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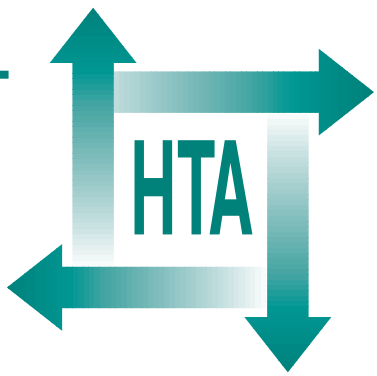
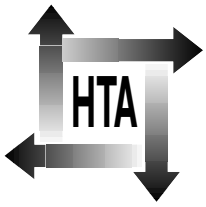
*Health Technology Assessment* 2002; Vol. 6: No. 5

# The clinical effectiveness and cost-effectiveness of inhaler devices used in the routine management of chronic asthma in older children: a systematic review and economic evaluation

J Peters
M Stevenson
C Beverley
JNW Lim
S Smith

**Health Technology Assessment**
**NHS R&D HTA Programme**





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# The clinical effectiveness and cost-effectiveness of inhaler devices used in the routine management of chronic asthma in older children: a systematic review and economic evaluation

J Peters[1*]
M Stevenson[1]
C Beverley[1]
JNW Lim[2]
S Smith[3]

[1] School of Health and Related Research (ScHARR), University of Sheffield, UK
[2] Nuffield Institute for Health, University of Leeds, UK
[3] Easington Primary Care Group, Peterlee, UK

[*] Corresponding author

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# Contents


**List of abbreviations** ..... i

**Executive summary** ..... iii

**1 Background** ..... 1
Description of underlying health problem .. 1
Current service provision ..... 3
Description of intervention ..... 4
Scope of the review ..... 13

**2 Effectiveness** ..... 15
Methods for reviewing effectiveness ..... 15
Results ..... 16

**3 Economic analysis** ..... 27
Methods for economic analysis ..... 27
Review of the economic submissions and published literaure ..... 27
Review group model ..... 34

**4 Implications for other parties** ..... 37

**5 Factors relevant to the NHS** ..... 39

**6 Discussion** ..... 41

**7 Conclusions** ..... 43

**8 Budgetary impact modelling** ..... 45

**Acknowledgements** ..... 47

**References** ..... 49

**Appendix 1** Management of chronic asthma in adults and schoolchildren ..... 61

**Appendix 2** Electronic bibliographic databases searched ..... 63

**Appendix 3** Other sources searched ..... 65

**Appendix 4** Search strategies used ..... 67

**Appendix 5** Excluded studies ..... 73

**Appendix 6** pMDIs with or without spacer vs pMDIs with or without spacer, with the same propellants, delivering bronchodilating drugs ..... 77

**Appendix 7** pMDIs with or without spacer vs DPIs, delivering bronchodilating drugs .. 83

**Appendix 8** DPIs vs DPIs, delivering bronchodilating drugs ..... 93

**Appendix 9** pMDIs with or without spacer vs pMDIs with or without spacer, with the same propellants, delivering corticosteroids 97

**Appendix 10** pMDIs with or without spacer vs DPIs, delivering corticosteroids ..... 99

**Appendix 11** DPIs vs DPIs, delivering corticosteroids ..... 105

**Appendix 12** pMDIs with or without spacer vs breath-actuated devices, delivering anti-inflammatory drugs: sodium cromoglicate .. 109

**Appendix 13** pMDIs with or without spacer vs pMDIs with or without spacer, with different propellants, delivering the same bronchodilating drugs ..... 111

**Appendix 14** pMDIs with or without spacer vs pMDIs with or without spacer, with different propellants, delivering corticosteroids or combined therapy..... 117

**Appendix 15** Breath-actuated inhalers with different propellants, delivering corticosteroids ..... 121

**Appendix 16** pMDIs with or without spacer vs pMDIs with or without spacer, with different propellants, delivering cromoglicate therapy ..... 123

**Appendix 17** Ease of use, patient/carer preference and compliance for alternative devices ..... 125

**Appendix 18** Review group model..... 145

**Health Technology Assessment reports published to date** ..... 159

**Health Technology Assessment Programme** ..... 165

# List of abbreviations

| | |
|---|---|
| ACORN | a classification of residential neighbourhoods |
| AUC | area under the curve* |
| BDP | beclometasone dipropionate* |
| BNF | *British National Formulary* |
| BP | blood pressure* |
| BTS | British Thoracic Society |
| CFC | chlorofluorocarbon (pMDI propellant) |
| CI | confidence interval* |
| DIN-Link | Doctors Independent Network-Link |
| DPI | dry powder inhaler |
| EIA | exercise-induced asthma* |
| EIB | exercise-induced bronchoconstriction* |
| F | female* |
| $FEF_{25–75\%}$ | forced expiratory flow over 25% to 75% of expiration |
| $FEV_1$ | forced expiratory volume in first second of expiration |
| $FEV_{25–75\%}$ | forced expiratory volume over 25% to 75% of expiration |
| FU | follow-up* |
| FVC | forced vital capacity |
| HFA | hydrofluoroalkane (pMDI propellant, replacement for CFC) |
| HR | heart rate* |
| ICS | inhaled corticosteroids* |
| ITT | intention-to-treat* |
| LYG | life-years gained |
| M | male* |
| MDI | metered dose inhaler |
| mean $max_{5–60}$ | mean maximum value during 5–60 minutes* |
| MIMS | *Monthly Index of Medical Specialities* |
| N/A | not applicable* |
| NICE | National Institute for Clinical Excellence |
| PEF | peak expiratory flow |
| PIF | peak inspiratory flow* |
| PEFR | peak expiratory flow rate |
| PIFR | peak inspiratory flow rate* |
| PII | package insert instructions* |
| PP | per protocol* |
| pMDI | pressurised metered dose inhaler |
| QALY | quality-adjusted life-year |
| RCT | randomised controlled trial* |
| SD | standard deviation* |
| SE | standard error* |
| SIGN | Scottish Intercollegiate Guideline Network |
| T | treatment arm* |
| $V_{25(50)(75)}$ | flow at 25%(50%)(75%) of vital capacity |
| VTG | volume of trapped gas (measure of small airways obstruction)* |

* Used only in tables

# Executive summary

## Background

This review examines the clinical effectiveness and cost-effectiveness of hand-held inhalers to deliver medication for the routine management of chronic asthma in children aged between 5 and 15 years.

Asthma is a common disease of the airways, with a prevalence of treated asthma in 5–15-year-olds of around 12% and an 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 the 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 5 years and the comparison in the second was made between pressurised metered dose inhalers and other types only.

## Objectives

This review examines the clinical effectiveness 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 5 and 15 years.

## Methods

Two previous HTA reviews have compared the effectiveness of inhaler devices, one focusing on asthma in children aged under 5 years and the other on asthma and chronic obstructive airways disease in all age groups. For the current review, a literature search was carried out to identify all evidence relating to the use of inhalers in older children with chronic asthma. A search of *in-vitro* studies undertaken for one of the previous reviews was also updated.

The data sources used were: 15 electronic bibliographic databases; the reference lists of one of the previous HTA reports and other relevant articles; health services research-related internet resources; and all sponsor submissions.

Studies were selected according to strict inclusion and exclusion criteria, and relevant information concerning effectiveness and patient compliance and preference was extracted directly on to an extraction/evidence table. Quality assurance was monitored.

Economic evaluation was undertaken by reviewing existing cost-effective evidence. Further economic modelling was carried out, and tables constructed to determine device cost-minimisation and incremental quality-adjusted life-year (QALY) thresholds between devices.

## Results

### Number and quality of studies, and direction of evidence

Fourteen randomised controlled studies were identified relating to the clinical effectiveness of inhaler devices for delivering $\beta_2$-agonists. A further five were on devices delivering corticosteroids and one concerned the delivery of cromoglicate. Overall, there were no differences in clinical efficacy between inhaler devices, but a pressurised metered dose inhaler with a spacer would appear to be more effective than one without. These findings endorse those of a previous HTA review but extend them to other inhaler devices.

Seven randomised controlled trials examined the impact on clinical effectiveness of using a non-chlorofluorocarbon (CFC) propellant in place of a CFC propellant 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 12 randomised controlled trials to non-controlled studies, were identified that concerned the impact of use by, and preference for, inhaler type, and treatment adherence in children. Differences between the studies, and limitations in comparative data between various inhaler device types, make it difficult to draw any firm conclusions from this evidence.

### Summary of benefits

No obvious benefits for one inhaler device type over another for use in children aged 5–15 years were identified.

### Costs and cost per quality-adjusted life-year

Two approaches have been taken: cost-minimisation and QALY threshold. In the QALY threshold approach, additional QALYs that each device must produce compared with a cheaper device to achieve an acceptable cost per QALY were calculated. Using the cheapest and most expensive devices for delivering 200 μg of beclometasone per day, assuming no cost offset for any device, and a threshold of £5000, the largest QALY needed was 0.00807. With such a small QALY increase, no intervention can be categorically rejected as not cost-effective.

## Conclusions

### Generalisability of findings

On the available evidence there are no obvious benefits for one inhaler device over another when used by children aged 5–15 years with chronic asthma. However, the evidence, in the majority of cases, was compiled on children with mild to moderate asthma and restricted to a limited number of drugs. Therefore the findings may not be generalisable to those at the more severe end of the spectrum of the disease or to inhaler devices delivering some of the drugs used in the management of asthma.

### Need for further research

Many of the previous studies are likely to have been underpowered. 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 owing to the large numbers of patients required.

# Chapter 1
# Background

## Description of underlying health problem

### 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 of the airways (bronchoconstriction) leads to a reduction in the flow of gases between air and the 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. 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 childhood asthma population and is associated with somewhat more frequent attacks and wheezing on moderate exercise, which can be prevented by predosing 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 wakening or chest tightness in the morning. There is nearly always evidence of airflow limitation between episodes. Prophylactic treatment is essential.[1]

#### *Acute asthma*

At any of these three levels of chronic morbidity a child may also suffer acute episodes of asthma, which range from mild (in which there will be coughing, audible wheezing, but peak expiratory flow (PEF) or forced expiratory volume in the first second of expiration ($FEV_1$) 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 who are not experiencing an acute episode, actual lung function should not restrict the effective use of breath-actuated inhaler devices.

### Epidemiology

#### *Mortality*

Although deaths from asthma-related causes are rare in children, there were 17 in England and Wales in 1999[3] in those aged 5–14 years, the majority of which were likely to have been preventable.

#### *Incidence and prevalence*

The prevalence of doctor-diagnosed asthma in children in Great Britain is around 10–23%. In 8–9-year-olds in Sheffield, it was found to be 10%[4] and in 11–16-year-olds in Nottingham it was 13%.[5] A national survey across Great Britain of 12–14-year-olds identified a prevalence of 21% in 1998,[6] which endorses the findings of the Health Survey for England of 1995–1997.[7] This survey reported a prevalence of doctor-diagnosed asthma of around 18% in girls aged 5–15 years and 24% in boys aged 5–12 years, dropping to 22% in those aged 15.[8] However, the condition is considerably undertreated, as not all people who have asthma are currently receiving therapy. *Table 1* shows the number of those treated for asthma per 1000 population for England and Wales, subdivided by age and sex.[9]

In the UK, asthma treatment is strongly influenced by the guidelines of the British Thoracic Society (BTS),[10] which currently promotes a step-wise management to increasingly severe asthma

***TABLE 1*** *Prevalence of patients treated for asthma per 1000 population (Office of National Statistics, 1996[9])*

| Age band (yr) | M | F |
|---|---|---|
| 0–4 | 94.1 | 59.5 |
| 5–15 | 122.9 | 97.2 |
| 16–24 | 70.7 | 81.7 |
| 25–34 | 49.1 | 57.8 |
| 35–44 | 41.8 | 54.1 |
| 45–54 | 38.6 | 55.1 |
| 55–64 | 52.9 | 67.7 |
| 65–74 | 69.0 | 74.6 |
| 75–84 | 72.1 | 66.7 |
| 85≥ | 54.6 | 42.4 |
| All ages | 66.2 | 67.7 |

*M, male; F, female*

***TABLE 2*** *Estimated percentages of patients with asthma by BTS step and age (derived from Hoskins* et al., *2000[11])*

| | % aged <5 yr | % aged 5–15 yr | % aged ≥16 yr |
|---|---|---|---|
| Medication below step 1 | 2 | 11 | 12 |
| BTS step 1 | 47 | 20 | 18 |
| BTS step 2 | 44 | 44 | 38 |
| BTS step 3 | 7 | 19 | 22 |
| BTS step 4 | 0 | 3 | 9 |
| BTS step 5 | 0 | 3 | 1 |
| Total | 100 | 100 | 100 |

(appendix 1). The percentages of patients in each of the five BTS steps have been derived from an article by Hoskins and colleagues[11] and are shown in *Table 2*.

By applying these data to a district serving 500,000 people, the numbers with asthma in each age range have been estimated. These are shown in *Figure 1*.

Using the prevalence rate for patients treated for asthma and a standard population profile, in a district of 500,000 people,[12] there would be 33,505 expected asthma sufferers, distributed by age band and BTS step as shown in *Table 3*.

## Significance in terms of ill health

Since there is no cure for asthma, these children

***TABLE 3*** *Expected number of people with asthma, by age band and severity, in a district serving a population of 500,000 (Office of National Statistics, 1994[12])*

| | 0–4 yr | 5–15 yr | ≥16 yr |
|---|---|---|---|
| Medication below step 1 | 57 | 845 | 2,790 |
| BTS step 1 | 1,204 | 1,536 | 4,184 |
| BTS step 2 | 1,147 | 3,379 | 8,834 |
| BTS step 3 | 172 | 1,459 | 5,114 |
| BTS step 4 | 0 | 230 | 2,092 |
| BTS step 5 | 0 | 230 | 232 |
| Total | 2,580 | 7,679 | 23,246 |

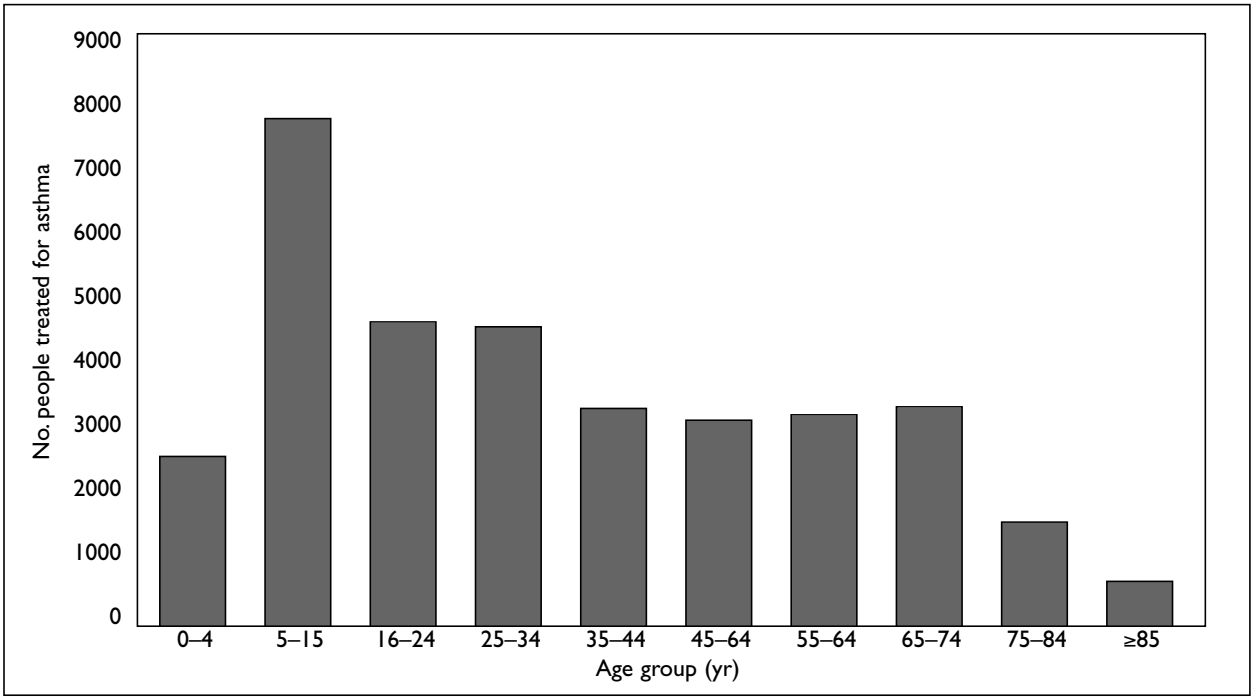


***FIGURE 1*** *Estimated number of people treated for asthma in a district serving a population of 500,000 (using an England and Wales population profile) (Derived from Office of National Statistics, 1996[9]; 1994[12])*

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. The goal of treatment is therefore 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 quality of life for these individuals and satisfaction with their care.[13] The ability to provide an early, effective treatment is also particularly important in children because it may provide longer-term advantages, in terms of both improved management and reductions in the social burden of disease caused through lost school days and reduced activity levels.[14–17]

## 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 the drug acts more quickly and smaller amounts are required, thus reducing the potential for adverse effects. Topically delivered therapy is usually via the inhaled route using devices delivering drugs such as $\beta_2$-agonists, corticosteroids and cromoglicate-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 regarding potential side-effects associated with high doses of steroids. Currently there are a number of different inhaler devices available that can deliver a range of drugs for the treatment of asthma in children aged 5–15 years.

### 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,[18] and a recent HTA report considered the clinical and cost-effectiveness of inhaler devices for children aged under 5 years with chronic asthma.[19] Finally, Brocklebank and co-workers[20] 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 HTA 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 with any hand-held inhaler (usually a pMDI) in stable asthma in children and adults
- inhaler technique with different inhaler devices.

### 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 healthcare professionals working with patients with asthma are most likely to be aware:

- BTS guidelines for the management of asthma.[10]
- Scottish Intercollegiate Guideline Network (SIGN) guidelines,[21] which contain 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. The National Institute for Clinical Excellence (NICE) was considering the development of a guideline on asthma, but instead will await publication of the SIGN guideline and will work with SIGN and the BTS on any subsequent amendments.
- National Heart, Lung, and Blood Institute (USA) guidelines for the diagnosis and management of asthma.[13]

The BTS guidelines[10] 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 the management of chronic asthma in adults and children, starting with bronchodilators and introducing anti-inflammatory agents, with increased doses of these if control is not maintained with the previous drug and dose regimen. For most of the recommendations, school children (aged 5 years and over) and adults are considered to require a similar therapeutic approach (see appendix 1).[10]

***National Heart, Lung and Blood Institute, USA 1997***
These guidelines were produced by an expert panel who revised and updated a set of previous (1991) guidelines. They also take a four-step approach for managing asthma in children older than 5 years of age and adults. 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.[13]

## Other evidence

***Drug and Therapeutics Bulletin***
These Bulletins are commissioned independent reviews produced by the Consumers' Association for clinicians and pharmacists. They are widely circulated to clinicians. The treatment of asthma in children by using inhaled steroids was addressed in 1999;[22] adults were considered in 2000.[23] The choice of inhaler devices for children was addressed, but without any specific recommendations, although inhaler devices themselves were also reviewed in 2000[24] and age-specific recommendations were then made (presented in *Table 4*).

***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 healthcare systems with a reasonable chance of compliance. Their recommendations for management and treatment are based upon symptom presence and frequency in children (ages not stated). 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 and colleagues,[20] in their recent HTA systematic review on inhaler devices for asthma, concluded that:

> "There appears to be a lack of consensus and guidance for an individual prescriber faced with a wide range of possible inhaler devices. The current guidelines are either vague, absent and where present, possibly contradictory" (p. 12).

# Description of intervention

For use in a population of children aged 5–15 years 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 (DPIs). In addition, there is also discussion on the combined devices of spacers or extension tubes used with either pressurised metered dose or breath-actuated aerosol inhalers and, finally, metered dose inhalers (MDIs) pressurised with either chlorofluorocarbon (CFC) or hydrofluoroalkane (HFA) propellants.

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

***TABLE 4*** *Inhaler devices: age-specific recommendations (modified from* Drug and Therapeutics Bulletin *2000;**38**(2):9–13.[24])*

| Age (yr) | First choice | Second choice |
|---|---|---|
| 0–2 | pMDI + spacer + face mask | Nebuliser |
| 3–6 | pMDI + spacer | Nebuliser |
| 6–12 bronchodilators | pMDI + spacer or DPI or breath-actuated pMDI | |
| 6–12 corticosteroids | pMDI + spacer | DPI or breath-actuated pMDI for low-dose corticosteroids only |
| >12 bronchodilators | pMDI | DPI or breath-actuated pMDI |
| >12 corticosteroids | pMDI (+ spacer for moderate or high doses) | DPI or breath-actuated pMDI for low-dose corticosteroids only |
| All ages; acute asthma | pMDI + spacer or nebuliser | |

*pMDI, pressurised metered dose inhaler; DPI, dry powder inhaler*

to molecular oxygen, with implications for depletion of the ozone layer, although medical aerosols use only 0.5% of worldwide consumption. The Montreal protocol,[25] signed by 27 nations in 1987, proposed a 50% reduction in CFC production by 1999. This was subsequently amended to achieve elimination of CFCs by 2000. Potential costs to the NHS of this transition of bronchodilators and corticosteroid inhalers from CFC to non-CFC versions have been estimated to be as high as £270 million. However, the transition has also provided an opportunity to review prescribing policies and develop strategies that offer maximum benefit to both patients and the health service, sometimes resulting in cost savings.[26] Manufacturers and pharmaceutical companies have been working over the past few years to produce non-CFC propellant MDIs. Alternative propellants now available include the HFAs.

There is some evidence that use of HFA propellants with beclometasone has led to improved lung deposition,[27] and a reduction in dose may become possible when changing a child with stable asthma from a CFC to an HFA-propelled inhaler.

## Inhaler devices

For the purpose of this review, the three different inhaler device types have been compared between and also within type. In the tables in the following section on pMDIs, information is provided on all the inhaler devices currently marketed in the UK,[28] grouped by drug delivered (type and generics). Furthermore, for the purpose of this report, 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.[29]

### *Pressurised metered dose aerosol inhalers*

A list of currently available pMDI devices (not breath actuated) is given in *Table 5*.

In England in 1995, the majority of all prescriptions for inhaler medication containing short-acting ($\beta_2$-agonists (83%) or inhaled steroids (78%) used a pMDI delivery mechanism.[30] Although, for children aged 5–12 years living in the West Midlands, bronchodilator prescriptions for pMDIs accounted for only 57%, with the other 43% being for DPIs.[31] 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 it to re-suspend 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 holding for 10 seconds.

A number of common local side-effects, such as mild throat irritation, cough, mouth dryness and paradoxical bronchospasm, have been reported to be associated with the CFC propellants and the lubricants.[32] However, after the decision taken at Montreal in 1987,[25] CFC propellants are now being phased out and replaced with CFC-free alternatives.

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

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 can occur with a standard 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% of patients.[33]
3. The effective delivery of a dose using a pMDI requires coordination between actuation and dose inhalation. A number of users have problems in coordinating their inhalation with their action to release the drug from the pMDI; this can result in excessive deposition of the drug in the oropharynx.[32] Deposition of corticosteroids in the oropharynx is associated with local side-effects such as oral candidiasis[32] and hoarseness due to muscle weakness. These two complications are known to be relatively rare in children, although they are more common in adults.

Spacer systems were developed to surmount these problems, while breath-actuated devices were designed to overcome the third problem specifically and also another problem that 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 with or without a one-way valve, or as tube extenders.

***TABLE 5*** *PMDIs (excluding breath actuated) by drug type, for children aged 5–15 years for routine management of chronic asthma*

| Drug type | Generic drug | Device brand name | Manufacturer | Users |
|---|---|---|---|---|
| Adrenoceptors: short-acting $\beta_2$-agonists | Salbutamol | **Maxivent® aerosol (CFC)** | APS | Children >2 yr |
| | | **Asmaven® aerosol (CFC)** | Berk | Children >2 yr |
| | | Salamol® aerosol (non-CFC) | Baker Norton | Children >2 yr |
| | | Airomir® aerosol (non-CFC) | 3M | Children >2 yr |
| | | Salbulin® aerosol (non-CFC) | 3M | Children >2 yr |
| | | Ventolin® Evohaler® (non-CFC) | GlaxoSmithKline[a] | Children >2 yr |
| | Terbutaline sulphate | Bricanyl® aerosol (CFC) | AstraZeneca | Adults and children; no age given |
| | Reproterol hydrochloride | Bronchodil® aerosol (CFC) | ASTA Medica | Adults and children aged ≥6 yr |
| Adrenoceptors: long-acting $\beta_2$-agonists | Salmeterol | Serevent® aerosol (CFC) | GlaxoSmithKline[a] | Adults and children aged ≥4 yr |
| Antimuscarinic bronchodilators | Ipratropium bromide | Atrovent® aerosol (CFC) | Boehringer Ingelheim | Adults and children 1 month upwards |
| | | Atrovent Forte aerosol (CFC) | Boehringer Ingelheim | Adults and children ≥6 yr |
| | Oxitropium bromide | Oxivent® aerosol (CFC) | Boehringer Ingelheim | Not recommended for children; no age given |
| | Ipratropium and fenoterol | Duovent® aerosol (CFC) | Boehringer Ingelheim | Children aged >6 yr |
| Corticosteroids | Beclometasone dipropionate | Beclazone® aerosol (50, 100, 200) (CFC) | Baker Norton | Adults and children; no age given |
| | | Beclazone aerosol (250) (CFC) | Baker Norton | Not recommended for children; no age given |
| | | Filair® aerosol (50, 100) (CFC) | Generics and 3M | Adults and children; no age given |
| | | Filair Forte aerosol (250) (CFC) | Generics and 3M | Not recommended for children; no age given |
| | | Becotide® aerosol (50, 100) (CFC) | GlaxoSmithKline[a] | Adults and children; no age given |
| | | Becloforte® aerosol (250) (CFC) | GlaxoSmithKline[a] | Not recommended for children; no age given |
| | | Qvar® aerosol (50, 100) (non-CFC) | 3M | Adults and children aged ≥12 yr |
| | Budesonide | Pulmicort® aerosol (CFC) | AstraZeneca | Adults and children; no age given |
| | Fluticasone propionate | Flixotide® aerosol (CFC) | GlaxoSmithKline[a] | Children aged ≥4 yr |
| | | **Flixotide Evohaler (50) (non-CFC)** | GlaxoSmithKline[a] | Children aged ≥4 yr |
| | | **Flixotide Evohaler (125, 250) (non-CFC)** | GlaxoSmithKline[a] | Not indicated for children; age unknown |
| Compound preparations | Beclometasone dipropionate and salbutamol | Ventide® aerosol (CFC) | GlaxoSmithKline[a] | Adults and children; no age given |
| | **Fluticasone and salmeterol** | **Seretide® Evohaler® (non-CFC)** | GlaxoSmithKline[a] | Children aged >12 yr and adults |

*continued*

***TABLE 5 contd*** *PMDIs (excluding breath actuated) by drug type, for children aged 5–15 years for routine management of chronic asthma*

| Drug type | Generic drug | Device brand name | Manufacturer | Users |
|---|---|---|---|---|
| Cromoglicate therapy | **Sodium cromoglicate** | **Cromogen® aerosol** | Baker Norton | Adults and children; no age given |
| | | Intal® aerosol (CFC) | Rhône-Poulenc Rorer | Adults and children; no age given |
| | | **Intal® Syncroner®** (with integral open-tube spacer) **(CFC and non-CFC)** | Rhône-Poulenc Rorer (Aventis Pharma Ltd) | Adults and children; no age given |
| | Nedocromil sodium | Tilade® aerosol (CFC) | Pantheon | Children aged >6 yr and adults |
| | | Tilade Syncroner (with integral open-tube spacer) (CFC) | Pantheon | Children aged >6 yr and adults |
| Compound preparations | Sodium cromoglicate and salbutamol | **Aerocrom® aerosol (CFC)** | Castlemead | Not recommended for children; no age given |
| | | Aerocrom aerosol Syncroner (CFC) | Castlemead | Not recommended for children; no age given |

*Items in normal typeface were found in the recent systematic review by Brocklebank and colleagues[20] and the BNF* (British National Formulary)*;[25] those in* **bold** *appear in the BNF now[25] but not in the review[20]*
*[a]GlaxoSmithKline includes Allen and Hanburys*

Some spacers are integral to the pMDI and form a single unit, whereas others have a flexible opening designed to accommodate either all or most available pMDIs or only those of the same manufacturer. Evidence on the efficacy and safety of use of attached spacers versus integrated modules appears to be lacking.

All spacers work on the same principle and with the same intended end-point and outcome. They address some of the problems that occur with pMDI use. However, there are a number of factors that can reduce the effectiveness of the pMDI–spacer combination. A list of spacer devices that are not integral to specific inhalers is given in *Table 6*.

**Electrostatic charge.** Plastic spacers cause a rapid loss of delivery to the lungs of drug aerosol particles owing to their deposition, because of electrostatic charge, on the walls of the spacer. Elimination of the charge results in an increase in the aerosol half-life, thus reducing the requirements for good and swift coordination between actuation of the inhaler and inhalation, which is 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 antistatic paint, washing the spacer in detergent but not drying it with a cloth, building up the antistatic layer through repeated use of the pMDI, or neutralising the electrostatic charge with benzalkonium chloride.[34] 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.[34] 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 250 ml device, is to be launched in the UK (AstraZeneca communication).[35]

### *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 coordination. 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 with a finger a button on the top of the device and having to synchronise inhalation with this action. With the pressurised component retained, little additional force is needed to trigger the device. Although some recommend that a spacer is also used with this inhaler type in order 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

***TABLE 6*** *Spacer devices available as units for attachment to inhaler devices*

| Name (manufacturer) | Type | Use with: |
|---|---|---|
| Able Spacer® (Clement Clarke) | Small-volume device | Any pressurised aerosol inhaler |
| AeroChamber® (Trudell Medical; UK distributor 3M) | Medium-volume device, adult, child and infant models, 145 ml, rigid plastic tube Compatible with all shapes of pMDI | Airomir, Salbulin, Qvar |
| Babyhaler® (Allen and Hanburys) | Paediatric device | Becotide and Ventolin inhalers |
| E-Z Spacer® (Vitalograph) | Large-volume device, collapsible | Any pressurised aerosol inhaler |
| Nebuhaler® (AstraZeneca) | Large-volume device, 750 ml, plastic pear-shaped cone | Bricanyl, Pulmicort |
| Volumatic® (GlaxoSmithKline) | Large-volume device, 750 ml reservoir | Compatible with all GlaxoSmithKline corticosteroid and bronchodilator MDIs |
| Optimiser™ (Norton) | Small-volume tubular attachment | Easi-Breathe® steroid inhalers |
| Fisonair® (Aventis) | Large-volume device | Intal (sodium cromoglicate) |

are two breath-actuated CFC-free inhaler devices currently licensed for use in the UK, although the inhaler delivering a corticosteroid (beclometasone) is licensed only for 12-year-olds and older.

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, beclometasone dipropionate.

**Easi-Breathe**
This breath-actuated device consists of an aluminium canister 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 beclometasone dipropionate, and sodium cromoglicate.

### *Dry powder inhalers*

DPI devices contain the drug in the form of a dry powder. They 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.[36] DPIs work on the principle of mechanical inhalation driven by the user's own inspiratory efforts (i.e. they are breath activated by the user). The energy imparted to the system by the user is used to disperse the drug particles. Dispersion is aided through the use of a carrier in many of the devices, together with a variety of physical forces, depending on the device, such as turbulence and/or a grille. Individual DPIs have varying internal resistance and require different minimum flow rates. However, with all current DPIs, patients should inhale forcefully because it is the inspiratory effort rather than the resistance that is crucial to the effectiveness of 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 coordination 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 a pMDI reduces its portability as a delivery system.

A list of currently available DPIs is given in *Table 8*.

**Rotahaler® and Spinhaler®**
Two DPIs, Rotahaler and Spinhaler, were introduced over 10 years ago. Both are unit-dose DPIs,

***TABLE 7*** *Breath-actuated MDIs, 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 $\beta_2$-agonists | Salbutamol | **Aerolin® Autohaler® (CFC)** | 3M | Children aged >2 yr |
| | | **Airomir Autohaler (non-CFC)** | 3M | Children aged >2 yr |
| | | **Salamol Easi-Breathe (CFC)** | Baker Norton | Children aged >2 yr |
| Antimuscarinic bronchodilators | Ipratropium bromide | Atrovent Autohaler (CFC) | Boehringer Ingelheim | Adults and children ≥1 months |
| | Oxitropium bromide | Oxivent Autohaler (CFC) | Boehringer Ingelheim | Not recommended for children; no age given |
| Combined therapy | Ipratropium and fenoterol | Duovent Autohaler (CFC) | Boehringer Ingelheim | Children aged >6 yr |
| Corticosteroids | Beclometasone dipropionate | AeroBec® Autohaler® (50, 100) (CFC) | 3M | Adults and children; age unknown |
| | | AeroBec Forte Autohaler (250) (CFC) | 3M | Not indicated for children; age unknown |
| | | Beclazone Easi-Breathe | Baker Norton | Adults and children |
| | | **Qvar Autohaler (50, 100) (non-CFC)** | 3M | Adults and children aged ≥12 yr |
| Cromoglicate therapy | Sodium cromoglicate | **Cromogen Easi-Breathe (CFC)** | Baker Norton | Adults and children; age unknown |

*Items in normal typeface were found in the recent systematic review by Brocklebank and colleagues[20] and the BNF;[25] those in* **bold** *appear in the BNF now[25] but not in the review[20]*

with each 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 or split in two. 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 having limited dexterity, as in younger children. The Rotahaler, and its later derivative, the Diskhaler®, which contains four or eight doses of individual plastic and foil bubble blister packs of the drug (depending on the drug), and the Spinhaler operate under two different principles. The Rotahaler and Diskhaler operate on the cyclone principle, whereas Spinhaler capsules are attached to a turbine that rotates on inhalation.[36] Powder becomes deposited on various parts of the inhaler and regular cleaning with a brush or scraper is advised. One problem with the older DPIs that use gelatin capsules is that the gelatin can soften at high temperatures and in high humidity, making it harder to pierce.

Rotahalers and Diskhalers deliver either salbutamol (a short-acting $\beta_2$-agonist, a bronchodilator) or beclometasone dipropionate (an anti-inflammatory corticosteroid). In addition, the Diskhaler can deliver salmeterol (a long-acting $\beta_2$-agonist, a bronchodilator) and fluticasone. The Spinhaler delivers sodium cromoglicate, a non-steroidal anti-inflammatory drug.

More recently, other multidose DPIs incorporating new design approaches have been introduced.

**Diskus® (Accuhaler®)**

The Diskus (alternative name Accuhaler) is another multidose DPI. It is a disk-shaped plastic device approximately 9 cm in diameter and 3 cm wide. A built-in dose 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 is 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.[36]

The Diskus delivers salbutamol and salmeterol (short- and long-acting $\beta_2$-agonists respectively,

***TABLE 8*** *DPIs 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 $\beta_2$-agonists | Salbutamol | Asmasal® Clickhaler® | Medeva | Children aged >2 yr |
| | | Ventodisks® Diskhaler® | GlaxoSmithKline | |
| | | Ventolin® Accuhaler® | GlaxoSmithKline | |
| | | Ventolin® Rotahaler® | GlaxoSmithKline | |
| | | Pulvinal® | Trinity | Children aged ≥6 yr |
| | Terbutaline sulphate | Bricanyl® Turbohaler® | AstraZeneca | |
| Long-acting $\beta_2$-agonists | Formoterol fumarate/ eformoterol fumarate | Foradil® | Novartis | Adults and children aged >5 yr |
| | | Oxis® Turbohaler® | AstraZeneca | Adults and children aged >12 yr |
| | Salmeterol | Serevent® Accuhaler® | GlaxoSmithKline | Adults and children aged ≥4 yr |
| | | Serevent Diskhaler | GlaxoSmithKline | Adults and children aged ≥4 yr |
| Antimuscarinic bronchodilators | Ipratropium bromide | Atrovent® Aerocaps® (with Atrovent® Aerohaler®) | Boehringer Ingelheim | Adults and children aged ≥12 yr |
| Corticosteroids | Beclometasone dipropionate | Asmabec Clickhaler® (50, 100) | Medeva | Adults and children; no age given |
| | | Asmabec Clickhaler (250) | Medeva | Not recommended for children |
| | | Becodisks® Diskhaler® | GlaxoSmithKline | Adults and children; age not given |
| | | Becotide® Rotacaps® (100, 200, 400) (with Rotahaler) | GlaxoSmithKline | Adults and children; age not given |
| | | Becloforte (400) (with Diskhaler) | GlaxoSmithKline | Not recommended for children; age unknown |
| | | Pulvinal | Trinity | Children aged ≥6 yr |
| | Budesonide | Pulmicort Turbohaler | AstraZeneca | Adults and children; age not given |
| | Fluticasone propionate | Flixotide Accuhaler | GlaxoSmithKline | Children aged 4–16 yr and adults |
| | | Flixotide Diskhaler | GlaxoSmithKline | Children aged ≥4 yr |
| Compound preparations | Beclometasone and salbutamol | Ventide Rotacaps (with Rotahaler) including Paediatric Rotacaps | GlaxoSmithKline | Adult and paediatric; no age given |
| | Fluticasone and salmeterol | Seretide (100) Accuhaler | GlaxoSmithKline | Children aged >4 yr and adults |
| | | Seretide (250 and 500) Accuhaler | GlaxoSmithKline | Children aged >12 yr and adults |
| Cromoglicate therapies | Sodium cromoglicate | Intal® Spincaps® (with Spinhaler insufflator®) | Rhône-Poulenc Rorer (Adventis Pharma Ltd submission) | Adults and children; no age given |
| | | Intal Syncroner | Rhône-Poulenc Rorer | |

*Items in normal typeface were found in the recent systematic review by Brocklebank and colleagues[20] and the BNF;[25] those in* ***bold*** *appear in the BNF now[25] but not in the review[20]*

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, while the Turbohaler®* and Clickhaler® are both reservoir devices.

**Turbohaler**

The Turbohaler is a multidose DPI that contains 50–200 metered doses of the drug, depending on drug strength. Unlike other DPIs and pMDIs, it does not contain any propellants, additives or lubricants except lactose. The inhaler device assembly consists of moulded plastic 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. A single dose is added (in the upright position) by twisting the base of the device fully in one direction and then back again. With each twist of the end of the unit, a dose of powder is shaved off from a drug reservoir. Inhalation forces air through the dosing holes, while spiral channels in the mouthpiece create turbulence and agitate the dry-air mixture, ensuring that a large proportion of the drug is delivered as free particles. 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.[37]

The Turbohaler functions at an inspiratory flow rate of 30 l/min, but ideally requires 60 l/min. This is a more powerful flow than that required with the Rotahaler and the Diskhaler because of in-built areas of resistance in the Turbohaler structure.

The Turbohaler is used to deliver terbutaline sulphate and formoterol fumarate (short-acting and long acting $\beta_2$-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 the drug and the dose; it has a dose counter and locks when empty. Children aged 7–16 years with mild to moderate stable asthma have been shown to generate inspiratory rates of 60 l/min or more when using this device.[38]

The Clickhaler delivers salbutamol (a short-acting $\beta_2$-agonist bronchodilator) or beclometasone dipropionate (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®**

Pulvinal is a new DPI recently launched in the UK. It is a multidose DPI comprising: a rotating mouthpiece with a dose-lock button to prevent unintentional priming; a drug chamber, containing the drug and a lactose carrier; and metering and distribution systems. The drug chamber is transparent, thus enabling the user to see the amount of drug remaining. Priming, activation and inspiration are independent steps, so precise coordination is not required for successful inhalation. Pulvinal delivers the anti-inflammatory corticosteroid, beclometasone dipropionate and the short-acting $\beta_2$-agonist salbutamol.

## Drugs

A person's asthmatic condition can be managed by 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 the inhaler devices described above. The drugs included are bronchodilators (short- and long-acting $\beta_2$-agonists, other adrenoceptors, antimuscarinic bronchodilators) and anti-inflammatory drugs (corticosteroids, cromoglicates) that are licensed for use in 5–15-year-old children.

### *Main types*

**Bronchodilators (relievers)**

The principal action of the $\beta_2$-agonists is to relax the airway smooth muscle by stimulating the $\beta_2$-receptors, which increases cyclic adenosine monophosphate and produces 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 $\beta_2$-agonists cause a prompt increase in airflow, peaking at 20–30 minutes and then fading rapidly, whereas long-acting inhaled $\beta_2$-agonists have a longer duration of bronchodilation of at least 12 hours after a

*"Turbuhaler" may occur as an alternative spelling for this product.

single dose. With formoterol, the onset of action is similar to that seen in short-acting $\beta_2$-agonists, but with salmeterol the onset of action is slower.

The prompt response seen after the inhalation of most short-acting $\beta_2$-agonists provides immediate feedback to the patient that the device has delivered some drug to the relevant sites. Short-acting $\beta_2$-agonists are usually inhaled as required.

**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 in the UK: fluticasone propionate, budesonide and beclometasone dipropionate, although not all are available through all three of the inhaler delivery devices under review: pressurised metered dose, breath-actuated metered dose, and dry powder. Standard dose corticosteroids are usually inhaled twice daily (morning and evening).

