

Does not compare devices Small sample size Generalisability?
<table>
<thead>
<tr>
<th>Study</th>
<th>Inhaler Type</th>
<th>Characteristics</th>
<th>N</th>
<th>Results</th>
<th>Relevance to the UK?</th>
</tr>
</thead>
<tbody>
<tr>
<td>White Adolescents</td>
<td></td>
<td>185 had diagnosed asthma</td>
<td></td>
<td>26% were not allowed to carry their inhaler at school</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age 13 to 14 years</td>
<td></td>
<td>Girls were more likely to be allowed to carry their inhaler at school and diagnosed asthmatic girls had a higher prevalence of wheezing the in the last year 47% compared with diagnosed asthmatic boys (26%).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>34% African-American</td>
<td></td>
<td>Smoking prevalence was higher in inhaler users (26%) compared to the study population (19%). (p=0.001)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>26% were not allowed to carry their inhaler at school</td>
<td></td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Vichyanond P et al</td>
<td>Turbohaler terbutaline 500μg three times daily</td>
<td>Multi-centre outpatient clinics throughout East Asia</td>
<td>N = 86 (58 had used pMDIs previously)</td>
<td>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 than written instructions at all times (p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exclusions: Hypersensitivity to β agonist drugs Concomitant disease such as cardiovascular disease, renal disease or hepatic disease.</td>
<td></td>
<td>90% considered use of Turbohaler to be easy and effective in affording symptom relief.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inclusions: Children with mild to moderate asthma, as classified according to the international consensus for the diagnosis and treatment of asthma.</td>
<td></td>
<td>Improvements in PEFR (p&lt;0.01) and reduction in asthma symptom scores (p&lt;0.005 for morning scores, p=&lt;0.0001 for evening scores) were observed during treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Handling assessed objectively by investigator and subjectively by patient/parent</td>
<td></td>
<td>All patients tolerated the study medication well without any serious adverse events.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Efficacy from PEFR (% of predicted) and asthma symptom score (diary records and clinic assessment)</td>
<td></td>
<td>Does not directly compare devices</td>
<td></td>
</tr>
<tr>
<td>Vichyanond P et al</td>
<td>Albuterol via DPI (Diskhaler) at equivalent dose in place of usual β agonist (78% were using pMDI alone)</td>
<td>Primary and respiratory practices</td>
<td>N= 4529 2219 male</td>
<td>54% preferred the DPI over their usual inhaler device (29%) (p=0.001). 17% expressed no preference.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exclusions: Hypersensitivity to β agonist drugs</td>
<td></td>
<td>The majority of paediatric patients preferred the disk delivery system to their previous inhalation device. (p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inclusions: Patients over 6 years of age requiring inhaled β agonist for stable reversible obstructive airways disease.</td>
<td></td>
<td>After instruction 98.5% demonstrated adequate technique at the initial visit</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Open, non-randomised study</td>
<td></td>
<td>At the conclusion of the trial incorrect use was noted in 10.2% of the elderly and 3.2% of all</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N= 4529 2219 male</td>
<td></td>
<td>Does not compare devices</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean age 39 ± 22 years</td>
<td></td>
<td>Generalisability?</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
<td>Methods</td>
<td>Outcomes</td>
<td></td>
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<td>-------</td>
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<td></td>
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<tr>
<td>Wilkelstein ML&lt;sup&gt;117&lt;/sup&gt;</td>
<td>Convenience sample of 30 families whose children were using daily inhaled asthma medications via MDI participating in community-based research study in US</td>
<td>N = 30 school age Urban, African-American 18 male Age 6-14 years</td>
<td>Medication concordance and discordance between parent and child and parent and physician reports of asthma medications Sociodemographic factors associated with early self-administration</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Gracia-Antequera M and Morales Suarez-Varela MM&lt;sup&gt;122&lt;/sup&gt;</td>
<td>DPI vs pMDI vs pMDI plus extension chamber</td>
<td>N = 255 142 included in per protocol analysis 103 male Mean age 10.5 years 7-12 years olds made up 57% of the sample</td>
<td>Mean follow-up period 10.5 months</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Kelloway Shepard J et al&lt;sup&gt;103&lt;/sup&gt;</td>
<td>Autohaler Use and design of package insert instructions (PII)</td>
<td>N = 40 (20 x naïve 20 x previous pMDI) Adults and Children (12-17 years)</td>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pederson S et al&lt;sup&gt;104&lt;/sup&gt;</td>
<td>DPI (rotahaler) vs pMDI vs pMDI plus spacer</td>
<td>N = 256 172 boys Baseline assessment of FEV&lt;sub&gt;1&lt;/sub&gt; plus</td>
<td>In 43% of patients, the demonstration of inhaler technique was deemed efficient.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arshad et al 1993</td>
<td>T1: Breath-actuated (Autohaler)</td>
<td>T2: MDI</td>
<td></td>
<td></td>
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<td>------------------</td>
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</tr>
<tr>
<td>Drug: sodium cromoglycate, 2 puffs (10mg), 4 times/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Design: Randomised, open, crossover, controlled.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jadad's score = 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multicentre, UK</td>
<td>In: stable asthma, airways reversibility of &gt; 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.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Study participants considered goo co-ordinators for pMD technique</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Out: not stated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Power calculation</td>
<td>150/group, at power 90%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 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 function, daily diary cards with 4 named symptoms symptom 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. | 