Differences in the relative potency and efficacy of each compound have been reviewed.[39] There is substantial evidence to suggest that significant variation in potency exists between the corticosteroid compounds, although this can be overcome by giving equipotent doses. Although individual laboratories report different relative potencies, the rank order of beclometasone dipropionate < budesonide < fluticasone propionate has been shown in a review to be consistent across laboratories.[39] With respect to efficacy, the same review concluded that current evidence does not support an efficacy difference among inhaled corticosteroids.[39] There have been concerns over safety and health issues associated with steroid use.[40]

Sodium cromoglicate and nedocromil sodium also provide effective non-steroidal anti-inflammatory treatment for some children.[41]

**Other**
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 5–15-year-old children.

### *Drug delivery*
This is currently believed to be achieved best 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 physical mode of delivery of asthma drugs there are 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 non-uniform drug deposition across the lungs while, with systemic 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 delivered systemically. Similarly, for corticosteroids, the improvement seen in the therapeutic index in the last few years has been as the result of using inhaled rather than systemic delivery of corticosteroid therapy.

In terms of patient-related issues, there are 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 molecules that is actually inhaled or delivered, and also the amount of drug deposition in the lungs. 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 coordination of actuation and inhalation. Poor inhalation can also lead to increased side-effects from drugs, particularly in the case of corticosteroids causing oral mucosa-related problems. Again, this can lead to additional treatment-related costs. However, in his review of inhaler use in children with asthma, Pedersen concluded that most children older than 5 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 to either 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.

- 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.
- Preference: Inhaler users often express a preference for a specific type of device or a particular device. Although this may encourage better adherence to treatment, in some patients it does not automatically result in better compliance or more effective/efficient use of the device. A number of devices are now being launched that record the date and time of actuation; this may have an impact on patient adherence.[42]

Thus, 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 the one most appropriate to the child's own lifestyle and physical, cognitive and emotional needs.[24]

In terms of disease management, poorly controlled asthma results in increased numbers of exacerbations, which are associated with increased healthcare costs. In one study it was found that 50% of the total resource use costs were accounted for by 22% of the patients who had experienced asthma attacks.[11] One predictor of an attack was poor inhalation technique, which would be due partly to the device, its design and its availability, and partly due to the patient and the healthcare professional who is promoting inhaler competence in terms of adherence and ability to use. Thus, the dose reaching the lungs of a person with asthma has little to do with the prescribed dose and is influenced by the factors described above, such as choice of device, inhaler technique, and adherence.[41] This relationship is further compromised in that variations occur in deposition of the drug in the patient's lungs with different types of inhalers, with or without spacers. The drug delivery system is a 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 beclometasone dipropionate by MDI in combination with a spacer, using the products of three different manufacturers, ranged from 21% to 33%.[39] Some data demonstrating variation in drug deposition by different inhaler devices are shown in *Table 9*.[43]

Although less *in-vivo* evidence is available, that which exists also supports variations in pulmonary delivery by inhaler device, although the results by drug and device do not all move in the same direction in all studies.[39] The dose prescription therefore needs to relate to the expected lung dose for a specific device–drug combination rather than to 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 children.[44] 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 for or toleration of the device by the user; and a device–drug combination that minimises the systemic effects for a given clinical benefit.[41] With $\beta_2$-agonists, because of their wide therapeutic index, the first two factors and issues of cost are important, whereas, for inhaled steroids, the third issue becomes more significant.[41]

## 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".

For the purpose of this question, inhaler devices are defined as pMDIs, breath-actuated pMDIs, and DPIs, with the first two considered with or without the use of a spacer and using CFC or non-CFC propellants.
There is also a 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.

***TABLE 9*** *Pattern of drug deposition with different inhalers: percentage total drug use (modified from Bandolier Drug Watch, 1994 (Feb)[43])*

| | | DPI | MDI | MDI with large-volume spacer |
|---|---|---|---|---|
| Patient | | 95 | 95 | 35 |
| | Lung | 10–15 | 10–15 | 20 |
| | Oropharynx | 80 | 80 | 15 |
| Device | | 5 | 5 | 65 |

# Chapter 2

# Effectiveness

## Methods for reviewing effectiveness

### Search strategy

The search aimed to identify all articles relating to childhood asthma inhalers and outcomes previously addressed in the systematic review by Brocklebank and colleagues[20] and published subsequent to that review. It also aimed to identify all articles 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.) that were not covered in Brocklebank and co-workers' review.[20] An update of these authors'[20] search on *in-vitro* studies was also undertaken. All literature searches were conducted between April and 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 Brocklebank and colleagues'[20] review and other relevant articles were checked. Various health services research-related resources were consulted via the Internet. These included health economics and health technology assessment organisations, guideline producing agencies, generic research and trials registers, and specialist asthma sites. A list of these additional sources is given in appendix 3. All sponsor submissions to NICE were also handsearched.

#### *Search terms*

A combination of free-text and thesaurus terms was 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®, Nebuhaler®, Accuhaler, etc.). The search strategies used for the major databases are given 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 because earlier studies had already been identified by Brocklebank and co-authors'[20] review. No language restrictions were used in the search strategy.

### Inclusion and exclusion criteria

#### *Inclusion criteria*

- Participants: Human patients aged between 5 and 15 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 omitted "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), cromoglicate, nedocromil, or combination therapy, for the routine management of chronic asthma. This includes any inhaler devices delivering drugs not licensed for use in 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 a CFC or an HFA propellant, with or without a spacer (all sizes)
  - breath-actuated metered dose aerosols, using either a CFC or an 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 the device used to deliver it.
- Language: Any articles not available in the English

language (this review was subject to a very short timescale that precluded time for translation).
- Time: No date limits were imposed.
- Abstracts: Studies available only as abstracts were also excluded.

### Data extraction strategy

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

### Quality assessment strategy

Included articles 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.

- Randomised controlled trials were assessed with respect to randomisation procedures, blinding, and handling of withdrawals and drop-outs, by using the Jadad scoring system.[45]
- Non-randomised studies using quantitative data, such as case-control and cohort studies, case series and case reports, were assessed with respect to validity by using guidelines from the Centre for Health Evidence based upon the Users' Guides to Evidence-Based Medicine.[46]
- Qualitative evidence was assessed using the Critical Appraisal Skills Programme checklist for qualitative research.[47]

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

- The quality of the economic literature was assessed according to the 'Guidelines for authors and peer reviewers of economic submissions' to the BMJ.[48]

## Results

### Quantity and quality of research available

#### *Number of references*

A total of 7234 references were identified 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.

#### *Exclusions*

Details of all studies excluded and reasons for their exclusion are given in appendix 5.[29,38,49–214,272]

#### *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

***TABLE 10*** *Reference statistics*

| Topic | No. identified[a] | No. ordered/ contacted | No. used | | |
|---|---|---|---|---|---|
| | | | Reviews | RCTs | Non-RCTs |
| *In-vitro/in-vivo* update | 31 | 2 | 0 | 0 | 0 |
| Clinical effectiveness, reviews, guidelines | 375 | 17 | 1 | 0 | 0 |
| Clinical effectiveness trials | 5531 | | 0 | 27 | 0 |
| Patient preference, ease of use | 183 | 287 | 0 | 10 | 20 |
| Non-specific searches | 605 | | 0 | 0 | 0 |
| Cost-effectiveness | 369 | 16 | 0 | 0 | 0 |
| Current research | 140 | 4 | 0 | 0 | 0 |
| Total | | 326 | 1 | 37 | 20 |

[a]*Includes duplicates*
*RCT, randomised controlled trial*

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 this research, it is hoped that any published results from these studies, if relevant, would have been identified in the literature searches.

## Clinical effectiveness

### *Review question*

The study question for this current review was 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 clinical effectiveness, this review updates the available information on the *in-vitro* questions addressed by Brocklebank and colleagues in their recent review:[20]

- 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:

- Comparison between three hand-held inhaler device types delivering bronchodilatory drugs, corticosteroids, or cromoglicate compounds, for the routine treatment of chronic asthma in children aged between 5 and 15 years (building on Brocklebank and co-workers' findings[20] where available).

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

### In-vitro *evidence*

Information on this aspect was taken from the recently published review[20] and updated with new published evidence. Brocklebank and co-authors[20] identified three studies that met their review criteria; from these they concluded that:

> "Recent studies with modified *in vitro* techniques suggest that there is a relationship between *in vitro* measurements and lung deposition. This relationship is specific to the set (inhaler device and drug combination) for which the *in vitro/in vivo* parameters were conducted. Studies have also shown that there is a relationship between *in vitro* measurements and clinical effect measured by lung function ($FEV_1$ and PEFR [peak expiratory flow rate]). However, there is still an incomplete understanding of the relationship between *in vitro* techniques, particle size, aerodynamic diameter and drug mass (μg)" (p. 5).[20]

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

### *Delivery of drugs for children with chronic asthma*

Although the recent systematic review of inhaler devices for asthma and chronic obstructive pulmonary disease[20] will be used to inform this review, it did not address all of the issues defined for this report. Two of the five key areas addressed by Brocklebank and co-workers[20] are of relevance to this review:

- the delivery of corticosteroids by hand-held inhalers for the treatment of stable asthma in children
- the delivery of bronchodilators in the same manner and to the same patient group.

In both of the above areas, Brocklebank and co-workers considered only studies that 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 and colleagues[20] in terms of:

- Inhaler device comparisons: 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, the current review includes other anti-inflammatory drugs, the cromoglicates. For bronchodilators, the specification is also broader. Brocklebank and colleagues[20] 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 articles identified within each comparison is provided in *Table 11*.

Only one study[215] was found relating to any inhaler device comparisons with the same propellant delivering cromoglicates, and only one[215] on comparisons of other inhaler types with breath-actuated inhaler devices. The same study addressed both of these areas.

***TABLE 11*** *Evidence for systematic review*

| Comparison | | No. studies | |
|---|---|---|---|
| **Inhalers** | **Drug** | **Brocklebank *et al.* 2001[20]** | **This review** |
| pMDI with/without spacer vs pMDI with/ without spacer, same propellants | $\beta_2$-agonists | Not included | 7 |
| pMDI with/without spacer vs breath-actuated MDI | $\beta_2$-agonists | 0 | 0 |
| pMDI with/without spacer vs DPI | $\beta_2$-agonists | 9 | 4 |
| DPI vs DPI | $\beta_2$-agonists | Not included | 3 |
| pMDI with/without spacer vs pMDI with/ without spacer, same propellants | Corticosteroids | Not included | 1 |
| pMDI with/without spacer vs breath-actuated MDI | Corticosteroids | 0 | 0 |
| pMDI with/without spacer vs DPI | Corticosteroids | 3 | 2 |
| DPI vs DPI | Corticosteroids | Not included | 2 |
| pMDI with/without spacer vs breath-actuated MDI | Cromoglicates | Not included | 1 |
| pMDI with/without spacer vs pMDI with/ without spacer, different propellants | $\beta_2$-agonists | 1 | 4 |
| pMDI with/without spacer vs pMDI with/ without spacer, different propellants | Corticosteroids | 0 | 1 |
| Breath-actuated vs breath-actuated, different propellants | Corticosteroids | 0 | 1 |
| pMDI with/without spacer vs pMDI with/ without spacer, different propellants | Cromoglicates | 0 | 1 |

In presenting the findings from Brocklebank and co-workers' systematic review[20] we have chosen, with permission from the authors, to show their relevant extraction tables of evidence. The reason for this is that, because very little evidence was found with respect to children, they 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 findings alongside those of Brocklebank and colleagues enables the reader to compare all the evidence for comparisons of each set of inhaler devices rather than adding small pieces of additional evidence to previous summaries. Indeed, we found little further evidence for those comparisons of inhaler types that Brocklebank's team had already addressed. We did however identify a number of articles that examined some other comparisons, such as those between different DPIs, which had not been covered in the previous review. We also took the decision not to carry out any meta-analyses, given the limited amount of evidence available within each comparison group.

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

Nine studies[117,216–223] were found in total by Brocklebank and colleagues[20] that compared inhaler devices using the same propellant and delivering bronchodilating drugs. An additional 14 studies that fulfilled the inclusion criteria were identified for the current review. Details of all studies are given in appendices 6–8 (*Tables 12–15*).

- Comparisons of pMDIs with/without a spacer vs other pMDIs with/without a spacer (appendix 6, *Table 12*)

This comparison was not included in Brocklebank and co-authors' review.[20]

Seven articles were identified for the current review.[224–230]

In a randomised trial Kerac and colleagues[224] compared a pMDI against two other pMDI spacer combinations (Volumatic®, plastic bottle,) all delivering salbutamol, and a pMDI placebo, in 48 children and adults. However, with an age range of 10–75 years, few of the patients were likely to be within the 5–15-year age eligibility criteria for this review. Significant differences in PEFR ($p < 0.05$) were found between both the pMDI spacer combinations and the pMDI placebo at 30 minutes after inhalation, but there were no significant differences between the two spacerless pMDIs (salbutamol and placebo). A second study[225] using salbutamol, in which a pMDI was compared with a pMDI spacer combination (Volumatic) in

ten children aged 8 to 14 years, demonstrated no difference between inhaler devices over a 30-minute period after inhalation. In Lee and Evans'[229] cross-over study, the four treatment arms were comparisons of albuterol (US term for salbutamol) delivered by a pMDI compared with three other pMDI–spacer combinations in 23 children (of whom 20 completed the study) aged 8–15 years. These authors reported no differences, either overall or for 14 children who had the correct inhaler technique, in the increase in $FEV_1$ after 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 pMDI–spacer combinations compared with the pMDI alone ($p < 0.05$). In one further study,[227] in 16 children aged 5–12 years randomised to pMDI or pMDI plus spacer, both delivering the bronchodilator metaproterenol sulphate, or to a pMDI or pMDI plus spacer, both delivering a placebo, no differences were found in $FEV_1$ or the forced expiratory flow over 25% to 75% of expiration ($FEF_{25–75\%}$) between the two drug-delivering inhaler combinations. Metaproterenol sulphate is not available in the UK. The final three studies,[226,228,230] all in children, looked at a pMDI compared with a pMDI plus spacer delivering terbutaline sulphate. Becker and co-workers[226] found that the pMDI and spacer, and pMDI alone, were equally effective for improving pulmonary function. However, in both of the other two studies[228,230] the pMDI–spacer combination was significantly better for PEFR in the 60 minutes after inhalation. All study participants were aged between 4 and 14 years; 18 were between 4.9 and 13.7 years,[228] and 12 were between 7 and 11 years.[230]

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

- pMDIs with/without a spacer vs DPIs (appendix 7, *Tables 13* and *14*)

Nine studies[117,216–223] were identified by Brocklebank and co-workers.[20] In two the DPI used was a Rotahaler and salbutamol was delivered; in the other seven, the DPI was a Turbohaler and turbutaline was delivered, except for one study that used salbutamol. All except one were based on a cross-over design. The main outcomes reported were lung function variables and, overall, no significant differences were found in $FEV_1$, $FEF_{25–75\%}$, forced vital capacity (FVC) or PEFR between the pMDI and the DPI. The conclusions of the reviewers[20] 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, a dosing schedule of 1:1 was used, whereas the prescribing recommendations for salbutamol suggest doses of 100–200 μg by pMDI and 200–400 μg by Rotahaler, and for terbutaline, they indicate the use of 250–500 μg by pMDI and 500 μg by Turbohaler. The authors stated that these 1:1 dosing studies would tend to favour the Turbohaler and disadvantage the Rotahaler when compared with the pMDI.

Four additional studies were published between 1999 and 2001; two used a cross-over design[231,232] while the other two were based around parallel groups.[233,234] The Spiros® DPI was used in two of the studies,[231,233] an Easyhaler® in the third,[232] and a Diskus in the fourth.[234] Three studies[231–233] used salbutamol or albuterol, while the fourth[234] used a long-acting $\beta_2$-agonist, salmeterol. As with the nine earlier studies, no significant differences were found in $FEV_1$, in the area under the FEV curve, or in PEF. Although two studies had small numbers of participants (<32), the other two were much larger than many seen in this research area, with 283 and 498 recruited (240 and 395 completing the study) respectively.[233,234] However, the problems with all four of these studies as a source of evidence for this review were that the populations studied ranged in age from 7 to 79 years, with only a small proportion of children aged under 15 years included in each, and no subgroup analysis by age was available.

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

- DPIs vs DPIs (appendix 8, *Table 15*)

This comparison was not part of Brocklebank and colleagues' review.[20]

Two studies were identified[235,236] that compared the Diskus DPI with the Diskhaler DPI, both delivering salmeterol. One was a three-way cross-over study[235] while the second used parallel groups.[236] In neither study was any significant difference found between the percentage predicted $FEV_1$[235] or PEFR and symptoms.[236] However, Bronsky and co-workers[235] studied only 24 patients (mean age 9 years, standard deviation 2.1) and, although Boulet's group[236] had included 380 participants by the end of their study, their mean age was 39 years (range 12–70),

making it unlikely that many of them were within the age range of interest for this review. A third study[237] compared the single-dose Rotahaler with the multidose Pulvinal, both delivering salbutamol to 13 children aged 8–12 years. No differences were found between the two devices with respect to $FEV_1$ or PEFR.

**Delivery of corticosteroids by hand-held inhaler devices, using the same propellants**
Three studies[238–240] were identified by Brocklebank and colleagues[20] and a further five in this review. Details of all the studies are given in appendices 9–11 (*Tables 16–19*).

- pMDIs with/without spacer vs pMDIs with/without spacer (appendix 9, *Table 16*)

This comparison was not included in Brocklebank and co-authors' review.[20]

One study was identified[241] 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 years in this randomised cross-over trial. The metal spacer, which, at 250 ml, is one-third the size of the plastic spacer (750 ml) is currently not available in the UK, although its introduction into the UK marketplace is proposed.

- pMDIs with/without spacer vs DPIs (appendix 10, *Tables 17* and *18*)

Brocklebank and colleagues[20] identified three randomised controlled trials comparing pMDIs (two with spacers) with DPIs.[238–240] In two studies beclometasone dipropionate was used and in the third budesonide. The review authors' summary of one study[239] was:

> "… this large and well-designed study does support the equivalence of the pMDI + Nebuhaler versus Turbuhaler (sic) at half of the pMDI dose. However, it does not present any evidence for advantages over the accepted place of the pMDI + large volume spacer as the device of choice in childhood asthma management (p. 17)."

The other two studies were basically dismissed by the authors. One was in abstract form only.[238] In the other, inappropriate or unsuitable devices were used with children, such as no spacer and a Rotahaler DPI; the study was also underpowered.[240]

Two further studies were identified during the current review. In a study by Agertoft and co-workers,[242] 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 DPI Turbohaler in children aged 6–15 years but, for younger children aged 4 and 5 years, there were no differences between the two inhaler devices. Bateman and colleagues[243] compared an HFA pMDI versus a DPI (Diskus), both delivering a combination of fluticasone dipropionate and salmeterol. The patients were aged 11–79 years and no differences in lung function and symptoms were found.

- DPIs vs DPIs (appendix 11, *Table 19*)

Two studies were identified,[244,245] both of which compared the Diskus with the Diskhaler, with fluticasone propionate as the medication. In neither study were any differences found between the two inhaler devices for $FEV_1$, symptom scores, albuterol use, or night-time wakenings. Both studies had sufficient power according to the details given in each article. In one,[244] the number of patients within the age range of relevance for this review was low, as the 229 studied ranged from 12 to 76 years of age. However, in the second study,[245] the 437 children recruited were aged 4–11 years.

**Delivery of cromoglicates by hand-held inhaler devices using the same propellant** (appendix 12, *Table 20*)
One study was identified[215] that compared a pMDI with a breath-actuated inhaler device (Autohaler) in children aged 4–18 years (with one person aged 39). The drug used was sodium cromoglicate. 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 8-week follow-up, compared with the 150 participants per group required in the authors' power calculation.

**Delivery of bronchodilators or anti-inflammatory drugs by hand-held inhaler devices using different propellants**
The Montreal Protocol of 1987[25] proposed the phasing out of CFC propellants over the following few years. The UK Government became committed to the removal of CFCs from all medicinal products by 2000. 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 $\beta_2$-agonist inhaler became available in 1995 and further products have now been launched. Although there is some evidence that beclometasone dipropionate pMDIs with HFA give better drug deposition and that drug doses may be reduced compared with those given through pMDI CFC inhalers,[246] in this review our brief was not to examine the evidence for effectiveness of different drug doses. Therefore we have looked only at studies that compared inhaler devices that have delivered the same drug in equivalent doses. In this section the same approach has been applied.

Given the timescale for and the difficulties in the development of non-CFC inhalers, Brocklebank and co-authors[20] identified only one study examining this issue, while a further seven have been published in the last 2 years. Details of all these studies are to be found in appendices 13–16 (*Tables 21–25*).

- Delivery of $\beta_2$-agonist bronchodilators by pMDI using different propellants (appendix 13, *Tables 21* and *22*)

Brocklebank and colleagues[20] identified one study in their review,[247] 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[248–251] have been identified, all of which compared pMDI CFC-propelled albuterol with a pMDI HFA-propelled equivalent dose of albuterol. In one study[251] the patients recruited were over 12 years of age and, with an average age around 30 years, few of the 313 total would be within the age range for this review. However, in the other three studies the patients were aged 4–11[248,249] and 6–11 years.[250] No significant differences were found between CFC and HFA use with respect to mean percentage predicted $FEV_1$ or the mean percentage predicted PEF.[248,249] Colice and co-workers[250] examined the impact of the two pMDI devices in children with exercise-induced asthma and also found no significant differences in the percentage change in $FEV_1$ postexercise between the two groups.

A similar pattern of evidence was also seen in the study on older patients,[251] with no changes in pulmonary function, morning or night-time PEFR values, symptom scores, night-time awakenings, or use of back-up short-acting $\beta_2$-agonists, when patients switched from inhalers containing CFC to those containing HFA propellants.

- Delivery of corticosteroids by pMDI using different propellants (appendix 14, *Table 23*)

One study examined the impact on lung function of CFC versus non-CFC pMDIs delivering a corticosteroid, triamcinolone acetonide (not currently available in the UK), via a pMDI spacer.[252] The participants were aged 6–13 years. Pearlman and colleagues examined the effect of three different dose regimens (150 μg/day, 300 μg/day, 600 μg/day) each delivered by both a CFC- and an HFA-propelled pMDI, and found no differences in morning and evening PEFR, $FEV_1$, symptom scores, night-time wakening, or albuterol use.[252]

- Delivery of corticosteroid therapy by breath-actuated inhalers using different propellants (appendix 15, *Table 24*)

Of all the evidence found, only one study compared breath-actuated inhaler devices. Farmer and colleagues[253] looked at differences between two breath-actuated inhalers delivering beclometasone dipropionate to children aged 7 to 12 years, one of which used CFC and the second, an HFA propellant. The study may have been slightly underpowered based on their 90% power calculation for participant numbers 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.

- Delivery of cromoglicate therapy by pMDIs using different propellants (appendix 16, *Table 25*)

Only one study from all the evidence found compared inhaler devices delivering sodium cromoglicate,[254] using pMDIs and CFC compared with HFA propellants. The authors found no differences in symptom scores, the use of albuterol, and morning and evening PEF in 280 participants aged 12–79 years. The patients rated the effective-ness of their treatment similarly in the two treatment groups (73% for CFC, 77% for HFA, $p = 0.989$). However, the clinicians rated the CFC inhaler as more effective (63%) for patients than the HFA one (56%) ($p = 0.042$).

### *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, while pMDIs and DPIs have been compared both against each other and within type, only two studies have concerned breath-actuated inhalers,[215,253] one of which was not a comparison of device types but of the

propellants used.[253] Similarly, in terms of drugs, although short-acting $\beta_2$-agonists and corticosteroids are well represented in the evidence, only two studies[215,254] related to the difference between inhalers delivering sodium cromoglicate; one of these was a comparison of propellants.[254] Few studies have addressed the question of long-acting $\beta_2$-agonists alone[234] or in combination therapy.[243]

In general, from the evidence available, the impact of different asthma medication inhaler devices on lung function and symptoms in children with chronic asthma aged 5–15 years, and being treated in a randomised controlled trial situation, suggests that there are no obvious benefits to asthma symptom control when 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 pMDIs[224,228,230] and a suggestion that those made of metal may be more effective than those currently available in the UK, which are made of plastic.[241] There may also, however, be cost implications with this latter option.

The evidence from the earlier systematic review of Brocklebank and co-authors,[20] although not so comprehensive in scope as the current review, led to a similar conclusion that there was no evidence of an advantage for any one type of inhaler device over another.

Being unable to identify any significant differences when they may actually exist may be due to the studies being underpowered (Type 2 error). In most instances, no power calculations were reported and patient numbers were usually low (<50 per treatment arm). Where power calculations were reported, sample sizes were in the order of 70+ with one exception.[255] It would be illogical if, with most of the authors looking at the same primary outcomes, $FEV_1$, PEF, PEFR, presumably with similar levels of effect, in similar populations of children with a similar condition (mild to moderate asthma), the studies did not all require similar patient numbers to be sufficiently powered.

In a systematic review of studies of CFC MDIs compared with non-CFC MDIs delivering short-acting $\beta_2$-agonists, Hughes and co-authors[256] pointed out that many of the trials reviewed were underpowered. A second point made related to the ability of studies to demonstrate equivalence. That issue is relevant for this review also.

In 43% of the studies identified, the sample populations lay entirely within the age range of interest for this review.[225–230,235,237,241,250,252,253] However, 16 studies covered a much greater age range distribution, with the age band of interest lying in one tail of the distribution, so it is possible that any variation in response in children may be masked because of this wider age range. Subgroup analysis by age band was not available for any of the studies that concerned adolescents and adults; indeed, the studies may not have had sufficient power for such analyses. The exclusion from the review of all the studies in which the age range was not totally within the review criteria would have more than halved the amount of evidence available.

It is also possible that the populations studied do not represent the population profile for childhood asthma. For 50% of the studies, patients with mild to moderate asthma were recruited specifically; a number of them expressly 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).[10] It is not necessarily appropriate to assume that children with more severe asthma would have shown similar lung function responses with the various inhaler types to those seen in the children surveyed and reported in this evidence.

In terms of therapeutic benefit associated with the different inhaler devices, those studies that considered adverse effects reported few or none;[227–229,231–237,231] there also appeared to be no obvious differences in these by inhaler type irrespective of drug delivered, with one exception.[243]

The cost of replacing CFC with HFA inhalers was predicted to be high[26] but, in 2001, with most of these costs being non-recurring and the number of HFA devices in the marketplace 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. An example could be that, in one arm, a patient would be required to take a dose more times per day than a patient in another arm, although the final dose would be 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, independently of the research question. In the studies considered in this review, treatments in each 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.

### *Summary*

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

- There is no difference in benefit between pMDIs using either CFC or HFA propellants, between pMDIs and DPIs, or between DPIs, delivering either short-acting $\beta_2$-agonists or corticosteroids.
- There is some evidence of benefit from using a pMDI spacer combination rather than a pMDI alone, specifically a metal spacer.
- There is no evidence on the clinical advantages or disadvantages of breath-actuated inhalers compared with either pMDIs or DPIs.

### *Recommendations*

Further properly designed equivalence trials, adequately powered, could produce some non-equivalent evidence. However, the patient 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[41] when considering asthma drug delivery systems in children: suitability for age of the user; liking or tolerance of the device by the user; and 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 evidence on factors relating to patient adherence to inhaled asthma medication associated with different inhaler devices in children aged 5–15 years and their carers is considered. Adherence will be affected by the suitability of the device and the user's liking of it.

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

### *Review question*

In this section of the review, the impact of ease of use, preference for and adherence to different inhaler types on their clinical effectiveness in children aged 5–15 years is considered.

### *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 29 articles included in the review, plus one industry submission study (data summarised in appendix 17, *Table 26*), 12 studies (including an extension study)[197,215,218,226,236,237,240,257–261] amounted to randomised controlled trials, of which five (plus the extension study) were blinded.[226,236,240,257–259]

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

The remainder included large and small open, non-controlled studies concerned with various perceived adherence factors in addition to the choice and ease of use of the inhaler device or ability to use it after a training programme. Fourteen of the studies did not involve comparisons between two or more inhaler device types.[257,262–271,273–275] Five studies on instruction giving have been included because of their impact upon use, although not directly upon ease of use.[263,274,276–278] In 12 of the studies selected, lung function and symptom variables were the primary outcome measures used, together with patient compliance and use in some studies but not all.[197,215,218,226,236,237,240,262,267,269,274,275] In the other 18 studies the primary outcomes related to adherence factors only.

With respect to the age of participants, in eight studies the age range selected was within the 5–15-year age band of relevance to this review.[226,237,262,265,266,268,269,271] Patients much older than 15 years were included in seven studies[218,236,259,260,270,274,276] and much younger than 5 years in a further three.[263,267,279] In 11 studies the age ranges were between 4 and 18 years.[197,215,240,257,258,264,273,275,277,278,280] Patient numbers for all studies, with the exception of three, ranged between 13[237] and 463.[236] For the three exceptions, participant numbers were considerably higher at 1133,[275] 2056[268] and 4529.[270] Seventeen groups studied less than 100 patients.

The majority of studies were observational, with small numbers of participants who were older than 15 years, and they did not directly or robustly 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 years.

### *Use*

The most general finding was that adequate, individual (verbal) instruction was the key to correct inhaler technique[263,269,270,275,276] and improvement in lung function and symptoms,[269,274]

regardless of the choice of inhaler device.[263,276] Choice of inhaler device did not appear to represent a barrier to effective use in children over the age of 5 years, with the proviso that adequate (verbal) instruction and supervision were provided. Deciding upon an inhaler device in combination with lung function testing appeared to produce better outcomes in terms of efficiency of use.[278]

A range of problems have been identified associated with poor technique[273] that is not necessarily specific to the inhaler device.[226,260] Age may have an impact on ability to use, with younger children (4–6 years of age) having a less efficient technique than those somewhat older (7–16 years),[278] although, in a second study, improvements in ability to use after a training intervention were independent of age.[276]

In terms of ease of use, Ng and colleagues[279] reported that 22 of 31 adolescents rated the DPI (Diskus (Accuhaler)) as easiest to use, compared with three in favour of the DPI (Turbohaler) ($p = 0.002$) and six the breath-actuated Autohaler ($p = 0.0311$). In a comparison study of two other DPIs, patients ($n = 463$) rated the Diskus (85%) and Diskhaler (45%) as very easy to use.[236] The authors of a further study reported the investigators' assessment of their 13 patients. Ease of use was recorded as excellent in ten and good in three when using the DPI Pulvinal, compared with three excellent, eight good, and two fair when using the DPI Rotahaler.[237] One specific factor that impacts upon ease of use is the ability to load the device correctly; significant differences were found between the percentage of errors made when loading the DPI Turbohaler compared with the DPI Diskus ($p = 0.045$).[260]

(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.)

### Adherence

When examining adherence, measuring it in some way was consistently a far more accurate reflection than self-reporting methods. Self-reported adherence by patients to drug-dose schedules has been overestimated by as much as 100% when compared with records of actual use,[257,262,266] although correlation between self-reported and estimated actual use is often poor or non-existent.[264,265] Some discordance was also seen between parent/child and parent/physician reports of asthma medication use.[271]

Factors such as age,[258,270] socio-economic status,[266] and ethnicity[266,268] were also found to interplay with measured adherence, with adherence appearing to decline with progress into adolescence.[258] The current authors suggest 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.

### Preference

Patient preference, where expressed, tended to favour DPIs over MDIs, but comparative outcome data were sparse. In a comparison of a pMDI with a DPI (Rotahaler) the younger children in a study of 4–15-year-olds preferred the Rotahaler, but this was not one of the listed outcomes of the study and no data were reported.[240] The DPI Diskhaler was also preferred over the pMDI by the majority of the children in the Kesten and co-workers' study ($p < 0.001$).[270]

Most of the evidence found related to comparisons of different DPI devices. In Sharma and co-authors' report,[280] 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 that guided preference among 10–14-year-olds and ease of use among those aged 4–9.[280] The DPI Diskus was rated more favourably than the DPI Turbohaler in another study on similar features, that is, dose indicator and ease of correct use.[197] 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 two groups would not.[197] Patient preference was significantly in favour of the Diskus over the Turbohaler in the study by Ng and colleagues.[279] However, van der Palen and colleagues[260] noted the reverse finding, with more people preferring the Turbohaler (25) to the Diskus (17) (eight had no preference). These differences were not significant and the participants were an older group (15–74 years), 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.[259] In a study by Boulet and co-workers,[236]

73% preferred the Diskus and 15% the Diskhaler, while 12% expressed no preference. Another DPI comparison between the Pulvinal and the Rotahaler showed 11 of 13 patients preferring the Pulvinal, one preferring the Rotahaler, and two with no preference (data as presented by authors).[237]

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

The pMDI has also been compared with the breath-actuated Autohaler. Ninety of 181 children and adolescents found the Autohaler to be more acceptable that the pMDI, 24 opted for the reverse opinion, and 43 found both devices equally acceptable ($p < 0.001$).[215]

### *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 the data available are of a less than robust quality.

### *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 asthma inhaler devices. 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 to the management of children and adolescents with chronic asthma.

# Chapter 3

# Economic analysis

## 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.

## 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 articles request-ed and reviewed was either that different drugs were being used in addition to different devices, or that the study population did not match the 5–15-year age range specified in the review inclusion criteria.

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

Each submission was documented according to 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 analysis 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.

### Overview of economic analyses in submissions

Six of the eight submissions adopted a standard cost-minimisation approach, citing that no significant clinical differences between devices have been proved. Therefore, the cheapest option with which the patient is both compliant and proficient in using should be chosen.

The submission by Norton Healthcare[281] used a cost–consequence approach, using a retrospective observational database to look at resource usage between patients who had changed to their product (Easi-Breathe) and patients who had changed to pMDIs. The resulting data showed that there were significantly fewer GP consultations for 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 owing to Easi-Breathe treatment, however these were not quantified to provide a cost-effectiveness ratio.

The submission by GlaxoSmithKline[282] argued that, although no evidence was found to prove that the inhaler devices were significantly different, this did not mean that they were necessarily equivalent because 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 is that the devices are equivalent, then a cost-minimisation approach should be taken.

### Review of the economic analysis presented in submission 1[283]

- company name: 3M
- number of products detailed in the submission: two.

Product 1:

- name: Autohaler
- device type: breath-actuated pMDI
- drugs delivered: salbutamol (HFA and CFC), beclometasone dipropionate (HFA and CFC)
- comparators for economic analyses: pMDIs and DPIs.

Product 2:

- name: AeroChamber®
- device type: medium-volume spacer
- compatible with: all pMDIs
- comparator for economic analyses: other spacers.

Appraisal of economic analysis:

- analytical approach taken: cost-minimisation
- time horizon: 1 year
- discounting: none taken
- source for drug and device costs: *British National Formulary* (BNF) March 2001[284] or *Monthly Index of Medical Specialities* (MIMS) June 2001.[285]

### *Product 1 (Autohaler)*

**Assumptions made**

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

**Submission conclusion**

pMDIs are the cheapest device based on acquisition cost but, when patients are unable to adhere to the pMDI technique, Autohaler devices are the next cheapest option.

**Budgetary impact model presented**

A typical district of 500,000 people was used as the population base. If all patients were prescribed pMDIs (a relatively inexpensive device) then the estimated inhaler cost would be £919,000. This figure would be £1,477,000 if all patients used Diskhalers. The figure would be £1,065,000 if all patients were to be prescribed Autohalers. Scaling these data to the population of England and Wales, the figures are £96 million, £154 million and £112 million 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 microgram and then multiplied to calculate the daily cost. This presents a problem when the daily requirement is 400 µg per day and a puff contains 250 µg. Clearly, two puffs would be needed, not 1.6 as has been calculated.

Nevertheless, 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 aged under 12 years, and that the AeroBec® Autohaler is more expensive than a number of competitor devices.

The impact of the equivalence assumptions made with regard 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 to England and Wales.

**Reviewer comment**

The mathematics behind the calculations appear to be robust.

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

## Review of the economic analysis presented in submission 2[286]

- company name: Aventis
- number of products detailed in the submission: three.

Product 1:

- name: Fisonair®
- device type: large-volume spacer
- compatible with: Intal® pMDI (sodium cromoglicate)
- comparator for economic analyses: Intal pMDI.

Product 2:

- name: Syncroner®
- device type: pMDI with an integral open tube spacer.
- drug delivered: Intal (sodium cromoglicate) or Tilade® (nedocromil sodium)
- comparator for economic analyses: Intal pMDI or Tilade pMDI.

Product 3:

- name: Spinhaler
- device type: DPI
- drug delivered: Intal (sodium cromoglicate)
- comparator for economic analyses: Intal pMDI.

Appraisal of economic analysis:

- 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[284] or MIMS June 2001.[285]

### *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 one GP consultation, or indeed one GP consultation per two patients, becoming cost saving are correct. However, no evidence has been presented that GP consultations are reduced by the use of a Fisonair device.

The impact of the equivalence assumptions made with regard 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 (i.e. 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 the Tilade Syncroner and the 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 with the comparative pMDIs.

**Budgetary impact model presented**
None.

**Reviewer comment**
The cost difference between the Intal pMDI and the 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 regard 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**
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 regard to the QALY improvement necessary for the device to be cost-effective has been explored in the model presented by the review team.

## Review of the economic analysis presented in submission 3

There is no submission 3.

## Review of the economic analysis presented in submission 4[287]

- company name: Celltech
- number of products detailed in the submission: one.

Product 1:

- name: Clickhaler
- device type: DPI
- drug delivered: salbutamol or beclometasone dipropionate
- comparator for economic analyses: other DPIs.

Appraisal of economic analysis:

- analytical approach taken: cost-minimisation
- time horizon: 1 year
- discounting: none taken
- source for drug and device costs: MIMS March 2000.[288]

### *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**

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 £14 million in 1999. Up to a further £39 million could have been saved were all patients on beclometasone dipropionate, fluticasone or budesonide switched to a Clickhaler delivering beclometasone dipropionate.

**Reviewer comment**

The focus on HFA-only devices means that some types with HFA licences pending, such as Easi-Breathe, 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 were over 1 year old compared with the costs used in the other submissions and the review team model.

## Review of the economic analysis presented in submission 5[282]

- company name: GlaxoSmithKline
- number of products detailed in the submission: six.

Product 1:

- name: inhaler
- device type: pMDI (CFC)
- drugs delivered: beclometasone dipropionate, salmeterol dipropionate, beclometasone + salbutamol
- comparator for economic analyses: none.

Product 2:

- name: Evohaler®
- device type: pMDI (HFA)
- drugs delivered: salbutamol, fluticasone propionate, fluticasone propionate + salmeterol
- comparator for economic analyses: none.

Product 3:

- name: Diskhaler
- device type: DPI
- drugs delivered: beclometasone dipropionate, salmeterol, salbutamol, fluticasone
- comparator for economic analyses: none.

Product 4:

- name: Accuhaler
- device type: DPI
- drugs delivered: salbutamol, fluticasone propionate, salmeterol, fluticasone propionate + salmeterol
- comparator for economic analyses: none.

Product 5:

- name: Rotahaler
- device type: DPI
- drugs delivered: beclometasone dipropionate, beclometasone dipropionate + 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.

Appraisal of economic analysis:

- analytical approach taken: budgetary impact model only
- time horizon: 1 year
- discounting: none taken
- source for drug and device costs: BNF March 2001[284] or MIMS June 2001.[285]

GlaxoSmithKline did not undertake 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 £0.33 million 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 £0.43 million 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 £1.3 million 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 inhaler types are equivalent. The model produced by the review team allows some indication of the QALY gains needed for more expensive inhaler devices to be cost-effective compared with cheaper devices. However, if a pragmatic consensus was that the devices were equivalent, then a cost-minimisation approach should be taken.

## Review of the economic analysis presented in submission 6[281] and supplementary requested information[289]

- company name: Norton Healthcare
- number of products detailed in the submission: one.

Product 1:

- name: Easi-Breathe
- device type: breath-actuated inhaler
- drug delivered: salbutamol or beclometasone dipropionate
- comparator for economic analyses: pMDIs.

Appraisal of economic analysis:

- analytical approach taken: cost consequence
- time horizon: 5 years
- discounting: none taken
- source for drug and device costs: MIMS June 2001.[285]

### *Product 1 (Easi-Breathe)*

**Assumptions made**
The retrospective observational data from the Asthma Resource Use Study were 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, made up of reduced GP consultations for asthma-related illnesses. In a 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, $\beta_2$–agonists, oral steroids, antibiotics and GP consultations gave results that showed Easi-Breathe to be cheaper on 99.11% occasions compared with a pMDI.

**Budgetary impact model presented**
If all patients using a beclometasone or salbutamol pMDI were switched to Easi-Breathe, an extra device cost of £2.17 million per annum would be expected for an estimated 674,000 users. It was postulated that these patients would accrue a saving of £13.94 million per annum, resulting in a net saving of £11.77 million per annum. An analysis phasing in Easi-Breathe by 20% of pMDI use over the forthcoming 5 years was also presented.

**Reviewer comment**
This is 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-Link database (DIN-Link). DIN-Link is a large longitudinal database from 100 practices, equating with approximately 360 geographically representative GPs and 900,000 patients.

These cohorts were divided into a group of patients in whom all asthma medication (beclometasone dipropionate and salbutamol) was given via a pMDI and a second group in whom such medication was delivered by Easi-Breathe. Each group was then subdivided into whether patients were existing medication users or new sufferers. It appears that only the results for existing patients were presented in the submission.

It is shown that the baseline dose of beclometasone dipropionate was higher for the group on Easi-

Breathe than for those using a 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 of the patients using Easi-Breathe may be more conducive to better adherence rates than those using a pMDI. The reported reduction in combined resource usage may be accounted for more by the variation in adherence rates than by the different inhaler devices used. The extent of this bias was examined using the ACORN (A Classification Of Residential Neighbourhoods) socio-economic groups developed by CACI Limited,[290] presented by the sponsor.[289] There are six categories, with the last one divided into five groups: (1) older people, less prosperous areas; (2) council estate residents, better-off homes; (3) council estate residents, high unemployment; (4) council estate residents, greatest hardship; and (5) 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 using Easi-Breathe in the higher socio-economic groups, but it could be a factor were deprivation (i.e. category F) to influence device usage, while those in categories A–E could use a device correctly. Anecdotal evidence (Everard M, Sheffield Children's Hospital NHS Trust, Sheffield: personal communication, 2001) and evidence from the current review contained in the discussion of results in chapter 2 suggest that this may be a factor.

After further analysis[289] it was shown that patients who had remained either on a pMDI device or on the 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 the asthma.

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

Thus, 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 that were individually significant ($\beta_2$-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 patients on a beclometasone dipropionate or salbutamol pMDI switched to Easi-Breathe, to £6.28m per annum.

The sensitivity analysis presented needed further explanation. There was 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 upper distributions of both 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 industry submission (£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 of the submission 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 could be taken as valid only under the conditions of the study (i.e. patients who switch to a pMDI or switch to Easi-Breathe) 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.

## Review of the economic analysis presented in submission 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.)

## Review of the economic analysis presented in submission 8[35]

- company name: AstraZeneca
- number of products detailed in the submission: one.

Product 1:

- name: Turbohaler
- device type: DPI
- drugs delivered: budesonide, terbutaline sulphate, eformoterol fumarate, budesonide + eformoterol fumarate
- comparator for economic analysis: none.

Appraisal of economic analysis:

- analytical approach taken: no quantified analysis
- time horizon: none
- discounting: none taken
- source for drug and device costs: MIMS June 2001.[285]

### *Product 1 (Turbohaler)*

**Submission conclusion**

Turbohaler significantly reduces hospitalisation compared with a pMDI.

Budesonide Turbohaler reduces hospitalisation and increases the number of symptom-free days.

Eformoterol fumarate Turbohaler increases the number of symptom-free days.

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

**Budgetary impact model presented**

No quantitative data were presented. 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 could 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 owing to better compliance, together with the review team model, allows a more informed decision to be made on device selection.

## Review of the economic analysis presented in submission 9

There is no submission 9.

## Review of the economic analysis presented in submission 10[291]

- company name: Trinity Pharmaceuticals
- number of products detailed in the submission: three.

Product 1:

- name: Pulvinal
- device type: DPI
- drugs delivered: beclometasone dipropionate and salbutamol
- comparators for economic analyses: other DPIs.

Product 2:

- name: inhaler
- device type: pMDI
- drugs delivered: ipratropium bromide, ipratropium bromide + fenoterol hydrobromide
- comparators for economic analyses: none.

Product 3:

- name: Autohaler
- device type: breath-actuated inhaler
- drugs delivered: ipratropium bromide, ipratropium bromide + fenoterol hydrobromide
- comparators for economic analyses: none.

Appraisal of economic analysis – Product 1:

- analytical approach taken: cost-minimisation
- time horizon: 1 year
- discounting: none taken
- source for drug and device costs: MIMS January 2001.[292]

Appraisal of economic analysis – Products 2 and 3:

- analytical approach taken: none
- time horizon: none
- discounting: none taken
- source for drug and device costs: MIMS April 2001.[293]

#### *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 beclometasone dipropionate and between £4.56 and £19.96 per patient per annum on salbutamol.

**Budgetary impact model presented**
None, except individual patient data.

**Reviewer comment**
The Pulvinal device has recently been licensed in the UK, but the submission predicted its launch, so it is noted that the price quoted is a projected price only.

#### *Products 2 and 3 (pMDI and Accuhaler)*

**Submission conclusion**
The *Drug and Therapeutics Bulletin*[22] recommendations for ages 6–12 years are also applicable for the age group 5–15 years.

**Budgetary impact model presented**
None, except individual patient data.

**Reviewer comment**
No additional calculations have been conducted.

## Review group model

### Methodology

Little evidence has been presented showing that the clinical outcomes are different between inhaler devices. The review group has therefore 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) because it gives an indication of a patient's health in the LYG to be considered, allowing distinctions to be made between those enjoying full health and those who are severely disabled. In this subject area there are very few 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 that any treatment can improve this rate. Explicit cost per QALY values have therefore not been calculated. The QALY threshold approach allows calculation of the marginal gain in QALYs needed for a more expensive device to be purchased.

For both methodologies, all unit costs have been taken from the BNF 41 March 2001[284] and MIMS May 2001.[294] These have been multiplied by the appropriate daily doses and are comparable with the prices in the submissions.[35,261,281–283,286,287,291] For devices that can be refilled, it has been assumed that two 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 two spacers per annum are required. It has also been assumed that the spacers will be used without a mask and, further, that, where a pMDI manufacturer does not also manufacture a spacer, a spacer made by a company that 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 £5000, 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 that patient's quality of life. If the estimations of the marginal QALYs were above the threshold values presented for device A in *Tables 27–38* in appendix 18, then that device should be purchased at the relevant cost per QALY threshold. Alternative sources of increased QALYs may occur by reducing the deposit of drug in the oropharynx or by the patient 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 of the drug prescribed. The analysis has therefore focused 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.

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

The exception is for Easi-Breathe products that deliver beclometasone dipropionate and salbutamol, for which the Norton Healthcare submission has provided some evidence that resources can be saved. Beclometasone dipropionate Easi-Breathe devices have therefore been modelled twice, once at their 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 this submission were due to the beclometasone dipropionate device solely, not to the salbutamol device. It is stressed that the cost offset attributed to the Easi-Breathe device is valid only 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 the patients studied.

## Results

Sample results are presented in *Tables 27–38* 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 beclometasone dipropionate device, the second device could be selected if the cost offset was not to be believed.

Although not presented, the results for terbutaline sulphate, reproterol hydrochloride, nedocromil sodium, beclometasone dipropionate + salbutamol, fluticasone propionate + salmeterol, ipratropium bromide + salbutamol, ipratropium bromide + fenoterol hydrobromide, salmeterol, eformoterol fumarate, and ipratropium bromide are similar to those presented in *Tables 27–30* in appendix 18.

The results presented are for relatively low dosage levels. *Tables 31* and *32* assume that a high dose of beclometasone dipropionate is given.

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

For *Tables 27, 28, 33–38*, the cheapest devices are those at the top of the vertical column. For example, in *Table 27*, the cheapest devices are Maxivent at £3.14 per annum, and Asmaven at the same price.

For beclometasone (*Tables 29–32*), the issue is not so clear, owing to evidence of resource savings presented by Norton Healthcare. Using acquisition prices alone, the cheapest devices are Qvar (50), Qvar Autohaler (50) and Filair (100), at £28.73 per annum. If, however, resource savings are produced by the use of Beclazone Easi-Breathe (100) that effectively price it at £10 less than the cheapest alternative device, Easi-Breathe would be the cheapest at £18.73.

Owing to uncertainty concerning the validity of the resource savings results, Beclazone Easi-Breathe has been included in *Tables 29–32* at both £18.73 and its true acquisition price of £30.08.

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

It is assumed that a daily dose of 200 µg of beclometasone dipropionate (100 µg for Qvar as per manufacturer's dosage levels) is required. (*Table 29* 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 £5000 cost per QALY level.

As an example, Filair® 100 would cost £28.73 per annum to provide the dose, assuming two puffs daily of 100 µg 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 £5000, 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 100 row, moving rightwards until the Filair 100 + AeroChamber column is reached.

Thus, were it believed that the additional AeroChamber produced more QALYs than this figure, it would be deemed cost-effective at the £5000 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. Beclazone 100 μg and 200 μg) 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 sometimes occurs in clinical practice (*Tables 31* and *32*).

## Calculating QALY threshold results

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

(device cost A – device cost B)/cost per QALY threshold selected

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

## Further research

The trial size needed to detect a QALY difference of 0.00807 at a 95% significance level and 80% power, assuming a general population QALY standard deviation of 0.1[295–297] has been calculated.

The approximate number needed can be calculated using the following formula:[298]

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

Substituting in the numbers from the example:

16/[0.00807/0.1]$^2$

which equals just under 2500 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 29* in appendix 18 that the largest QALY needed, assuming no Easi-Breathe cost offsets, for a cost per QALY ratio of £5000 at the 200 μg of beclometasone dipropionate dose per day is 0.01007. (This equates to an additional 88 hours of perfect health per annum.) It is clear that, with the small QALY increase required, no intervention can be categorically dismissed as not being cost-effective. Using a cost per QALY threshold of £20,000, the largest incremental QALY gain needed, assuming no Easi-Breathe cost offset, is 0.00202 (*Table 30* in appendix 18); many QALY increments required less than 0.001. (This latter figure is equivalent to less than 9 hours of perfect health per annum.)

It is noted that the maximum incremental QALYs needed for different devices delivering salbutamol (*Tables 27* and *28* in appendix 18) and budesonide, fluticasone and cromoglicate (*Tables 33–38* in appendix 18) have the same order of magnitude as the results for low-dose beclometasone (*Tables 29* and *30* in appendix 18).

To put such QALY increments into perspective, suffering a wrist fracture has a QALY loss of 0.01,[299] and suffering a vertebral fracture has a QALY loss of 0.092.[300]

It is stressed that these tables assume clinical equivalence. Were a device to prevent a hospitalisation when compared with another device delivering the same medication, due, for example, to a patient's reluctance to use a device, the cost-effectiveness would be significantly altered. The cost of an average hospitalisation for a patient aged over 5 years was calculated to be £857 per patient per stay at 1996 prices,[301] which is far in excess of the marginal costs presented. However, no submission, with the exception of that of Norton Healthcare, made any claim for a reduction in resources used according to 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. In cases where the patient and the clinician believe that 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.

# Chapter 4

## Implications for other parties

No implications for other parties were identified.

# Chapter 5

## Factors relevant to the NHS

With respect to CFC and HFA propellants, although, for a number of products, we are in the transition phase at present, with dual availability of both CFC and CFC-free versions of the same product, 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 in respiratory outcomes between the old CFC and new HFA devices delivering equivalent therapeutic doses of either reliever or anti-inflammatory asthma medication. The enforced change, although 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.

# Chapter 6

# 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 chronic asthma. There is some evidence to support an additional benefit of using a spacer with a pMDI rather than a 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 are sparse. It would appear that the choice of an inhaler device does not represent a barrier to effective use in children over 5 years of age if adequate instruction and supervision are provided.

In terms of cost-effectiveness, the largest QALY needed at a dose of 200 μg of beclometasone dipropionate per day was calculated to be 0.00807, 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 research, using double-blind randomised studies with adequate power are needed, together with participants representing the full profile of the condition, from the mild to moderate to those at the severe end of the disease spectrum. Such studies also need a qualitative component to try to understand the factors that underlie children's relationships with their condition and the 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.

# Chapter 7
# Conclusions

Only one submission[281] provided data supporting 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 one specific device compared with another.

The yearly costs of each device and drug type were calculated. Assuming cost per QALY threshold levels of £5000 or £20,000, it was seen that the marginal QALYs needed to be deemed cost-effective were very small.

No device type could be categorically rated as not cost-effective. *Tables 27–38* in appendix 18 provide indications of the marginal QALYs needed when comparing between devices.

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

# Chapter 8

## Budgetary impact modelling

The authors of this report conclude that none of the products considered could be deemed categorically not cost-effective. The QALY gains (from potential sources such as improved chronic quality of life or reduced side-effects) required to make a more expensive inhaler device cost-effective are very small. Given that no clear recommendations could be given on which inhaler device should be used it was deemed inappropriate to conduct a budgetary impact analysis.

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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 Beverley 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.

All responsibility for the content of this review remains with the authors.

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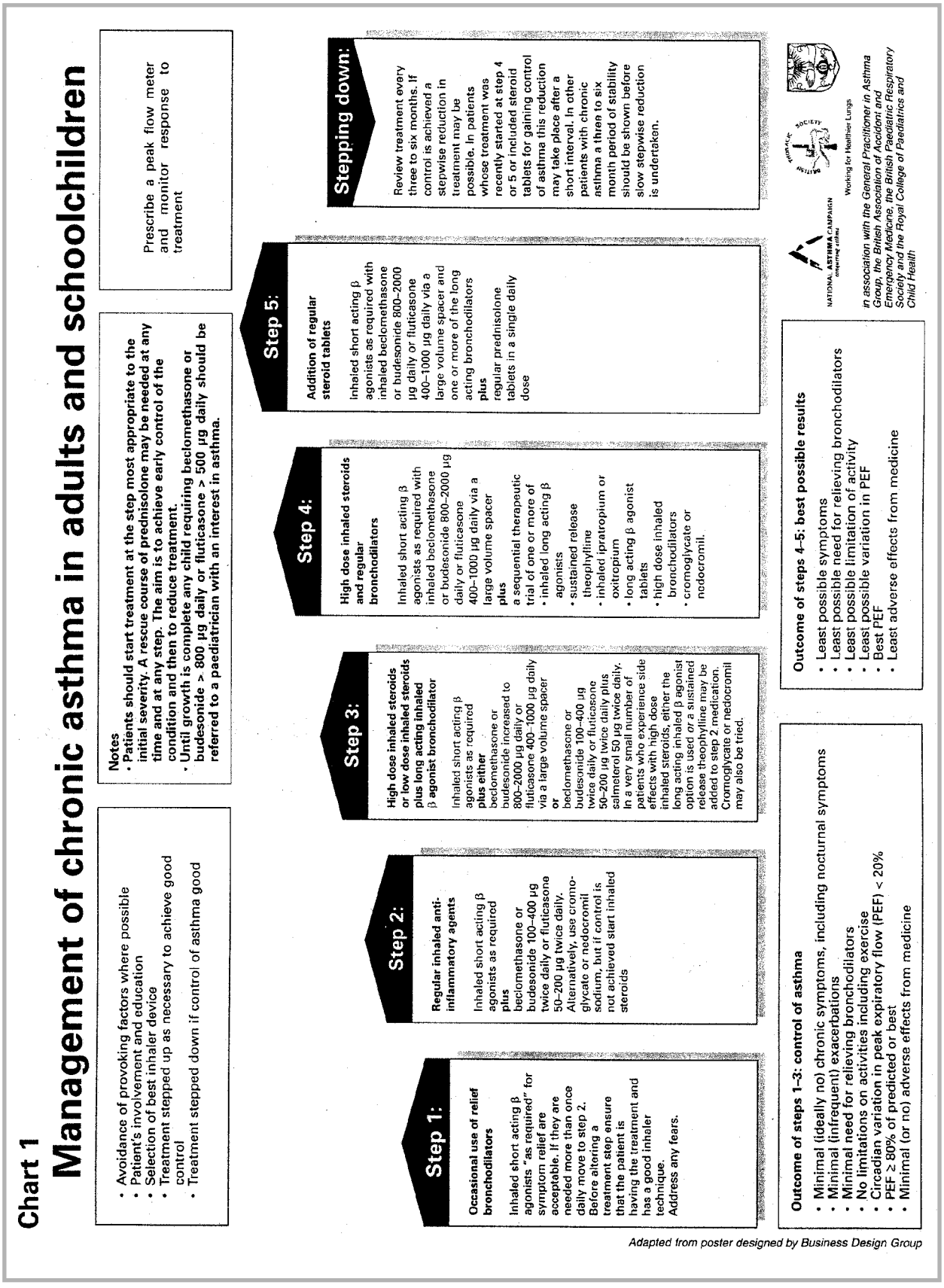
# Appendix 1

## Management of chronic asthma in adults and schoolchildren

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# Appendix 2

## Electronic bibliographic databases searched

Best Evidence
Biological Abstracts
CCTR (Cochrane Controlled Trials Register)
CDSR (Cochrane Database of Systematic Reviews)
EMBASE
HEED
HMIC (Health Information Management Consortium – comprising DH-Data, the King's Fund Database, and HELMIS)
MEDLINE
NHS DARE
NHS EED
NHS HTA
PsycINFO
PubMed (previous 90 days)
Science Citation Index
Social Sciences Citation Index

# Appendix 3

## Other sources searched

ABPI (Association of the British Pharmaceutical Industry)
AHRQ (Agency for Healthcare Research and Quality)
Alberta Clinical Guidelines Programme
American Thoracic Society
ARIF (Aggressive Research Intelligence Facility)
Bandolier
British Thoracic Society
CCOHTA (Canadian Co-ordinating Centre for Health Technology Assessment)
CCT (Current Controlled Trials)
CenterWatch Trials Register
Centre for Clinical Effectiveness, Monash University
Centre for Health Economics, University of York
ClinicalTrials.gov, National Institutes of Health Clinical Trials Database
CRiB (Current Research in Britain)
eMC (Electronic Medicines Compendium)
EMEA (European Agency for the Evaluation of Medicinal Products)
eGuidelines
HSTAT (Health Services/Technology Assessment Text, US National Library of Medicine)
INAHTA (International Network of Agencies for Health Technology Assessment) Clearinghouse
MCA (Medicines Control Agency)
MRC (Medical Research Council) Funded Projects Database
National Guideline Clearinghouse
National Heart, Lung and Blood Institute
National Research Register
NCCHTA (National Co-ordinating Centre for Health Technology Assessment)
NHS CRD (Centre for Reviews and Dissemination), University of York
NHS R&D Programmes
NIH (National Institutes of Health) Consensus Development Program
North of England Guidelines, University of Newcastle
OMNI (Organising Medical Networked Information)
ReFeR (Research Findings Register)
SBU (Swedish Council for Health Technology Assessment)
ScHARR (School of Health and Related Research) Library Catalogue
SIGN (Scottish Intercollegiate Guidelines Network)
SumSearch
Trent Working Group on Acute Purchasing
TRIP (Turning Research into Practice) Database
Health Evidence Bulletins, Wales
Wessex DEC (Development and Evaluation Committee) Reports
West Midlands DES (Development and Evaluation Services) Reports

# Appendix 4

## Search strategies used

### Best Evidence (Ovid Biomed 1991 – April 2001)

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

### Biological Abstracts (SilverPlatter WebSPIRS 1985 – May 2001)

#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 spacer*)
#1 asthma*

### CDSR and CCTR (The Cochrane Library 2001 Issue 2)

#1 asthma*:me
#2 asthma*
#3 #1 or #2
#4 administration-inhalation*:me
#5 nebulizers-and vaporizers*:me
#6 aerosols*:me
#7 aerosol*
#8 inhaler*
#9 nebuliz*
#10 nebulis*
#11 meter* near dose*
#12 mdi or mdis
#13 pmdi*
#14 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
#15 child*:me
#16 #3 and #14
#17 #16 and #15

### CINAHL (Ovid Biomed 1982 – May 2001)

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 or/15–21
23 14 and 22

## Citation Indexes (Science and Social Sciences) (Web of Science 1981 – April 2001)

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 – May 2001)

#37 #23 or #30 or #34 or #36
#36 #22 and #35
#35 spacer* or holding chamber* or aerochamber or babyhaler or haleraid or nebuhaler
#34 #22 and #33
#33 #31 or #32
#32 integra or fisonair or nebuhaler or aeroscopic or syncroner or nebuchamber or volumatic or rotahaler or spinhaler or turbuhaler or diskus or sidestream or ventstream or lc plus or lc star or halo lite or aerobec or aerolizer or pari baby
#31 maxivent or spacehaler or asmaven or salamol or autohaler or airomir or salbulin or easibreathe or easi-breathe or evohaler or ventolin or bricanyl or berotec or bronchodil or serevent or alupent or atrovent or oxivent or combivent or duovent or beclazone or filair or becotide or becloforte or qvar or pulmicort or flixotide or ventide or seretide or cromogen or intal or tilade or aerocrom or aerobec or asmasal or clickhaler or ventodisk* or diskhaler or Rotahaler or turbohaler or foradil or aerocap* or asmabec or rotacap* or accuhaler or steri-nab or ipratropium or respontin
#30 #22 and #29
#29 #24 or #25 or #26 or #27 or #28
#28 inhal* suspen*
#27 powder inhal*
#26 pmdi* in ti, ab
#25 (mdi or mdis) in ti, ab
#24 meter* dose*
#23 #22 and #13
#22 #3 and #21
#21 #14 or #15 or #16 or #17 or #18 or #19 or #20
#20 pediat*
#19 paediat*
#18 teenager*
#17 adolescent*
#16 infant*
#15 child*
#14 explode 'child-' / all subheadings
#13 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
#12 nebulis*
#11 nebuliz*
#10 powder*
#9 aerosol*
#8 explode 'nebulizer-' / all subheadings
#7 'aerosol-' / all subheadings
#6 'inhalational-drug-administration' / all subheadings
#5 'inhalation-' / all subheadings
#4 explode 'inhaler-' / all subheadings
#3 #1 or #2
#2 asthma* in ti, ab
#1 explode 'asthma-' / all subheadings

## HEED (OHE HEED CD-ROM – complete database)

### Search terms

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

### Fields searched

- Abstract
- All data
- Article title
- Book title
- Keywords
- Technology assessed

## HMIC (SilverPlatter WinSPIRS 1983 – May 2001)

#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 – May 2001)

1 exp asthma/
2 asthma$.tw
3 or/1–2
4 administration, inhalation/
5 "nebulizers and vaporizers"/
6 exp aerosols/
7 is.fs
8 aerosols.rw
9 powders.rw
10 nebuliz$.tw
11 nebulis$.tw
12 or/4–11
13 3 and 12
14 meter$ dose$.tw
15 (mdi or mdis).tw
16 pmdi$.tw
17 powder inhal$.tw
18 inhal$ suspens$.tw
19 or/14–18
20 3 and 19
21 maxivent.af
22 spacehaler.af
23 asmaven.af
24 salamol.af
25 autohaler.af
26 airomir.af
27 salbulin.af
28 easibreathe.af
29 easi-breathe.af
30 evohaler.af
31 ventolin.af
32 bricanyl.af
33 berotec.af
34 bronchodil.af
35 serevent.af
36 alupent.af
37 atrovent.af
38 oxivent.af
39 combivent.af
40 douvent.af
41 beclazone.af
42 filair.af
43 becotide.af
44 becloforte.af
45 qvar.af
46 pulmicort.af
47 flixotide.af
48 ventide.af
49 seretide.af
50 cromogen.af
51 intal.af
52 tilade.af
53 aerocrom.af
54 aerobec.af
55 asmasal.af
56 clickhaler.af
57 ventodisk$.af
58 diskhaler.af
59 Rotahaler.af
60 turbohaler.af
61 foradil.af
62 aerocap$.af
63 asmabec.af
64 rotacap$.af
65 accuhaler.af
66 steri-nab.af
67 ipratropium.af
68 respontin.af
69 or/21–68
70 3 and 69
71 integra.af
72 fisonair.af
73 nebuhaler.af
74 aeroscopic.af
75 syncroner.af
76 nebuchamber.af
77 volumatic.af
78 rotahaler.af
79 spinhaler.af
80 turbuhaler.af
81 diskus.af
82 sidestream.af
83 ventstream.af
84 lc plus.af
85 lc star.af
86 halo lite.af
87 aerobec.af
88 aerolizer.af
89 pari baby.af
90 or/71–89
91 3 and 90
92 spacer$.tw
93 holding chamber$.tw
94 aerochamber.tw

95 babyhaler.af
96 haleraid.af
97 nebuhaler.af
98 or/92–97
99 3 and 98
100 13 or 20 or 70 or 91 or 99
101 exp child/
102 child$.tw
103 infant$.tw
104 adolescent$.tw
105 teenager$.tw
106 paediat$.tw
107 pediat$.tw
108 or/101–107
109 100 and 108

## PsycINFO (SilverPlatter WebSPIRS 1967 – May 2001)

#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 May 2001)

#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 – July 2001)

### EMBASE (SilverPlatter WebSPIRS 2000 – July 2001)

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

### MEDLINE (Ovid Biomed 2000 – July 2001)

1 in vitro.af
2 exp asthma/
3 asthma$.tw
4 or/2–3
5 clinical trial.pt
6 4 and 5
7 limit 7 to yr=2000–2001

## Methodological search filters used in Ovid MEDLINE

### Guidelines

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

### Systematic reviews

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

### Randomized controlled trials

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

### Economic evaluations

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

### Unwanted effects

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

### Patient preference/compliance

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

### Quality of life (asthma)

1 exp quality of life/
2 quality of life.tw
3 life quality.tw
4 qaly$.tw
5 quality adjusted life year$.tw
6 (sf36 or sf 36 or short form 36).tw
7 (eq5d or eq 5d or euroqol).tw
8 asthma self-efficacy scale.tw
9 juniper.tw
10 asthma quality of life questionnaire.tw
11 aqlq.tw
12 living with asthma questionnaire.tw
13 asthma bother profile.tw
14 asthma symptom checklist.tw
15 childhood asthma questionnaire.tw
16 paediatric asthma quality of life questionnaire.tw
17 child asthma short form.tw
18 children$ health survey for asthma.tw
19 about my asthma.tw
20 or/1–19

# Appendix 5

## Excluded studies

| Study | Reason for exclusion |
|---|---|
| Agertoft and Pedersen, 1994[49] | Patients aged <5 years |
| Agertoft and Pedersen, 1998[50] | Inhaler technique training intervention |
| Ahonen *et al.*, 2000[51] | Some included articles in abstract form only |
| Ahrens *et al.*, 1995[52] | *In vitro*, wrong research question |
| Anhoj *et al.*, 2000[53] | Inappropriate study design |
| Argenti *et al.*, 2000[54] | Patients aged >15 years |
| Ayres *et al.*, 2000[55] | Patients aged >15 years |
| Barry and O'Callaghan, 1994[56] | *In vitro*, but wrong research question |
| Barry and O'Callaghan, 1996[57] | *In-vitro* drug delivery from 7 spacers – not in the criteria |
| Barry and O'Callaghan, 1997[58] | *In-vitro* drug delivery and spacer – not in the criteria |
| Barry and O'Callaghan, 1999[59] | *In vitro*, spacer devices – not in the criteria |
| Baumgarten *et al.*, 2000[60] | Patients aged >15 years |
| Berg *et al.*, 1998[63] | Patients aged >15 years |
| Bisgaard *et al.*, 1994[65] | No comparison device |
| Bisgaard *et al.*, 1998[66] | Different drugs used |
| Bloomfield *et al.*, 1979[67] | Patients aged >15 years |
| Boccuti *et al.*, 1996[68] | Assessment of technique |
| Boccuzzi *et al.*, 2000[69] | Cohort study |
| Böllert *et al.*, 1997[70] | Adults |
| Borgström *et al.*, 1996[71] | Patients aged >15 years |
| Bourne, 1996[72] | Not available from the British Library |
| Bousquet *et al.*, 2000[73] | Drug intervention |
| Brand *et al.*, 2001[74] | Patients aged <5 years |
| Brannan *et al.*, 1998[64] | *In vitro*, spacer and pMDI – not in the criteria |
| Burgess, 1993[75] | Abstract only |
| Busse *et al.*, 1999[76] | Patients aged >15 years |
| Cavagni *et al.*, 1993[77] | Spacer device (Jet disposable – Chiesi Farmaceutici SpA, Parma, Italy) not in criteria |
| Chan and DeBruyne, 2000[78] | Study population was parents |
| Chang *et al.*, 2000[79] | Asthma management |
| [a]Chapman and Brubaker, 1993[80] | Patients aged >15 year |
| Chapman, 1995[81] | Review |
| Chhabra, 1987[29] | Drug intervention |
| Chipps *et al.*, 1992[82] | Inappropriate study design |
| Chuffart *et al.*, 2001[83] | *In vitro*, spacers – not in the criteria |
| Clark and Lipworth, 1996[84] | Healthy volunteers |
| Conroy *et al.*, 2000[85] | Drug intervention |
| Corris, 1992[86] | Drug intervention |
| Crompton, 1982[272] | |
| Cunningham and Crain, 1994[87] | Patients with episodic emergency department visits for acute asthma attack |
| Dahl *et al.*, 1997[88] | Patients aged >15 years |
| Davies *et al.*, 1998[89] | Patients aged >15 years |
| Dawson *et al.*, 1985[90] | Different drug doses |
| de Benedictus *et al.*, 1994[62] | Drug intervention |
| Deenstra *et al.*, 1988[91] | Adults |
| Demedts *et al.*, 1999[92] | Patients mostly >15 years |
| [a]Diggory *et al.*, 1991[93] | Patients aged >15 years |
| Dinh Xuan *et al.*, 1989[198] | Drug not device |

| | |
|---|---|
| Dubus and Dolvich, 2000[94] | *In vitro*, wrong research question |
| Emeryk *et al.*, 1999[95] | Abstract only |
| Engel *et al.*, 1990[96] | Patients aged >15 years |
| Everard *et al.*, 1992[97] | *In vitro*, spacers – not in the criteria |
| Finlay and Zuberbuhler, 1998[98] | Patients aged <5 years |
| Finlay and Zuberbuhler, 1999[99] | Patients aged <5 years |
| Fuller, 1986[100] | Adults |
| Geoffroy *et al.*, 1999[101] | Patients aged >15 years |
| Giannini *et al.*, 2000[102] | Patients aged >15 years |
| Gillies, 1997[103] | Discussion article |
| Goh *et al.*, 1998[104] | Survey of CFC awareness |
| Goldberg *et al.*, 1996[105] | Inappropriate study design |
| Gross *et al.*, 1999[107] | Patients aged >15 years |
| [a]Grossman *et al.*, 1997[108] | Patients aged >15 years |
| Gunawardena *et al.*, 1997[109] | Adults |
| Gurwitz *et al.*, 1983[110] | Non-randomised controlled trial, acute and chronic asthma |
| Haahtela *et al.*, 1994[111] | Adults |
| [a]Hampson and Mueller, 1994[112] | Non-asthmatic participants |
| Haughney, 1995[113] | Discussion article |
| [a]Hendry *et al.*, 1995[114] | Patients aged >15 years |
| Hidinger and Dorow, 1984[115] | Adults |
| Hilton, 1990[116] | Study on technique |
| Jacobson *et al.*, 1999[118] | Patients aged >15 years |
| Jones *et al.*, 1992[119] | Asthma morbidity in primary care |
| Juntunen-Backman *et al.*, 1996[120] | Abstract only |
| Kassirer, 1994[121] | Editorial |
| [a]Kelloway and Wyatt, 1997[122] | Wrong age group |
| LaForce *et al.*, 1993[123] | Healthy volunteers |
| Langaker and Hidinger, 1982[124] | Patients aged >15 years |
| [a]Langley 1999[125] | Wrong age group |
| Laurikainen *et al.*, 1997[126] | Adults |
| Lees, 1988[127] | Drug device combination no longer available |
| [a]Lenney *et al.*, 2000[128] | Patients aged >15 years |
| Liam and Lim, 1998[129] | Included children with acute asthma |
| Liljas *et al.*, 1997[130] | Patients aged >15 years |
| Lipworth and Clark, 1997[131] | Healthy volunteers |
| Lipworth and Clark, 1997[132] | Abstract only |
| Lipworth *et al.*, 1998[133] | Drugs |
| Löfdahl *et al.*, 1994[134] | Abstract only |
| Magnussen, 2000[135] | Patients aged >15 years |
| Mahadewsingh *et al.*, 1996[136] | Adults |
| Mash *et al.*, 2002[137] | Patients aged >15 years |
| Mawhinney *et al.*, 1991[138] | Patients aged >15 years |
| Milanowski *et al.*, 1999[139] | Adult patients, comparing different drug doses |
| Mitchell and Nagel, 1997[140] | *In-vitro* testing of three spacers – not in the criteria |
| Muittari and Ahonen, 1979[141] | Patients aged >15 years |
| Nankani *et al.*, 1990[142] | Drug, not inhaler device intervention |
| Nantel and Newhouse, 1999[38] | No comparison device |
| Nantel *et al.*, 1996[143] | Device unknown, no drug delivered |
| Nelson and Loffert, 1994[144] | Adults |
| Newman *et al.*, 1991[145] | Adults |
| Newman *et al.*, 1982[146] | Patients had chronic obstructive pulmonary disease |
| Newman *et al.*, 1989[147] | Patients aged 21–76 years |
| Nielsen *et al.*, 1998[148] | Not comparing devices |
| O'Gorman *et al.*, 1990[106] | Drug intervention |
| O'Reilly *et al.*, 1986[149] | Adults |
| [a]Oldaeus *et al.*, 1994[150] | Drug intervention |

| | |
|---|---|
| Oliver *et al.*, 1982[151] | Non-randomised controlled trial, cross-over study |
| Pedersen and Hansen, 1990[152] | Abstract only |
| Pedersen and Hansen, 1995[153] | Drug intervention |
| Pedersen and Mortensen, 1990[154] | Non-asthmatic children |
| Pedersen, 1983[155] | Acute asthma |
| Pedersen, 1992[156] | Abstract only |
| Pederson, 1986[157] | No comparison group |
| Pederson *et al.*, 1990[158] | No comparison group |
| Perruchoud *et al.*, 2000[159] | Patients aged >15 years |
| Petrie *et al.*, 1990[160] | Adults only |
| Pierart *et al.*, 1999[161] | *In vitro*, participants were healthy adult volunteers |
| Price and Kemp, 1999[162] | On oral tablet therapy |
| Quezada *et al.*, 1999[163] | Comparing effects of different drugs |
| Quittner *et al.*, 2000[164] | Patients with cystic fibrosis |
| Repper *et al.*, 1994[165] | Drug intervention |
| Rivlin *et al.*, 1983[166] | Study of technique |
| Ruggins *et al.*, 1993[167] | Patients with acute asthma |
| Rutten-van Mölken *et al.*, 1992[168] | Review |
| [a]Rydman *et al.*, 1999[169] | Teaching technique |
| Salat *et al.*, 2000[170] | Patients aged >15 years |
| Samaranayake and Perera, 1998[171] | Acute asthma |
| Santanello *et al.*, 1999[172] | Patients aged >15 years |
| Schecker *et al.*, 1993[173] | Drug not available in UK |
| Schlaeppi *et al.*, 1996[174] | Patients aged >15 years |
| Seale and Harrison, 1998[175] | Patients aged >15 years |
| Shapiro *et al.*, 1998[176] | Different drug doses |
| Smith *et al.*, 1998[177] | Comparing different drugs |
| Solé *et al.*, 1993[178] | Acute asthma |
| Spector, 2000[179] | Review article on oral therapy |
| Ståhl *et al.*, 1996[180] | Drug, not device |
| Stenius-Aarniala *et al.*, 1993[181] | Adults |
| Tal *et al.*, 1996[182] | No comparison group |
| Terzano and Mannino, 1996[183] | *In vitro*, wrong research question |
| Thompson *et al.*, 1998[184] | Patients aged >15 years |
| Thorsson *et al.*, 1994[185] | Patients aged >15 years |
| Tonnel *et al.*, 2000[186] | Patients aged >15 years |
| Turgeon *et al.*, 1996[187] | Training intervention |
| Turpeinen *et al.*, 1999[188] | Patients aged <5 years |
| van Beerendonk *et al.*, 1998[61] | Patients aged >15 years |
| Vidgren *et al.*, 1988[189] | Healthy volunteers |
| Weinstein, 2000[190] | Discussion article |
| Wettengel *et al.*, 1998[191] | Patients aged >15 years |
| Wildhaber *et al.*, 1996[192] | *In vitro*, spacer device – not in the criteria |
| Wildhaber *et al.*, 1998[193] | Inappropriate study design |
| Wildhaber *et al.*, 2000[194] | No comparison group |
| Wildhaber *et al.*, 2000[195] | Patients aged >17 years |
| Wildhaber, *et al.*, 1996[196] | Patients aged <4 years |
| Williams and Richards, 1997[197] | Comparing different drugs and doses (400 μg budesonide vs 200 μg fluticasone propionate) |
| Yuksel and Greenough, 1994[199] | Patients aged <5 years |
| Zainudin *et al.*, 1990[200] | Adults |
| Zar *et al.*, 1999[201] | Acute asthma |
| Zar *et al.*, 1998[202] | Inappropriate study design |

## Foreign language articles – not extracted

Aceves-Vazquez-Guadalupa-De La Luz *et al.,* 1995[203]
Aguilar and Mallol, 2000[204]
Carrion *et al.,* 2000[206]
Chinet, 2000[207]
Dubus *et al.,* 1997[209]
Dubus, 2001[210]
Garcia-Marcos *et al.,* 2001[205]
Garde Garde and Medina Pomares, 1999[211]
Rufin *et al.,* 2000[212]
Sanchez-Jimenez *et al.,* 1998[213]
Vazquez Cordero *et al.,* 1987[208]
[a]Zureik and Delacourt, 1999[214]

[a]Identified from industry submissions

# 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 12*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Kerac *et al.*, 1998[224] | **T1**: MDI<br>**T2**: MDI + spacer (Volumatic)<br>**T3**: MDI + plastic 1-litre soft-drink bottle spacer<br>**T4**: MDI<br><br>**Drug**: Salbutamol (2 puffs) T1, T2, T3<br>Placebo T4<br><br>**Design**: Randomised, double-blind, placebo-controlled<br><br>**Jadad** = 3 | 1 site, Calcutta, India.<br><br>**In**: Chronic stable asthmatic outpatients<br><br>**Out**: None<br><br>**Power calculation**: No<br><br>**PP analysis**: Assumed | **At beginning**: *n* = 48<br><br>**At end**: *n* = 48<br><br>**Age**: 43.8 ± 3.5 (10–75)<br><br>**M/F**: 25/23 | **Run-in**: Salbutamol 4 mg + deriphyllin (bronchodilator) 100 mg taken orally t.d.s., withheld overnight Morning baseline PEFR <80% of predicted for age and height<br><br>**FU**: Patients attended on 4 occasions, each 2 weeks apart. All devices used on each occasion but only one contained active drug<br><br>**Primary**: PEFR measured 15 and 30 minutes after MDI administration | Mean ± SE baseline PEFR, 156.9 ± 8.4. No significant differences among the 4 groups ($p > 0.1$)<br><br>Significant % improvement in PEFR over baseline in T2 and T3 compared with T4, 30 minutes after inhalation, and in T2 vs T4 at 15 minutes after inhalation (both $p < 0.05$)<br><br>No differences between T1 and T4 | Mostly adult patients<br><br>Plastic bottle spacer was as effective as commercial spacer |
| Green and Price, 1991[225] | **T1**: MDI + spacer (Volumatic) and placebo via MDI<br><br>**T2**: MDI and placebo via MDI + spacer<br><br>**T3**: Placebo via both devices<br><br>**Drug**: Salbutamol, 200 μg<br><br>**Design**: Randomised, single-blind (patient), placebo-controlled<br><br>**Jadad** = 1 | 1 site, London, UK<br><br>**In**: Asymptomatic at the time of study, proficient in $FEV_1$ manoeuvres<br><br>**Power calculation**: No<br><br>**PP analysis**: Assumed | **At beginning**: *n* = 10<br><br>**At end**: n = 10<br><br>**Age**: 11 (8–14)<br><br>**M/F**: Not stated | **Run-in**: Stopped medication 24 h before study<br><br>**FU**: 3 occasions, 2–7 days apart and within 14 days<br><br>**Primary**: Baseline $FEV_1$, $FEV_1$ after 15 minutes, $FEV_1$ after a further 15 minutes | No significant difference in baseline $FEV_1$ for the study days ($p > 0.05$)<br><br>From baseline to 15 minutes, standardised $FEV_1$ rose significantly in T1 (mean +8.1%, 95% CI ±4.2%, $p = 0.0005$) and T2 (mean +5.9%, 95% CI ±1.8%, $p = 0.0005$) vs T3 (mean +0.25%, 95% CI ±2.5%, paired *t*-test) | No significant difference in bronchodilation between MDI + spacer and MDI<br><br>Retrospective power calculation, 75 patients needed |

*continued*

***TABLE 12 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr)<br>mean ± SD<br>(range)<br>M/F | Run-in<br>FU<br>Outcomes<br>(primary,<br>secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Lee and Evans, 1987[229] | **T1**: MDI<br>**T2**: MDI + spacer (InspirEase®)<br>**T3**: MDI + spacer (AeroChamber)<br>**T4**: MDI + spacer (aerosol bag)<br><br>**Drug**: Albuterol, 2 puffs, 180 μg<br>All operations were assisted by the examiner to ensure correct use of aids<br><br>**Design**: Randomised, double-blind, cross-over, placebo<br><br>**Jadad** = 3 | 1 centre, New York<br><br>**In**: Stable asthma, correct inhalation technique from a MDI, receiving $\beta_2$-agonist aerosol from MDI<br><br>**Power calculation**: No<br><br>**PP analysis**: Assumed | **At beginning**: *n* =23<br><br>**At end**: *n* = 20<br><br>**Age**: 12.5 (8–15)<br><br>**M/F**: Not stated | **Run-in**: Taught proper use of 3 inhalation aids (InspirEase, AeroChamber, aerosol bag) in laboratory<br><br>**FU**: 3 subsequent days<br><br>**Primary**: Pulmonary function ($FEV_1$) correct MDI technique | 14 children had correct inhalation technique while 6 had errors<br>Incorrect technique: 1 with MDI, 3 with InspirEase, 2 with InspirEase and AeroChamber, 0 for aerosol bag<br><br>Overall and for 14 children with correct technique, no significant differences in $FEV_1$ % increase from baseline over 3 h after inhalation in all treatment groups<br><br>For 6 children with incorrect MDI technique, significant difference ($p < 0.05$) in $FEV_1$ % increase from baseline, over 3 h after inhalation between T2, T3 and T4 compared with T1<br>Also, at 15 and 30 minutes only, T2 and T4 > T3 ($p < 0.05$)<br><br>Side-effects similar for all treatments | No additional benefits from T2, T3 and T4 for those with correct MDI technique, but benefit of spacer with incorrect MDI technique<br><br>AeroChamber requires slightly greater skill in its use than InspirEase and aerosol bag: the latter two aids allow re-breathing of aerosol while AeroChamber does not<br><br>All aids require some skill in use; teaching is important for effective use |