<p>| No significant differences found between autohaler and MDI in clinical efficacy |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Drug</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edmunds et al., 1984</td>
<td>T1: pMDI &amp; DPI placebo, T2 DPI (Rotahaler) &amp; pMDI placebo</td>
<td>Beclomethasone dipropionate. 2 puffs of aerosol 4 times/day; 1 capsule in the rotahaler 4 times/day.</td>
<td>All children require treatment with beclomethasone dipropionate</td>
</tr>
<tr>
<td></td>
<td>Design: Randomised, double-blind, crossover Jadad's score = 2</td>
<td></td>
<td>Power calculation: no Pre-protocol analysis</td>
</tr>
<tr>
<td></td>
<td>Run in: All patients taught how to use the pMDI and rotahaler before study. FU: 2 months, each month, one device contained active drug &amp; the other a placebo.</td>
<td></td>
<td>Mean symptom score was significantly &lt; with T1 vs. T2 (p&lt;0.04). There were no significant differences between the 2 periods for any of the other recorded parameters.</td>
</tr>
<tr>
<td></td>
<td>Primary: ability to use device, sum of diary recorded symptoms, no. of symptom-free days, am &amp; pm PEFR, &amp; rescue salbutamol use.</td>
<td></td>
<td>'Younger' children preferred to use rotahaler (not a predefined outcome).</td>
</tr>
<tr>
<td>Dal Col et al., 1995</td>
<td>T1: DPI (Pulvinal, multidose) T2: DPI (Rotahaler, single dose) T3: placebo via Pulvinal T4: Placebo via Rotahaler</td>
<td>Salbutamol powder, single dose, 200µg</td>
<td>stable asthma, at screening visit - FEV1 &amp; PEFR &gt; 75%; predicted normal, history of exercise-induced asthma &amp; reversible airway obstruction. On day 1 of study, with no treatment, patients had to have Fev1 &gt; 80% of predicted.</td>
</tr>
<tr>
<td></td>
<td>Run in: standard exercise same time on each trial day - 6 min on treadmill with 10° slope. Use of sodium cromoglycate, nedocromil sodium,</td>
<td></td>
<td>No significant difference between T1 and T2 (p&gt;0.05)</td>
</tr>
<tr>
<td></td>
<td>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 for 8 and fair for 2 patients. No patient reported a verdict of 'poor'; for ease of use for either T1 or T2.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Design: Randomised, crossover Jadad's score = 1</td>
<td>15% max fall in FEV₁ vs. baseline values to continue trial. <strong>Out:</strong> 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, &amp; impossibility to discontinue concomitant treatments 24h before testing. <strong>Power calculation:</strong> no Pre-protocol analysis</td>
<td>bronchodilators &amp; antihistamines stopped ≥ 24h before test, inhaled steroid use permitted, nose fixed. Instruction to use inhalers with drawings on correct technique <strong>FU:</strong> 4 consecutive days. <strong>Primary:</strong> FEV₁ &amp; PEFR before and after treatment &amp; exercise challenge, ease of use, correct handling technique</td>
<td>11 patients preferred T₁ while 1 patient preferred T₂, 2 patients had no preference. No adverse events reported throughout study.</td>
</tr>
<tr>
<td>Becker et al 1985</td>
<td><strong>T₁:</strong> MDI + spacer (tube 80ml, 10x3.2 cm) &amp; placebo via MDI <strong>T₂:</strong> MDI &amp; placebo via MDI + spacer <strong>T₃:</strong> placebo via both devices <strong>Drug:</strong> Terbutaline, 250µg/actuation, given in a total dose of 500µg. Placebo was the cfc propellant-surfactant mixture used in the active inhaler <strong>Design:</strong> randomised, double-blind, placebo-controlled Jadad's score = 2</td>
<td><strong>At beginning:</strong> 34 <strong>T₁:</strong> 12 <strong>T₂:</strong> 12 <strong>T₃:</strong> 10 <strong>At end:</strong> 34 <strong>Age</strong> <strong>T₁:</strong> 11.7±0.8 <strong>T₂:</strong> 10.2±0.6 **T₃:**10.5±0.6 <strong>M/F:</strong> nil</td>
<td><strong>Errors in inhaler technique</strong> 4/34 (11.7%) had no errors. Failure to pMDI pMDI+spacer (n=34) (n=34) Remove cap 0 not applicable Shake inhaler 3 7 Position device correctly 0 4 Extend neck 12 17 Slightly 0 0 Exhale completely 2 3 Hold breath while actuating not applicable Co-ord actuation early 13 1 &amp; inspiration late 9 Inhale slowly, deeply 7 9 Hold breath (10 sec) 3 3 Breathe out 3 2 Wait 30 sec 1 1 Before repeat</td>
</tr>
<tr>
<td>Boulet et al, 1995</td>
<td><strong>T₁:</strong> Diskus &amp; placebo via Diskhaler <strong>T₂:</strong> Diskhaler &amp; placebo via Diskus</td>
<td><strong>Run-in:</strong> stop oral medication for 12h or inhaled bronchodilator aerosol for 6h before study. Demonstration &amp; supervision given by investigator <strong>FU:</strong> 3 occasions - 2 to 7 days apart and within 14 days. <strong>Primary:</strong> pulmonary functions</td>
<td>Both MDI+spacer and pMDI were equally effective in improving pulmonary function from the baseline state</td>
</tr>
</tbody>
</table>