*continued*

***TABLE 12 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr)<br>mean ± SD<br>(range)<br>M/F | Run-in<br>FU<br>Outcomes<br>(primary,<br>secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Rachelefsky *et al.*, 1986[227] | **T1**: MDI placebo<br>**T2**: MDI<br>**T3**: MDI + spacer placebo<br>**T4**: MDI + spacer (AeroChamber)<br><br>**Drug**: T2 and T4 bronchodilator metaproterenol sulphate 130 μg, 2 puffs<br><br>**Design**: Randomised, double-blind, placebo-controlled<br><br>**Jadad** = 2 | 1 site, USA<br><br>**In**: Moderate asthma, fulfilled the American Thoracic Society criteria for reversible airway disease<br><br>**Power calculation**: No<br><br>**PP analysis**: Assumed | **At beginning**: *n* = 16<br><br>**At end**: *n* = 16<br><br>**Age**: 9 ± 2 (5–12)<br><br>**M/F**: Not stated | **Run-in**: Instruction given on proper closed-mouth technique at each visit, including 3-minute videotape viewing<br><br>All bronchodilators were stopped 12 h before and long-acting theophylline 24 h before time of study<br><br>**FU**: 4 separate days<br><br>**Primary**: $FEV_1$, FVC, mid-maximal expiratory volume ($FEF_{25–75\%}$) before, and 5, 14, 30 minutes and hourly for 6 h after drug administration<br><br>**Secondary**: Side-effects | No significant difference between T2 and T4 for $FEV_1$ and $FEF_{25–75\%}$<br><br>Both T2 and T4 significantly different from placebo (T1, T3)*<br><br>**% ± SD increases from baseline after 4 treatments over a 6-h period:**<br><br>**Time** / **$FEV_1$ T2** / **$FEV_1$ T4** / **$FEF_{25–75\%}$ T2** / **$FEF_{25–75\%}$ T4**<br>15 minutes: 26 ± 2* / 18 ± 12* / 56 ± 16* / 44 ± 45*<br>30 minutes: 25 ± 10* / 20 ± 14* / 56 ± 17* / 47 ± 54*<br>1 h: 32 ± 12* / 20 ± 18* / 74 ± 29* / 53 ± 63*<br>2 h: 27 ± 9* / 23 ± 23* / 62 ± 29* / 49 ± 74*<br>3 h: 17 ± 7 / 15 ± 22 / 37 ± 35* / 36 ± 51*<br>4 h: 14 ± 13 / 6 ± 15 / 34 ± 29* / 29 ± 38*<br>5 h: 9 ± 13 / 4 ± 21 / 21 ± 33 / 9 ± 21<br>6 h: 3 ± 10 / 1 ± 19 / 3 ± 21 / 6 ± 36<br><br>No obvious side-effects were noted | The pMDI tube spacer (AeroChamber) was as effective as the standard MDI device in administering metaproterenol to asthmatic children who, ideally, have been taught to use both correctly |

*continued*

***TABLE 12 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Becker *et al.*, 1985[226] | **T1**: MDI + spacer (tube 80 ml 10 × 3.2 cm) and placebo via MDI<br>**T2**: MDI and placebo via MDI + spacer<br>**T3**: Placebo via both devices<br><br>**Drug**: Terbutaline, 250 μg/actuation, given in a total dose of 500 μg<br>Placebo was the CFC propellant–surfactant mixture used in the active inhaler<br><br>**Design**: Randomised, double-blind, placebo-controlled<br><br>**Jadad** = 2 | 1 hospital, Canada<br><br>**In**: A history of asthma, documented reversibility of obstruction to airflow previously (increase $FEV_1$ >20% after a bronchodilator aerosol), $FEF_{25-75\%}$ <70% predicted normal<br><br>**Out**: Severe acute asthma on study day<br><br>**Power calculation**: No<br><br>**PP analysis**: Assumed | **At beginning**: *n* = 34<br>T1: 12<br>T2: 12<br>T3: 10<br><br>**At end**: *n* = 34<br><br>**Age**:<br>T1: 11.7 ± 0.8<br>T2: 10.2 ± 0.6<br>T3: 10.5 ± 0.6<br><br>**M/F**: Unknown | **Run-in**: Stopped oral medication for 12 h or inhaled bronchodilator aerosol for 6 h before study<br>Demonstration and supervision given by investigator<br><br>**FU**: 3 occasions, 2–7 days apart and within 14 days<br><br>**Primary**: Pulmonary function | Pulmonary function (mean ± SE % predicted normal for age, sex and height except for $FEV_1$/FVC, which is an absolute value)<br>T3 placebo results omitted from this table<br><br>**Test** / **Pre-treatment** / **Hours post-treatment**: 0.5 / 1.0 / 1.5 / 2.0<br>**$FEV_1$**<br>T1: 78.3 ± 6.1* / 93.3 ± 6.6 / 92.7 ± 6.4 / 90.8 ± 6.7 / 89.7 ± 6.2<br>T2: 87.0 ± 6.8 / 103.3 ± 8.3* / 101.8 ± 8.3* / 101.3 ± 8.1* / 100.4 ± 8.3*<br>**$FEV_1$/FVC**<br>T1: 66.8 ± 3.4 / 77.2 ± 3.8 / 77.3 ± 4.1 / 76.0 ± 4.0 / 74.5 ± 3.9<br>T2: 69.5 ± 2.2 / 78.4 ± 3.1 / 78.6 ± 3.1 / 77.8 ± 3.3 / 75.4 ± 2.8<br>**$FEF_{25-75}$**<br>T1: 38.3 ± 5.5 / 57.8 ± 8.4 / 62.1 ± 9.1 / 60.9 ± 10.4 / 58.7 ± 9.7<br>T2: 40.6 ± 4.8 / 63.8 ± 8.1 / 63.5 ± 8.4 / 64.4 ± 8.1 / 63.3 ± 8.1<br>**$V_{25}$**<br>T1: 60.4 ± 7.4 / 83.1 ± 9.3 / 82.5 ± 9.0 / 85.8 ± 10.2 / 86.3 ± 8.1<br>T2: 70.8 ± 7.6 / 92.2 ± 9.3 / 83.0 ± 9.0 / 85.8 ± 10.2 / 79.4 ± 10.2<br>**$V_{50}$**<br>T1: 41.7 ± 5.0 / 60.2 ± 8.4 / 64.2 ± 8.4 / 63.4 ± 9.0 / 61.2 ± 10.1<br>T2: 48.7 ± 5.0 / 71.0 ± 7.7* / 68.1 ± 7.8 / 71.2 ± 8.4 / 71.5 ± 8.6<br>**$V_{75}$**<br>T1: 26.0 ± 4.9 / 41.5 ± 7.6 / 47.2 ± 8.0 / 44.0 ± 9.8 / 43.1 ± 9.0<br>T2: 24.4 ± 4.9 / 42.3 ± 6.7 / 43.1 ± 7.6 / 50.3 ± 9.9 / 40.8 ± 7.1<br><br>*T1 vs T2 $p < 0.05$ | Both MDI + spacer and pMDI were equally effective in improving pulmonary function from the baseline state |

*continued*

***TABLE 12 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Hidinger and Kjellman, 1984[228] | **T1**: pMDI<br>**T2**: pMDI + spacer (750 ml collapsible spacer)<br><br>**Drug**: Terbutaline sulphate, 1 puff, 0.24 mg<br><br>**Design**: Randomised, open, cross-over<br><br>**Jadad** = 1 | 1 paediatric outpatient department, Sweden<br><br>**In**: Bronchial asthma. All children were regular users of $\beta_2$-receptor agonists<br>All children had used pMDI prior to study<br><br>**Out**: Not stated<br><br>**Power calculation**: No<br><br>**PP analysis** | **At beginning**: *n* = 18<br><br>**At end**: *n* = 18<br><br>**Age**: 8.0 (4.9–13.7)<br><br>**M/F**: 12/6 | **Run in**: $\beta_2$-agonists withheld ≤10 h prior to study; theophyllines also excluded for >24 h<br>Tea/coffee not allowed on the morning of study<br><br>**FU**: 2 days, 2–14 days apart<br><br>**Primary**: PEFR at 0, 5, 20 and 60 minutes after inhalation of the aerosol | 5 minutes after inhalation there was a significant increase over basal values in PEFR for T1 and T2 ($p < 0.001$) and the response persisted throughout the observation period (60 minutes)<br><br>Mean PEFR for T2 was significantly greater vs T1 at 5, 20 and 60 minutes after administering the aerosol ($p < 0.05$)<br><br>Mean $max_{5–60}$ for T2 was significantly greater vs T1 ($p < 0.01$)<br><br>**PEFR (mean ± SD) l/min:**<br><br>**Minutes after inhalation** / **T1** / **T2** / ***p*-value**<br>0 / 182 ± 69.4 / 194 ± 71.5 / Not sig.<br>5 / 216 ± 64.0 / 232 ± 68.7 / <0.05<br>20 / 217 ± 68.4 / 234 ± 69.5 / <0.05<br>60 / 219 ± 65.2 / 235 ± 62.5 / <0.05<br>Mean $max_{5–60}$ / 227 ± 65.5 / 243 ± 64.9 / <0.01<br><br>There were no differences in effects related to age | The use of a spacer attached to the usual actuator improved efficacy when patients inhaled 1 puff of terbutaline sulphate |
| Ellul-Micallef, 1980[230] | **T1**: pMDI<br>**T2**: pMDI + spacer (750 ml collapsible spacer)<br><br>**Drug**: Terbutaline sulphate, 1 puff, 0.25 mg<br><br>**Design**: Randomised, cross-over<br><br>**Jadad** = 1 | 1 site, Sweden<br><br>**In**: Moderate bronchial asthma<br><br>**Out**: Not stated<br><br>**Power calculation**: No<br><br>**PP analysis** | **At beginning**: *n* = 12<br><br>**Age**: 7–11<br><br>**M/F**: 8/4 | **Run in**: On 1st and 2nd visits, patients familiarised themselves with a peak flow meter<br><br>**FU**: 4 separate occasions at approximately weekly intervals<br><br>**Primary**: PEFR at 0, 5, 20 and 60 minutes after inhalation of the aerosol | PEFR was 181 ± 6 l/min (mean ± SE) for T1 vs T2 206 ± 6 l/min<br><br>The values obtained when the spacer was attached were significantly greater when measured at 20 minutes ($p < 0.001$) and 60 minutes ($p < 0.01$) after therapy but not at 5 minutes | Adding the spacer to a pMDI resulted in significantly better pulmonary function |

*T, treatment; PP, per protocol; M, male; F, female; SD, standard deviation; SE, standard error; FU, follow-up; CI, confidence interval;* $V_{25(50)(75)}$*, flow at 25%(50%)(75%) of vital capacity; mean* $max_{5–60}$*, mean maximum value during 5–60 minutes*

# Appendix 7

## pMDIs with or without spacer vs DPIs, delivering bronchodilating drugs (randomised controlled trials, physiological and clinical outcomes)

***TABLE 13*** *Evidence reported by Brocklebank* et al., *2001*[20]

| Reference | Methodology | Details | Results | Comments |
|---|---|---|---|---|
| Kemp *et al.*, 1989[216] | **Design**: 2 separate studies reported:<br>(a) randomised double-blind double-dummy cross-over study using 2 doses: 100 and 200 μg on separate days<br>(b) a parallel run study using 200 μg q.d.s. for 12 weeks<br><br>Used computer-coded treatment<br><br>**Device**: Rotahaler vs pMDI alone<br><br>**Drug**: Salbutamol<br><br>**Dose**:<br>(a) 90–100 and 180–200 μg<br>(b) 180–200 μg<br><br>**Duration**:<br>(a) 360 minutes<br>(b) 12 weeks | **Participants**:<br>(a) 30 children, mean age 9.4 yr; lung function measured from 5 to 360 minutes post-dose<br>(b) 204 (164 F) children, age range 4–11 yr, mean age 8.2 yr; lung function measured from 5 to 480 minutes post-dose<br><br>**Study quality**:<br>(a) Cochrane-A<br>(b) Cochrane-A | **(a) No significant differences in**: $FEV_1$, HR or BP<br><br>**(b) No significant differences in**: $FEV_1$, $FEF_{25-75\%}$, FVC, PEFR, drop-out rate or symptom scores<br><br>**(b) Significant difference in**: No. acute exacerbations (requiring intervention): 26 (25%) in pMDI group vs 13 (13%) in Rotahaler group ($p < 0.05$) | Analyses of baseline mean $FEV_1$ (using unpaired two-tailed *t*-test) showed that the pMDI group had significantly lower $FEV_1$ when compared with the Rotahaler group<br>This may explain the higher rate of acute exacerbations seen in the pMDI group |
| Bronsky *et al.*, 1995[217] | **Design**: Randomised double-blind double-dummy cross-over study using Latin-square treatment schedule<br>Exercise challenge used<br><br>**Device**: Rotahaler vs pMDI alone<br><br>**Drug**: Salbutamol<br><br>**Dose**: pMDI 180 μg vs Rotahaler 200 μg<br><br>**Duration**: 51 minutes | **Participants**: 44 children, age range 4–11 yr, mean age 8 yr<br>Pulmonary function test performed up to 51 minutes after taking the drug and running on a treadmill for 6 minutes at predetermined target rates (85% of $HR_{max}$)<br>Study also reported 15-minute post-dose $FEV_1$ (i.e. pre-exercise)<br><br>**Study quality**: Cochrane-B | **No significant differences in**:<br>Pre- and post-exercise $FEV_1$ after drug administration | Study used exercise challenge to show that the two devices are equally effective against EIA |

*continued*

***TABLE 13 contd*** *Evidence reported by Brocklebank* et al., *2001*[20]

| Reference | Methodology | Details | Results | Comments |
|---|---|---|---|---|
| Ahlström *et al.*, 1989[218] | **Design**: Open randomised cross-over study<br><br>**Device**: Turbuhaler® vs MDI + Nebuhaler<br><br>**Drug**: Terbutaline<br><br>**Dose**: 0.5 mg q.d.s. (both devices)<br><br>**Duration**: 14 days | **Participants**: 21 children (7 F), age range 2–5 yr, mean age 3.9 yr<br>PEFR measured 15 minutes after drug administration<br><br>**Study quality**: Cochrane-B | **No significant differences in**: Day or night symptom scores, day or night side-effects or additional use of beta-2 medication<br><br>**Significant difference in**: Morning PEFR favouring Turbuhaler over pMDI + Nebuhaler ($p$ = 0.046) | PEFR result to be treated with caution as evening baseline PEFR was significantly ($p$ = 0.03) higher in the Turbuhaler group |
| Fuglsang and Pedersen, 1989[219] | **Design**: Single-blinded double-dummy, cross-over study<br>Used computer-generated schedule<br><br>**Device**: Turbuhaler vs pMDI alone<br><br>**Drug**: Terbutaline<br><br>**Dose**: 2.0 mg (both devices)<br><br>**Duration**: Cumulative dosing study, giving a total dose of 2.0 mg within 80 minutes | **Participants**: 13 children (3 F), age range 7–15 yr, mean age 10.5 yr<br>Pulmonary function testing at 15 minutes post-dose<br><br>**Study quality**: Cochrane-B | **No significant differences in**: $FEV_1$, $FEF_{25–75\%}$, PEFR or FVC<br><br>**Significant differences in**: HR when using pMDI but not with Turbuhaler<br>More children complained of tremor in the pMDI (7) group than in the Turbuhaler group (0) | |
| Hultquist *et al.*, 1989[220] | **Design**: Randomised double-blind double-dummy cross-over study<br><br>**Device**: Turbuhaler vs pMDI alone<br><br>**Drug**: Terbutaline<br><br>**Dose**: 0.5 mg + p.r.n. (both devices)<br><br>**Duration**: 2 weeks | **Participants**: 57 children, age range 6–18 yr, mean age 11 yr; PEFR was measured 10 minutes post-dose<br><br>**Study quality**: Cochrane-B | **No significant differences in**: PEFR (morning and evening) and symptom scores<br><br>**Significant differences in**: Preference for device; more children preferred the Turbuhaler (49%) than the pMDI (23%) | |

*continued*

***TABLE 13 contd*** *Evidence reported by Brocklebank* et al., *2001*[20]

| Reference | Methodology | Details | Results | Comments |
|---|---|---|---|---|
| Laberge *et al.*, 1994[221] | **Design**: Randomised double-blind double-dummy cross-over study<br>Used random numbers<br><br>**Device**: Turbuhaler vs pMDI + Nebuhaler<br><br>**Drug**: Terbutaline<br><br>**Dose**: Cumulative dosing study, giving a total dose of 2.0 mg within 80 minutes, then followed by nebulised salbutamol 5 mg | **Participants**: 10 children, age range 3–6 yr, mean age 4.6 yr<br>Lung function measured 15 minutes after each dose of medication<br><br>**Study quality**: Cochrane-A | **No significant differences in**: HR, BP, tremor or airway resistance | |
| Svenonius *et al.*, 1994[222] | **Design**: Randomised double-blind double-dummy cross-over study<br>Exercise challenge used<br><br>**Device**: Turbuhaler vs pMDI alone<br><br>**Drug**: Terbutaline<br><br>**Dose**: 1 mg (both devices)<br><br>**Duration**: 15 minutes | **Participants**: 12 children (2 F), age range 9–17 yr, mean age 13.8 yr<br>Lung function measured before exercise then given the drug and measured again up to 15 minutes post-dose to observe reversibility of EIA<br><br>**Study quality**: Cochrane-B | **No significant differences in**: $FEV_1$ and VTG | |
| Hirsch *et al.*, 1997[117] | **Design**: Randomised double-blind double-dummy parallel study<br>Used drawing lots<br><br>**Device**: Turbuhaler vs pMDI alone<br><br>**Drug**: Terbutaline<br><br>**Dose**: 0.5 mg (both devices)<br><br>**Duration**: 10 minutes | **Participants**: 118 children, age range 8–15 yr, mean age 11.3 yr<br>Pulmonary function testing done during 10 minutes post-dose<br><br>**Study quality**: Cochrane-A | **No significant differences in**: Change from baseline $FEV_1$ and FVC<br><br>**Significant differences in**: $V_{50}$ favouring pMDI | |

*continued*

***TABLE 13 contd*** *Evidence reported by Brocklebank* et al., *2001*[20]

| Reference | Methodology | Details | Results | Comments |
|---|---|---|---|---|
| Razzouk *et al.*, 1999[223] | **Design**: Randomised double-blind double-dummy cross-over study<br><br>**Device**: Turbuhaler vs pMDI alone<br><br>**Drug**: Salbutamol<br><br>**Dose**: 100 μg (both devices)<br><br>**Duration**: 240 minutes | **Participants**: 40 children (9 F), age range 6–12 yr, mean age 9 yr<br>Pulmonary function testing performed from 15 to 240 minutes post-dose<br><br>**Study quality**: Cochrane-B | **No significant differences in**: Geometric means of $FEV_1$ and $FEV_{1max}$<br><br>Study also used Turbuhaler 50 μg vs Turbuhaler 100 μg and pMDI 100 μg, showing no significant differences | |

*HR, heart rate; EIA, exercise-induced asthma; BP, blood pressure; VTG, volume of trapped gas (a measure of small airways obstruction)*

***TABLE 14*** *Additional evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Koskela *et al.*, 2000[232] | **T1**: DPI (Easyhaler®) (Buventol® Easyhaler®)<br>**T2**: pMDI + spacer (Volumatic)<br>**T3**: Easyhaler<br>**T4**: pMDI + spacer<br><br>**Drug**: Salbutamol 100 μg T1, T2<br>Placebo T3, T4<br><br>**Design**: Randomised, cross-over, double-blind, double-dummy<br><br>**Jadad** = 2 | 1 hospital, Finland<br><br>**In**: Mild to moderate asthma, 7–65 yr old, no smoking during 6 months to study; 4 weeks to study $FEV_1$ or PEF ≥15%<br><br>**Power calculation**: Yes, 90%, $p = 0.05$<br><br>**Analysis**: ITT and PP | **At beginning**: $n = 22$<br><br>**At end**: $n = 21$<br><br>**Age**: 19 (7–65)<br><16 yr: $n = 12$<br><br>**M/F**: 10/12 | **Run in**: Abstained from controlled-release theophylline preparation ≥48 h, and from oral and inhaled long-acting sympathomimetics ≥6 h<br>No caffeine-containing drinks 4 h before lung function tests<br>Correct inhalation technique taught<br><br>**FU**: 2 study days – interval ≥24 h<br><br>**Primary**: $FEV_{1max}$<br><br>**Secondary**: AUC $FEV_1$ before and at 15, 30 and 60 minutes; $FEV_{1max}$ as % of predicted value at baseline (during the first study day); $FVC_{max}$; $PEF_{max}$ | No significant differences in primary or secondary efficacy variables between T1 and T2<br><br>**Mean (SD) ITT analysis:**<br><br>**T1** / **T2**<br>**Baseline** / **60 minutes** / **Baseline** / **60 minutes**<br>$FEV_{1max}$(l): 2.44 (0.9) / 2.69 (0.93) / 2.43 (0.9) / 2.67 (0.97)<br>$FEV_1$ predicted (%): 80.9 (10.9) / 89.5 (10.7) / 80 (12.3) / 88 (11.7)<br>AUC $FEV_1$ (l/min): – / 10.2 (9.1) / – / 10.1 (9.0)<br>FVC (l): 3.26 (1.17) / 3.35 (1.19) / 3.25 (1.17) / 3.31 (1.18)<br><br>No correlation with age, or PIFR and relative treatment effect of the 2 devices<br>Even a PIFR as low as 23 l/min via Easyhaler was sufficient to obtain a similar treatment effect to normal inhalation from a pMDI + spacer<br><br>No adverse effects | A reasonably low inspiratory flow rate (30 l/min) via Easyhaler produced an equivalent improvement in lung function to a correctly used pMDI + spacer |

*continued*

***TABLE 14 contd*** *Additional evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr)<br>mean ± SD<br>(range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes<br>(primary,<br>secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Ahrens *et al.*, 1999[231] | T1, T2: DPI (Spiros®)<br>T3, T4: MDI<br><br>**Drug**:<br>T1, T2 albuterol sulphate (108 μg = 90 μg of albuterol base/actuation); T1 1, T2 3 actuations<br>T3, T4 Ventolin (90 μg albuterol base/actuation); T3 1, T4 3 actuations<br><br>**Design**: Randomised, double-blind, cross-over, double-dummy<br><br>**Jadad** = 3 | USA<br><br>**In**: Mild to moderate asthma; age ≥12 years; $FEV_1$ ≥65% and $PD_{20}$ ≤4 mg/ml; $PD_{20}$ to increase 8-fold after 2 actuations of Ventolin At subsequent visits, $FEV_1$ ≥65% and $PD_{20}$ to be within 2-fold of screening value Non-smokers<br><br>**Out**: Used ≥ an average of 1 $\beta_2$-agonist inhaler/month, respiratory tract infection within last 30 days, oral corticosteroid within last 3 months of screening, history of life-threatening asthma, other significant illness, clinically significant respiratory disorders, current/ex smokers, seasonal allergic asthma, use of other named medication within specific time-frame of visit 1 (ICS, oral or parenteral steroid, theophylline, ipratropium bromide, | **At beginning**: *n* = 31<br><br>**At end**: *n* = 24<br><br>**Age**: 26.2 (12–46)<br><br>**M/F**: 15/9 | **FU**: 4 study days<br><br>**Primary**: $PD_{20}$ measured by methacholine challenge<br><br>**Secondary**: Adverse events | No significant differences in $PD_{20}$ $FEV_1$ dose–response curves between all treatments Adverse events profiles were similar for the two inhalers | 4 aged ≤15 yr (3 = 13 yr; 1 = 12 yr)<br><br>In this patient group, the dose delivered by Spiros DPI was comparable with that delivered by Ventolin MDI Each actuation of Spiros = 1.12 actuations of Ventolin in the delivery of albuterol (90% CI 0.68 to 1.94) |

*continued*

***TABLE 14 contd*** *Additional evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| *continued*<br>Ahrens *et al.*, 1999[231] | | oral or nebulised $\beta_2$-agonists, salmeterol, nedocromil sodium)<br><br>**Power calculation**: No<br><br>**Analysis**:<br>PP for efficacy<br>ITT for safety analysis | | | | |
| Nelson *et al.*, 1999[233] | **T1**: DPI (Spiros) + pMDI placebo<br>**T2**: pMDI + DPI (Spiros) placebo<br>**T3**: DPI (Spiros) + MDI<br><br>**Drug**: Albuterol sulphate, T1 (108 μg/actuation = 90 μg/actuation)<br>Albuterol, T2 (90 μg/actuation)<br>2 actuations q.d.s. for each inhaler<br>T3, lactose placebo<br><br>**Design**: Randomised, double-blind, double-dummy, placebo-controlled 3-way-parallel group, Phase III<br><br>**Jadad** = 3 | 20 centres, USA<br><br>**In**: Non-smokers, mild to moderate asthma, age ≥12 years, minimum 1 yr of asthma documentation, healthy (medical history, physical examination, 12-lead ECG, clinical laboratory test), no hospital admission within 4 weeks prior to study, $FEV_1$ 40–80% predicted normal on restricted asthma medication, $FEV_1$ ≥12% 30 minutes after 2 inhalations from albuterol MDI<br><br>**Out:** Administration of oral steroid<br><br>**Power calculation**: No<br><br>**PP analysis**: Assumed | **At beginning**:<br>*n* = 283<br>T1: 97<br>T2: 92<br>T3: 94<br><br>**At end**:<br>*n* = 238<br>T1: 81<br>T2: 80 (79 AUC above baseline)<br>T3: 77 (76 AUC above baseline)<br><br>**Age**:<br>T1: 34.2 (±13.4)<br>T2: 34.6 (±15.4)<br>T3: 32.4 (±14.2)<br><br>**M/F**:<br>T1: 37/60<br>T2: 47/45<br>T3: 42/52 | **Run-in**: 7–14 days, instruction and training to use and record PEF on diary card<br>Training with Spiros inhalation system and MDI<br><br>**FU**: 12 weeks<br><br>**Primary**: $FEV_{1max}$; AUC $FEV_1$ above baseline<br><br>**Secondary**: Rescue albuterol use; episodes of exacerbation; daily PEF; nocturnal asthma symptom scores from self-recorded diary cards | The Spiros and MDI groups were comparable in all $FEV_1$ parameters and superior over the placebo group ($p$ = 0.0001)<br><br>With exception of treatment week 0 for the maximum % change in $FEV_1$, the duration of effect and the AUC above baseline, no statistically significant differences between T1 and T2 for any $FEV_1$ parameters<br><br>**Week 0, mean change:**<br>T1 / T2<br>Baseline $FEV_1$ (%): 37.71 / 31.29<br>AUC above baseline (l/min): 141.50 / 181.73<br>Duration of effect (minutes): 192.0 / 162.7<br><br>**Week 12, mean change, $p$ = 0.0001:**<br>T1 / T2<br>Baseline $FEV_1$ (%): 30 / 29<br>AUC above baseline (l/min): 126.29 / 126.85<br>Duration of effect (minutes): 150 / 144<br><br>Statistically significant differences for a.m. and p.m. PEF values among all groups but they were small and not considered to be clinically important<br><br>No statistically significant differences among groups for asthma exacerbation, daily use of rescue albuterol or asthma symptom scores | No difference in clinical benefit for Spiros DPI and albuterol MDI with same medication and same dose<br><br>5 withdrawals for treatment-related adverse effects (T1 3, T2 1, T3 1); the incidence pattern is consistent with that expected in a generally healthy asthmatic population over a period of time<br><br>Asthma exacerbation due to change in medication: T1 6, T2 4, T3 7 |

*continued*

***TABLE 14 contd*** *Additional evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Wolfe *et al.*, 2000[234] | **T1**: DPI (Diskus®) + MDI placebo<br>**T2**: MDI + DPI (Diskus) placebo<br>**T3**: DPI (Diskus) + MDI<br><br>**Drug**: Salmeterol<br>T1: 50 μg, twice daily<br>T2: 42 μg, twice daily<br>T3: Placebo<br><br>**Design**: Randomised, multicentre, double-blind, double-dummy, placebo-controlled parallel group<br><br>**Jadad** = 3 | 27 centres, USA<br><br>**In**:<br>**Screening**: Age ≥12 years; ≥6-month history of mild to moderate asthma that required pharmacotherapy; baseline $FEV_1$ 50–85% predicted normal value after abstaining from asthma medications, ≥15% reversibility of airway obstruction within 30 minutes after 2 actuations of albuterol aerosol (180 μg)<br><br>**Treatment day 1**: About 2 weeks after screening visit, reproducible lung function within 15% of the best screening visit pre-albuterol $FEV_1$ and within 50–85% of the predicted normal value<br><br>Patients with stable regimen of inhaled or intranasal corticosteroids, cromolyn (sodium cromoglicate) or nedocromil started at least 1 month before screening and regimen | **At beginning**:<br>*n* = 498<br>T1: 165<br>T2: 166<br>T3: 167<br><br>**At end**:<br>*n* = 395<br>T1: 134<br>T2: 139<br>T3: 122<br><br>**Age**:<br>T1: 33 (12–74)<br>T2: 35 (12–79)<br>T3: 34 (12–74)<br><br>**M/F**:<br>T1: 79/86<br>T2: 78/88<br>T3: 78/89<br><br>**Ethnic**:<br>White/Black/Hispanic/other:<br>T1: 131/18/15/1<br>T2: 135/12/18/1<br>T3: 128/19/19/1 | **Baseline period**:<br>2-week period<br>All patients received both a Diskus and a MDI device<br>Instruction given on use<br>Supplement aerosol MDI given to all patients<br><br>**FU**: 12 weeks<br><br>**Primary**: 12-h serial measurements at day 1, and weeks 4 and 12, of $FEV_1$, PEF, self-rated asthma symptom scores, night-time awakenings and supplemental albuterol use<br><br>**Secondary**: Adverse events | No significant differences between T1 and T2 in improvement in pulmonary function<br><br>Compared with T3 placebo, significant decreases demonstrated in T1 and T2 in albuterol use, night-time awakenings and increases in % days with no asthma symptoms for the entire study period<br><br>**Mean change from week 1 to week 12 (±SE):**<br>**T1** / **T2** / **T3**<br>$FEV_1$(%): 23 / 22 / 9<br>PEF a.m. (l/min): 17–31 / 22–30 / 7–17<br>Albuterol use (puffs/day): –2.1 ± 0.2 / –1.9 ± 0.2 / –0.7 ± 0.2<br>Nights without awakenings (%): 12 ± 2 / 16 ± 2 / 4 ± 2<br>Symptom scores (no.): –0.4 ± 0.1 / –0.4 ± 0.1 / –0.2 ± 0.1<br><br>No significant differences in adverse events related to study drug among the groups. (T1 11 (7%), T2 9 (5%), T3 6 (4%)) | No difference shown in clinical benefit for Diskus vs. MDI with same dose and drug<br><br>No differences between gender, ethnicity, or patients with ICS vs those without |

*continued*

***TABLE 14 contd*** *Additional evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr)<br>mean ± SD<br>(range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes<br>(primary,<br>secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| *continued*<br>Wolfe *et al.*, 2000[234] | | constant throughout study<br><br>**Out**: Upper or lower respiratory tract or middle ear infections within 6 weeks of study entry; evidence of pulmonary abnormalities unrelated to asthma; > a 10-pack year history of smoking; smoking within 1 yr prior to study entry; exposure to secondary tobacco smoke (≥4 h/day); and presenting clinically significant concurrent disease<br><br>**Power calculation**: Yes, 90% power, $p < 0.05$<br><br>**Analysis**: ITT | | | | |

*ITT, intention-to-treat; AUC, area under the curve; PIFR, peak inspiratory flow rate; $PD_{20}$, 20% decrease in $FEV_1$; ICS, inhaled corticosteroids*

# Appendix 8

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

***TABLE 15*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr)<br>mean ± SD<br>(range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes<br>(primary,<br>secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Dal Col *et al.*, 1995[237] | **T1**: DPI (Pulvinal, multidose)<br>**T2**: DPI (Rotahaler, single dose)<br>**T3**: Placebo via Pulvinal<br>**T4**: Placebo via Rotahaler<br><br>**Drug**: Salbutamol powder, single dose, 200 μg<br><br>**Design**: Randomised, cross-over<br><br>**Jadad** = 1 | 1 site, USA<br><br>**In**: Stable asthma<br>At screening visit: $FEV_1$ and PEFR >75% predicted normal; history of EIA and reversible airway obstruction<br>On day 1 of study, with no treatment, patients had to have ≥15% max fall in $FEV_1$ vs baseline values to continue trial<br><br>**Out**: In case of possible exposure to sensitising agents during the course of the study: acute attacks of asthma in prior 2 months; presence of concomitant disease, or of cardiac, hepatic, renal or endocrine disorders; use of oral steroids during previous 2 months; and impossibility of discontinuing concomitant treatments 24 h before testing<br><br>**Power calculation**: No<br><br>**PP analysis** | **At beginning**: *n* = 13<br><br>**Age**: 10.9 (8–12)<br><br>**M/F**: 9/4 | **Run in**: Standard exercise performed at the same time on each trial day – 6 minutes on a treadmill with a 10° slope<br><br>Use of sodium cromoglicate, nedocromil sodium, bronchodilators and antihistamines stopped for ≥24h before each test<br><br>Inhaled steroid use permitted, but dose to remain constant throughout study<br><br>Instructions on inhaler use with drawings to illustrate correct inhalation technique<br><br>**FU**: 4 consecutive days, 15 minutes before standardised exercise test<br><br>**Primary**: $FEV_1$ and PEFR before and between treatment and exercise challenge test, and after exercise challenge test; ease of use and correct handling technique | No significant difference between T1 and T2 ($p \geq 0.05$)<br><br>Investigator's opinion on ease of use for T1 was excellent for 10 patients and good for the other 3<br>Opinion for T2 was excellent for 3 patients, good for 8 and fair for 2<br>No patient reported a verdict of "poor" for ease of use for either T1 or T2<br><br>11 patients preferred T1; 1 patient preferred T2; 2 patients had no preference (data as presented by authors)<br><br>No adverse events reported throughout study | |

*continued*

***TABLE 15 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Bronsky *et al.*, 1999[235] | **T1**: DPI (Diskus)<br>**T2**: DPI (Diskhaler)<br>**T3**: DPI (Diskhaler)<br><br>**Drug**: T1, T2 salmeterol 50 μg T3 placebo<br><br>**Design**: Randomised, double-blind, double-dummy, placebo-controlled, single-dose, three-way cross-over<br><br>**Jadad** = 3 | 2 sites<br><br>**In**: Mild to moderate asthma; presence of EIA; aged 4–11 yr; $FEV_1$ ≥70% predicted; asthma triggers other than exercise (cold, air, allergens, tobacco smoke)<br><br>**Out**: Received any short-acting $\beta_2$-agonists at ≤8 h of screening visit, oral short-acting $\beta_2$-agonists at ≤12 h, oral extended-release $\beta_2$-agonists or inhaled long-acting $\beta_2$-agonists at ≤24 h; or required $\beta_2$-agonists other than study drug and supplemental albuterol during trial<br><br>Upper/lower respiratory tract/middle ear infections at ≤6 weeks of study entry; clinically significant concurrent disease; abnormalities in complete blood count, or renal or hepatic profiles; abnormal 12-lead ECG; pulmonary abnormalities unrelated to asthma; or secondary exposure to tobacco for ≥8 h/day<br><br>**Power calculation**: No<br><br>**Analysis**: ITT | **At beginning**: *n* = 24<br><br>**At end**: *n* = 24<br><br>**Age**: 9 (±2.1)<br><br>**M/F**: 14/10<br><br>**Ethnicity**: White/Black 22/2 | **FU**: 3 treatment visits + post-treatment FU visit, 2–14 days apart<br><br>**Primary**: Serial $FEV_1$ at 1, 6, and 12 h after study drug administration<br><br>**Secondary**: Adverse events | No significant differences found between T1 and T2 in mean % predicted $FEV_1$ after EIB at 1, 6 and 12 h<br>No difference in the magnitude of bronchoprotection provided by salmeterol from the two devices<br><br>**Mean % predicted $FEV_1$:**<br><br>**T1** 85.2 — **T2** 85.2 — **T3** 83.2<br>Baseline (1 h pre-exercise)<br><br>**Mean % predicted $FEV_1$ fall after exercise challenge at:**<br><br>1 h: 1.4 ± 2.6 ($p$ = 0.002 vs T3) — 0.0 ± 3.0 ($p$ < 0.001 vs T3) — 10.5 ± 2.6<br>6 h: 5.4 ± 1.4 ($p$ = 0.03 vs T3) — 5.7 ± 1.3 ($p$ = 0.07 vs T3) — 11.1 ± 2.0<br>12 h: 5.6 ± 2.1 ($p$ < 0.02 vs T3) — 4.0 ± 1.3 ($p$ = 0.01 vs T3) — 12.1 ± 3.2<br><br>3 adverse events but not study drug related | Salmeterol powder delivered via Diskus and Diskhaler gave equivalent and long-lasting broncho-protection against EIB in children |

*continued*

***TABLE 15 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr)<br>mean ± SD<br>(range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes<br>(primary,<br>secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Boulet *et al.*, 1995[236] | **T1**: Diskus + placebo via Diskhaler<br>**T2**: Diskhaler + placebo via Diskus<br><br>**Drug**: Salmeterol, 50 μg b.d.<br><br>**Design**: Randomised, double-blind, double-dummy, parallel-group, multicentre<br><br>**Jadad** = 3 | 16 sites, USA<br><br>**In**: Age ≥12 yr; $FEV_1$ between 60% and 90% predicted normal; receiving adequate anti-inflammatory and inhaled $\beta_2$-agonist<br>Last 7 days of baseline period: mean morning PEFR 60–80% 15 minutes after inhalation of 800 μg albuterol<br>No methylxanthines, anti-cholinergics, oral/parenteral corticosteroids/other routine $\beta_2$-agonist during study<br><br>**Power calculation**: 99%, 150/group<br><br>**PP analysis**: Assumed | **At beginning**: *n* = 463<br><br>**At end**: *n* = 380<br>**T1**: 190<br>**T2**: 190<br><br>**Age**:<br>**T1**: 39 (12–70)<br>**T2**: 39 (12–69)<br><br>**M/F**:<br>**T1**: 77/113<br>**T2**: 78/112 | **Run-in**: 2 weeks; instruction leaflet and taught by physician on the use of study devices<br><br>**FU**: 4 weeks; questionnaires completed on 4 visits (screening visit, after run-in period, 6th and 12th weeks of study)<br><br>**Primary**: Self-filled daily record of a.m. and p.m. PEFR, a.m. and p.m. asthma symptom scores, and use of albuterol<br>Clinic-recorded pulmonary function tests and adverse effects | Increase in mean a.m. PEFR during treatment, T1 = T2<br>No significant differences observed for p.m. PEFR, a.m. and p.m. symptoms, and albuterol back-up use<br><br>No unexpected adverse events | Majority aged >15 yr<br><br>Diskus and Diskhaler, both with salmeterol, produced similar clinical effects |

*EIB, exercise-induced bronchoconstriction*

# Appendix 9

## pMDIs with or without spacer vs pMDIs with or without spacer, with the same propellants, delivering corticosteroids (randomised controlled trials, physiological and clinical outcomes)

***TABLE 16*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr)<br>mean ± SD<br>(range)<br>M/F | Run-in<br>FU<br>Outcomes<br>(primary,<br>secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Janssens *et al.*, 1999[241] | **T1**: pMDI + spacer (NebuChamber®), metal, 250 ml, no facemask<br>**T2**: pMDI + spacer (Volumatic) polycarbonate, 750 ml + plastic connector to fit pMDI<br><br>**Drug**: Budesonide 200 μg b.d. (Pulmicort)<br>Filter between mouth and spacer<br><br>**Design**: Randomised cross-over<br><br>**Jadad** = 2 | 1 hospital, Australia<br><br>**In**: Stable asthma; no exacerbation requiring oral corticosteroids or change in medication in last 1 month; age 1–8 yr; no other lung function related disorder<br><br>**Power calculation**: No<br><br>**PP analysis**: Assumed | **At beginning**: Not stated<br><br>At end:<br>*n* = 16<br><br>**Age**: 83 months (65–104)<br><br>**M/F**: 12/4<br><br>All used pMDI/spacer >6 months: Breath-a-Tech® 3, Volumatic 12, Turbuhaler 1 | **Run-in**: 1 weeks' instruction and practice with spacer and pMDI<br><br>**FU**: 2 weeks – 1 week with each spacer + new filters for every use<br><br>**Primary**: Filter dose (budesonide deposited on filter) as % of nominal dose<br><br>**Secondary**: Asthma symptom scores (from diary) | Filter doses higher in T1 vs T2 ($p < 0.0001$)<br><br>Mean ±SD in % of nominal dose:<br>T1: 50.3 ± 9.2<br>T2: 19.4 ± 7.2<br><br>Children with higher filter doses for T1 also had higher filter doses for T2 ($r = 0.79$, $p = 0.0003$)<br>No correlation between filter dose and sample number for T1 or T2<br><br>Within-patient variation was smaller for T1 than T2 ($p = 0.003$), but children with higher variation in T1 also had higher variation in T2 ($r = 0.7$, $p = 0.028$)<br>No change with age.<br><br>Mean ±SD within-patient variation in % of nominal dose:<br>T1: 23.1 ± 9.1<br>T2: 34.0 ± 6.5<br><br>No difference in mean asthma scores for T1 vs T2 (0.4% not cooperative)<br><br>Some mistakes in use, no analysis by treatment | Split into 2 age groups: 1–4, 5–8 yr<br>Results for second group only included in this table<br><br>Within-patient variation considerable and not spacer or age dependent, but actual doses delivered to mouth higher with metal spacer |