| **At beginning:** 463 | **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** | |
| **At end:** 380 | **T₁:** 190 | | |

16 sites, USA **In:** ≥ 12 yrs old, FEV₁ between 60% - 90% predicted normal, receiving adequate anti-inflammatory & inhaled **Power protocol analysis** | Both MDI+spacer and pMDI were equally effective in improving pulmonary function from the baseline state | 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

**Design:** randomised, double-blind, double-dummy, parallel-group, multicenter.

Jadad’s score = 3

**Per protocol analysis:**

**Power calculation:**

90%

**Baseline period:**

none

**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

Very easy to use, % 

85

45

**Easier to tell, % 

91

61

15

(12% with no preference)

No unexpected adverse events.

**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.

Inhalation technique than Diskhaler. Diskus is also rated as easy to learn to use than Diskhaler.
| Mahajan & Okamoto, 1997 | 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** | **At beginning:**  
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 satisfied**  
| Diskhaler  
At screening, 1st exposure (n=210)  
After wk-12 of use (n=154)  
Wk-12 at time of withdrawal (n=154)  
**Global assessments, %**  
| Diskus  
At screening, 1st exposure (n=210)  
Wk-12 (n=154)  
Wk-12 at time of withdrawal (n=154)  
**Preference of device (n=189)**  
at wk-12 (13% had no preference)  |

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

| Cost per Qaly threshold | £5.00 | £5.14 | £5.60 | £5.60 | £5.70 | £5.90 | £6.00 | £6.99 | £7.10 | £7.10 | £7.10 | £7.14 | £7.88 | £7.88 | £8.22 | £8.78 | £9.70 | £10.99 | £11.50 | £11.53 | £11.54 | £12.00 | £17.37 | £18.32 | £29.36 | £30.00 | £30.42 | £53.21 |
|-------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Cost per annum          | £3.14 | £3.60 | £3.60 | £3.60 | £4.20 | £4.20 | £4.20 | £4.20 | £7.88 | £7.88 | £7.88 | £9.22 | £9.70 | £10.99 | £11.50 | £11.53 | £11.54 | £12.00 | £17.37 | £18.32 | £29.36 | £30.00 | £30.42 | £53.21 |
| Device name(s)          |        |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |
| Asmaven                 |        |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |
| Salamol                 |        |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |
| Airomir                 |        |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |
| Salbulin                |        |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |
| Ventolin Exhaler        |        |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |
| Ventolin Exhaler with Nebulizer |   |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |
| Asma inhaler            |        |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |
| Salbutrin               |        |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |
| Ventolin with AbleSpacer |        |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |
| Aerolin Autohaler       |        |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |
| Ventolin Rotahaler (200) |        |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |
| Ventolin Rotahaler (400) |        |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |
| Ventolin Diskehaler (200) |        |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |
| Ventolin Diskehaler (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>
<thead>
<tr>
<th>Cost per Qaly threshold</th>
<th>Asmaven</th>
<th>Salamol</th>
<th>Airomir</th>
<th>Salbulin</th>
<th>Ventolin Evohaler</th>
<th>Airomir with AeroChamber</th>
<th>Salbulin with Aer Amber</th>
<th>Pulvinal</th>
<th>Ventolin Evohaler with Nebulhler</th>
<th>Airomir Autohaler</th>
<th>Salomol Easi-breathe</th>
<th>Asmaven with Able-Spacer</th>
<th>Salamol with Able-Spacer</th>
<th>Ventolin Rotahaler (200)</th>
<th>Ventolin Rotahaler (400)</th>
<th>Ventolin Diskhaler (200)</th>
<th>Ventolin Accuhaler</th>
<th>Ventolin Diskhaler (400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>£20.00</td>
<td>£3.14</td>
<td>£3.60</td>
<td>£3.60</td>
<td>£3.60</td>
<td>£4.20</td>
<td>£7.88</td>
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<td>£9.70</td>
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<td>£12.00</td>
<td>£17.37</td>
<td>£18.32</td>
<td>£29.36</td>
<td>£30.00</td>
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<tr>
<td>Device name(s)</td>
<td>Asmaven</td>
<td>Salamol</td>
<td>Airomir</td>
<td>Salbulin</td>
<td>Ventolin Evohaler</td>
<td>Airomir with Aero Chamber</td>
<td>Salbulin with Aer Amber</td>
<td>Pulvinal</td>
<td>Ventolin Evohaler with Nebulhler</td>
<td>Airomir Autohaler</td>
<td>Salomol Easi-breathe</td>
<td>Asmaven with Able-Spacer</td>
<td>Salamol with Able-Spacer</td>
<td>Ventolin Rotahaler (200)</td>
<td>Ventolin Rotahaler (400)</td>
<td>Ventolin Diskhaler (200)</td>
<td>Ventolin Accuhaler</td>
<td>Ventolin Diskhaler (400)</td>
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Committee, but this information has been removed from this current document]
Table 3. QALY thresholds for 200 ug daily dose (or equivalent) of Beclamethasone

<table>
<thead>
<tr>
<th>Cost per Qaly threshold (£/1000)</th>
<th>Cost per annum (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>£5,000</td>
<td>£28.62 - £28.73</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Device name(s)</th>
<th>Cost per annum (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclazone (200)</td>
<td>£28.62</td>
</tr>
<tr>
<td>Filair (200)</td>
<td>£28.73</td>
</tr>
<tr>
<td>Qvar (50)</td>
<td>£28.73</td>
</tr>
<tr>
<td>Qvar Autohaler (50)</td>
<td>£28.73</td>
</tr>
<tr>
<td>Beclazone (100)</td>
<td>£30.08</td>
</tr>
<tr>
<td>Beclazone Easi-breathe (100)</td>
<td>£30.22</td>
</tr>
<tr>
<td>Filair (100)</td>
<td>£31.41</td>
</tr>
<tr>
<td>Qvar (100)</td>
<td>£31.41</td>
</tr>
<tr>
<td>Qvar Autohaler (100)</td>
<td>£33.01</td>
</tr>
<tr>
<td>Filair (200) + Aerochamber</td>
<td>£33.01</td>
</tr>
<tr>
<td>Qvar (50) + Aerochamber</td>
<td>£34.50</td>
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<tr>
<td>Filair (100) + Aerochamber</td>
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<tr>
<td>Filair (200) + Able Spacer</td>
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<td>Pulvinal (200)</td>
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<td>Qvar (100)</td>
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<tr>
<td>Qvar Autohaler (100)</td>
<td>£38.51</td>
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<tr>
<td>Filair (200) + Able Spacer</td>
<td>£40.73</td>
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<td>Pulvinal (200)</td>
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<tr>
<td>Beclazone (100)</td>
<td>£69.06</td>
</tr>
</tbody>
</table>

* 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

<table>
<thead>
<tr>
<th>Cost per Qaly</th>
<th>Cost per annum</th>
</tr>
</thead>
<tbody>
<tr>
<td>£20,000</td>
<td>£28.62 - £38.51</td>
</tr>
<tr>
<td>£28.62</td>
<td>Beclazone (200)</td>
</tr>
<tr>
<td>£28.73</td>
<td>Filair (200)</td>
</tr>
<tr>
<td>£28.73</td>
<td>Qvar (100)</td>
</tr>
<tr>
<td>£30.08</td>
<td>Beclazone (100)</td>
</tr>
<tr>
<td>£30.22</td>
<td>Filair (100)</td>
</tr>
<tr>
<td>£31.41</td>
<td>Qvar (200) + Aerocambr</td>
</tr>
<tr>
<td>Cost per Qaly threshold</td>
<td>Cost per annum</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>£114.40 Beclamethasone (100)</td>
<td>£114.40 Filair (100)</td>
</tr>
<tr>
<td>£114.90 Beclamethasone (200)</td>
<td>£119.18 Beclamethasone (100)</td>
</tr>
<tr>
<td>£125.63 Beclamethasone (100)</td>
<td>£126.73 Beclamethasone (50)</td>
</tr>
<tr>
<td>£128.70 Beclamethasone (100)</td>
<td>£133.65 Beclamethasone (100)</td>
</tr>
<tr>
<td>£148.60 Filair (100)</td>
<td>£150.60 Filair (100) + Filair (100)</td>
</tr>
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<td>£150.20 Filair (100) + Filair (100)</td>
<td>£156.17 Filair (100) + Filair (100)</td>
</tr>
</tbody>
</table>

*not licensed for children under 12  *assuming a 0.12 cost offset compared with the cheapest option
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<th>Price per Daily Dose</th>
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<th>Cost per annum</th>
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<tr>
<td>£114.90</td>
<td>Qvar Autohaler (100)</td>
<td>£114.90</td>
</tr>
<tr>
<td>£119.18</td>
<td>Filair (100) with AeroChamber</td>
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<td>£126.73</td>
<td>Beclazone Easi-Breathe (50)</td>
<td>£126.73</td>
</tr>
<tr>
<td>£143.15</td>
<td>Becotide (200)</td>
<td>£143.15</td>
</tr>
<tr>
<td>£188.19</td>
<td>Aerobic Autohaler (100)</td>
<td>£188.19</td>
</tr>
<tr>
<td>£199.06</td>
<td>Becotide Rotacaps (400)</td>
<td>£199.06</td>
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<tr>
<td>£272.80</td>
<td>Becodisks Diskhaler (100)</td>
<td>£272.80</td>
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</table>