# Appendix 10

## pMDIs with or without spacer vs DPIs, delivering corticosteroids (randomised controlled trials, physiological and clinical outcomes)

***TABLE 17*** *Evidence reported by Brocklebank* et al., *2001*[20]

| Reference | Methodology | Details | Results | Comments |
|---|---|---|---|---|
| Adler *et al.*, 1997[238] | **Design**: Parallel, double-blind, double-dummy RCT<br><br>**Device**: pMDI + Volumatic vs Clickhaler<br><br>**Drug**: Beclometasone<br><br>**Dose**: Up to 400 μg/day<br><br>**Duration**: 4 weeks | **Participants**: 144 asthmatic children, mean age 10.9 yr, range 6–17<br><br>**Study quality**: Cochrane-B | **No significant differences in**: Change in morning PEFR<br><br>Other outcomes unspecified and reported as non-significant without details | Published in abstract form only |
| Agertoft and Pedersen, 1993[239] | **Design**: Parallel, open RCT<br><br>**Device** : pMDI + Nebuhaler vs Turbuhaler<br><br>**Drug** : Budesonide<br><br>**Dose** : pMDI + Nebuhaler: run-in dose Turbuhaler: half of run-in dose<br><br>**Duration** : 9 weeks | **Participants**: 126 asthma patients, 87 M, 39 F, mean age 9.2 yr, range 4–15<br><br>241 children screened by halving their steroid dosage<br>126 whose asthma control deteriorated went forward to randomisation<br><br>**Study quality**: Cochrane-B | **No significant differences in**:<br>**Clinic**:<br>Change from baseline of: $FEV_1$, FVC, $FEF_{25–75\%}$, and % falls in $FEV_1$, FVC, $FEF_{25–75\%}$ and PEFR in response to exercise; 24-h urinary cortisol<br>**Home diary cards**:<br>PEFR (a.m. and p.m.); day and night symptom score<br><br>**Statistical difference in**: Relief medication use, puffs/week | This study supports equivalence of pMDI + Nebuhaler vs 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-h urinary cortisol between the groups, implying a similar delivered dose of medication<br><br>Relief medication usage was statistically different between groups but the effect was small (less than 1 extra puff/week)<br><br>Ranked ahead of Edmunds, 1979 (below), owing to much larger study size |
| Edmunds *et al.*, 1979[240] | **Design**: Cross-over RCT, double-blind, double-dummy<br><br>**Device**: pMDI vs Rotahaler<br><br>**Drug**: Beclometasone<br><br>**Dose**: 2 puffs q.d.s. vs 1 capsule q.d.s. (presumed each 200 μg q.d.s.)<br><br>**Duration**: 2 × 1 month | **Participants**: 14 asthma patients, 7 M, 7 F, mean age 9.7 yr, range 4.8–15.1<br><br>**Study quality**: Cochrane-A | **No significant differences in**: PEFR (a.m. and p.m.), symptom-free days and relief salbutamol use<br><br>**Significant difference in**: Mean symptom scores in favour of pMDI ($p = 0.04$)<br><br>8 patients preferred aerosol, 2 preferred Rotahaler | Poorly presented study with no statistical results given (author states "no significance")<br><br>Rotahaler (Rotacaps) is an unusual device to use now and would normally be considered to need twice the pMDI dosage<br><br>This study is presumed to be 1:1 dosing |

***TABLE 18*** *Additional evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr)<br>mean ± SD<br>(range)<br>M/F | Run-in<br>FU<br>Outcomes<br>(primary,<br>secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Agertoft *et al.*, 1999[242] | **T1**: DPI (Turbuhaler)<br>**T2**: pMDI + spacer (Nebuhaler, 750 ml)<br><br>**Drug**: Budesonide 200 μg<br><br>**Design**: Randomised, cross-over, controlled<br>Filter between inhaler system and lips to collect drug as inhaled<br><br>**Jadad** = 2 | 1 outpatient clinic, Denmark<br><br>**In**: Asthma requiring continuous treatment with ICS; age 3–15 yr; no diseases that might influence the ability to inhale normally<br><br>**Power calculation**: No<br><br>**PP analysis**: Assumed | **At beginning**: Not stated<br><br>**At end**: *n* = 198<br><br>**Age**: 9 (3–15)<br><br>**M/F**: 132/66<br><br>No. children in each of the 13 age groups ranged from 15 to 24 | **Run-in**: Demonstration of correct use of pMDI Nebuhaler and Turbuhaler given by nurse<br>Each child given one try<br>All children received continuous inhaled therapy with pMDI Nebuhaler for several months before start<br>All children >5 yr had experience of using Turbuhaler for rescue terbutaline or daily budesonide treatment<br><br>**FU**: Not stated<br><br>**Primary**: Mean filter doses<br><br>**Secondary**: PIF, fine-particle fractions using *in-vitro* test | A statistically significant correlation between dose and age was seen for T1 ($r$ = 0.51, $p$ = 0.001) and T2 ($r$ = 0.16, $p$ = 0.03)<br>Filter dose via T1 = T2 for children aged 4 and 5 yr<br>In children >5 yr, T1 delivered a significantly higher dose than T2 ($p$ < 0.03 to $p$ = 0.001)<br><br>Children with higher filter doses for T1 also had higher filter doses for T2 (r = 0.79, p = 0.0003)<br><br>Within-patient variation for T1 = T2 for older children who had experience of using both devices<br><br>The estimated inhaled dose of particle size with a mass medium aerodynamic diameter of ≤5 μm was higher in T1 than T2 for older children | Results for children aged 3–4 yr not included<br><br>No explanation of why older children had a significantly higher dose delivered with Turbuhaler than with pMDI Nebuhaler |

*continued*

***TABLE 18 contd*** *Additional evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr)<br>mean ± SD<br>(range)<br>M/F | Run-in<br>FU<br>Outcomes<br>(primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Bateman *et al.*, 2001[243] | **T1**: pMDI (HFA) and Diskus placebo<br>**T2**: Diskus and pMDI (HFA) placebo<br>**T3**: MDI (CFC) and Diskus (HFA) placebo<br><br>**Drug**: Salmeterol/fluticasone propionate 100/200 μg/day<br><br>**Design**: Randomised, multicentre, double-blind, double-dummy, parallel-group<br><br>**Jadad** = 3 | 69 centres, 10 countries<br><br>**In**: Age ≥12 years, mild to moderate asthma, reversible airway obstruction, smoking history of <10 pack-years, used ICS (beclometasone dipropionate, budesonide/flunisolide 400–500 μg/day or fluticasone propionate 200-250 μg/day) ≥4 weeks before entering study<br>During run-in period: last 7 days, mean a.m. PEF 50–85% after inhaling salbutamol 400 μg, symptomatic (i.e. cumulative total symptom score >8 and taking salbutamol ≤800 μg/day), $FEV_1$ >50% predicted normal<br><br>**Out**: Had received a long-acting/oral $\beta_2$-agonist ≤2 weeks of run-in period; changed asthma medication; had a lower respiratory tract infection at ≤4 weeks of run-in period; acute asthma exacerbation requiring hospitalisation | **At beginning**:<br>*n* = 724 but 497 randomised<br>T1: 165<br>T2: 167<br>T3: 165<br><br>**At end**:<br>*n* = 430<br>T1: 145<br>T2: 145<br>T3: 140<br><br>**PP pop.**:<br>*n* = 383<br>T1: 128<br>T2: 131<br>T3: 124<br><br>**Age**:<br>T1: 40.7 (11–78)<br>T2: 38.6 (11–79)<br>T3: 39.5 (12–76)<br><br>**M/F**:<br>T1: 73/92<br>T2: 79/88<br>T3: 67/98 | **Run-in**: 2 weeks; continued with usual ICS therapy and symptomatic relief with salbutamol (Ventolin)<br>At end, discontinued current ICS therapy<br><br>**FU**: 12 weeks treatment + 2 weeks FU<br><br>**Primary**: Mean a.m. PEF over weeks 1–12<br><br>**Secondary**: p.m. PEF; a.m. and p.m. symptom scores; back-up salbutamol use; clinic $FEV_1$ | No significant differences between T1 and T2<br><br>Improvements were similar in all variables: lung function (a.m. and p.m. PEF), clinic $FEV_1$, symptom scores, use of rescue salbutamol, adverse events<br><br>**T1** **T2**<br>During the 12-week period, a.m. PEF increase (l/min) 42 43<br>Adjusted mean a.m. PEF increase from baseline (l/min) 43 46<br>Mean p.m. PEF (l/min) 38 35<br>Clinic $FEV_1$, increase from baseline at week 12 (%) 17 15<br>Clinic $FEV_1$, adjusted mean change from baseline weeks 1–12 (% predicted) 10 10<br>No. symptom-free a.m., weeks 1–12, medium proportions (%) 55 52<br>No. symptom-free p.m., weeks 1–12, medium proportions (%) 71 78<br>No. back-up salbutamol-free a.m., weeks 1–12, medium proportions.(%) 73 75<br>No. back-up salbutamol-free p.m., weeks 1–12, medium proportions (%) 90 93<br>Adverse event, no. patients (%) 82(50) 95(57) | Likely that majority of patients aged >15 yrs<br><br>Included only data comparing MDI (T1) and Diskus (T2)<br><br>Patients were allowed the use of a spacer (T1 24, T2 22, T3 26)<br><br>Comparable clinical efficacy for HFA MDI vs Diskus with same medication and same dose<br><br>Drug-related adverse event highest in T2 (18) vs T1 (13) |

*continued*

***TABLE 18 contd*** *Additional evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr)<br>mean ± SD<br>(range)<br>M/F | Run-in<br>FU<br>Outcomes<br>(primary,<br>secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| *continued*<br>Bateman *et al.*, 2001[243] | | ≤12 weeks of study entry; prior treatment with oral, depot/par-enteral ICS/combination therapy (containing $\beta_2$-agonist/ICS)<br><br>**Power calculation**: At 90% power<br><br>**Analysis**: PP and ITT | | | | |
| *PIF, peak inspiratory flow* | | | | | | |

# Appendix 11

## DPIs vs DPIs, delivering corticosteroids (randomised controlled trials, physiological and clinical outcomes)

***TABLE 19*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Non-compliance<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Peden *et al.*, 1998[245] | **T1**: DPI (Diskus)<br>**T2**: DPI (Diskus)<br>**T3**: DPI (Diskhaler)<br>**T4**: DPI (Diskhaler)<br>**T5**: Placebo<br><br>**Drug**: Fluticasone propionate<br>T1, T3: 50 μg b.d.<br>T2, T4: 100 μg b.d.<br>Patients had to withhold theophylline treatment, if any, for 24–36 h before clinic visits and albuterol use for ≥6 hours before clinic visits<br><br>**Design**: Randomised, double-blind, double-dummy, parallel-group, placebo-controlled<br><br>**Jadad** = 3 | 34 centres, USA<br><br>**In**: Children aged 4–11 yr, chronic asthma, symptoms requiring maintenance treatment >3 months immediately before study, PEF ≤85% (age 4–5 yr), $FEV_1$ 50–85% (age 6–11 yr), ≥15% reversibility in $FEV_1$ within 30 minutes after 2 puffs of albuterol or documentation of this reversibility within 6 months before study<br><br>**Out**: Life-threatening asthma or other severe concurrent disease, exposed to or had chickenpox ≤3 weeks before study, lower respiratory tract infection ≤ previous 2 weeks, used oral or parenteral corticosteroids ≤1 month before study, used methotrexate or gold salts or any other prescriptions or over-the-counter medication, participated in previous clinical trial with Diskus or Diskhaler devices, $FEV_1$ values < $FEV_1$ stability limit, PEF values < PEF stability limit at each clinic visit and in 7 days preceding each visit, ≤2 days of ≤12 puffs of albuterol aerosol per day or ≤6 albuterol powder per day, >2 night-time asthma awakenings and requiring albuterol, and ≤2 days with an a.m. or p.m. PEF above PEF stability limit | **At beginning**: Not stated<br><br>**At end**: *n* = 437<br><br>**At end**:<br>T1: 90<br>T2: 87<br>T3: 91<br>T4: 83<br>T5: 86<br><br>**Age** 4–5 yr: *n* = 57<br>T1: 11<br>T2: 14<br>T3: 13<br>T4: 12<br>T5: 7<br><br>**Age 6–11 yr**: *n* = 380<br>T1: 79<br>T2: 73<br>T3: 78<br>T4: 71<br>T5: 79<br><br>**M/F (%)**:<br>T1: 59/41<br>T2: 68/32<br>T3: 55/45<br>T4: 60/40<br>T5: 71/29 | **Run-in**: 2-week single-blind, placebo<br>Instruction for proper use of device given<br><br>**Baseline**: Parents/caregivers completed 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<br><br>**FU**: 12 weeks<br><br>**Primary**: $FEV_1$, a.m. PEF, p.m. PEF, asthma symptoms, night-time awakenings requiring albuterol, albuterol use<br><br>**Secondary**: Patient compliance | No significant differences between T1, T2, T3, T4 for $FEV_1$ mean (%) change from baseline and % predicted, PEF, albuterol use, night-time awakenings and asthma symptom scores<br><br>**Mean % change ±SE, 50 μg b.d.:**<br>**Diskus (*n* = 90)** / **Diskhaler (*n* = 91)** / **Placebo (*n* = 86)**<br>$FEV_1$: 15.77 ± 1.97 / 17.89 ± 2.28 / 6.96 ± 2.45<br>PEF: 26 ± 3 / 30 ± 3 / 14 ± 4<br>Albuterol use (puffs/day): –0.75 ± 0.23 / –1.02 ± 0.18 / 0.08 ± 0.23<br>Night-time awakenings/night: –0.03 ± 0.01 / –0.04 ± 0.01 / 0.07 ± 0.04<br>Symptom scores: –0.36 ± 0.07 / –0.41 ± 0.07 / –0.02 ± 0.09<br><br>**Mean % change ±SE, 100 μg b.d.:**<br>**Diskus (*n* = 90)** / **Diskhaler (*n* = 91)** / **Placebo (*n* = 86)**<br>$FEV_1$: 17.93 ± 2.44 / 18.61 ± 3.08 / 6.96 ± 2.45<br>PEF: 27 ± 3 / 33 ± 4 / 14 ± 4<br>Albuterol use (puffs/day): –1.04 ± 0.20 / –0.90 ± 0.23 / 0.08 ± 0.23<br>Night-time awakenings/night: –0.06 ± 0.02 / –0.06 ± 0.02 / 0.07 ± 0.04<br>Symptom scores: –0.41 ± 0.07 / –0.36 ± 0.07 / –0.02 ± 0.09<br><br>(Symptom score: 0 = none, 1 = mild, 2 = moderate, 3 = severe) | Diskus and Diskhaler were comparable in efficacy<br><br>Details on results of device satisfaction from parents/caregivers not included in article |

*continued*

***TABLE 19*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Non-compliance<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr)<br>mean ± SD<br>(range)<br>M/F | Run-in<br>FU<br>Outcomes<br>(primary,<br>secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| *continued*<br>Peden *et al.*, 1998[245] | | 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, and ≥3 night-time awakenings requiring albuterol<br><br>**Non-compliance**: ≤70% of placebo, and did not complete diary cards<br><br>**Power calculation**: 80% power<br><br>**Analysis**: ITT | | | | |
| | | | | | | *continued* |

***TABLE 19 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Non-compliance<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Galant *et al.*, 1999[244] | **T1**: DPI (Diskus) and Diskhaler placebo<br>**T2**: DPI (Diskhaler) and Diskus placebo<br>**T3**: Diskus and Diskhaler placebo<br><br>**Drug**: Fluticasone propionate 500 μg<br><br>**Design**: Randomised, double-blind, double-dummy, parallel-group, placebo-controlled<br><br>**Jadad** = 4 | 16 sites, USA<br><br>**In**: Mild to moderate asthma, children aged ≥12 yr, stratified by baseline therapy of ICS for 3 months prior to study, or $\beta_2$-agonist therapy alone, forced $FEV_1$ = 50–80%, ≥15% reversibility $FEV_1$ (30 minutes after up to 4 puffs of albuterol at screening), or ≥15% variability in $FEV_1$ ≤6 months prior to study<br><br>**Out**: Pregnancy or lactation, severe chronic disease, used methotrexate or gold salts, nedocromil or sodium cromolyn, oral or parenteral corticosteroid <4 weeks prior to study, any prescription or over-the-counter medication that might affect the course of asthma or its treatment<br><br>Lack of efficacy after run-in period ($FEV_1$ values > $FEV_1$ stability limit, ≤3 days where PEF < PEF stability limit during 7 days preceding a study visit, ≤2 days of ≥12 puffs albuterol/day, or ≤2 night-time awakenings requiring albuterol and exacerbation requiring hospitalisation and drug excluded by study protocol)<br><br>**Power calculation**: 80% power<br><br>**Analysis**: ITT | **At beginning**: *n* = 229<br><br>**At end**: *n* = 213<br>T1: 64<br>T2: 79<br>T3: 70<br><br>**Age**:<br>T1: 32 (12–62)<br>T2: 34 (12–76)<br>T3: 32 (13–73)<br><br>**Patients aged 12–17 yr**:<br>T1: 10<br>T2: 7<br>T3: 13<br><br>**M/F (%)**:<br>T1: 56/44<br>T2: 54/46<br>T3: 54/46 | **Baseline**: 3 months' therapy with ICS or $\beta_2$-agonists alone<br><br>**Run-in**: 2 weeks, single-blind, assessing compliance and familiarisation with devices<br><br>**FU**: 12 weeks<br><br>**Primary**: a.m. predose $FEV_1$, probability of remaining in study, patient-rated asthma symptoms for wheeze, cough and breath shortness, patient-measured a.m. and p.m. PEF, albuterol use and night-time awakening requiring albuterol, adverse events<br><br>**Secondary**: Systemic exposure to fluticasone propionate, drug compliance | No significant differences between Diskus and Diskhaler groups for $FEV_1$, symptom scores, use of albuterol, lung function ($p \geq 0.05$) except for a.m. PEF ($p \leq 0.05$)<br><br>**Mean change ± SE:**<br><br>**Diskus** / **Diskhaler** / **Placebo**<br>$FEV_1$ a.m. predose (l): 0.52 ± 0.06 (*n* = 59) / 0.40 ± 0.06 (*n* = 73) / 0.05 ± 0.07 (*n* = 63)<br>$FEV_1$ (%): 22.37 ± 2.38 (*n* = 59) / 16.61 ± 2.24 (*n* = 73) / 3.01 ± 3.03 (*n* = 63)<br>a.m. PEF (l/min): 12 ± 2 (*n* = 58) / 7 ± 1 (*n* = 71) / –3 ± 1 (*n* = 62)<br>p.m. PEF (l/min): 6 ± 1 (*n* = 59) / 5 ± 1 (*n* = 71) / –1 ± 1 (*n* = 60)<br>Albuterol use (puffs/day): –1.54 ± 0.36 (*n* = 59) / –1.41 ± 0.32 (*n* = 58) / 0.76 ± 0.31 (*n* = 71)<br>Night-time awakenings (no./week): –0.03 ± 0.02 (*n* = 60) / 0.00 ± 0.04 (*n* = 58) / 0.10 ± 0.05 (*n* = 72)<br>Total symptom scores: –0.20 ± 0.05 (*n* = 59) / –0.10 ± 0.05 (*n* = 72) / 0.04 ± 0.05 (*n* = 61)<br><br>(Total symptom score: 0 = none, 1 = mild, 2 = moderate, 3 = severe)<br><br>No significant differences in probability of remaining in study over time between device groups<br><br>Potential drug-related adverse events were 14%, 16% and 23% for placebo, Diskus and Diskhaler respectively<br><br>Compliance rate for Diskus and Diskhaler = 94% scheduled doses | Both Diskus and Diskhaler produced comparable benefits with same medication and same dose<br><br>No age details of withdrawn patients<br><br>Withdrawal from study: 5% T1, T2; 34% T3 |

# Appendix 12

## pMDIs with or without spacer vs breath-actuated devices delivering anti-inflammatory drugs: sodium cromoglicate (randomised controlled trials, physiological and clinical outcomes)

***TABLE 20*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr)<br>mean ± SD<br>(range)<br>M/F | Run-in<br>FU<br>Outcomes<br>(primary,<br>secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Arshad, 1993[215] | **T1**: Breath-actuated (Autohaler)<br>**T2**: MDI<br><br>**Drug**: Sodium cromoglicate, 2 puffs (10 mg) q.d.s.<br><br>**Design**: Randomised, open, cross-over, controlled<br><br>**Jadad** = 1 | Multicentre, UK<br><br>**In**: Stable asthma, airways reversibility of ≥15% to an inhaled bronchodilator, currently treated with sodium cromoglicate, duration 10 weeks to 15 yr (mean 6.5 yr), ability to use the MDI<br><br>**Out**: Not stated<br><br>**Power calculation** 150/group, at power 90%<br><br>**PP analysis** | **At beginning**:<br>*n* = 181<br>T1: 90<br>T2: 91<br><br>**At end**:<br>*n* = 166<br><br>**Age**: 10.4 (4–18) except 1 patient aged 39 yr<br><br>**M/F**: 181/0 | **Run in**: All medications for treatment of asthma permitted, but, apart from inhaled broncho-dilators, dose to remain the same throughout study period<br><br>**FU**: 8 weeks (4-week treatment period before cross-over), 3 clinical visits<br><br>Primary: Spirometry pre- and post-$\beta_2$ inhaler, daily diary cards with 4 named-symptom scores, bronchodilator use and PEFR twice a day, overall assessment of severity of asthma over the previous 4 weeks by clinician, treatment efficacy assessed by patient and clinician, self-assessed acceptability of device, unusual events<br><br>**Secondary**: Ease of use, coordination of actuation with inhalation and control of asthma in the 2 treatment periods | No statistically significant differences for pulmonary function tests (PEFR, $FEV_1$, $FEV_1$ reversibility and FVC) between T1 and T2<br><br>Morning PEFR and differential (a.m.–p.m. PEFR) significantly higher ($p < 0.05$) for second device period (whichever inhaler was used after cross-over)<br>No significant differences between devices could be detected<br><br>No significant differences between devices or period for mean numbers of puffs of inhaled bronchodilator used during night and day<br><br>Clinician's opinion: overall severity of asthma did not differ for the 2 devices; no difference in number and distribution of unusual events<br><br>Both patients' and clinicians' opinions of sodium cromoglicate effectiveness significantly better for Autohaler vs MDI ($p < 0.01$)<br><br>56 patients found Autohaler better; 67 found no difference; 35 found MDI better (assumed data missing) | No significant differences in clinical efficacy found between Autohaler and MDI |

# Appendix 13

## pMDIs with or without spacer vs pMDIs with or without spacer, with different propellants, delivering the same bronchodilating drugs (randomised controlled trials, physiological and clinical outcomes)

***TABLE 21*** *Evidence reported by Brocklebank* et al., *2001*[20]

| Reference | Methodology | Details | Results | Comments |
|---|---|---|---|---|
| Custovic *et al.*, 1995[247] | **Design**: Randomised double-blind double-dummy cross-over study<br>Computer-generated schedule<br>Histamine challenge used<br><br>**Device**: HFA pMDI alone vs CFC pMDI alone<br><br>**Drug**: Salbutamol<br><br>**Dose**: 200 μg (both devices)<br><br>**Duration**: 30 minutes | **Participants**: 25 children, age range 6–14 yr, mean age 10 yr<br>Pulmonary function test performed 30 minutes post-dose, then histamine challenge performed and $FEV_1$ measured until $FEV_1$ decreased by 20% ($PD_{20}$)<br><br>**Study quality**: Cochrane-A | **No significant differences in**: $FEV_1$ or protection against histamine-induced bronchoconstriction as measured by $PD_{20}$ | |

***TABLE 22*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Shapiro *et al.*, 2000[249] | **T1**: HFA pMDI<br>**T2**: CFC pMDI<br>**T3**: Placebo, HFA propellant only<br><br>**Drug**: Albuterol, 2 puffs, 4–6 h (1 puff Ventolin HFA (108 μg albuterol sulphate) = 1 puff Ventolin CFC (90 μg albuterol base))<br><br>**Design**: Randomised, double-blind, placebo-controlled<br><br>**Jadad** = 3 | 11 sites (USA and Puerto Rico)<br><br>**In**: Ages 4–11 yr, asthma requiring physician-prescribed chronic pharmacotherapy ≥6mths, no significant pulmonary disease/serious chronic disease, PEF or $FEV_1$ = 50–80% predicted, $FEV_1$ reversibility ≥15%<br><br>**Out**: Signs of unstable asthma during run-in, life-threatening asthma, not allowed medications with potential impact on the analyses of cardiovascular end-points<br><br>**Power calculation**: 80%, a difference of 10% in % predicted $FEV_1$, $p \leq 0.5$<br><br>**PP analysis**: Assumed | **At beginning**:<br>*n* = 135<br>T1: 46<br>T2: 46<br>T3: 43<br><br>**At end**:<br>*n* = 118<br><br>**Age**:<br>T1: 9.0<br>T2: 8.5<br>T3: 9.0<br><br>**Sex (M%)**:<br>T1: 54<br>T2: 72<br>T3: 53 | **Run-in**: 1–2 weeks, instruction on proper use of MDI and peak flow meter<br><br>**FU**: 2 weeks<br><br>**Primary**: Mean % predicted PEF during 6-h serial tests (day 1 and week 2)<br>Mean % predicted $FEV_1$ for patients aged 6–11 yr and 4–5 yr<br><br>**Secondary**: Daily self-measured a.m. and p.m. PEF, guardian/self-rated asthma symptoms, % nocturnal awakenings requiring albuterol, asthma exacerbation frequency | T1 and T2 produced comparable bronchodilation as assessed by mean increase in % predicted PEF: better than placebo<br>No significant differences between T1 and T2 in mean increases<br>Serial $FEV_1$ values similar to those calculated for PEF<br>Improvement in all diary card variables – no significant differences between T1 and T2<br><br>**6-h serial PEF (%):**<br><br>**T1** (Day 1 (*n* = 46), Week 2 (*n* = 41)); **T2** (Day 1 (*n* = 46), Week 2 (*n* = 41)); **T3** (Day 1 (*n* = 43), Week 2 (*n* = 36))<br><br>Baseline PEF, predicted: 71.5 ± 2.4 | 78.5 ± 3.1 | 71.0 ± 2.2 | 76.7 ± 2.8 | 69.7 ± 2.1 | 72.3 ± 2.8<br>Changes in PEF, predicted: 13.9 ± 1.4 | 10.8 ± 1.4 | 12.6 ± 1.4 | 10.8 ± 1.4 | 6.3 ± 1.7 | 4.5 ± 0.9<br><br>**Mean change from baseline in diary card variables:**<br><br>**T1** (*n* = 46); **T2** (*n* = 46); **T3** (*n* = 41)<br><br>a.m. PEF (l/min): 17 ± 4* | 9 ± 4 | 2 ± 3<br>p.m. PEF (l/min): 15 ± 3* | 11 ± 4 | 3 ± 3<br>Albuterol use (mean puffs/day): −1.8 ± 0.4* | −2.0 ± 0.4* | −0.8 ± 0.4<br>Days with no albuterol (%): 36.4 ± 6.1* | 39.5 ± 5.6* | 11.5 ± 6.2<br><br>Night-time without awakenings (%): 1 ± 4 | 4 ± 2 | 5 ± 4<br>Asthma symptom scores: −0.3 ± 0.1* | −0.1 ± 0.1 | 0.1 ± 0.1<br><br>(*$p < 0.03$ vs T3) | Ventolin HFA produced bronchodilation that is clinically comparable with the effects of inhaled Ventolin CFC |

*continued*

***TABLE 22 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Colice *et al.*, 1999[250] | **T1**: HFA pMDI<br>**T2**: CFC pMDI<br>**T3**: CFC pMDI<br>**T4**: Placebo HFA pMDI<br><br>**Drug**: Albuterol or Ventolin, 2 puffs<br><br>**Design**: Randomised, single-blind, placebo-controlled, four-period cross-over<br><br>**Jadad** = 3 | 1 site, USA<br><br>**In**: Age 6–11 yr; stable asthma (no episode of emergency care within 4 weeks of pre-study visit) requiring short-acting $\beta_2$-agonists for control of symptoms; chronic asthma (≥6 months); presence of EIB within 30 minutes after a standardised exercise; withhold medication and methylxanthine-containing foods and beverages for ≥6 h; $FEV_1$ ≥70% predicted; demonstrated proper technique in using a press and breathe MDI; not obese; no lower/upper respiratory tract infections; not using salmeterol (48 h), theophylline products (48 h), cromolyn sodium/nedocromil sodium (1 week), oral/injectable steroids (8 weeks), antihistamine treatment (3 months) prior to pre-study visit; no use of these medications throughout study<br><br>**Out**: Failure to confirm EIB by pre-study exercise challenge, withdrawal of consent, and baseline $FEV_1$ <70% predicted<br><br>**Power calculation**: No<br><br>**PP analysis**: Assumed | **At beginning**: *n* = 16<br><br>**At end**: *n* = 15<br><br>**Age**: 9.4 (6–11)<br><br>**M/F**: 11/5 | **FU**: 4 treatment visits 3–7 days apart<br><br>**Primary**: Smallest % change from pre-dose $FEV_1$ post-exercise<br><br>**Secondary**: % and absolute change from pre-dose $FEV_1$ post-exercise | No significant differences found among active treatment results<br><br>**T1** / **T2** / **T3** / **T4**<br>Smallest % change in $FEV_1$ post- exercise*: 1.9 ± 16.4 / –0.3 ± 11.4 / –0.7 ± 13.5 / –25.5 ± 16.0<br>No. (%) patients protected from EIB: 14 (93) / 15 (100) / 14 (93) / 5 (33)<br><br>(*T1, T2 and T3 vs T4 all $p < 0.001$) | Albuterol HFA had similar broncho-dilator efficacy and safety profile as CFC albuterol |

*continued*

***TABLE 22 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Shapiro *et al.*, 2000[248] | **T1**: HFA pMDI<br>**T2**: CFC pMDI<br><br>**Drug**: Albuterol, 2 puffs<br><br>**Design**: Open-label, parallel-group, randomised<br><br>**Jadad** = 1 | Multicentre, USA<br><br>**In**: Stable asthma, age 4–11 yr, using short-acting inhaled $\beta_2$-agonists for 6 months, $FEV_1$ ≥50% predicted after withholding short-acting inhaled $\beta_2$-agonists for 6 h, increase in $FEV_1$ ≥12% within 30 minutes after 2 puffs CFC albuterol<br><br>**Out**: Other pulmonary disease; clinically significant concomitant non-pulmonary disease; upper respiratory tract infection ≤4 weeks of screening; lower respiratory tract infection ≤2 weeks of screening or a known idiosyncratic reaction to sympathomimetic drug; theophylline use (≤3 days); oral $\beta_2$-agonists (≤1 week); inhaled corticosteroid (≤4 weeks); monoamine oxidase inhibitors, tricyclic antidepressants and $\beta_2$-antagonist (≤6 wks); and antihistamine treatment (≤80 days) prior to study entry; ipratropium bromide, oral or nebulised $\beta_2$-agonists, salmeterol, nedocromil sodium<br><br>**Power calculation**: Requiring 30/group, at 90% power<br><br>**PP analysis**: Assumed | **At beginning**:<br>*n* = 63<br>T1: 33<br>T2: 30<br><br>**Age**:<br>T1: (4–7) (*n* = 9) and (8–11) (*n* = 24)<br><br>**T2**: (4–7) (*n* = 6) and (8–11) (*n* = 24) | **Run-in**: ≥7 days<br><br>**FU**: 4 weeks<br><br>**Primary**: actual and % change from pre-dose $FEV_1$ at study day 1 and week 4, AUC for bronchodilation effect<br><br>**Secondary**: Symptom scores, PEF a.m. and p.m., nocturnal awakenings scores, average albuterol use | No significant differences between T1 and T2 for $FEV_1$ at day 1 and week 4, a.m. and p.m. PEF<br><br>No significant differences between T1 and T2 for individual asthma symptom scores, night-time asthma sleep disturbance scores and rescue study drug use over 4-week study period | No difference in clinical benefit for CFC vs HFA with same medication and dose |

*continued*

***TABLE 22 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Lumry *et al.*, 2001[251] | **T1**: CFC pMDI<br>**T2**: HFA pMDI<br>**T3**: MDI placebo (HFA propellant alone, q.d.s.)<br><br>**Drug**: Albuterol 180 μg q.d.s.<br><br>**Design**: Randomised, multicentre, double-blind, parallel-groups<br><br>**Jadad** = 3 | 25 outpatient centres, USA<br><br>**In**: Mild to moderate bronchial asthma, aged ≥12 yr, a 6-month history of asthma, a medication-free forced $FEV_1$ 50–80% normal predicted, ≥15% $FEV_1$ increase in 30 minutes of Ventolin inhalation (2 puffs, 180 μg)<br><br>**Out**: Requiring asthma medication other than Ventolin during study or having significant other concurrent illnesses<br><br>**Power calculation**: Requiring 80/group, at 80% power, $p = 0.05$<br><br>**PP analysis**: Assumed | **At beginning**:<br>*n* = 313<br>T1: 108<br>T2: 101<br>T3: 104<br><br>**At end**:<br>*n* = 276<br>T1: 99<br>T2: 91<br>T3: 86<br><br>**Age**:<br>T1: 32 ± 14.8<br>T2: 30.6 ± 12.2<br>T3: 29.7 ± 13.8<br><br>**M/F %**:<br>T1: 56/44<br>T2: 55/45<br>T3: 50/50<br><br>**Ethnicity % (Caucasian/ Black/other)**:<br>T1: 79/13/8<br>T2: 75/13/12<br>T3: 81/12/7 | **Baseline period**: 3 weeks, Ventolin CFC via MDI, 180 μg q.d.s.<br><br>**FU**: 12 weeks<br><br>**Primary**: Serial pulmonary function testing<br><br>**Secondary**: Mean change a.m. and p.m. PEF, back-up Ventolin use, asthma symptoms, nocturnal awakenings | Pulmonary function, a.m. and p.m. PEFR values, back-up Ventolin use, symptom scores and nocturnal awakenings all remained unchanged relative to baseline levels when switched from T1 to T2<br><br>**Serial pulmonary function results: day 1**<br><br>**T1 (*n* = 100) / T2 (*n* = 91) / T3 (*n* = 95)**<br>% patients ≥15% improvement: 82 / 77 / 19<br>Median onset of effect (h): 0.06 / 0.07 / 6.0<br>Mean duration (h) of effect (SE): 3.26 (0.24) / 3.07 (0.25) / 0.57 (0.17)<br>% max effect (SE): 30.1 (1.83) / 28.4 (1.34) / 14.4 (1.05)<br>Median time max effect (h): 1.0 / 1.0 / 3.0<br>Mean change from baseline in AUC l/h (SE): 0.84 (0.16) / 2.48 (0.19) / 2.65 (0.18)<br><br>No significant difference between T1 and T2 for all serial pulmonary function results but difference with placebo ($p < 0.001$) at day 1 (shown) and all other visits ($p < 0.001$) | Likely that majority of patients aged >15 yr<br><br>Comparable clinical efficacy for CFC vs HFA propellant in an MDI with same medication and same dose<br><br>Ventolin CFC and Ventolin HFA have similar adverse event profiles<br>Treatment-related adverse events highest in T3 (9%) vs T1 (2%), T2 (4%) |

# Appendix 14

## pMDIs with or without spacer vs pMDIs with or without spacer, with different propellants, delivering corticosteroids or combined therapy (randomised controlled trials, physiological and clinical outcomes)

***TABLE 23*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Pearlman *et al.,* 1999[252] | **T1**: MDI CFC (75 μg/puff), 150 μg/day, 1 puff b.d.<br>**T2**: MDI CFC (75 μg/puff), 300 μg/day, 2 puffs b.d.<br>**T3**: MDI CFC (75 μg/puff), 600 μg/day, 4 puffs b.d.<br>**T4**: MDI HFA (75 μg/puff), 150 μg/day, 1 puff b.d.<br>**T5**: MDI HFA (75 μg/puff), 300 μg/day, 2 puffs b.d.<br>**T6**: MDI HFA (75 μg/puff), 600 μg/day, 4 puffs b.d.<br><br>**Drug**: Triamcinolone acetonide<br>A built-in spacer-mouthpiece was used for both the HFA and CFC formulations<br><br>**Design**: Randomised, double-blind<br><br>**Jadad** = 3 | 43 centres, USA<br><br>**In**: Age 6–13 yr, 1-yr history of perennial asthma requiring daily medication and inhaled $\beta_2$-agonists for at least previous month, $FEV_1$ = 50–100% of predicted<br><br>**Out**: Life-threatening asthma, anoxic seizures, significant hypercapnia, recent hospitalisation for asthma, systemic corticosteroid use once within previous month or >2 courses during previous year, any significant clinical/laboratory abnormalities/clinical conditions<br><br>**Power calculation**: No<br><br>**Analysis**: ITT | **At beginning**:<br>*n* = 473<br>T1: 75<br>T2: 82<br>T3: 82<br>T4: 76<br>T5: 83<br>T6: 75<br><br>**At end**:<br>*n* = 374<br><br>**Age**:<br>T1: 10.2 (6–13)<br>T2: 9.6 (6.1–13)<br>T3: 9.9 (6–26.1)[a]<br>T4: 9.9 (6.1–13)<br>T5: 9.7 (5.9–13)<br>T6: 9.6 (6.1–12.5)<br><br>**M/F**:<br>T1: 48/27<br>T2: 62/20<br>T3: 56/26<br>T4: 51/25<br>T5: 50/33<br>T6: 53/22 | **Baseline period**: 3–28 days, instructions given on the use of portable meter to measure a.m. and p.m. PEFR<br><br>**FU**: 12-week treatment period<br><br>**Primary**: Mean % change from baseline to end-point<br><br>**Secondary**: Mean % change in $FEF_{25–75\%}$ from baseline to end-point, changes in a.m. and p.m. PEFR, nocturnal awakenings, patient efficacy ratings, asthma symptom scores | Comparison between HFA and CFC formulations within dose levels showed 2 formulations therapeutically equivalent at all 3 doses for albuterol use, a.m. and p.m. PEFR and nocturnal awakenings Differences in $FEV_1$ and 24-h symptom scores between formulations, but not significant<br><br>No significant differences for comparisons across dose levels for albuterol use (rescue medication), 24-h symptom scores/nocturnal awakenings<br><br>Significant improvements in $FEV_1$ for all doses, both formulations<br><br>**$FEV_1$ (mean ± SE):**<br>CFC T1: 1.59 ± 0.05; 13.53 ± 3.24<br>T2: 1.44 ± 0.05; 19.40 ± 2.67<br>T3: 1.45 ± 0.04; 22.62 ± 2.67<br>HFA T4: 1.48 ± 0.04; 12.17 ± 3.24<br>T5: 1.47 ± 0.04; 21.39 ± 3.10<br>T6: 1.43 ± 0.05; 22.02 ± 3.26<br>(Baseline (l); % change)<br><br>**PEFR (ml/min) a.m. (mean ± SE); PEFR (ml/min) p.m. (mean ± SE); $FEF_{25–75\%}$ % change (mean ± SE)**<br>CFC T1: 19.0 ± 4.5; 15.2 ± 4.2; 23.2 ± 10.8<br>T2: 23.0 ± 4.3; 15.8 ± 4.2; 42.8 ± 10.3<br>T3: 30.2 ± 4.3; 25.6 ± 4.1; 42.3 ± 10.3<br>HFA T4: 24.2 ± 4.3; 20.2 ± 4.3; 29.9 ± 8.7<br>T5: 20.5 ± 4.0; 18.8 ± 4.1; 33.0 ± 8.3<br>T6: 27.4 ± 4.3; 24.3 ± 4.3; 53.6 ± 8.7<br><br>Albuterol use decreased across dose levels for both HFA and CFC, but overall treatment effect significant with HFA formulation ($p$ = 0.001), not CFC formulation ($p$ = 0.270) | Therapeutic equivalent found at all 3 dose levels between HFA and CFC propellants |

*continued*

***TABLE 23 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr)<br>mean ± SD<br>(range)<br>M/F | Run-in<br>FU<br>Outcomes<br>(primary,<br>secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| *continued*<br>Pearlman<br>*et al.,* 1999[252] | | | | | Significant improvements ($p < 0.05$) from baseline for a.m. and p.m. asthma symptom scores, 24-h symptom scores and no. nocturnal awakenings in HFA groups; CFC groups demonstrated significant changes ($p < 0.05$) from baseline for only a.m. and p.m. asthma symptoms and 24-h symptom scores | |