*Not licensed for children under 12

**assuming a 0.1% cost offset compared with the cheapest pMDI**
### Table 7. QALY thresholds for 200 ug daily dose (or equivalent) of Budesonide

<table>
<thead>
<tr>
<th>Cost per Qaly threshold</th>
<th>Cost per annum</th>
<th>Pulmicort Aerosol</th>
<th>Pulmicort Aerosol with Nebuhaler</th>
<th>Pulmicort Turbohaler (100)</th>
<th>Pulmicort Turbohaler (200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>£5,000</td>
<td>£34.68</td>
<td>£34.68</td>
<td>£87.53</td>
<td>£87.53</td>
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</tr>
<tr>
<td>Cost per annum</td>
<td>Device name(s)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>£24.31</td>
<td>Pulmicort LS</td>
<td>0.00207</td>
<td>0.002073</td>
<td>0.008643</td>
<td>0.00864</td>
</tr>
<tr>
<td>£34.68</td>
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<td>0.00657</td>
<td>0.00657</td>
<td>0.00657</td>
</tr>
<tr>
<td>£34.68</td>
<td>Pulmicort Aerosol with Nebuhaler</td>
<td>0</td>
<td>0.00657</td>
<td>0.00657</td>
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<tr>
<td>£67.53</td>
<td>Pulmicort Turbohaler (100)</td>
<td>0</td>
<td>0.00657</td>
<td>0.00657</td>
<td>0.00657</td>
</tr>
<tr>
<td>£67.53</td>
<td>Pulmicort Turbohaler (200)</td>
<td>0</td>
<td>0.00657</td>
<td>0.00657</td>
<td>0.00657</td>
</tr>
</tbody>
</table>

[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

<table>
<thead>
<tr>
<th>Cost per Qaly threshold</th>
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<th>£67.53</th>
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<td>Cost per annum</td>
<td>Device name(s)</td>
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<td>Pulmicort Turbohaler (100)</td>
<td>Pulmicort Turbohaler (200)</td>
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<td>£20,000</td>
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<tr>
<td>£67.53</td>
<td>Pulmicort Turbohaler (200)</td>
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<td>0</td>
<td>0.001643</td>
<td>0.00164</td>
</tr>
</tbody>
</table>

[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>
<thead>
<tr>
<th>Cost per Daily Dose (£5,000)</th>
<th>Cost per annum</th>
<th>£35.59</th>
<th>£44.15</th>
<th>£44.15</th>
<th>£58.40</th>
<th>£69.53</th>
<th>£78.09</th>
<th>£83.46</th>
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<th>£107.28</th>
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<td><strong>Cost per annum</strong></td>
<td><strong>Device name(s)</strong></td>
<td>Flixotide Evohaler (50)</td>
<td>Flixotide (50) with Nebuhaler</td>
<td>Flixotide Evohaler (125)</td>
<td>Flixotide (125) with Nebuhaler</td>
<td>Flixotide (125)</td>
<td>Flixotide Accuhaler (100)</td>
<td>Flixotide (25)</td>
<td>Flixotide (25) with Nebuhaler</td>
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<td>Flixotide (50)</td>
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<td>0.006799</td>
<td>0.006789</td>
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<td>0.011287</td>
</tr>
<tr>
<td></td>
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<td>0.001712</td>
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<td>0.006799</td>
<td>0.006789</td>
<td>0.006601</td>
<td>0.006575</td>
<td>0.006575</td>
<td>0.011287</td>
</tr>
<tr>
<td></td>
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<td>0.001712</td>
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<td>0.005039</td>
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<td>0.001712</td>
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<td>0.006799</td>
<td>0.006789</td>
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<td>0.006799</td>
<td>0.006789</td>
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<td>0.006575</td>
<td>0.006575</td>
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</tr>
<tr>
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<td>Flixotide (25) with Nebuhaler</td>
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<td>0.001712</td>
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<td>0.003052</td>
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<td>6.95E-06</td>
<td>6.95E-06</td>
<td>6.95E-06</td>
<td>6.95E-06</td>
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*p* not indicated for children
<table>
<thead>
<tr>
<th>Cost per Daily Dose (or equivalent) of Fluticasone</th>
<th>Device name(s)</th>
<th>Cost per QALY</th>
<th>Cost per annum</th>
</tr>
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<td>£35.59 Flutotide (50) with Nebuhaler</td>
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<td>£0.000428</td>
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<td>£35.59 Flutotide Evohaler (50) with Nebuhaler</td>
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<td>£0.000713</td>
</tr>
<tr>
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<td>£0.000713</td>
</tr>
<tr>
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<td>£0.000557</td>
</tr>
<tr>
<td>£69.53 Flutotide (125) with Nebuhaler</td>
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<td>£0.000428</td>
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<tr>
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*not indicated for children
Table 11. QALY thresholds for 20 mg daily dose (or equivalent) of Sodium Cromoglycate

<table>
<thead>
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<th>Cost per Qaly threshold</th>
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<td>£60.77</td>
<td>Intal with synchroner</td>
<td>0.0002073</td>
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<td>0</td>
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</table>
10. REFERENCES


8. Office for National Statistics Key Health Statistics from General Practice. 1996; No. 1


24. Royal Pharmaceutical Society of Great Britain WeBNF Number 41. [http://bnf.org](http://bnf.org) 2001;

26. *IMS Medical Data Index* 1995; 3


32. Slack, R, Ward, S, McCabe, C, Peters, J, and Akehurst, R The Transition to CFC-Free Inhalers. 1998; 98/1


41. Chrystyn, H. Anatomy and physiology in delivery: can we define our targets? *Allergy* 1999; 54 82-87.


63. Bateman, E. D., Silins, V., and Bogolubov, M. Clinical equivalence of salmeterol/fluticasone propionate in combination (50/100 microg twice daily) when administered via a chlorofluorocarbon-free metered dose inhaler or dry powder inhaler to patients with mild-to-moderate asthma. *Respir Med* 2001; 95 136-146.


71. Pearlman, D. S., Kane, R. E., and Banerji, D. Comparative dose-ranging study of triamcinolone acetonide inhalation aerosol using propellants hydrofluoroalkane 134a or P-12 in children with chronic asthma. *Current Therapeutic Research - Clinical and Experimental* 1999; 60 595 -606.


86. Van der, Palen J., Klein, J. J., and Schildkamp, A. M. Comparison of a new multidose powder inhaler (Diskus registered /Accuhaler registered ) and the Turbuhaler registered regarding preference and ease of use. *Journal of Asthma* 1998; 35 147-152.


108. Williams, J. and Richards, K. A. Ease of handling and clinical efficacy of fluticasone propionate Accuhaler/Diskus inhaler compared with the Turbuhaler in paediatric patients. UK Study Group. *Br J Clin Pract* 1997; 51 153-


110. GlaxoSmithKline Submission to NICE. 2001;

111. 3M Submission for NICE. 2001;


114. Aventis Submission to NICE. 2001;

115. Celltech Submission to NICE. 2001;


118. CACI Limited ACORN data used to classify the sample were provided by CACI Limited on the basis of 1991 Census Small Area Statistics obtained from the Office of National Statistics (ONS). 1997;

119. Yamanouchi Submission to NICE. 2001;

120. AstraZeneca Submission to NICE. 2001;

121. Trinity Pharmaceuticals Submission to NICE. 2001;


123. MIMS April 2001. 2001;


128. Machin, D, Campbell, MJ, Fayers, PM, and Pinol, AYJ Sample sizes Tables for Clinical Studies. 1997;

129. Dolan, P, Torgerson, D, and Kakarlapudi, TK Health Related Quality of Life of Colles' Fracture Patients. *Osteoporosis Int* 1999; 9 199-


131. Stevenson, MD, Richards, RG, and Beard, SM The Role of Antileukotrienes in the Treatment of Chronic Asthma. 1999;