**Change in asthma symptoms (mean ± SE):**

| | a.m. symptom score | p.m. symptom score | 24-h symptom score | Nocturnal awakenings (no./day) |
|---|---|---|---|---|
| CFC T1 | –0.5 ± 0.1 | –0.4 ± 0.1 | –1.0 ± 0.2 | –0.2 ± 0.1 |
| T2 | –0.7 ± 0.1 | –0.6 ± 0.1 | –1.3 ± 0.2 | –0.4 ± 0.1 |
| T3 | –0.9 ± 0.1 | –0.8 ± 0.1 | –1.7 ± 0.2 | –0.4 ± 0.1 |
| *p*-value | 0.044 | 0.044 | 0.045 | 0.105 |
| HFA T4 | –0.5 ± 0.1 | –0.5 ± 0.1 | –0.9 ± 0.2 | –0.1 ± 0.1 |
| T5 | –0.8 ± 0.1 | –0.7 ± 0.1 | –1.6 ± 0.2 | –0.2 ± 0.1 |
| T6 | –1.1 ± 0.1 | –1.0 ± 0.1 | –2.0 ± 0.2 | –0.5 ± 0.1 |
| *p*-value | 0.002 | 0.007 | 0.002 | 0.001 |

[a]*Age range actually 6–13 years; 1 older patient accidentally enrolled and subsequently excluded*

# Appendix 15

## Breath-actuated inhalers with different propellants, delivering corticosteroids (randomised controlled trials, physiological and clinical outcomes)

***TABLE 24*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Farmer *et al.*, 2000[253] | **T1**: Breath-actuated MDI HFA<br>**T2**: Breath-actuated MDI CFC<br><br>**Drug**: BDP, 100 μg<br><br>**Design**: Randomised, multicentre, double-blind, parallel-group<br><br>**Jadad** = 4 | 44 general practice and hospital sites, UK, South Africa, Czech Republic, Yugoslavia, Hungary<br><br>**In**: Age 7–12 yr, $FEV_1$ ≥60% predicted for height and gender, $FEV_1$ reversibility ≥10% after inhaling 200 μg salbutamol via pMDI, documented $FEV_1$ reversibility ≥10% in previous 12 months, currently using inhaled bronchodilator $\beta_2$-agonist/sodium cromoglicate or constant dose of nedocromil sodium<br><br>**Out**: Currently using inhaled/oral corticosteroids, unstable asthma, significant medical/psychological conditions<br><br>**Power calculation** 90%, 105 patients/group<br><br>**PP analysis**: Assumed | **At beginning**: *n* = 229<br><br>**At end**: *n* = 199<br><br>**Age**: T1: 10.0 (7–12.9) T2: 9.8 (6.6–12.8)<br><br>**M/F**: T1: 71/45 T2: 75/38 | **Run-in**: 2-week placebo, 1 puff b.d. from CFC placebo Easi-Breathe inhaler<br><br>End of run-in, required the use of relief bronchodilator (≥2 puffs on ≥3 of last 7 days of run-in)<br><br>**FU**: 4 treatment visits: 1, 4, 8 and 12 weeks<br><br>**Primary**: Lung function (PEF and $FEV_1$), self-recorded symptom scores and relief medication use | Equivalent results for all lung function parameters obtained for mean a.m. and p.m. PEF, with estimated treatment difference being 2.6% and 2.1% respectively<br><br>Exception was mean daily variability in PEF, which decreased from 21 to 16% in T1 and from 22 to 16% in T2<br><br>Compared with baseline, significant decreases in proportions of patients reporting a.m. and p.m. symptoms and use of relief medication in both T1 and T2<br><br>**T1 mean (SD) / T2 mean / Estimate (95% CI): (SD) HFA/CFC (%)**<br><br>a.m. PEF (l/min): Baseline 299 (56) 294 (62)<br>End-point 340 (61) 328 (54)<br>End-point[a] 338 330 102.6 (99.1 to 106.2)<br><br>p.m. PEF (l/min): Baseline 302 (57) 297 (61)<br>End-point 340 (61) 329 (51)<br>End-point[a] 338 331 102.1 (98.1 to 105.6)<br><br>Clinic PEF (l/min): Baseline 308 (60) 305 (69)<br>End-point 335 (59) 335 (59)<br>End-point[a] 337 333 101.2 (97.3 to 105.1)<br><br>Clinic $FEV_1$ (l/min): Baseline 1.82 (0.42) 1.77 (0.42)<br>End-point 1.98 (0.45) 1.92 (0.40)<br>End-point[a] 1.97 1.91 103.5 (99.6 to 107.5)<br><br>Daily variability PEF (%): Baseline 20.8 (11.7) 22.3 (11.6)<br>End-point 16.1 (13.6) 16.5 (10.9)<br>End-point[a] 16.2 16.3 99.4 (78.6 to 116.9)<br><br>[a]Least square | HFA inhaler was therapeutically equivalent to CFC inhaler at similar dose (BDP 100 μg b.d.) |

*BDP, beclometasone dipropionate*

# Appendix 16

## pMDIs with or without spacer vs pMDIs with or without spacer, with different propellants, delivering cromoglicate therapy (randomised controlled trials, physiological and clinical outcomes)

***TABLE 25*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Furukawa *et al.,* 1999[254] | **T1**: MDI CFC<br>**T2**: MDI HFA<br>**T3**: Placebo with HFA propellant<br><br>**Drug**: Cromolyn sodium, 2 mg q.d.s.<br>Albuterol MDI used as needed in all groups<br><br>**Design**: Randomised, double-blind placebo-controlled parallel-group<br><br>**Jadad** = 3 | 29 sites, USA<br><br>**In**: Mild to moderate bronchial asthma, age ≥12 yr, cromolyn sodium use for ≥2 months, inhaled $\beta_2$-agonists use for ≥1 month, $FEV_1$ ≥60% normal predicted<br><br>**Out**: Other clinically significant respiratory disorders, current/ex-smokers, history of life-threatening asthma exacerbation, seasonal allergic asthma, use of other named medication within specific time-frame of visit 1: ICS, oral or parenteral steroid, theophylline, ipratropium bromide, oral or nebulised $\beta_2$-agonists, salmeterol, nedocromil sodium<br><br>**Power calculation**: Requiring 100/group, at 90% power<br><br>**PP analysis**: Assumed | **At beginning**:<br>*n* = 280<br>T1: 91<br>T2: 94<br>T3: 95<br><br>**At end**:<br>*n* = 256<br>T1: 84<br>T2: 88<br>T3: 84<br><br>**Age**:<br>T1: 30.3 (12–79)<br>T2: 30 (12–62)<br>T3: 26.9 (12–68)<br><br>**M/F**:<br>T1: 40/51<br>T2: 39/55<br>T3: 48/47 | **Baseline period**: 2–4 weeks<br><br>**FU**: 12 weeks<br><br>**Primary**: Symptom summary score (daytime + night-time asthma scores)<br><br>**Secondary**: Lung function, albuterol use, symptom scores a.m. and p.m., PEFs, self- and clinician-rated effectiveness or treatment-related events | No significant differences in symptom score decreases, use of albuterol, lung function, treatment-related events T1 vs T2 ($p \geq 0.05$)<br><br>**Mean change (%):**<br>**T1 (*n* = 84)** / **T2 (*n* = 88)**<br>Symptom score: –22 / –27<br>Daytime score: –25 / –29<br>Night-time score: –18 / –23<br>a.m. PEF: 1.3 / 5.3<br>p.m. PEF: 0.1 / 4.7<br>Albuterol use: –13 / –27<br><br>Clinician-rated T1 effective for 63% patients vs T2 (56%) ($p = 0.042$); no difference for patient-rated T1 (73%) and T2 (77%) ($p = 0.989$) | Likely that majority of patients were aged >15 yr<br><br>No difference in clinical benefit for CFC vs HFA propellant in an MDI with same medication and same dose<br><br>Differences between clinician and patient ratings on effectiveness<br><br>4 withdrawals for treatment-related adverse effects (T1 1, T2 2, T3 1) |

# Appendix 17

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

***TABLE 26*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Non-compliance<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Milgrom *et al.*, 1996[262] | Volunteer/convenience sample for comparison of diary records, electronic monitoring and disease exacerbation in relation to adherence with inhaled corticosteroids and $\beta_2$-agonists via pMDI | Outpatient clinic<br><br>**In**: Children requiring both ICS and $\beta_2$-agonists via pMDI, and who reliably kept clinic appointments<br><br>**Out**: Known non-compliance<br>Use of spacers and nebulisers<br>$\beta_2$-agonists only as needed | *n* = 24<br><br>14 M<br><br>Age: (8–12) | 13 weeks<br><br>Diary records compared with electronic monitoring<br><br>Disease exacerbations requiring oral corticosteroids | Diary compliance records:<br>78.2% for $\beta_2$-agonists<br>95.4% for corticosteroids<br><br>Electronic compliance records:<br>48.0% for $\beta_2$-agonists<br>32.0% for corticosteroids<br><br>Compliance with inhaled steroids was 13.7% in 8 patients who needed additional oral steroids, and 68.2% in those who did not ($p = 0.008$) | Did not compare devices<br><br>Small selective sample |
| Kamps *et al.*, 2000[263] | DPI or pMDI plus spacer<br><br>Case-control study comparing effectiveness of repeated inhalation instructions (control) versus no systematic inhalation instructions (cases) | Outpatient clinic | *n* = 66 newly referred patients<br><br>Age: 5 (1–14)<br><br>37 M<br><br>vs:<br><br>*n* = 29 in clinical trial (controls)<br><br>Age: 7 (5–10)<br><br>21 M | Inhalation technique score according to criteria defined by Netherlands Asthma Foundation | 60 patients had received inhalation instructions prior to referral:<br>29% using DPI correctly<br>67% using pMDI plus spacer correctly<br>($p < 0.01$)<br><br>Repeated comprehensive inhalation instruction in clinical trial setting or at the pharmacy resulted in:<br>79% using DPI correctly<br>93% using pMDI plus spacer correctly<br>versus 39% who had received a single instruction by a GP<br>($p < 0.01$) | Study not designed to differentiate between devices<br><br>Generalisability? |

*continued*

***TABLE 26 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Non-compliance<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Celano *et al.*, 1998[264] | pMDI use and pMDI/pMDI + spacer technique | Urban hospital outpatient clinic<br><br>**In**: Age 6–17 yr with moderate/severe asthma Albuterol via pMDI + at least one anti-inflammatory agent via pMDI +spacer<br><br>**Out**: Current immunotherapy or oral corticosteroids for significant periods over previous year | *n* = 55 families<br><br>98% African-American<br><br>Age 10.8 ± 2.7 (6–17)<br><br>Children 57% M | FU 2–20 weeks (mean 10)<br><br>Estimated MDI adherence (from canister weight)<br><br>Self-reported adherence<br><br>MDI/MDI + spacer technique (from MDI checklist)<br><br>Assessed at FU after instruction at study entry | 34 sets of data for estimated adherence (range 0–100% (mean 44%))<br><br>Poor or no correlation between self-reported and estimated use<br><br>MDI checklist available data for 49 patients: 27% scored zero; remainder demonstrated varying technique but achieved minimum criteria to ensure at least some drug delivery<br>Interrelationship between measured adherence behaviours not significant | Did not compare inhaler devices<br><br>Several study limitations |
| Zora *et al.*, 1989[265] | Maintenance $\beta_2$-agonists (metaproterenol 2 sprays 3–5 times daily via pMDI no spacer)<br><br>Study of compliance assessed by canister weighings and patient records of daily inhaler use and symptom scores | Outpatient clinic<br><br>**In**: Diagnosis of asthma confirmed by 15% reversibility in the $FEV_1$<br><br>Maintenance $\beta_2$-agonists | *n* = 17<br><br>Age: (5–13)<br><br>13 M | 5 children for 2 weeks<br>12 children for 2 consecutive 2-week periods<br><br>Compliance as assessed by canister weight | 2/5 deemed compliant during 2-week study<br>1/12 deemed compliant during 4-week study<br>1/5 had diary correlating with actual use during 2-week study<br>0/12 had diary correlating with actual use during 4-week study<br><br>Symptom scores indicated a non-significant improvement in relation to more compliant use | Non-comparative<br><br>Small study numbers<br><br>Did not compare inhaler devices |

*continued*

***TABLE 26 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Non-compliance<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Jonasson *et al.*, 1999[257] | Turbohaler budesonide 100 μg or 200 μg or placebo in 2 divided doses<br><br>Group I:<br>Budesonide 200 μg a.m. and placebo 100 μg p.m.<br><br>Group II:<br>Budesonide 100 μg a.m. and placebo 100 μg p.m.<br><br>Group III:<br>Budesonide 100 μg a.m. and budesonide 100 μg p.m.<br><br>Group IV:<br>Placebo 100 μg a.m. and placebo 100 μg p.m.<br><br>Double-blind randomised study of patient compliance assessed by diary/dose count/symptom score | 1 centre<br><br>**In**: Mild asthma (mean baseline $FEV_1$ 103% of predicted)<br><br>No documented power calculation<br><br>Compliance level assessed by Student's two-sample *t*-test<br>Analysis of co-variance was used to determine the degree of association with any demographic variables | *n* = 163<br><br>Age: 9.9 (7–16)<br><br>107 M | 2-week open run-in period followed by 12-week study period<br><br>Compliance assessed by diary records and dose counts | Results available from 161 participants<br><br>Significant difference between self-reported and measured compliance<br>a.m.: 93% diary, 76% measured ($p < 0.001$)<br>p.m.: 94% diary, 77% measured ($p < 0.001$)<br><br>86% had higher self-reported than measured compliance for a.m. medication compared with 94% for p.m. medication<br><br>No correlation between symptom scores and adherence or placebo treatment and adherence | Mild asthma<br><br>Did not compare devices |
| Jonasson *et al.*, 2000[258] (Extension study of ref. 257 above) | As above | As above | *n* = 122<br><br>Age: (7–16)<br><br>80 M | 27 months' treatment<br><br>Measured drug adherence at 6-month intervals | Adherence decreased with time and with use of placebo treatment (significant level of difference after 21 months)<br><br>Adherence better in p.m. than in a.m., a difference that became significant after 3 months' treatment<br><br>Adherence in two different age groups (7–9 versus 10–16 yr at baseline) was on all occasions higher in the younger age group, but only significantly so during the first 3 months' treatment | As above |

*continued*

***TABLE 26 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Non-compliance<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Bender B *et al.*, 2000[266] | Measured adherence in relation to use of pMDI<br><br>Comparison between:<br>Mother's report<br>Child's report<br>Canister weight<br><br>Electronic measurement (clinical trial: electronic doser attached to inhaled steroid pMDI) | 1 centre<br><br>**In**: Mild to moderate asthma including at least twice-weekly asthma symptoms and requiring daily inhaled anti-inflammatory medicines<br><br>**Out**: Severe asthma or other serious medical conditions<br><br>Non-randomised, non-controlled study | *n* = 27<br><br>Age: 10.9 ± 2.5 (7–12)<br><br>16 M<br><br>African-American *n* = 6<br>Hispanic *n* = 4 | 6 months with assessment at 2-month intervals | Mothers and children reported, on average, over 80% adherence with the prescribed inhaled steroid<br><br>Canister weight revealed, on average, adherence of 69%, significantly lower than self-report<br><br>Adherence: showed trend towards lower adherence in older children, children with poorer functioning families, boys, children in homes with a smoker or a pet, and non-white children (significant difference)<br><br>Favours electronic doser as means of estimating adherence | Did not compare devices<br><br>Small sample size<br><br>Generalisability? |
| Goren *et al.*, 1994[267] | Use of Turbohaler terbutaline by children aged 3–6 yr<br><br>Open, non-controlled study | Consecutive attenders at outpatient asthma clinic | *n* = 59<br><br>Age: (3–6)<br><br>39 M | Efficiency of inhalation technique (scored) after instruction/ demonstration and pharmacological effect of the terbutaline (sum of clinical symptom scores) in the inhaler, measured at a single visit | 0%, 43%, 67% and 80% of 3-, 4-, 5- and 6-year-olds respectively used the Turbohaler efficiently (statistically significant between 3-year-olds and combined other age groups)<br><br>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; 3 asymptomatic patients not included) | Did not compare devices<br><br>Small sample size<br><br>Selective sample<br><br>Restricted age range<br><br>Generalisability? |

*continued*

***TABLE 26 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Non-compliance<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Yeatts *et al.*, 2000[268] | Study of barriers to inhaler use amongst non-white (African-American) and white adolescents | Population-based sample (public school system in North Carolina, USA) | *n* = 2056<br><br>296 had used an inhaler in the previous year<br><br>185 had been diagnosed with asthma<br><br>Age: (13–14)<br><br>34% African-American | Sociodemographics of inhaler users | 14% reported using an inhaler in the previous 12 months, with no differences among African-American and white children<br><br>26% were not allowed to carry their inhaler at school<br><br>Girls were more likely to be allowed to carry their inhalers at school and diagnosed asthmatic girls had a higher prevalence of wheezing in the last year (47%) compared with diagnosed asthmatic boys (26%)<br><br>Smoking prevalence was higher in inhaler users (26%) compared with the study population (19%) ($p = 0.001$)<br><br>African-Americans were slightly more likely to take their inhaler medication only when needed (83%) compared with white children (75%) (Note: only small numbers involved) | Did not compare devices<br><br>Relevance to the UK? |
| Vichyanond *et al.*, 1994[269] | Turbohaler terbutaline 500 μg t.d.s.<br><br>Open non-comparative study of handling and efficacy (symptom scores and PEFR) after verbal and written instruction | Multicentre outpatient clinics throughout East Asia<br><br>**In**: Children with mild to moderate asthma, as classified according to the international consensus for the diagnosis and treatment of asthma<br><br>**Out**: Hypersensitivity to $\beta_2$-agonist drugs<br>Concomitant conditions, such as cardiovascular, renal or hepatic disease<br><br>83 included in PP analysis | *n* = 86<br>(58 had used pMDIs previously)<br><br>Age: 8.7 (5–14)<br><br>Asian children | 1 week run-in<br>4-week study<br><br>Handling assessed objectively by investigator and subjectively by patient/parent<br><br>Efficacy from PEFR (% predicted) and asthma symptom score (diary records and clinic assessment) | Maximum scores for inhalation were achieved by 73% of patients after combined verbal and written instructions at the start of the study and by 99% ($p < 0.001$) at the end of the 4-week treatment period<br><br>Verbal instructions yielded better results for inhalation technique scores than written instructions at all times ($p < 0.001$)<br><br>90% considered use of Turbohaler to be easy and effective in affording symptom relief<br><br>Improvements in PEFR ($p < 0.01$) and reduction in asthma symptom scores ($p < 0.005$ for a.m. scores; $p \leq 0.0001$ for p.m. scores) were observed during treatment<br><br>All patients tolerated the study medication well without any serious adverse events | Did not compare devices<br><br>Generalisability? |

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***TABLE 26 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Non-compliance<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Kesten *et al.*, 1994[270] | Albuterol via DPI (Diskhaler) at equivalent dose in place of usual $\beta_2$-agonist (78% were using pMDI alone)<br><br>Non-comparative open assessment | Primary and respiratory practices<br><br>**In**: Patients aged >6 yr requiring inhaled $\beta_2$-agonist for stable reversible obstructive airways disease<br><br>Open, non-randomised study<br><br>No documented power calculation<br><br>Fisher's exact test used for comparisons among 3 age groups; significance level was <0.05 | *n* = 4529<br><br>Age: 39 ± 22<br>653 between 6 and 12 yr<br>Age bands:<br><13<br>13–64<br>>64<br><br>43 excluded on initial screening<br><br>2219 M | 2 weeks<br><br>Patient preference over usual inhaler device<br><br>Adequate demonstration of 6 device-handling steps after initial instruction and at end of study period | The majority of paediatric patients preferred the disk delivery system to their previous inhalation device ($p < 0.001$)<br><br>After instruction 98.5% demonstrated adequate technique at the initial visit<br><br>At the conclusion of the trial, incorrect use was noted in 10.2% of the elderly patients and 3.2% of all other age groups combined ($p \leq 0.001$)<br><br>112 patients withdrawn owing to adverse events (100 non-major, 12 major, 88 considered drug related)<br><br>3 major adverse events considered to be drug related | Did not directly compare devices |
| Winkelstein *et al.*, 2000[271] | Convenience sample of 30 families whose children were using daily inhaled asthma medication via MDI, participating in a US community-based research study | Domiciliary, structured interviews relating to usage, technique and knowledge of asthma medication by both parent and child | *n* = 30<br><br>School-age (6–14) urban African-American children<br><br>18 M | Medication concordance and discordance between parent and child and parent and physician reports of asthma medications<br><br>Sociodemographic factors associated with early self-administration | 93% took inhaled medication without parental supervision<br><br>Early self-administration was associated with parental employment status and childhood behaviours<br><br>Only 7% had effective MDI skills<br><br>Considerable discordance between parent/child and parent/physician reports of asthma medications | Did not compare devices<br><br>Small sample size<br><br>Generalisability? |

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***TABLE 26 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Non-compliance<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Gracia-Antequera and Morales Suarez-Varela, 1999[276] | DPI vs pMDI vs pMDI + extension chamber<br><br>Non-randomised intervention study<br><br>After baseline assessment, intervention was instruction (structured sessions of correct use and handling of inhalers with new assessment at FU) | Paediatric outpatient department<br><br>142 included in PP analysis (i.e. remained on same inhaler device) | *n* = 255<br><br>**Age**: 10.5<br>7–12-year-olds made up 57% of the sample<br><br>103 M | Mean FU period 10.5 months | An increase in correct manoeuvres was observed for all 3 devices:<br><br>**Relative risk and 95% CI of incorrect post-intervention use**:<br>DPI 0.59 (0.38 to 0.92)<br>MDI 0.23 (0.10 to 0.56)<br>MDI/spacer 0.54 (0.32 to 0.90)<br><br>Multivariate analysis suggests that the improvement was observed irrespective of gender and age interval and was better when parents cooperated with nursing and medical staff | |
| Kelloway *et al.*, 1993[277] | Autohaler<br><br>Use and design of PII | | *n* = 40<br><br>Naive *n* = 20<br><br>Previous pMDI *n* = 20<br><br>Adults and children<br><br>Age: (12–17) | | Using only PII for guidance, 5/20 (25%) failed to trigger the device<br><br>Using revised PII (based on patient feedback) 1/20 (5%) of different participants failed to trigger the device<br><br>85% thought that the device was easier to use than an MDI | |

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***TABLE 26 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Non-compliance<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Pedersen *et al.,* 1986[278] | DPI (Rotahaler) vs pMDI vs pMDI + spacer<br><br>Open, non-randomised study | Outpatient clinic with recruitment over a 4-month period<br><br>**In**: Children with perennial asthma who agreed, with informed consent, to participate<br><br>Receiving inhalation therapy on a regular basis with the inhaler prescribed since treatment was started | *n* = 256<br><br>Age: 9.7 (4–16)<br><br>MDI *n* = 132<br>MDI + spacer *n* = 85<br>Rotahaler *n* = 39<br><br>172 M | Baseline assessment of $FEV_1$ + demonstration and details of inhaler technique and instruction<br><br>If $FEV_1$ ≥15% 10 minutes after the demonstration, then inhalation technique assessed as efficient; evaluated only in children with pre-treatment $FEV_1$ ≤85% of predicted on day of study | In 43%, demonstration of inhaler technique deemed efficient<br><br>In 52%, demonstration of inhaler technique deemed inefficient<br><br>5% did not have reversible asthma on the day of the study<br><br>No statistically significant, systematic variation with age found when results for all inhaler types grouped together or considered separately<br><br>Comparison of results from those aged <6 yr with all other age groups showed a significantly lower frequency of efficient technique (0% vs 47%) and a higher mean % of errors (5.9% vs 3.3%) in the lower age group ($p < 0.01$) for both variables<br>Nasal inhalation in particular was more common in younger than older children ($p < 0.01$)<br><br>Important variables:<br>Person who had taught the child how to use the inhaler<br>Initial choice of inhaler device controlled by use of pulmonary function tests | |

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***TABLE 26 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Non-compliance<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Arshad, 1993[215] | **T1**: Breath-actuated (Autohaler)<br>**T2**: MDI<br><br>**Drug**: Sodium cromoglicate, 2 puffs (10 mg) q.d.s.<br><br>**Design**: Randomised, open, cross-over, controlled<br><br>**Jadad** = 1 | Multicentre, UK<br><br>**In**: Stable asthma, airways reversibility of >15% to an inhaled bronchodilator, currently treated with sodium cromoglicate, duration of asthma varied between 10 weeks and 15 yr (mean 6.5 yr), ability to use the MDI<br><br>Study participants considered good coordinators for pMDI technique<br><br>**Out**: Not stated<br><br>**Power calculation**: 150/group, at power 90%<br><br>**PP analysis** | **At beginning**: *n* = 181<br>T1: 90<br>T2: 91<br><br>**At end**: *n* = 166<br><br>**Age**: 10.4 (4–18) (except 1 patient aged 39 yr)<br><br>**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<br><br>**FU**: 8 weeks (4-week treatment period before cross-over); 3 clinical visits<br><br>**Primary**: Lung function, daily diary cards with 4 named symptom scores, bronchodilator use; PEFR b.d., clinician assessment of severity, treatment efficacy assessed by patient and clinician, self-assessed acceptability of device, unusual events<br><br>**Secondary**: Ease of use, coordination of actuation with inhalation, control of asthma in the 2 treatment periods | In the clinicians' opinion, overall severity of asthma did not differ for the 2 devices, nor were there any differences in the number and distribution of unusual events<br><br>Both patients' and clinicians' opinions of sodium cromoglicate effectiveness were significantly better for Autohaler vs MDI ($p < 0.01$)<br><br>56 patients found Autohaler better; 67 found no difference between devices; 35 found MDI better<br><br>90 patients found Autohaler to be more acceptable than MDI, 24 found MDI more acceptable ($p < 0.001$); 43 found both devices equally acceptable | No significant differences in clinical efficacy found between Autohaler and MDI |

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***TABLE 26 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Non-compliance<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Edmunds *et al.,* 1979[240] | **T1**: pMDI and DPI placebo<br>**T2**: DPI (Rotahaler) and pMDI placebo<br><br>**Drug**: BDP 2 puffs of aerosol q.d.s.; 1 capsule in the Rotahaler q.d.s.<br><br>**Design**: Randomised, double-blind, cross-over<br><br>**Jadad** = 2 | 1 site, UK<br><br>**In**: Severe asthma; all children requiring treatment with BDP<br><br>**Out**: Not stated<br><br>**PP analysis**: No | **At beginning**: *n* = 14<br><br>**Age**: 9.7 (4.8–15.1)<br><br>**M/F**: 7/7 | **Run in**: All patients taught how to use the pMDI and Rotahaler before study<br><br>**FU**: 2 months; each month, 1 device contained active drug and the other a placebo<br><br>**Primary**: Ability to use device, sum of diary recorded symp-toms, no. symptom-free days, a.m. and p.m. PEFR, and rescue salbutamol use | Mean symptom score was significantly less with T1 vs T2 ($p$ = 0.04)<br>No significant differences between the 2 periods for any of the other recorded parameters<br><br>"Younger" children preferred to use Rotahaler (not a predefined outcome) | |

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***TABLE 26 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Non-compliance<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Dal Col *et al.*, 1995[237] | **T1**: DPI (Pulvinal, multidose)<br>**T2**: DPI (Rotahaler, single dose)<br>**T3**: Placebo via Pulvinal<br>**T4**: Placebo via Rotahaler<br><br>**Drug**: Salbutamol powder, single dose, 200 μg<br><br>**Design**: Randomised, cross-over<br><br>**Jadad** = 1 | 1 site, USA<br><br>**In**: Stable asthma, at screening visit $FEV_1$ and PEFR >75% predicted normal, history of exercise-induced asthma and reversible airway obstruction<br>On day 1 of study, with no treatment, patients had to have ≥15% maximum fall in $FEV_1$ vs baseline values to continue trial<br><br>**Out**: In case of possible exposure to sensitising agents during the study: acute attacks of asthma in the 2 months prior to study; presence of concomitant disease, or of cardiac, hepatic, renal or endocrine disorders; use of oral steroids during the previous 2 months; and impossibility of discontinuing concomitant treatments 24 h before testing<br><br>**Power calculation**: No<br><br>**PP analysis** | **At beginning**: *n* = 13<br><br>**Age**: 10.9 (8–12)<br><br>**M/F**: 9/4 | **Run in**: Standard exercise same time on each trial day: 6 minutes on treadmill with 10° slope<br>Use of sodium cromoglicate, nedocromil sodium, bronchodilators and antihistamines stopped ≥24 h before test; inhaled steroid use permitted, dose fixed<br>Instruction on how to use inhalers, with drawings on correct technique<br><br>**FU**: 4 consecutive days<br><br>**Primary**: $FEV_1$ and PEFR before and after treatment and exercise challenge, ease of use, correct handling technique | No significant difference between T1 and T2 ($p > 0.05$)<br><br>Investigator's opinion on ease of use for T1 was excellent for 10 patients and good for 3<br>The opinion for T2 was excellent for 3 patients, good for 8 and fair for 2<br><br>No patient reported a verdict of "poor" for ease of use for either T1 or T2<br><br>11 patients preferred T1 while 1 preferred T2; 2 patients had no preference (data as presented by authors)<br><br>No adverse events reported throughout study | |

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***TABLE 26 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Non-compliance<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Becker *et al.*, 1985[226] | **T1**: pMDI + spacer (tube 80 ml, 10 × 3.2 cm) and placebo via pMDI<br>**T2**: pMDI and placebo via pMDI + spacer<br>**T3**: Placebo via both devices<br><br>**Drug**: Terbutaline, 250 μg/actuation, given in a total dose of 500 μg<br>Placebo was the CFC propellant–surfactant mixture used in the active inhaler<br><br>**Design**: Randomised, double-blind, placebo-controlled<br><br>**Jadad** = 2 | 1 hospital, Canada<br><br>**In**: History of asthma, documented reversibility of obstruction to airflow previously (increase $FEV_1$ >20% after bronchodilator aerosol), $FEF_{25–75\%}$ <70% predicted normal<br><br>**Out**: Severe acute asthma on study day<br><br>**Power calculation**: No<br><br>**PP analysis**: Assumed | **At beginning**:<br>*n* = 34<br>T1: 12<br>T2: 12<br>T3: 10<br><br>**At end**:<br>*n* = 34<br><br>**Age**:<br>T1: 11.7 ± 0.8<br>T2: 10.2 ± 0.6<br>T3: 10.5 ± 0.6<br><br>**M/F**: Not stated | **Run-in**: Stopped oral medication for 12 h or inhaled bronchodilator aerosol for 6 h before study<br>Demonstration and supervision given by investigator<br><br>**FU**: 3 occasions, 2–7 days apart and within 14 days<br><br>**Primary**: Pulmonary function | 4/34 (11.7%) had no errors in inhaler technique<br><br>**No. patients who failed to:** / **pMDI (*n* = 34)** / **pMDI + spacer (*n* = 34)**<br>Remove cap: 0 / N/A<br>Shake inhaler: 3 / 7<br>Position device correctly: 0 / 4<br>Extend neck slightly: 12 / 17<br>Close lips: 0 / 0<br>Exhale completely: 2 / 3<br>Hold breath while actuating: N/A / N/A<br>Co-ordinate actuation and inspiration early: 13 / 1<br>Co-ordinate actuation and inspiration late: 9<br>Inhale slowly, deeply: 9 / 7<br>Hold breath (10 s): 3 / 3<br>Breathe out: 3 / 2<br>Wait 30 s before repeat: 1 / 1 | Both pMDI + spacer and pMDI were equally effective in improving pulmonary function from the baseline state |
| Boulet *et al.*, 1995[236] | **T1**: Diskus and placebo via Diskhaler<br>**T2**: Diskhaler and placebo via Diskus<br><br>**Drug**: Salmeterol, 50 μg b.d.<br><br>**Design**: Randomised, double-blind, double-dummy, parallel-group, multicentre<br><br>**Jadad** = 3 | 16 sites, USA<br><br>**In**: Aged ≥12 yr, $FEV_1$ between 60% and 90% predicted normal, receiving adequate anti-inflammatory and inhaled $\beta_2$-agonist<br>Last 7 days of baseline period, mean a.m. PEFR 60–80% 15 minutes after inhalation of 800 μg albuterol<br>No methylxanthines, anticholinergics, oral/parenteral corticosteroids/other routine $\beta_2$-agonist during study<br><br>**Power calculation**: 90%<br><br>**PP analysis**: Assumed | **At beginning**:<br>*n* = 463<br><br>**At end**:<br>*n* = 380<br>T1: 190<br>T2: 190<br><br>**Age**:<br>T1: 39 (12–70)<br>T2: 39 (12–69)<br><br>**M/F**:<br>T1: 77/113<br>T2: 78/112 | **Run-in**: 2-weeks, instruction leaflet and taught by physician on the use of study devices given<br><br>**FU**: 4 weeks<br><br>**Primary**: Self-filled daily record of a.m. and p.m. PEFR, a.m. and p.m. asthma symptom scores, and use of albuterol; clinic-recorded pulmonary function tests and adverse effects | For all ease of use, ease of monitoring remaining doses and preference, Diskus > Diskhaler ($p < 0.001$)<br><br>**Ease of use** / **Diskus (%)** / **Diskhaler (%)**<br>Use correctly after 1st training: >80 / 70<br>Use correctly at end of treatment: 99 / 98<br>Very easy to use: 85 / 45<br>Easier to count remaining doses: 91 / 61<br>Preference: 73 / 15<br><br>(12% with no preference)<br><br>No unexpected adverse events | Majority of patients aged >15 yr<br><br>Diskus rated as easier to use and to tell remaining doses than Diskhaler<br><br>Diskus also rated as easier to learn to use than Diskhaler |

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***TABLE 26 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Non-compliance<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| van der Palen *et al.,* 1998[260] | **T1**: DPI (Turbuhaler)<br>**T2**: DPI Diskus (Accuhaler)<br><br>**Drug**: Not stated<br><br>**Design**: Open, randomised, cross-over<br><br>**Jadad** = 1 | 1 site, Belgium<br><br>**In**: Aged ≥15 yr, naive to Diskus/Accuhaler and Turbuhaler, but currently using inhaled medication<br><br>**Out**: Limited ability to understand and speak Dutch<br><br>**Power calculation**: No<br><br>**PP analysis**: Not stated | **At beginning**: *n* = 50<br><br>**At end**: *n* = 50<br><br>**Age**: 49 (15–74) | **Baseline period**: None<br><br>**FU**: Same-day assessment: patients shown and asked to read inhaler-specific instruction leaflet and then use the inhaler<br>Inhalation technique assessed using a purpose-designed inhaler-specific checklist<br>Same procedure repeated for second inhaler<br>Patients asked to scale the importance of the inhaler's features and state preference<br><br>**Primary**: Ease of use and preference<br>Mean checklist scores of inhalation technique | Mean checklist scores of inhalation technique were not significant between Diskus/Accuhaler (92.7%) and Turbuhaler (92.0%) ($p$ = 0.52)<br><br>From the essential checklist items, statistical difference in errors with "loading" the device: Turbuhaler (93.5%) < Diskus/Accuhaler (97.3%) ($p$ = 0.045)<br><br>% patients performing all items correctly: Diskus/Accuhaler (25, 50%) and Turbuhaler (23, 46%) ($p$ = 0.75)<br><br>% patients performing all essential items correctly: 46 (92%) for Diskus/Accuhaler vs 37 (74%) for Turbuhaler<br><br>98% patients considered a clear instruction leaflet to be important/very important<br><br>>90% considered important: ease of holding the device, overall perceived ease of use, ease of use in acute exacerbation, and a clear counting mechanism<br><br>Preference: 17 patients Diskus/Accuhaler vs 25 Turbuhaler; 8 no preference ($p$ > 0.05)<br><br>Significant differences ($p$ < 0.001): favoured Turbuhaler > Diskus/Accuhaler for ease of carrying, size, inconspicuousness, and reading remaining doses | Inhalation technique with both devices was equally good<br><br>Error in loading device > for Turbuhaler than Diskus/Accuhaler (Turbuhaler requires 2 critical steps in loading, while Diskus has 1 correct action)<br><br>More patients preferred Turbuhaler than Diskus/Accuhaler for size, ease of carrying and counting remaining doses |

*continued*

***TABLE 26 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Non-compliance<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Mahajan and Okamoto, 1997[259] | **T1**: DPI Diskus and placebo via Diskhaler<br>**T2**: Diskhaler and placebo via Diskus<br>**T3**: placebo via Diskus and Diskhaler<br><br>**Drug**: Fluticasone propionate 500 µg<br><br>**Design**: Randomised, double-blind, double-masked, placebo-controlled<br><br>**Jadad** = 3 | 16 sites, USA<br><br>**In**: Age ≥12 yr, $FEV_1$ between 50% and 80% predicted<br><br>**Power calculation**: No<br><br>**PP analysis**: Assumed | **At beginning**:<br>*n* = 213<br>T1: 64<br>T2: 79<br>T3: 70<br><br>**At end**:<br>*n* = 155 (but only 154 completed questionnaire at week 12)<br>T1: 33<br>T2: 54<br>T3: 68<br><br>**Age**: 33 (12–76)<br><br>**M/F**: Not stated | **Run-in**: 2-week familiarisation with placebo via Diskhaler and Diskus inhalers in single-masked manner and to assess compliance<br><br>**FU**: 12 weeks: questionnaires completed on 4 visits (screening visit, after run-in period, the 6th week and 12th week of study)<br><br>**Primary**: Performance assessment based on criteria: convenient to carry, durability, ease of use, ease of loading, ease of holding and operating, ease of cleaning, ease of telling number of doses left | **Performance assessment of the 7 attributes (% satisfied/very satisfied):**<br><br>**Diskhaler** / **Diskus**<br>At screening, 1st exposure (*n* = 210): 60–95 / 72–95<br>After week 12 of use (*n* = 154): 57–88 / 76–96<br>Week 12/at time of withdrawal (*n* = 154): 60–89 / 74–95<br><br>**Global assessments (%):**<br><br>**Diskhaler** / **Diskus**<br>*Comfortable/very comfortable:*<br>At screening, 1st exposure (*n* = 210): 60 / 72<br>Week 12 (*n* = 154): 79 / 85<br>*Like/strongly like:*<br>Week 12 (*n* = 154): 67 / 85<br>*Satisfied/very satisfied:*<br>Week 12 (*n* = 154): 72 / 82–84<br>*Preference for device* (n = *189):*<br>Week 12 (13% had no preference): 25 / 61<br><br>No statistically significant difference between T1 and T2 for treatment effects<br><br>Also showed that patients were rating only devices, not the medication they received | Diskus inhaler was preferred over Diskhaler, possibly due to characteristics of Diskus inhaler (convenience of not having to load Diskus with medication) |

*continued*

***TABLE 26 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Non-compliance<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr)<br>mean ± SD<br>(range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes<br>(primary,<br>secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Ahlström *et al.,* 1989[218] | **T1**: DPI Turbuhaler<br>**T2**: pMDI + spacer (Nebuhaler)<br><br>**Drug**: Terbutaline<br>T1: 0.5 mg/dose;<br>1 inhalation t.d.s.<br>T2: 0.25 mg/dose,<br>2 inhalations t.d.s.<br><br>**Design**: Open, cross-over, randomised<br><br>**Jadad** = 2 | 2 centres, Sweden<br><br>**In**: Not stated<br><br>**Power calculation**: No<br><br>**PP analysis**: Assumed | **At beginning**:<br>*n* = 26<br><br>**At end**:<br>*n* = 21<br><br>**Age**: 3.9 (2–5)<br><br>**M/F**: 14/7 | **Run-in**: 1 week<br>Patients and their parents acquainted themselves with the diaries<br>Patients were trained how to use device<br>All treatment, except $\beta_2$-agonists, kept constant during the study<br><br>**FU**: 2 treatment periods, each of 14 days<br><br>**Primary**: Asthma symptom score, PEF, extra inhalation of same drug, side-effects<br><br>**Secondary**: Children and parents' preference for the 2 devices | Inhalation with T1 and T2 resulted in a significant increase in PEF ($p < 0.001$)<br>PEF values 15 minutes after inhalation in a.m. for T1 > T2 ($p = 0.046$)<br>Baseline PEF values after inhalation in p.m. for T1 > T2 ($p = 0.03$)<br><br>No statistical difference found between T1 and T2 for asthma symptoms when present and extra medication<br><br>Mild side-effects experienced by few children; no significant difference between T1 and T2<br><br>Parents' assessments of efficacy, side-effects and ease of use for each treatment period:<br>Significantly fewer side-effects found with T1 vs T2<br>No significant difference in efficacy between T1 and T2, but was considered easier to use ($p = 0.002$)<br>19 parents wanted their children to use T1 in the future while 2 parents preferred T2 ($p < 0.001$) | Turbuhaler was as effective as pMDI + Nebuhaler in treatment of bronchial asthma in small children |

*continued*

***TABLE 26 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Non-compliance<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr)<br>mean ± SD<br>(range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes<br>(primary,<br>secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Sharma RK *et al.,* 1996[280] | Accuhaler versus Turbohaler in "powder naive" asthmatic children aged 4–14 yr<br><br>Cross-over assessment at a single visit of each device in turn<br>Randomised with respect to order in which devices presented | Outpatient clinic<br><br>**In**: Children aged 4–14 yr requiring ICS and/or $\beta_2$-agonists via pMDI "Powder naive" | *n* = 162<br><br>*n* = 84 (4–9 yr)<br><br>*n* = 78 (10–14 yr)<br><br>95 M | Spontaneous and prompted assessment of pMDI<br><br>Views on properties of ideal inhaler (prompted)<br><br>Comparison of Accuhaler and Turbohaler:<br>Attractiveness<br>Attached cover<br>Indicator of doses left<br>Shape<br>Perceived ease of use<br>Ease of holding<br>Mouthpiece<br>Hygiene<br>Instructions<br>Weight<br>Discreetness<br>Ease of carrying<br>Size | Patients/parents stated ease of use and effectiveness as desirable features of current pMDI<br><br>With prompting, the most desirable features of an ideal inhaler included ease of use and the presence of a dose counter<br><br>The Accuhaler scored more highly than the Turbohaler on all prompted features apart from size | Most commonly cited reason for overall preference was perceived ease of use among the parents of 4–9-year-olds and overall design amongst the 10–14-year-olds |

*continued*

***TABLE 26 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Non-compliance<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Northfield *et al.*, 1991[275] | Turbohaler terbutaline p.r.n. in inhaler naive asthmatics<br><br>Open study to assess efficacy, acceptability and effect on lifestyle | General practice<br><br>**In**: Newly diagnosed or receiving oral bronchodilator alone and not in need of urgent treatment | *n* = 1133 adults and children<br><br>*n* = 345 (6–16 yr) | 1-week run-in<br><br>4-week treatment period<br><br>Efficacy:<br>PEFR<br>Symptom diary<br>Lifestyle index changes | After terbutaline treatment, PEFR rose significantly and severity (scored) of each asthma symptom was reduced by between 45% and 47% (all $p < 0.001$)<br>The purported adverse effect of asthma on lifestyle was reduced by 51% ($p < 0.001$)<br>These results were comparable for all age-related subgroups<br><br>Physicians' assessment of inhaler technique indicated that:<br>It was easy or fairly easy to teach the technique to 96% of patients;<br>99% learnt the correct technique;<br>99% demonstrated a good or acceptable technique at the end of the study<br><br>Patients' assessment of terbutaline treatment via Turbohaler indicated that:<br>90% found it to be beneficial;<br>98% found it easy to use | Terbutaline preferred by 91% of the patients who had previously received oral anti-asthma therapy<br><br>$p < 0.001$ for all of the findings |
| Williams and Richards, 1997[197] | Randomised, multicentre open-label, parallel-group study<br><br>Accuhaler fluticasone 500 μg b.d.<br><br>versus<br><br>Turbohaler budesonide 200 μg b.d. | UK hospitals and UK general practice<br><br>**In**: Children aged 4–11 yr who were receiving or had symptoms indicating a clinical requirement for ICS at a daily dose of 400 μg budesonide or 200 μg fluticasone | *n* = 323<br><br>Age: (4–11) | Primary efficacy parameter was mean % predicted a.m. PEF<br><br>Secondary measures included patient assessment of device handling | Change from baseline to week 4 of treatment in mean % predicted a.m. PEF was higher in the fluticasone propionate Accuhaler group (median 100.2% vs 98.8%, $p < 0.012$)<br><br>Accuhaler was rated more favourably than Turbohaler in terms of:<br>Ease of use<br>Ease of telling no. doses left<br>Ease of knowing whether the dose had been inhaled<br>Overall liking of the device<br><br>More patients in the Accuhaler (85%) than in the Turbohaler (58%) group said that they would be happy to receive the same device again, while 8% and 25% respectively said that they would not | |

*continued*

***TABLE 26 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Non-compliance<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Baciewicz and Kyllonen, 1989[273] | Ability of children aged 4–18 yr to use a pressurised inhaler<br><br>Open assessment regardless of drug type | Sample of outpatients attending paediatric respiratory clinic over 3-month study period<br><br>**In**: Children who had used pressurised inhalers for >6 months<br><br>**Out**: Children who had received formal instruction in the use of the inhaler during the previous 6 months and children who used tube spacers | *n* = 25<br><br>Age: (7.5–18)<br><br>13 M | Assessment by a clinical pharmacist of steps required to ensure efficient inhaler technique | No child was observed to have completed all inhaler techniques correctly; patients had an average of 5.1 errors | Small sample size<br><br>Some subjectivity in assessment |
| Hawksworth *et al.*, 2000[274] | Open intervention (counselling) with aim of improving inspiratory flow rates for patients using Turbohaler | Sample of patients attending community pharmacy with prescription for inhalers | *n* = 24<br><br>Age: 59 ± 19.2 (10–76) | Measured inspiratory inhalation rate via Turbohaler converted to cumulative inspired volume followed by $FEV_1$ (best of 3 manoeuvres) | Mean (SD) inhalation rate (l/min):<br>Pre-counselling: 48.0 (16.8)<br>Post-counselling: 54.7 (17.6)<br><br>Mean (SD) inhaled volume (l):<br>Pre-counselling: 1.75 (0.68)<br>Post-counselling: 1.94 (0.62)<br><br>Mean (SD) $FEV_1$ (% of predicted):<br>Inspiration rate ≥60 l/min: 60.3 (20.2)<br>Inspiration rate <60 l/min: 53.7 (19.4)<br>Median difference –9.0 (95% CI –26.0 to 10.0) | Small sample size<br><br>Mean age suggests inclusion of few patients relevant to current review |

*continued*

***TABLE 26 contd*** *Evidence from the current review*

| Reference | Treatment inhaler type<br>Drug and dose<br>Study design<br>Jadad score | Location, setting<br>Inclusion/exclusion<br>Non-compliance<br>Power calculation<br>Type of analysis | No. patients<br>Age (yr) mean ± SD (range)<br>M/F<br>Ethnicity | Run-in<br>FU<br>Outcomes (primary, secondary) | Results | Comments |
|---|---|---|---|---|---|---|
| Ng *et al.*, 1999[279] | Open study comparing three breath-actuated inhalation devices in terms of perception of ease of use and preference by patients, and the perception of ease of teaching by nurses<br><br>Accuhaler (Diskus)<br>Autohaler<br>Turbohaler | Sample of paediatric inpatients, Kwong Wah Hospital, Hong Kong<br><br>**In**: Children (not necessarily asthmatic) aged >6 yr who had never been taught to use or had ever used any inhalation device before the study | *n* = 31<br><br>Age: 10.6 ± 2.8<br><br>19 M | Perception of ease of use and preference by patients<br><br>Perception of ease of teaching by nurses | Ease of use by patients:<br>Accuhaler 22 ($p$ = 0.0311 vs Autohaler)<br>Autohaler 6 ($p$ = 0.2516 vs Turbohaler)<br>Turbohaler 3 ($p$ = 0.002 vs Accuhaler)<br><br>Patient preference:<br>Accuhaler 23 ($p$ = 0.0104 vs Autohaler)<br>Autohaler 6 ($p$ = 0.2289 vs Turbohaler)<br>Turbohaler 2 ($p$ = 0.0008 vs Accuhaler)<br><br>Ease of teaching by nurses:<br>Accuhaler 15 ($p$ = 0.7024 vs Autohaler)<br>Autohaler 15 ($p$ = 0.019 vs Turbohaler)<br>Turbohaler 1 ($p$ = 0.0048 vs Accuhaler) | Small sample size |

*PII, package insert instructions; N/A, not applicable*
*(Yamanouchi provided confidential information, which was included in the version of the report that was sent to the Appraisals Committee, but this information has been removed from this current document)*

# Appendix 18

## Review group model

***TABLE 27*** *QALY thresholds for salbutamol (assumed 100 µg dose equivalence): cost per QALY threshold £5000*

| Cost per annum (£) | | 3.14 | 3.60 | 3.60 | 3.60 | 4.20 | 7.88 | 7.88 | 9.70 | 10.99 | 11.50 | 11.53 | 11.54 | 11.54 | 12.00 | 17.37 | 18.32 | 18.43 | 30.00 | 30.42 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Device name(s)** | **Asmaven** | **Salamol** | **Airomir** | **Salbulin** | **Ventolin Evohaler** | **Airomir with AeroChamber** | **Salbulin with AeroChamber** | **Ventolin Evohaler with Nebuhaler** | **Airomir Autohaler** | **Salamol Easi-Breathe** | **Asmasal Clickhaler** | **Maxivent with Able Spacer** | **Asmaven with Able Spacer** | **Salamol with Able Spacer** | **Ventolin Rotahaler (200)[a]** | **Aerolin Autohaler** | **Pulvinal** | **Ventodisks (200)[a]** | **Ventolin Accuhaler (200)[a]** |
| **3.14** | **Maxivent** | 0.00000 | 0.00009 | 0.00009 | 0.00009 | 0.00021 | 0.00095 | 0.00095 | 0.00131 | 0.00157 | 0.00167 | 0.00168 | 0.00168 | 0.00168 | 0.00177 | 0.00285 | 0.00304 | 0.00306 | 0.00537 | 0.00546 |
| **3.14** | **Asmaven** | | 0.00009 | 0.00009 | 0.00009 | 0.00021 | 0.00095 | 0.00095 | 0.00131 | 0.00157 | 0.00167 | 0.00168 | 0.00168 | 0.00168 | 0.00177 | 0.00285 | 0.00304 | 0.00306 | 0.00537 | 0.00546 |
| **3.60** | **Salamol** | | | 0.00000 | 0.00000 | 0.00012 | 0.00086 | 0.00086 | 0.00122 | 0.00148 | 0.00158 | 0.00159 | 0.00159 | 0.00159 | 0.00168 | 0.00275 | 0.00295 | 0.00297 | 0.00528 | 0.00536 |
| **3.60** | **Airomir** | | | | 0.00000 | 0.00012 | 0.00086 | 0.00086 | 0.00122 | 0.00148 | 0.00158 | 0.00159 | 0.00159 | 0.00159 | 0.00168 | 0.00275 | 0.00295 | 0.00297 | 0.00528 | 0.00536 |
| **3.60** | **Salbulin** | | | | | 0.00012 | 0.00086 | 0.00086 | 0.00122 | 0.00148 | 0.00158 | 0.00159 | 0.00159 | 0.00159 | 0.00168 | 0.00275 | 0.00295 | 0.00297 | 0.00528 | 0.00536 |
| **4.20** | **Ventolin Evohaler** | | | | | | 0.00074 | 0.00074 | 0.00110 | 0.00136 | 0.00146 | 0.00147 | 0.00147 | 0.00147 | 0.00156 | 0.00263 | 0.00283 | 0.00285 | 0.00516 | 0.00524 |
| **7.88** | **Airomir with AeroChamber** | | | | | | | 0.00000 | 0.00036 | 0.00062 | 0.00072 | 0.00073 | 0.00073 | 0.00073 | 0.00082 | 0.00190 | 0.00209 | 0.00211 | 0.00442 | 0.00451 |
| **7.88** | **Salbulin with AeroChamber** | | | | | | | | 0.00036 | 0.00062 | 0.00072 | 0.00073 | 0.00073 | 0.00073 | 0.00082 | 0.00190 | 0.00209 | 0.00211 | 0.00442 | 0.00451 |
| **9.70** | **Ventolin Evohaler with Nebuhaler** | | | | | | | | | 0.00026 | 0.00036 | 0.00037 | 0.00037 | 0.00037 | 0.00046 | 0.00153 | 0.00173 | 0.00175 | 0.00406 | 0.00414 |
| **10.99** | **Airomir Autohaler** | | | | | | | | | | 0.00010 | 0.00011 | 0.00011 | 0.00011 | 0.00020 | 0.00128 | 0.00147 | 0.00149 | 0.00380 | 0.00389 |
| **11.50** | **Salamol Easi-Breathe** | | | | | | | | | | | 0.00001 | 0.00001 | 0.00001 | 0.00010 | 0.00117 | 0.00137 | 0.00139 | 0.00370 | 0.00378 |
| **11.53** | **Asmasal Clickhaler** | | | | | | | | | | | | 0.00000 | 0.00000 | 0.00009 | 0.00117 | 0.00136 | 0.00138 | 0.00369 | 0.00378 |
| **11.54** | **Maxivent with Able Spacer** | | | | | | | | | | | | | 0.00000 | 0.00009 | 0.00117 | 0.00136 | 0.00138 | 0.00369 | 0.00378 |
| **11.54** | **Asmaven with Able Spacer** | | | | | | | | | | | | | | 0.00009 | 0.00117 | 0.00136 | 0.00138 | 0.00369 | 0.00378 |
| **12.00** | **Salamol with Able Spacer** | | | | | | | | | | | | | | | 0.00107 | 0.00127 | 0.00129 | 0.00360 | 0.00368 |
| **17.37** | **Ventolin Rotahaler (200)[a]** | | | | | | | | | | | | | | | | 0.00019 | 0.00021 | 0.00253 | 0.00261 |
| **18.32** | **Aerolin Autohaler** | | | | | | | | | | | | | | | | | 0.00002 | 0.00233 | 0.00242 |
| **18.43** | **Pulvinal** | | | | | | | | | | | | | | | | | | 0.00231 | 0.00240 |
| **30.00** | **Ventodisks (200)[a]** | | | | | | | | | | | | | | | | | | | 0.00008 |
| **30.42** | **Ventolin Accuhaler (200)[a]** | | | | | | | | | | | | | | | | | | | |

[a]*These devices provide 200 µg equivalent of salbutamol; the costs of the other drugs must be doubled where 200 µg is provided*
*(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 28*** *QALY thresholds for salbutamol (assumed 100 µg dose equivalence): cost per QALY threshold £20,000*

| Cost per annum (£) | | 3.14 | 3.60 | 3.60 | 3.60 | 4.20 | 7.88 | 7.88 | 9.70 | 10.99 | 11.50 | 11.53 | 11.54 | 11.54 | 12.00 | 17.37 | 18.32 | 18.43 | 30.00 | 30.42 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Device name(s)** | **Asmaven** | **Salamol** | **Airomir** | **Salbulin** | **Ventolin Evohaler** | **Airomir with AeroChamber** | **Salbulin with AeroChamber** | **Ventolin Evohaler with Nebuhaler** | **Airomir Autohaler** | **Salamol Easi-Breathe** | **Asmasal Clickhaler** | **Maxivent with Able Spacer** | **Asmaven with Able Spacer** | **Salamol with Able Spacer** | **Ventolin Rotahaler (200)[a]** | **Aerolin Autohaler** | **Pulvinal** | **Ventodisks (200)[a]** | **Ventolin Accuhaler (200)[a]** |
| **3.14** | **Maxivent** | 0.00000 | 0.00002 | 0.00002 | 0.00002 | 0.00005 | 0.00024 | 0.00024 | 0.00033 | 0.00039 | 0.00042 | 0.00042 | 0.00042 | 0.00042 | 0.00044 | 0.00071 | 0.00076 | 0.00076 | 0.00134 | 0.00136 |
| **3.14** | **Asmaven** | | 0.00002 | 0.00002 | 0.00002 | 0.00005 | 0.00024 | 0.00024 | 0.00033 | 0.00039 | 0.00042 | 0.00042 | 0.00042 | 0.00042 | 0.00044 | 0.00071 | 0.00076 | 0.00076 | 0.00134 | 0.00136 |
| **3.60** | **Salamol** | | | 0.00000 | 0.00000 | 0.00003 | 0.00021 | 0.00021 | 0.00031 | 0.00037 | 0.00040 | 0.00040 | 0.00040 | 0.00040 | 0.00042 | 0.00069 | 0.00074 | 0.00074 | 0.00132 | 0.00134 |
| **3.60** | **Airomir** | | | | 0.00000 | 0.00003 | 0.00021 | 0.00021 | 0.00031 | 0.00037 | 0.00040 | 0.00040 | 0.00040 | 0.00040 | 0.00042 | 0.00069 | 0.00074 | 0.00074 | 0.00132 | 0.00134 |
| **3.60** | **Salbulin** | | | | | 0.00003 | 0.00021 | 0.00021 | 0.00031 | 0.00037 | 0.00040 | 0.00040 | 0.00040 | 0.00040 | 0.00042 | 0.00069 | 0.00074 | 0.00074 | 0.00132 | 0.00134 |
| **4.20** | **Ventolin Evohaler** | | | | | | 0.00018 | 0.00018 | 0.00028 | 0.00034 | 0.00040 | 0.00037 | 0.00037 | 0.00037 | 0.00039 | 0.00066 | 0.00071 | 0.00071 | 0.00129 | 0.00131 |
| **7.88** | **Airomir with AeroChamber** | | | | | | | 0.00000 | 0.00009 | 0.00016 | 0.00018 | 0.00018 | 0.00018 | 0.00018 | 0.00021 | 0.00047 | 0.00052 | 0.00053 | 0.00111 | 0.00113 |
| **7.88** | **Salbulin with AeroChamber** | | | | | | | | 0.00009 | 0.00016 | 0.00018 | 0.00018 | 0.00018 | 0.00018 | 0.00021 | 0.00047 | 0.00052 | 0.00053 | 0.00111 | 0.00113 |
| **9.70** | **Ventolin Evohaler with Nebuhaler** | | | | | | | | | 0.00006 | 0.00009 | 0.00009 | 0.00009 | 0.00009 | 0.00011 | 0.00038 | 0.00043 | 0.00044 | 0.00101 | 0.00104 |
| **10.99** | **Airomir Autohaler** | | | | | | | | | | 0.00003 | 0.00002 | 0.00003 | 0.00003 | 0.00005 | 0.00032 | 0.00037 | 0.00037 | 0.00095 | 0.00097 |
| **11.50** | **Salamol Easi-Breathe** | | | | | | | | | | | 0.00000 | 0.00000 | 0.00000 | 0.00002 | 0.00029 | 0.00034 | 0.00035 | 0.00092 | 0.00095 |
| **11.53** | **Asmasal Clickhaler** | | | | | | | | | | | | 0.00000 | 0.00000 | 0.00002 | 0.00029 | 0.00034 | 0.00034 | 0.00092 | 0.00094 |
| **11.54** | **Maxivent with Able Spacer** | | | | | | | | | | | | | 0.00000 | 0.00002 | 0.00029 | 0.00034 | 0.00034 | 0.00092 | 0.00094 |
| **11.54** | **Asmaven with Able Spacer** | | | | | | | | | | | | | | 0.00002 | 0.00029 | 0.00034 | 0.00034 | 0.00092 | 0.00094 |
| **12.00** | **Salamol with Able Spacer** | | | | | | | | | | | | | | | 0.00027 | 0.00032 | 0.00032 | 0.00090 | 0.00092 |
| **17.37** | **Ventolin Rotahaler (200)[a]** | | | | | | | | | | | | | | | | 0.00005 | 0.00005 | 0.00063 | 0.00065 |
| **18.32** | **Aerolin Autohaler** | | | | | | | | | | | | | | | | | 0.00001 | 0.00058 | 0.00060 |
| **18.43** | **Pulvinal** | | | | | | | | | | | | | | | | | | 0.00058 | 0.00060 |
| **30.00** | **Ventodisks (200)[a]** | | | | | | | | | | | | | | | | | | | 0.00002 |
| **30.42** | **Ventolin Accuhaler (200)[a]** | | | | | | | | | | | | | | | | | | | |

*[a]These devices provide 200 µg equivalent of salbutamol; the costs of the other drugs must be doubled where 200 µg is provided*
*(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 29*** *QALY thresholds for 200 μg daily dose (or equivalent) of beclometasone: cost per QALY threshold £5000*

| Cost per annum (£) | | 28.73 | 28.73 | 28.73 | 30.08 | 30.08 | 31.41 | 31.41 | 33.01 | 33.01 | 35.69 | 37.67 | 38.48 | 38.51 | 40.73 | 43.17 | 47.05 | 55.21 | 69.06 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Device name(s)** | **Qvar (50)[b]** | **Qvar Autohaler (50)[b]** | **Filair (100)** | **Beclazone (100)** | **Beclazone Easi-Breathe (100)** | **Qvar (100)[b]** | **Qvar Autohaler (100)[b]** | **Qvar (50) with AeroChamber[b]** | **Filair (100) with AeroChamber** | **Qvar (100) with AeroChamber[b]** | **Becotide (100)** | **Beclazone (100) with Able Spacer** | **Asmabec Clickhaler (100)** | **Pulvinal (100)** | **Becotide (100) with Volumatic** | **AeroBec Autohaler (100)** | **Becotide Rotacaps (100)** | **Becodisks Diskhaler (100)** |
| **18.73**[a] | **Beclazone Easi-Breathe (100)** | 0.00200 | 0.00200 | 0.00200 | 0.00227 | 0.00227 | 0.00254 | 0.00254 | 0.00286 | 0.00286 | 0.00339 | 0.00379 | 0.00395 | 0.00396 | 0.00440 | 0.00489 | 0.00566 | 0.00730 | 0.01007 |
| **28.73** | **Qvar (50)[b]** | | 0.00000 | 0.00000 | 0.00027 | 0.00027 | 0.00054 | 0.00054 | 0.00086 | 0.00086 | 0.00139 | 0.00179 | 0.00195 | 0.00196 | 0.00240 | 0.00289 | 0.00366 | 0.00530 | 0.00807 |
| **28.73** | **Qvar Autohaler (50)[b]** | | | 0.00000 | 0.00027 | 0.00027 | 0.00054 | 0.00054 | 0.00086 | 0.00086 | 0.00139 | 0.00179 | 0.00195 | 0.00196 | 0.00240 | 0.00289 | 0.00366 | 0.00530 | 0.00807 |
| **28.73** | **Filair (100)** | | | | 0.00027 | 0.00027 | 0.00054 | 0.00054 | 0.00086 | 0.00086 | 0.00139 | 0.00179 | 0.00195 | 0.00196 | 0.00240 | 0.00289 | 0.00366 | 0.00530 | 0.00807 |
| **30.08** | **Beclazone (100)** | | | | | 0.00000 | 0.00027 | 0.00027 | 0.00059 | 0.00059 | 0.00112 | 0.00152 | 0.00168 | 0.00169 | 0.00213 | 0.00262 | 0.00339 | 0.00503 | 0.00780 |
| **30.08** | **Beclazone Easi-Breathe (100)** | | | | | | 0.00027 | 0.00027 | 0.00059 | 0.00059 | 0.00112 | 0.00152 | 0.00168 | 0.00169 | 0.00213 | 0.00262 | 0.00339 | 0.00503 | 0.00780 |
| **31.41** | **Qvar (100)[b]** | | | | | | | 0.00000 | 0.00032 | 0.00032 | 0.00086 | 0.00125 | 0.00141 | 0.00142 | 0.00187 | 0.00235 | 0.00313 | 0.00476 | 0.00753 |
| **31.41** | **Qvar Autohaler (100)[b]** | | | | | | | | 0.00032 | 0.00032 | 0.00086 | 0.00125 | 0.00141 | 0.00142 | 0.00187 | 0.00235 | 0.00313 | 0.00476 | 0.00753 |
| **33.01** | **Qvar (50) with AeroChamber[b]** | | | | | | | | | 0.00000 | 0.00054 | 0.00093 | 0.00109 | 0.00110 | 0.00155 | 0.00203 | 0.00281 | 0.00444 | 0.00721 |
| **33.01** | **Filair (100) with AeroChamber** | | | | | | | | | | 0.00054 | 0.00093 | 0.00109 | 0.00110 | 0.00155 | 0.00203 | 0.00281 | 0.00444 | 0.00721 |
| **35.69** | **Qvar (100) with AeroChamber[b]** | | | | | | | | | | | 0.00040 | 0.00056 | 0.00056 | 0.00101 | 0.00150 | 0.00227 | 0.00390 | 0.00667 |
| **37.67** | **Becotide (100)** | | | | | | | | | | | | 0.00016 | 0.00017 | 0.00061 | 0.00110 | 0.00188 | 0.00351 | 0.00628 |
| **38.48** | **Beclazone (100) with Able Spacer** | | | | | | | | | | | | | 0.00001 | 0.00045 | 0.00094 | 0.00171 | 0.00335 | 0.00612 |
| **38.51** | **Asmabec Clickhaler (100)** | | | | | | | | | | | | | | 0.00045 | 0.00093 | 0.00171 | 0.00334 | 0.00611 |
| **40.73** | **Pulvinal (100)** | | | | | | | | | | | | | | | 0.00049 | 0.00126 | 0.00289 | 0.00566 |
| **43.17** | **Becotide (100) with Volumatic** | | | | | | | | | | | | | | | | 0.00078 | 0.00241 | 0.00518 |
| **47.05** | **AeroBec Autohaler (100)** | | | | | | | | | | | | | | | | | 0.00163 | 0.00440 |
| **55.21** | **Becotide Rotacaps (100)** | | | | | | | | | | | | | | | | | | 0.00277 |
| **69.06** | **Becodisks Diskhaler (100)** | | | | | | | | | | | | | | | | | | |

[a]*Assuming a £10 cost offset compared with the cheapest pMDI is validated*
[b]*Not licensed for children aged under 12 yr*

***TABLE 30*** *QALY thresholds for 200 μg daily dose (or equivalent) of beclometasone: cost per QALY threshold £20,000*

| Cost per annum (£) | | 28.73 | 28.73 | 28.73 | 30.08 | 30.08 | 31.41 | 31.41 | 33.01 | 33.01 | 35.69 | 37.67 | 38.48 | 38.51 | 40.73 | 43.17 | 47.05 | 55.21 | 69.06 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Device name(s)** | **Qvar (50)[b]** | **Qvar Autohaler (50)[b]** | **Filair (100)** | **Beclazone (100)** | **Beclazone Easi-Breathe (100)** | **Qvar (100)[b]** | **Qvar Autohaler (100)[b]** | **Qvar (50) with AeroChamber[b]** | **Filair (100) with AeroChamber** | **Qvar (100) with AeroChamber[b]** | **Becotide (100)** | **Beclazone (100) with Able Spacer** | **Asmabec Clickhaler (100)** | **Pulvinal (100)** | **Becotide (100) with Volumatic** | **AeroBec Autohaler (100)** | **Becotide Rotacaps (100)** | **Becodisks Diskhaler (100)** |
| **18.73[a]** | **Beclazone Easi-Breathe (100)** | 0.00050 | 0.00050 | 0.00050 | 0.00057 | 0.00057 | 0.00063 | 0.00063 | 0.00071 | 0.00071 | 0.00085 | 0.00095 | 0.00099 | 0.00099 | 0.00110 | 0.00122 | 0.00142 | 0.00182 | 0.00252 |
| **28.73** | **Qvar (50)[b]** | | 0.00000 | 0.00000 | 0.00007 | 0.00007 | 0.00013 | 0.00013 | 0.00021 | 0.00021 | 0.00035 | 0.00045 | 0.00049 | 0.00049 | 0.00060 | 0.00072 | 0.00092 | 0.00132 | 0.00202 |
| **28.73** | **Qvar Autohaler (50)[b]** | | | 0.00000 | 0.00007 | 0.00007 | 0.00013 | 0.00013 | 0.00021 | 0.00021 | 0.00035 | 0.00045 | 0.00049 | 0.00049 | 0.00060 | 0.00072 | 0.00092 | 0.00132 | 0.00202 |
| **28.73** | **Filair (100)** | | | | 0.00007 | 0.00007 | 0.00013 | 0.00013 | 0.00021 | 0.00021 | 0.00035 | 0.00045 | 0.00049 | 0.00049 | 0.00060 | 0.00072 | 0.00092 | 0.00132 | 0.00202 |
| **30.08** | **Beclazone (100)** | | | | | 0.00000 | 0.00007 | 0.00007 | 0.00015 | 0.00015 | 0.00028 | 0.00038 | 0.00042 | 0.00042 | 0.00053 | 0.00065 | 0.00085 | 0.00126 | 0.00195 |
| **30.08** | **Beclazone Easi-Breathe (100)** | | | | | | 0.00007 | 0.00007 | 0.00015 | 0.00015 | 0.00028 | 0.00038 | 0.00042 | 0.00042 | 0.00053 | 0.00065 | 0.00085 | 0.00126 | 0.00195 |
| **31.41** | **Qvar (100)[b]** | | | | | | | 0.00000 | 0.00008 | 0.00008 | 0.00021 | 0.00031 | 0.00035 | 0.00035 | 0.00047 | 0.00059 | 0.00078 | 0.00119 | 0.00188 |
| **31.41** | **Qvar Autohaler (100)[b]** | | | | | | | | 0.00008 | 0.00008 | 0.00021 | 0.00031 | 0.00035 | 0.00035 | 0.00047 | 0.00059 | 0.00078 | 0.00119 | 0.00188 |
| **33.01** | **Qvar (50) with AeroChamber[b]** | | | | | | | | | 0.00000 | 0.00013 | 0.00023 | 0.00027 | 0.00028 | 0.00039 | 0.00051 | 0.00070 | 0.00111 | 0.00180 |
| **33.01** | **Filair (100) with AeroChamber** | | | | | | | | | | 0.00013 | 0.00023 | 0.00027 | 0.00028 | 0.00039 | 0.00051 | 0.00070 | 0.00111 | 0.00180 |
| **35.69** | **Qvar (100) with AeroChamber[b]** | | | | | | | | | | | 0.00010 | 0.00014 | 0.00014 | 0.00025 | 0.00037 | 0.00057 | 0.00098 | 0.00167 |
| **37.67** | **Becotide (100)** | | | | | | | | | | | | 0.00004 | 0.00004 | 0.00015 | 0.00028 | 0.00047 | 0.00088 | 0.00157 |
| **38.48** | **Beclazone (100) with Able Spacer** | | | | | | | | | | | | | 0.00000 | 0.00011 | 0.00023 | 0.00043 | 0.00084 | 0.00153 |
| **38.51** | **Asmabec Clickhaler (100)** | | | | | | | | | | | | | | 0.00011 | 0.00023 | 0.00043 | 0.00083 | 0.00153 |
| **40.73** | **Pulvinal (100)** | | | | | | | | | | | | | | | 0.00012 | 0.00032 | 0.00072 | 0.00142 |
| **43.17** | **Becotide (100) with Volumatic** | | | | | | | | | | | | | | | | 0.00019 | 0.00060 | 0.00129 |
| **47.05** | **AeroBec Autohaler (50)** | | | | | | | | | | | | | | | | | 0.00041 | 0.00110 |
| **55.21** | **Becotide Rotacaps (100)** | | | | | | | | | | | | | | | | | | 0.00069 |
| **69.06** | **Becodisks Diskhaler (100)** | | | | | | | | | | | | | | | | | | |

[a] *Assuming a £10 cost offset compared with the cheapest pMDI is validated*
[b] *Not licensed for children aged under 12 yr*

***TABLE 31*** *QALY thresholds for 800 µg daily dose (or equivalent) of beclometasone: cost per QALY threshold £5000*

| Cost per annum (£) | | 114.46 | 114.90 | 114.90 | 114.90 | 119.18 | 119.18 | 120.30 | 120.30 | 122.86 | 125.63 | 125.63 | 126.73 | 128.70 | 128.99 | 129.91 | 133.27 | 133.65 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Device name(s)** | **Beclazone (200)** | **Filair (100)** | **Qvar (50)[b]** | **Qvar Autohaler (50)[b]** | **Qvar (50) with AeroChamber[b]** | **Filair (100) with AeroChamber** | **Beclazone (100)** | **Beclazone Easi-Breathe (100)** | **Beclazone (200) with Able Spacer** | **Qvar (100)[b]** | **Qvar Autohaler (100)[b]** | **Beclazone Easi-Breathe (50)** | **Beclazone (100) with Able Spacer** | **Filair (250)** | **Qvar (100) with AeroChamber[b]** | **Filair (250) with AeroChamber** | **Becodisks Diskhaler (400)** |
| **104.46[a]** | **Beclazone Easi-Breathe (100)** | 0.00200 | 0.00209 | 0.00209 | 0.00209 | 0.00294 | 0.00294 | 0.00317 | 0.00317 | 0.00368 | 0.00423 | 0.00423 | 0.00445 | 0.00485 | 0.00491 | 0.00509 | 0.00576 | 0.00584 |
| **114.46** | **Beclazone (200)** | | 0.00009 | 0.00009 | 0.00009 | 0.00094 | 0.00094 | 0.00117 | 0.00117 | 0.00168 | 0.00223 | 0.00223 | 0.00245 | 0.00285 | 0.00291 | 0.00309 | 0.00376 | 0.00384 |
| **114.90** | **Filair (100)** | | | 0.00000 | 0.00000 | 0.00086 | 0.00086 | 0.00108 | 0.00108 | 0.00159 | 0.00215 | 0.00215 | 0.00237 | 0.00276 | 0.00282 | 0.00300 | 0.00367 | 0.00375 |
| **114.90** | **Qvar (50)[b]** | | | | 0.00000 | 0.00086 | 0.00086 | 0.00108 | 0.00108 | 0.00159 | 0.00215 | 0.00215 | 0.00237 | 0.00276 | 0.00282 | 0.00300 | 0.00367 | 0.00375 |
| **114.90** | **Qvar Autohaler (50)[b]** | | | | | 0.00086 | 0.00086 | 0.00108 | 0.00108 | 0.00159 | 0.00215 | 0.00215 | 0.00237 | 0.00276 | 0.00282 | 0.00300 | 0.00367 | 0.00375 |
| **119.18** | **Qvar (50) with AeroChamber[b]** | | | | | | 0.00000 | 0.00022 | 0.00022 | 0.00074 | 0.00129 | 0.00129 | 0.00151 | 0.00190 | 0.00196 | 0.00215 | 0.00282 | 0.00289 |
| **119.18** | **Filair (100) with AeroChamber** | | | | | | | 0.00022 | 0.00022 | 0.00074 | 0.00129 | 0.00129 | 0.00151 | 0.00190 | 0.00196 | 0.00215 | 0.00282 | 0.00289 |
| **120.30** | **Beclazone (100)** | | | | | | | | 0.00000 | 0.00051 | 0.00107 | 0.00107 | 0.00128 | 0.00168 | 0.00174 | 0.00192 | 0.00259 | 0.00267 |
| **120.30** | **Beclazone Easi-Breathe (100)** | | | | | | | | | 0.00051 | 0.00107 | 0.00107 | 0.00128 | 0.00168 | 0.00174 | 0.00192 | 0.00259 | 0.00267 |
| **122.86** | **Beclazone (200) with Able Spacer** | | | | | | | | | | 0.00055 | 0.00055 | 0.00077 | 0.00117 | 0.00123 | 0.00141 | 0.00208 | 0.00216 |
| **125.63** | **Qvar (100)[b]** | | | | | | | | | | | 0.00000 | 0.00022 | 0.00061 | 0.00067 | 0.00086 | 0.00153 | 0.00160 |
| **125.63** | **Qvar Autohaler (100)[b]** | | | | | | | | | | | | 0.00022 | 0.00061 | 0.00067 | 0.00086 | 0.00153 | 0.00160 |
| **126.73** | **Beclazone Easi-Breathe (50)** | | | | | | | | | | | | | 0.00040 | 0.00045 | 0.00064 | 0.00131 | 0.00138 |
| **128.70** | **Beclazone (100) with Able Spacer** | | | | | | | | | | | | | | 0.00006 | 0.00024 | 0.00091 | 0.00099 |
| **128.99** | **Filair (250)** | | | | | | | | | | | | | | | 0.00018 | 0.00086 | 0.00093 |
| **129.91** | **Qvar (100) with AeroChamber[b]** | | | | | | | | | | | | | | | | 0.00067 | 0.00075 |
| **133.27** | **Filair (250) with AeroChamber** | | | | | | | | | | | | | | | | | 0.00008 |
| **133.65** | **Becodisks Diskhaler (400)** | | | | | | | | | | | | | | | | | |
| **143.15** | **Becotide (200)** | | | | | | | | | | | | | | | | | |
| **148.65** | **Becotide (200) with Volumatic** | | | | | | | | | | | | | | | | | |
| **148.99** | **Pulvinal (400)** | | | | | | | | | | | | | | | | | |
| **150.23** | **Pulvinal (200)** | | | | | | | | | | | | | | | | | |
| **150.67** | **Becotide (100)** | | | | | | | | | | | | | | | | | |
| **154.03** | **Asmabec Clickhaler (100)** | | | | | | | | | | | | | | | | | |
| **156.17** | **Becotide (100) with Volumatic** | | | | | | | | | | | | | | | | | |
| **162.94** | **Pulvinal (100)** | | | | | | | | | | | | | | | | | |
| **188.19** | **AeroBec Autohaler (100)** | | | | | | | | | | | | | | | | | |
| **209.48** | **Becotide Rotacaps (200)** | | | | | | | | | | | | | | | | | |
| **209.66** | **Asmabec Clickhaler (50)** | | | | | | | | | | | | | | | | | |
| **220.83** | **Becotide Rotacaps (100)** | | | | | | | | | | | | | | | | | |
| **266.16** | **Becodisks Diskhaler (200)** | | | | | | | | | | | | | | | | | |
| **266.16** | **Becotide Rotacaps (400)** | | | | | | | | | | | | | | | | | |
| **272.80** | **Becodisks Diskhaler (100)** | | | | | | | | | | | | | | | | | |

*continued*

***TABLE 31 contd*** *QALY thresholds for 800 μg daily dose (or equivalent) of beclometasone: cost per QALY threshold £5000*

| Cost per annum (£) | | 143.15 | 148.65 | 148.99 | 150.23 | 150.67 | 154.03 | 156.17 | 162.94 | 188.19 | 209.48 | 209.66 | 220.83 | 266.16 | 266.16 | 272.80 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Device name(s)** | **Becotide (200)** | **Becotide (200) with Volumatic** | **Pulvinal (400)** | **Pulvinal (200)** | **Becotide (100)** | **Asmabec Clickhaler (100)** | **Becotide (100) with Volumatic** | **Pulvinal (100)** | **AeroBec Autohaler (100)** | **Becotide Rotacaps (200)** | **Asmabec Clickhaler (50)** | **Becotide Rotacaps (100)** | **Becodisks Diskhaler (200)** | **Becotide Rotacaps (400)** | **Becodisks Diskhaler (100)** |
| **104.46**[a] | **Beclazone Easi-Breathe (100)** | 0.00774 | 0.00884 | 0.00891 | 0.00915 | 0.00924 | 0.00991 | 0.01034 | 0.01169 | 0.01675 | 0.02100 | 0.02104 | 0.02327 | 0.03234 | 0.03234 | 0.03367 |
| **114.46** | **Beclazone (200)** | 0.00574 | 0.00684 | 0.00691 | 0.00715 | 0.00724 | 0.00791 | 0.00834 | 0.00969 | 0.01475 | 0.01900 | 0.01904 | 0.02127 | 0.03034 | 0.03034 | 0.03167 |
| **114.90** | **Filair (100)** | 0.00565 | 0.00675 | 0.00682 | 0.00707 | 0.00715 | 0.00783 | 0.00825 | 0.00961 | 0.01466 | 0.01892 | 0.01895 | 0.02118 | 0.03025 | 0.03025 | 0.03158 |
| **114.90** | **Qvar (50)**[b] | 0.00565 | 0.00675 | 0.00682 | 0.00707 | 0.00715 | 0.00783 | 0.00825 | 0.00961 | 0.01466 | 0.01892 | 0.01895 | 0.02118 | 0.03025 | 0.03025 | 0.03158 |
| **114.90** | **Qvar Autohaler (50)**[b] | 0.00565 | 0.00675 | 0.00682 | 0.00707 | 0.00715 | 0.00783 | 0.00825 | 0.00961 | 0.01466 | 0.01892 | 0.01895 | 0.02118 | 0.03025 | 0.03025 | 0.03158 |
| **119.18** | **Qvar (50) with AeroChamber**[b] | 0.00479 | 0.00589 | 0.00596 | 0.00621 | 0.00630 | 0.00697 | 0.00740 | 0.00875 | 0.01380 | 0.01806 | 0.01809 | 0.02033 | 0.02939 | 0.02940 | 0.03072 |
| **119.18** | **Filair (100) with AeroChamber** | 0.00479 | 0.00589 | 0.00596 | 0.00621 | 0.00630 | 0.00697 | 0.00740 | 0.00875 | 0.01380 | 0.01806 | 0.01809 | 0.02033 | 0.02939 | 0.02940 | 0.03072 |
| **120.30** | **Beclazone (100)** | 0.00457 | 0.00567 | 0.00574 | 0.00599 | 0.00607 | 0.00675 | 0.00717 | 0.00853 | 0.01358 | 0.01784 | 0.01787 | 0.02010 | 0.02917 | 0.02917 | 0.03050 |
| **120.30** | **Beclazone Easi-Breathe (100)** | 0.00457 | 0.00567 | 0.00574 | 0.00599 | 0.00607 | 0.00675 | 0.00717 | 0.00853 | 0.01358 | 0.01784 | 0.01787 | 0.02010 | 0.02917 | 0.02917 | 0.03050 |
| **122.86** | **Beclazone (200) with Able Spacer** | 0.00406 | 0.00516 | 0.00523 | 0.00547 | 0.00556 | 0.00623 | 0.00666 | 0.00801 | 0.01307 | 0.01732 | 0.01736 | 0.01959 | 0.02866 | 0.02866 | 0.02999 |
| **125.63** | **Qvar (100)**[b] | 0.00350 | 0.00460 | 0.00467 | 0.00492 | 0.00501 | 0.00568 | 0.00611 | 0.00746 | 0.01251 | 0.01677 | 0.01680 | 0.01904 | 0.02810 | 0.02811 | 0.02943 |
| **125.63** | **Qvar Autohaler (100)**[b] | 0.00350 | 0.00460 | 0.00467 | 0.00492 | 0.00501 | 0.00568 | 0.00611 | 0.00746 | 0.01251 | 0.01677 | 0.01680 | 0.01904 | 0.02810 | 0.02811 | 0.02943 |
| **126.73** | **Beclazone Easi-Breathe (50)** | 0.00329 | 0.00439 | 0.00445 | 0.00470 | 0.00479 | 0.00546 | 0.00589 | 0.00724 | 0.01229 | 0.01655 | 0.01659 | 0.01882 | 0.02789 | 0.02789 | 0.02922 |
| **128.70** | **Beclazone (100) with Able Spacer** | 0.00289 | 0.00399 | 0.00406 | 0.00431 | 0.00439 | 0.00507 | 0.00549 | 0.00685 | 0.01190 | 0.01616 | 0.01619 | 0.01842 | 0.02749 | 0.02749 | 0.02882 |
| **128.99** | **Filair (250)** | 0.00283 | 0.00393 | 0.00400 | 0.00425 | 0.00434 | 0.00501 | 0.00544 | 0.00679 | 0.01184 | 0.01610 | 0.01613 | 0.01837 | 0.02743 | 0.02743 | 0.02876 |
| **129.91** | **Qvar (100) with AeroChamber**[b] | 0.00265 | 0.00375 | 0.00382 | 0.00406 | 0.00415 | 0.00482 | 0.00525 | 0.00660 | 0.01166 | 0.01591 | 0.01595 | 0.01818 | 0.02725 | 0.02725 | 0.02858 |
| **133.27** | **Filair (250) with AeroChamber** | 0.00198 | 0.00308 | 0.00314 | 0.00339 | 0.00348 | 0.00415 | 0.00458 | 0.00593 | 0.01098 | 0.01524 | 0.01528 | 0.01751 | 0.02658 | 0.02658 | 0.02791 |
| **133.65** | **Becodisks Diskhaler (400)** | 0.00190 | 0.00300 | 0.00307 | 0.00332 | 0.00340 | 0.00408 | 0.00450 | 0.00586 | 0.01091 | 0.01517 | 0.01520 | 0.01744 | 0.02650 | 0.02650 | 0.02783 |
| **143.15** | **Becotide (200)** | | 0.00110 | 0.00117 | 0.00142 | 0.00150 | 0.00218 | 0.00260 | 0.00396 | 0.00901 | 0.01327 | 0.01330 | 0.01553 | 0.02460 | 0.02460 | 0.02593 |
| **148.65** | **Becotide (200) with Volumatic** | | | 0.00007 | 0.00032 | 0.00040 | 0.00108 | 0.00150 | 0.00286 | 0.00791 | 0.01217 | 0.01220 | 0.01443 | 0.02350 | 0.02350 | 0.02483 |
| **148.99** | **Pulvinal (400)** | | | | 0.00025 | 0.00034 | 0.00101 | 0.00144 | 0.00279 | 0.00784 | 0.01210 | 0.01213 | 0.01437 | 0.02343 | 0.02343 | 0.02476 |
| **150.23** | **Pulvinal (200)** | | | | | 0.00009 | 0.00076 | 0.00119 | 0.00254 | 0.00759 | 0.01185 | 0.01188 | 0.01412 | 0.02318 | 0.02319 | 0.02451 |
| **150.67** | **Becotide (100)** | | | | | | 0.00067 | 0.00110 | 0.00245 | 0.00750 | 0.01176 | 0.01180 | 0.01403 | 0.02310 | 0.02310 | 0.02443 |
| **154.03** | **Asmabec Clickhaler (100)** | | | | | | | 0.00043 | 0.00178 | 0.00683 | 0.01109 | 0.01113 | 0.01336 | 0.02243 | 0.02243 | 0.02375 |
| **156.17** | **Becotide (100) with Volumatic** | | | | | | | | 0.00135 | 0.00640 | 0.01066 | 0.01070 | 0.01293 | 0.02200 | 0.02200 | 0.02333 |
| **162.94** | **Pulvinal (100)** | | | | | | | | | 0.00505 | 0.00931 | 0.00934 | 0.01158 | 0.02064 | 0.02064 | 0.02197 |
| **188.19** | **AeroBec Autohaler (100)** | | | | | | | | | | 0.00426 | 0.00429 | 0.00653 | 0.01559 | 0.01559 | 0.01692 |
| **209.48** | **Becotide Rotacaps (200)** | | | | | | | | | | | 0.00003 | 0.00227 | 0.01133 | 0.01134 | 0.01266 |
| **209.66** | **Asmabec Clickhaler (50)** | | | | | | | | | | | | 0.00223 | 0.01130 | 0.01130 | 0.01263 |
| **220.83** | **Becotide Rotacaps (100)** | | | | | | | | | | | | | 0.00907 | 0.00907 | 0.01040 |
| **266.16** | **Becodisks Diskhaler (200)** | | | | | | | | | | | | | | 0.00000 | 0.00133 |
| **266.16** | **Becotide Rotacaps (400)** | | | | | | | | | | | | | | | 0.00133 |
| **272.80** | **Becodisks Diskhaler (100)** | | | | | | | | | | | | | | | |

[a] *Assuming a £10 cost offset compared with the cheapest pMDI is validated*
[b] *Not licensed for children aged under 12 yr*

***TABLE 32*** *QALY thresholds for 800 µg daily dose (or equivalent) of beclometasone: cost per QALY threshold £20,000*

| Cost per annum (£) | | 114.46 | 114.90 | 114.90 | 114.90 | 119.18 | 119.18 | 120.30 | 120.30 | 122.86 | 125.63 | 125.63 | 126.73 | 128.70 | 128.99 | 129.91 | 133.27 | 133.65 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Device name(s)** | **Beclazone (200)** | **Filair (100)** | **Qvar (50)[b]** | **Qvar Autohaler (50)[b]** | **Qvar (50) with AeroChamber[b]** | **Filair (100) with AeroChamber** | **Beclazone (100)** | **Beclazone Easi-Breathe (100)** | **Beclazone (200) with Able Spacer** | **Qvar (100)[b]** | **Qvar Autohaler (100)[b]** | **Beclazone Easi-Breathe (50)** | **Beclazone (100) with Able Spacer** | **Filair (250)** | **Qvar (100) with AeroChamber[b]** | **Filair (250) with AeroChamber** | **Becodisks Diskhaler (400)** |
| **104.46**[a] | **Beclazone Easi-Breathe (100)** | 0.00050 | 0.00052 | 0.00052 | 0.00052 | 0.00074 | 0.00074 | 0.00079 | 0.00079 | 0.00092 | 0.00106 | 0.00106 | 0.00111 | 0.00121 | 0.00123 | 0.00127 | 0.00144 | 0.00146 |
| **114.46** | **Beclazone (200)** | | 0.00002 | 0.00002 | 0.00002 | 0.00024 | 0.00024 | 0.00029 | 0.00029 | 0.00042 | 0.00056 | 0.00056 | 0.00061 | 0.00071 | 0.00073 | 0.00077 | 0.00094 | 0.00096 |
| **114.90** | **Filair (100)** | | | 0.00000 | 0.00000 | 0.00021 | 0.00021 | 0.00027 | 0.00027 | 0.00040 | 0.00054 | 0.00054 | 0.00059 | 0.00069 | 0.00070 | 0.00075 | 0.00092 | 0.00094 |
| **114.90** | **Qvar (50)[b]** | | | | 0.00000 | 0.00021 | 0.00021 | 0.00027 | 0.00027 | 0.00040 | 0.00054 | 0.00054 | 0.00059 | 0.00069 | 0.00070 | 0.00075 | 0.00092 | 0.00094 |
| **114.90** | **Qvar Autohaler (50)[b]** | | | | | 0.00021 | 0.00021 | 0.00027 | 0.00027 | 0.00040 | 0.00054 | 0.00054 | 0.00059 | 0.00069 | 0.00070 | 0.00075 | 0.00092 | 0.00094 |
| **119.18** | **Qvar (50) with AeroChamber[b]** | | | | | | 0.00000 | 0.00006 | 0.00006 | 0.00018 | 0.00032 | 0.00032 | 0.00038 | 0.00048 | 0.00049 | 0.00054 | 0.00070 | 0.00072 |
| **119.18** | **Filair (100) with AeroChamber** | | | | | | | 0.00006 | 0.00006 | 0.00018 | 0.00032 | 0.00032 | 0.00038 | 0.00048 | 0.00049 | 0.00054 | 0.00070 | 0.00072 |
| **120.30** | **Beclazone (100)** | | | | | | | | 0.00000 | 0.00013 | 0.00027 | 0.00027 | 0.00032 | 0.00042 | 0.00043 | 0.00048 | 0.00065 | 0.00067 |
| **120.30** | **Beclazone Easi-Breathe (100)** | | | | | | | | | 0.00013 | 0.00027 | 0.00027 | 0.00032 | 0.00042 | 0.00043 | 0.00048 | 0.00065 | 0.00067 |
| **122.86** | **Beclazone (200) with Able Spacer** | | | | | | | | | | 0.00014 | 0.00014 | 0.00019 | 0.00029 | 0.00031 | 0.00035 | 0.00052 | 0.00054 |
| **125.63** | **Qvar (100)[b]** | | | | | | | | | | | 0.00000 | 0.00005 | 0.00015 | 0.00017 | 0.00021 | 0.00038 | 0.00040 |
| **125.63** | **Qvar Autohaler (100)[b]** | | | | | | | | | | | | 0.00005 | 0.00015 | 0.00017 | 0.00021 | 0.00038 | 0.00040 |
| **126.73** | **Beclazone Easi-Breathe (50)** | | | | | | | | | | | | | 0.00010 | 0.00011 | 0.00016 | 0.00033 | 0.00035 |
| **128.70** | **Beclazone (100) with Able Spacer** | | | | | | | | | | | | | | 0.00001 | 0.00006 | 0.00023 | 0.00025 |
| **128.99** | **Filair (250)** | | | | | | | | | | | | | | | 0.00005 | 0.00021 | 0.00023 |
| **129.91** | **Qvar (100) with AeroChamber[b]** | | | | | | | | | | | | | | | | 0.00017 | 0.00019 |
| **133.27** | **Filair (250) with AeroChamber** | | | | | | | | | | | | | | | | | 0.00002 |
| **133.65** | **Becodisks Diskhaler (400)** | | | | | | | | | | | | | | | | | |
| **143.15** | **Becotide (200)** | | | | | | | | | | | | | | | | | |
| **148.65** | **Becotide (200) with Volumatic** | | | | | | | | | | | | | | | | | |
| **148.99** | **Pulvinal (400)** | | | | | | | | | | | | | | | | | |
| **150.23** | **Pulvinal (200)** | | | | | | | | | | | | | | | | | |
| **150.67** | **Becotide (100)** | | | | | | | | | | | | | | | | | |
| **154.03** | **Asmabec Clickhaler (100)** | | | | | | | | | | | | | | | | | |
| **156.17** | **Becotide (100) with Volumatic** | | | | | | | | | | | | | | | | | |
| **162.94** | **Pulvinal (100)** | | | | | | | | | | | | | | | | | |
| **188.19** | **AeroBec Autohaler (100)** | | | | | | | | | | | | | | | | | |
| **209.48** | **Becotide Rotacaps (200)** | | | | | | | | | | | | | | | | | |
| **209.66** | **Asmabec Clickhaler (50)** | | | | | | | | | | | | | | | | | |
| **220.83** | **Becotide Rotacaps (100)** | | | | | | | | | | | | | | | | | |
| **266.16** | **Becodisks Diskhaler (200)** | | | | | | | | | | | | | | | | | |
| **266.16** | **Becotide Rotacaps (400)** | | | | | | | | | | | | | | | | | |
| **272.80** | **Becodisks Diskhaler (100)** | | | | | | | | | | | | | | | | | |

*continued*

***TABLE 32 contd*** *QALY thresholds for 800 μg daily dose (or equivalent) of beclometasone: cost per QALY threshold £20,000*

| Cost per annum (£) | | 143.15 | 148.65 | 148.99 | 150.23 | 150.67 | 154.03 | 156.17 | 162.94 | 188.19 | 209.48 | 209.66 | 220.83 | 266.16 | 266.16 | 272.80 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Device name(s)** | **Becotide (200)** | **Becotide (200) with Volumatic** | **Pulvinal (400)** | **Pulvinal (200)** | **Becotide (100)** | **Asmabec Clickhaler (100)** | **Becotide (100) with Volumatic** | **Pulvinal (100)** | **AeroBec Autohaler (100)** | **Becotide Rotacaps (200)** | **Asmabec Clickhaler (50)** | **Becotide Rotacaps (100)** | **Becodisks Diskhaler (200)** | **Becotide Rotacaps (400)** | **Becodisks Diskhaler (100)** |
| **104.46**[a] | **Beclazone Easi-Breathe (100)** | 0.00193 | 0.00221 | 0.00223 | 0.00229 | 0.00231 | 0.00248 | 0.00259 | 0.00292 | 0.00419 | 0.00525 | 0.00526 | 0.00582 | 0.00808 | 0.00808 | 0.00842 |
| **114.46** | **Beclazone (200)** | 0.00143 | 0.00171 | 0.00173 | 0.00179 | 0.00181 | 0.00198 | 0.00209 | 0.00242 | 0.00369 | 0.00475 | 0.00476 | 0.00532 | 0.00758 | 0.00758 | 0.00792 |
| **114.90** | **Filair (100)** | 0.00141 | 0.00169 | 0.00170 | 0.00177 | 0.00179 | 0.00196 | 0.00206 | 0.00240 | 0.00366 | 0.00473 | 0.00474 | 0.00530 | 0.00756 | 0.00756 | 0.00790 |
| **114.90** | **Qvar (50)**[b] | 0.00141 | 0.00169 | 0.00170 | 0.00177 | 0.00179 | 0.00196 | 0.00206 | 0.00240 | 0.00366 | 0.00473 | 0.00474 | 0.00530 | 0.00756 | 0.00756 | 0.00790 |
| **114.90** | **Qvar Autohaler (50)**[b] | 0.00141 | 0.00169 | 0.00170 | 0.00177 | 0.00179 | 0.00196 | 0.00206 | 0.00240 | 0.00366 | 0.00473 | 0.00474 | 0.00530 | 0.00756 | 0.00756 | 0.00790 |
| **119.18** | **Qvar (50) with AeroChamber**[b] | 0.00120 | 0.00147 | 0.00149 | 0.00155 | 0.00157 | 0.00174 | 0.00185 | 0.00219 | 0.00345 | 0.00452 | 0.00452 | 0.00508 | 0.00735 | 0.00735 | 0.00768 |
| **119.18** | **Filair (100) with AeroChamber** | 0.00120 | 0.00147 | 0.00149 | 0.00155 | 0.00157 | 0.00174 | 0.00185 | 0.00219 | 0.00345 | 0.00452 | 0.00452 | 0.00508 | 0.00735 | 0.00735 | 0.00768 |
| **120.30** | **Beclazone (100)** | 0.00114 | 0.00142 | 0.00143 | 0.00150 | 0.00152 | 0.00169 | 0.00179 | 0.00213 | 0.00339 | 0.00446 | 0.00447 | 0.00503 | 0.00729 | 0.00729 | 0.00763 |
| **120.30** | **Beclazone Easi-Breathe (100)** | 0.00114 | 0.00142 | 0.00143 | 0.00150 | 0.00152 | 0.00169 | 0.00179 | 0.00213 | 0.00339 | 0.00446 | 0.00447 | 0.00503 | 0.00729 | 0.00729 | 0.00763 |
| **122.86** | **Beclazone (200) with Able Spacer** | 0.00101 | 0.00129 | 0.00131 | 0.00137 | 0.00139 | 0.00156 | 0.00167 | 0.00200 | 0.00327 | 0.00433 | 0.00434 | 0.00490 | 0.00716 | 0.00716 | 0.00750 |
| **125.63** | **Qvar (100)**[b] | 0.00088 | 0.00115 | 0.00117 | 0.00123 | 0.00125 | 0.00142 | 0.00153 | 0.00187 | 0.00313 | 0.00419 | 0.00420 | 0.00476 | 0.00703 | 0.00703 | 0.00736 |
| **125.63** | **Qvar Autohaler (100)**[b] | 0.00088 | 0.00115 | 0.00117 | 0.00123 | 0.00125 | 0.00142 | 0.00153 | 0.00187 | 0.00313 | 0.00419 | 0.00420 | 0.00476 | 0.00703 | 0.00703 | 0.00736 |
| **126.73** | **Beclazone Easi-Breathe (50)** | 0.00082 | 0.00110 | 0.00111 | 0.00118 | 0.00120 | 0.00137 | 0.00147 | 0.00181 | 0.00307 | 0.00414 | 0.00415 | 0.00470 | 0.00697 | 0.00697 | 0.00730 |
| **128.70** | **Beclazone (100) with Able Spacer** | 0.00072 | 0.00100 | 0.00101 | 0.00108 | 0.00110 | 0.00127 | 0.00137 | 0.00171 | 0.00297 | 0.00404 | 0.00405 | 0.00461 | 0.00687 | 0.00687 | 0.00721 |
| **128.99** | **Filair (250)** | 0.00071 | 0.00098 | 0.00100 | 0.00106 | 0.00108 | 0.00125 | 0.00136 | 0.00170 | 0.00296 | 0.00402 | 0.00403 | 0.00459 | 0.00686 | 0.00686 | 0.00719 |
| **129.91** | **Qvar (100) with AeroChamber**[b] | 0.00066 | 0.00094 | 0.00095 | 0.00102 | 0.00104 | 0.00121 | 0.00131 | 0.00165 | 0.00291 | 0.00398 | 0.00399 | 0.00455 | 0.00681 | 0.00681 | 0.00714 |
| **133.27** | **Filair (250) with AeroChamber** | 0.00049 | 0.00077 | 0.00079 | 0.00085 | 0.00087 | 0.00104 | 0.00115 | 0.00148 | 0.00275 | 0.00381 | 0.00382 | 0.00438 | 0.00664 | 0.00664 | 0.00698 |
| **133.65** | **Becodisks Diskhaler (400)** | 0.00048 | 0.00075 | 0.00077 | 0.00083 | 0.00085 | 0.00102 | 0.00113 | 0.00146 | 0.00273 | 0.00379 | 0.00380 | 0.00436 | 0.00663 | 0.00663 | 0.00696 |
| **143.15** | **Becotide (200)** | | 0.00028 | 0.00029 | 0.00035 | 0.00038 | 0.00054 | 0.00065 | 0.00099 | 0.00225 | 0.00332 | 0.00333 | 0.00388 | 0.00615 | 0.00615 | 0.00648 |
| **148.65** | **Becotide (200) with Volumatic** | | | 0.00002 | 0.00008 | 0.00010 | 0.00027 | 0.00038 | 0.00071 | 0.00198 | 0.00304 | 0.00305 | 0.00361 | 0.00588 | 0.00588 | 0.00621 |
| **148.99** | **Pulvinal (400)** | | | | 0.00006 | 0.00008 | 0.00025 | 0.00036 | 0.00070 | 0.00196 | 0.00302 | 0.00303 | 0.00359 | 0.00586 | 0.00586 | 0.00619 |
| **150.23** | **Pulvinal (200)** | | | | | 0.00002 | 0.00019 | 0.00030 | 0.00064 | 0.00190 | 0.00296 | 0.00297 | 0.00353 | 0.00580 | 0.00580 | 0.00613 |
| **150.67** | **Becotide (100)** | | | | | | 0.00017 | 0.00028 | 0.00061 | 0.00188 | 0.00294 | 0.00295 | 0.00351 | 0.00577 | 0.00577 | 0.00611 |
| **154.03** | **Asmabec Clickhaler (100)** | | | | | | | 0.00011 | 0.00045 | 0.00171 | 0.00277 | 0.00278 | 0.00334 | 0.00561 | 0.00561 | 0.00594 |
| **156.17** | **Becotide (100) with Volumatic** | | | | | | | | 0.00034 | 0.00160 | 0.00267 | 0.00267 | 0.00323 | 0.00550 | 0.00550 | 0.00583 |
| **162.94** | **Pulvinal (100)** | | | | | | | | | 0.00126 | 0.00233 | 0.00234 | 0.00289 | 0.00516 | 0.00516 | 0.00549 |
| **188.19** | **AeroBec Autohaler (100)** | | | | | | | | | | 0.00106 | 0.00107 | 0.00163 | 0.00390 | 0.00390 | 0.00423 |
| **209.48** | **Becotide Rotacaps (200)** | | | | | | | | | | | 0.00001 | 0.00057 | 0.00283 | 0.00283 | 0.00317 |
| **209.66** | **Asmabec Clickhaler (50)** | | | | | | | | | | | | 0.00056 | 0.00283 | 0.00283 | 0.00316 |
| **220.83** | **Becotide Rotacaps (100)** | | | | | | | | | | | | | 0.00227 | 0.00227 | 0.00260 |
| **266.16** | **Becodisks Diskhaler (200)** | | | | | | | | | | | | | | 0.00000 | 0.00033 |
| **266.16** | **Becotide Rotacaps (400)** | | | | | | | | | | | | | | | 0.00033 |
| **272.80** | **Becodisks Diskhaler (100)** | | | | | | | | | | | | | | | |

[a]*Assuming a £10 cost offset compared with the cheapest pMDI is validated*
[b]*Not licensed for children aged under 12 yr*

***TABLE 33*** *QALY thresholds for 400 μg daily dose (or equivalent) of budesonide: cost per QALY threshold £5000*

| Cost per annum (£) | | 69.35 | 97.24 | 135.05 | 135.05 | 135.05 |
|---|---|---|---|---|---|---|
| | **Device name(s)** | **Pulmicort Aerosol with Nebuhaler** | **Pulmicort LS** | **Pulmicort Turbohaler (100)** | **Pulmicort Turbohaler (200)** | **Pulmicort Turbohaler (400)** |
| **69.35** | **Pulmicort Aerosol** | 0.00000 | 0.00558 | 0.01314 | 0.01314 | 0.01314 |
| **69.35** | **Pulmicort Aerosol with Nebuhaler** | | 0.00558 | 0.01314 | 0.01314 | 0.01314 |
| **97.24** | **Pulmicort LS** | | | 0.00756 | 0.00756 | 0.00756 |
| **135.05** | **Pulmicort Turbohaler (100)** | | | | 0.00000 | 0.00000 |
| **135.05** | **Pulmicort Turbohaler (200)** | | | | | 0.00000 |
| **135.05** | **Pulmicort Turbohaler (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 34*** *QALY thresholds for 400 μg daily dose (or equivalent) of budesonide: cost per QALY threshold £20,000*

| Cost per annum (£) | | 69.35 | 97.24 | 135.05 | 135.05 | 135.05 |
|---|---|---|---|---|---|---|
| | **Device name(s)** | **Pulmicort Aerosol with Nebuhaler** | **Pulmicort LS** | **Pulmicort Turbohaler (100)** | **Pulmicort Turbohaler (200)** | **Pulmicort Turbohaler (400)** |
| **69.35** | **Pulmicort Aerosol** | 0.00000 | 0.00139 | 0.00329 | 0.00329 | 0.00329 |
| **69.35** | **Pulmicort Aerosol with Nebuhaler** | | 0.00139 | 0.00329 | 0.00329 | 0.00329 |
| **97.24** | **Pulmicort LS** | | | 0.00189 | 0.00189 | 0.00189 |
| **135.05** | **Pulmicort Turbohaler (100)** | | | | 0.00000 | 0.00000 |
| **135.05** | **Pulmicort Turbohaler (200)** | | | | | 0.00000 |
| **135.05** | **Pulmicort Turbohaler (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 35*** *QALY thresholds for 200 μg daily dose (or equivalent) of fluticasone: cost per QALY threshold £5000*

| Cost per annum (£) | | 71.18 | 76.68 | 76.68 | 116.80 | 139.07 | 139.07 | 144.57 | 144.57 | 166.86 | 166.86 | 166.93 | 166.93 | 166.93 | 172.43 | 172.43 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Device name(s)** | **Flixotide Evohaler (50)** | **Flixotide (50) with Accuhaler** | **Flixotide Evohaler (50) with Accuhaler** | **Flixotide Accuhaler (100)** | **Flixotide (125)** | **Flixotide Evohaler (125)** | **Flixotide (125) with Accuhaler[a]** | **Flixotide Evohaler (125) with Accuhaler[a]** | **Flixotide Diskhaler (100)** | **Flixotide Diskhaler (50)** | **Flixotide (25)** | **Flixotide Evohaler (25)** | **Flixotide Accuhaler (50)** | **Flixotide (25) with Accuhaler** | **Flixotide Evohaler (25) with Accuhaler** |
| **71.18** | **Flixotide (50)** | 0.00000 | 0.00110 | 0.00110 | 0.00912 | 0.01358 | 0.01358 | 0.01468 | 0.01468 | 0.01914 | 0.01914 | 0.01915 | 0.01915 | 0.01915 | 0.02025 | 0.02025 |
| **71.18** | **Flixotide Evohaler (50)** | | 0.00110 | 0.00110 | 0.00912 | 0.01358 | 0.01358 | 0.01468 | 0.01468 | 0.01914 | 0.01914 | 0.01915 | 0.01915 | 0.01915 | 0.02025 | 0.02025 |
| **76.68** | **Flixotide (50) with Accuhaler** | | | 0.00000 | 0.00802 | 0.01248 | 0.01248 | 0.01358 | 0.01358 | 0.01804 | 0.01804 | 0.01805 | 0.01805 | 0.01805 | 0.01915 | 0.01915 |
| **76.68** | **Flixotide Evohaler (50) with Accuhaler** | | | | 0.00802 | 0.01248 | 0.01248 | 0.01358 | 0.01358 | 0.01804 | 0.01804 | 0.01805 | 0.01805 | 0.01805 | 0.01915 | 0.01915 |
| **116.80** | **Flixotide Accuhaler (100)** | | | | | 0.00445 | 0.00445 | 0.00555 | 0.00555 | 0.01001 | 0.01001 | 0.01003 | 0.01003 | 0.01003 | 0.01113 | 0.01113 |
| **139.07** | **Flixotide (125)** | | | | | | 0.00000 | 0.00110 | 0.00110 | 0.00556 | 0.00556 | 0.00557 | 0.00557 | 0.00557 | 0.00667 | 0.00667 |
| **139.07** | **Flixotide Evohaler (125)** | | | | | | | 0.00110 | 0.00110 | 0.00556 | 0.00556 | 0.00557 | 0.00557 | 0.00557 | 0.00667 | 0.00667 |
| **144.57** | **Flixotide (125) with Accuhaler[a]** | | | | | | | | 0.00000 | 0.00446 | 0.00446 | 0.00447 | 0.00447 | 0.00447 | 0.00557 | 0.00557 |
| **144.57** | **Flixotide Evohaler (125) with Accuhaler[a]** | | | | | | | | | 0.00446 | 0.00446 | 0.00447 | 0.00447 | 0.00447 | 0.00557 | 0.00557 |
| **166.86** | **Flixotide Diskhaler (100)** | | | | | | | | | | 0.00000 | 0.00001 | 0.00001 | 0.00001 | 0.00111 | 0.00111 |
| **166.86** | **Flixotide Diskhaler (50)** | | | | | | | | | | | 0.00001 | 0.00001 | 0.00001 | 0.00111 | 0.00111 |
| **166.93** | **Flixotide (25)** | | | | | | | | | | | | 0.00000 | 0.00000 | 0.00110 | 0.00110 |
| **166.93** | **Flixotide Evohaler (25)** | | | | | | | | | | | | | 0.00000 | 0.00110 | 0.00110 |
| **166.93** | **Flixotide Accuhaler (50)** | | | | | | | | | | | | | | 0.00110 | 0.00110 |
| **172.43** | **Flixotide (25) with Accuhaler** | | | | | | | | | | | | | | | 0.00000 |
| **172.43** | **Flixotide Evohaler (25) with Accuhaler** | | | | | | | | | | | | | | | |

[a] *Not indicated for children*

***TABLE 36*** *QALY thresholds for 200 µg daily dose (or equivalent) of fluticasone: cost per QALY threshold £20,000*

| Cost per annum (£) | | 71.18 | 76.68 | 76.68 | 116.80 | 139.07 | 139.07 | 144.57 | 144.57 | 166.86 | 166.86 | 166.93 | 166.93 | 166.93 | 172.43 | 172.43 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Device name(s)** | **Flixotide Evohaler (50)** | **Flixotide (50) with Accuhaler** | **Flixotide Evohaler (50) with Accuhaler** | **Flixotide Accuhaler (100)** | **Flixotide (125)** | **Flixotide Evohaler (125)** | **Flixotide (125) with Accuhaler[a]** | **Flixotide Evohaler (125) with Accuhaler[a]** | **Flixotide Diskhaler (100)** | **Flixotide Diskhaler (50)** | **Flixotide (25)** | **Flixotide Evohaler (25)** | **Flixotide Accuhaler (50)** | **Flixotide (25) with Accuhaler** | **Flixotide Evohaler (25) with Accuhaler** |
| **71.18** | **Flixotide (50)** | 0.00000 | 0.00028 | 0.00028 | 0.00228 | 0.00339 | 0.00339 | 0.00367 | 0.00367 | 0.00478 | 0.00478 | 0.00479 | 0.00479 | 0.00479 | 0.00506 | 0.00506 |
| **71.18** | **Flixotide Evohaler (50)** | | 0.00028 | 0.00028 | 0.00228 | 0.00339 | 0.00339 | 0.00367 | 0.00367 | 0.00478 | 0.00478 | 0.00479 | 0.00479 | 0.00479 | 0.00506 | 0.00506 |
| **76.68** | **Flixotide (50) with Accuhaler** | | | 0.00000 | 0.00201 | 0.00312 | 0.00312 | 0.00339 | 0.00339 | 0.00451 | 0.00451 | 0.00451 | 0.00451 | 0.00451 | 0.00479 | 0.00479 |
| **76.68** | **Flixotide Evohaler (50) with Accuhaler** | | | | 0.00201 | 0.00312 | 0.00312 | 0.00339 | 0.00339 | 0.00451 | 0.00451 | 0.00451 | 0.00451 | 0.00451 | 0.00479 | 0.00479 |
| **116.80** | **Flixotide Accuhaler (100)** | | | | | 0.00111 | 0.00111 | 0.00139 | 0.00139 | 0.00250 | 0.00250 | 0.00251 | 0.00251 | 0.00251 | 0.00278 | 0.00278 |
| **139.07** | **Flixotide (125)** | | | | | | 0.00000 | 0.00028 | 0.00028 | 0.00139 | 0.00139 | 0.00139 | 0.00139 | 0.00139 | 0.00167 | 0.00167 |
| **139.07** | **Flixotide Evohaler (125)** | | | | | | | 0.00028 | 0.00028 | 0.00139 | 0.00139 | 0.00139 | 0.00139 | 0.00139 | 0.00167 | 0.00167 |
| **144.57** | **Flixotide (125) with Accuhaler[a]** | | | | | | | | 0.00000 | 0.00111 | 0.00111 | 0.00112 | 0.00112 | 0.00112 | 0.00139 | 0.00139 |
| **144.57** | **Flixotide Evohaler (125) with Accuhaler[a]** | | | | | | | | | 0.00111 | 0.00111 | 0.00112 | 0.00112 | 0.00112 | 0.00139 | 0.00139 |
| **166.86** | **Flixotide Diskhaler (100)** | | | | | | | | | | 0.00000 | 0.00000 | 0.00000 | 0.00000 | 0.00028 | 0.00028 |
| **166.86** | **Flixotide Diskhaler (50)** | | | | | | | | | | | 0.00000 | 0.00000 | 0.00000 | 0.00028 | 0.00028 |
| **166.93** | **Flixotide (25)** | | | | | | | | | | | | 0.00000 | 0.00000 | 0.00028 | 0.00028 |
| **166.93** | **Flixotide Evohaler (25)** | | | | | | | | | | | | | 0.00000 | 0.00028 | 0.00028 |
| **166.93** | **Flixotide Accuhaler (50)** | | | | | | | | | | | | | | 0.00028 | 0.00028 |
| **172.43** | **Flixotide (25) with Accuhaler** | | | | | | | | | | | | | | | 0.00000 |
| **172.43** | **Flixotide Evohaler (25) with Accuhaler** | | | | | | | | | | | | | | | |

[a] *Not indicated for children*

***TABLE 37*** *QALY thresholds for 20 mg daily dose (or equivalent) of sodium cromoglicate: cost per QALY threshold £5000*

| Cost per annum (£) | | 32.71 | 34.68 | 34.68 | 60.77 | 60.77 |
|---|---|---|---|---|---|---|
| | Device name(s) | Cromogen with Able Spacer | Cromogen Easi-Breathe | Intal | Intal with Synchroner | Intal Spincaps |
| 24.31 | Cromogen | 0.00168 | 0.00207 | 0.00207 | 0.00729 | 0.00729 |
| 32.71 | Cromogen with Able Spacer | | 0.00039 | 0.00039 | 0.00561 | 0.00561 |
| 34.68 | Cromogen Easi-Breathe | | | 0.00000 | 0.00522 | 0.00522 |
| 34.68 | Intal | | | | 0.00522 | 0.00522 |
| 60.77 | Intal with Synchroner | | | | | 0.00000 |
| 60.77 | Intal Spincaps | | | | | |

***TABLE 38*** *QALY thresholds for 20 mg daily dose (or equivalent) of sodium cromoglicate: cost per QALY threshold £20,000*

| Cost per annum (£) | | 32.71 | 34.68 | 34.68 | 60.77 | 60.77 |
|---|---|---|---|---|---|---|
| | Device name(s) | Cromogen with Able Spacer | Cromogen Easi-Breathe | Intal | Intal with Synchroner | Intal Spincaps |
| 24.31 | Cromogen | 0.00042 | 0.00052 | 0.00052 | 0.00182 | 0.00182 |
| 32.71 | Cromogen with Able Spacer | | 0.00010 | 0.00010 | 0.00140 | 0.00140 |
| 34.68 | Cromogen Easi-Breathe | | | 0.00000 | 0.00130 | 0.00130 |
| 34.68 | Intal | | | | 0.00130 | 0.00130 |
| 60.77 | Intal with Synchroner | | | | | 0.00000 |
| 60.77 | Intal Spincaps | | | | | |

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Director,
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Professor of Therapeutics
University of Leicester

Professor Bruce Campbell
Consultant General Surgeon
Royal Devon & Exeter Hospital

Professor Shah Ebrahim
Professor of Epidemiology
of Ageing
University of Bristol

Dr John Reynolds
Clinical Director
Acute General Medicine SDU
Oxford Radcliffe Hospital

Dr Ron Zimmern
Director, Public Health
Genetics Unit
Strangeways Research
Laboratories, Cambridge

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**Members**

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Director, NHS HTA
Programme, &
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University of Bristol

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NHS R&D
Clinical Scientist
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Institute of Health Sciences
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Director, MRC Institute
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University of Nottingham

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School of Psychology
University of Leeds

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London School of Hygiene
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University of Oxford

Professor Ala Szczepura
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Services Studies
University of Warwick

Dr Gillian Vivian
Consultant in Nuclear
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Truro

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Department of
General Practice
University of Glasgow

Dr Jeremy Wyatt
Senior Fellow
Health Knowledge
Management Centre
University College London



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*continued*

## Diagnostic Technologies & Screening Panel

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Director, Public Health Genetics Unit
Strangeways Research Laboratories
Cambridge

Dr Philip J Ayres
Consultant in Epidemiology & Public Health
The Leeds Teaching Hospitals NHS Trust

Mrs Stella Burnside
Chief Executive, Altnagelvin Hospitals Health & Social Services Trust
Londonderry
Northern Ireland

Dr Paul O Collinson
Consultant Chemical Pathologist & Senior Lecturer
St George's Hospital, London

Dr Barry Cookson
Director, Laboratory of Hospital Infection
Public Health Laboratory Service, London

Professor Howard Cuckle
Professor of Reproductive Epidemiology
University of Leeds

Dr Carol Dezateux
Senior Lecturer in Paediatric Epidemiology
Institute of Child Health
London

Professor Adrian K Dixon
Professor of Radiology
Addenbrooke's Hospital
Cambridge

Mr Steve Ebdon-Jackson
Head, Diagnostic Imaging & Radiation Protection Team
Department of Health, London

Dr Tom Fahey
Senior Lecturer in General Practice
University of Bristol

Dr Andrew Farmer
General Practitioner & NHS Clinical Scientist
Institute of Health Sciences
University of Oxford

Mrs Gillian Fletcher
Antenatal Teacher & Tutor
National Childbirth Trust
Reigate

Professor Jane Franklyn
Professor of Medicine
University of Birmingham

Dr JA Muir Gray
Joint Director, National Screening Committee
NHS Executive, Oxford

Dr Peter Howlett
Executive Director – Development
Portsmouth Hospitals NHS Trust

Professor Alistair McGuire
Professor of Health Economics
City University, London

Mrs Kathlyn Slack
Professional Support
Diagnostic Imaging & Radiation Protection Team
Department of Health
London

Mr Tony Tester
Chief Officer, South Bedfordshire Community Health Council
Luton

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Clinical Director – Acute General Medicine SDU
Oxford Radcliffe Hospital

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Milford-on-Sea, Hants

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Leicester Royal Infirmary

Dr Alastair Gray
Director, Health Economics Research Centre
Institute of Health Sciences
University of Oxford

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Senior Principal Pharmacist
Department of Health, London

Dr Andrew Mortimore
Consultant in Public Health Medicine
Southampton & South West Hants Health Authority

Mr Nigel Offen
Head of Clinical Quality
NHS Executive – Eastern
Milton Keynes

Professor Robert Peveler
Professor of Liaison Psychiatry
Royal South Hants Hospital
Southampton

Mrs Marianne Rigge
Director, College of Health
London

Dr Frances Rotblat
Manager, Biotechnology Group
Medicines Control Agency
London

Mr Bill Sang
Chief Executive
Salford Royal Hospitals NHS Trust

Dr Eamonn Sheridan
Consultant in Clinical Genetics
St James's University Hospital
Leeds

Mrs Katrina Simister
New Products Manager
National Prescribing Centre
Liverpool

Dr Ross Taylor
Senior Lecturer
Department of General Practice & Primary Care
University of Aberdeen

Dr Richard Tiner
Medical Director
Association of the British Pharmaceutical Industry
London

Professor Jenifer Wilson-Barnett
Head, Florence Nightingale Division of Nursing & Midwifery
King's College, London

Mr David J Wright
Chief Executive
International Glaucoma Association, London

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Consultant General Surgeon
Royal Devon & Exeter Hospital

Professor John Bond
Professor of
Health Services Research
University of Newcastle-upon-Tyne

Ms Judith Brodie
Head of Cancer
Support Service
Cancer BACUP, London

Ms Tracy Bury
Head of Research
& Development
Chartered Society of
Physiotherapy, London

Mr Michael Clancy
Consultant in A&E Medicine
Southampton General Hospital

Professor Collette Clifford
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Dr Katherine Darton
Information Unit
MIND – The Mental Health
Charity, London

Mr John Dunning
Consultant Cardiothoracic
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Cambridge

Mr Jonothan Earnshaw
Consultant Vascular Surgeon
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The Leicester Royal Infirmary
NHS Trust

Professor FD Richard Hobbs
Professor of Primary Care
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University of Birmingham

Mr Richard Johanson
Consultant & Senior Lecturer
North Staffordshire Infirmary
NHS Trust, Stoke-on-Trent

Dr Duncan Keeley
General Practitioner
Thame, Oxon

Dr Phillip Leech
Principal Medical Officer
Department of Health, London

Professor James Lindesay
Professor of Psychiatry for
the Elderly
University of Leicester

Professor Rajan Madhok
Director of Health Policy
& Public Health
East Riding & Hull
Health Authority

Dr Mike McGovern
Branch Head
Department of Health
London

Dr John C Pounsford
Consultant Physician
Frenchay Healthcare Trust
Bristol

Dr Mark Sculpher
Senior Research Fellow in
Health Economics
University of York

Dr Ken Stein
Consultant in Public
Health Medicine
North & East Devon
Health Authority, Exeter

## Expert Advisory Network

**Members**

Professor John Brazier
Director of Health Economics
University of Sheffield

Mr Shaun Brogan
Chief Executive, Ridgeway
Primary Care Group
Aylesbury, Bucks

Mr John A Cairns
Director, Health Economics
Research Unit
University of Aberdeen

Dr Nicky Cullum
Reader in Health Studies
University of York

Professor Pam Enderby
Chair of Community
Rehabilitation
University of Sheffield

Mr Leonard R Fenwick
Chief Executive
Freeman Hospital
Newcastle-upon-Tyne

Ms Grace Gibbs
Deputy Chief Executive
West Middlesex
University Hospital

Dr Neville Goodman
Consultant Anaesthetist
Southmead Hospital, Bristol

Professor Robert E Hawkins
CRC Professor & Director of
Medical Oncology
Christie Hospital NHS Trust
Manchester

Professor Allen Hutchinson
Director of Public Health &
Deputy Dean, ScHARR
University of Sheffield

Professor David Mant
Professor of General Practice
Institute of Health Sciences
University of Oxford

Professor Alexander Markham
Director
Molecular Medicine Unit
St James's University Hospital
Leeds

Dr Chris McCall
General Practitioner
Corfe Mullen, Dorset

Dr Peter Moore
Freelance Science Writer
Ashtead, Surrey

Dr Sue Moss
Associate Director, Cancer
Screening Evaluation Unit
Institute of Cancer Research
Sutton, Surrey

Mrs Julietta Patnick
National Coordinator
NHS Cancer Screening
Programmes, Sheffield

Professor Jennie Popay
Professor of Sociology &
Community Health
University of Salford

Professor Chris Price
Professor of
Clinical Biochemistry
St Bartholomew's & The
Royal London School of
Medicine & Dentistry

Mr Simon Robbins
Chief Executive
Camden & Islington
Health Authority, London

Dr William Rosenberg
Senior Lecturer &
Consultant in Medicine
University of Southampton

Dr Sarah Stewart-Brown
Director, Health Services
Research Unit
University of Oxford

Dr Gillian Vivian
Consultant in Nuclear
Medicine & Radiology
Royal Cornwall Hospitals Trust
Truro

Mrs Joan Webster
Former Chair
Southern Derbyshire
Community Health Council
Nottingham

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The HTA programme and the authors would like to know your views about this report.

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***We look forward to hearing from you.***

Copies of this report can be obtained from:

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

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