

# CLINICAL AND COST EFFECTIVENESS OF INHALER DEVICES FOR CHILDREN WITH CHRONIC ASTHMA

**Report commissioned  
by:**

NHS R&D HTA Programme

**On behalf of:**

The National Institute for Clinical Excellence

**Produced by:**

Trent Institute for Health Services Research, School of Health  
& Related Research (SchARR). The University of Sheffield.

**Authors:**

Nick Payne Senior Lecturer in Public Health Medicine<sup>1</sup>

Stephen Beard, Senior Operational Research Analysts<sup>1</sup>

David Brocklebank, Respiratory Research Registrar<sup>2</sup>

Felix Ram, Respiratory Research Fellow<sup>2</sup>

John Wright, Consultant in Clinical Epidemiology and Public  
Health<sup>2</sup>

Rod Taylor, Head of Appraisal<sup>3</sup>

<sup>1</sup>ScHARR

<sup>2</sup>Bradford Hospitals NHS Trust

Department of Epidemiology and Public Health

<sup>3</sup>National Institute for Clinical Excellence

**Final revision completed:** August 2000

**Expiry Date:** August 2003

## 1.0 Introduction

### 1.1 Epidemiology

Asthma is a common disease that produces symptoms of wheeziness and breathlessness. It affects the lower airways and results in narrowing (bronchoconstriction) of the airways with consequent reduction in the flow of gases between the air and lung alveoli and symptoms of wheeze and breathlessness. It can be triggered by a variety of environmental factors such as infection, allergy, airborne chemicals and also exercise. There are a number of patterns of lower airways disease in early childhood that results in two predominant clinical patterns (acute wheezy episodes and recurrent day to day symptoms) that may occur separately or together in the child. It has a wide range of severity, is the cause of considerable morbidity and a rare cause of death.

In the UK, asthma treatment is strongly influenced by the guidelines of the British Thoracic Society (BTS)<sup>2</sup> which promote a step-wise management of increasingly severe asthma. Therapy consists predominantly of the use of inhalers, delivering beta<sub>2</sub>-agonists, corticosteroids and cromoglycate-like drugs in various doses. The use of increasing doses of inhaled corticosteroids is the mainstay of preventive therapy.

### 1.2 Incidence and Pathology

The prevalence of asthma in England is around 8-12%,<sup>3,4</sup> but not all people who have asthma are currently being treated. Table 1 shows the number of those treated for asthma per 1,000 population for England and Wales, subdivided by age and sex.<sup>5</sup> Patients aged 0 to 4 years constitute 7.7% of all those with the condition.

Table 1. The prevalence of those treated for asthma per 1,000 population

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

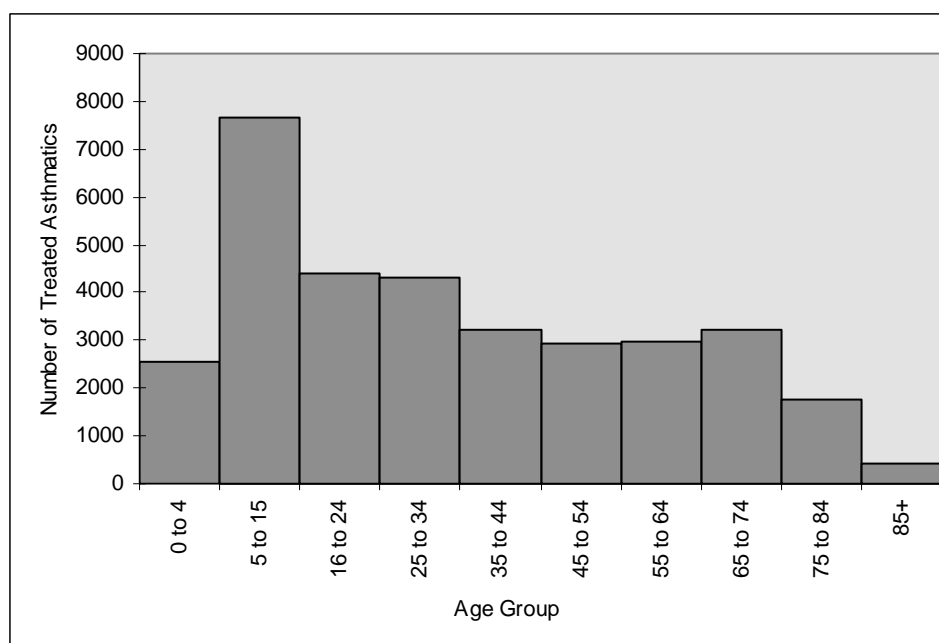
The severity of asthma has been divided into five BTS steps. The percentage of patients in each BTS step has been derived from Hoskins et al.<sup>6</sup> and is shown in Table 2.

**Table 2. The estimated proportion of people with asthma by BTS step**

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

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

**Figure 1. Estimated number treated for asthma in a health authority serving a population of 500,000.**



Using the prevalence rate for treated asthmatics and standard population in a district of 500,000 people,<sup>5,7</sup> there would be 33,500 expected asthmatics - 2,580 of these would be expected to be in the age range 0 to 4 years, and 30,920 in the age range of five years and over. This information, broken down by BTS step, is given in Table 3.

**Table 3. The expected number of people with asthma, by broad age band and severity, in a health authority of 500,000 people**

|                         | Aged 0 - 4 years | Aged 5-15 years | Aged 16 years and over |
|-------------------------|------------------|-----------------|------------------------|
| Medication below step 1 | 57               | 845             | 2,790                  |
| BTS step 1              | 1,204            | 1,536           | 4,184                  |
| BTS step 2              | 1,147            | 3,379           | 8,834                  |
| BTS step 3              | 172              | 1,459           | 5,114                  |
| BTS step 4              | 0                | 230             | 2,092                  |
| BTS step 5              | N/A              | 230             | 232                    |
| <b>Total Number</b>     | <b>2,580</b>     | <b>7,679</b>    | <b>23,246</b>          |

### 1.3 An estimate of the costs of drugs used in treating chronic asthma in children

The Prescribing Analysis and Costs (PACT) data are one possible source of information about the quantity of drugs prescribed for asthma in children. It is not yet clear whether these data can be analysed in this way but this issue is being explored with the Prescriptions Pricing Authority (PPA). In any event, we have assumed that the division of the drug costs by BTS step cannot be determined by the use of PACT data.

Another way of providing an approximate estimate of the number and costs of drugs prescribed for asthma, is to assume that the patients are prescribed drugs consistent with their position within BTS guidelines. The assumed drug regimens for those on each BTS step are given in table 4.

**Table 4. The assumed drug regimens per BTS step for patients aged 5 years and over. Children under 5 years are assumed to have a similar regime but at half the dose**

| BTS step     | Assumed drug use   |
|--------------|--|
| Below Step 1 | Salbutamol 0.5 puffs a day.  |
| Step 1       | Salbutamol 1 puff a day.   |
| Step 2       | Beclomethasone 200ug twice daily + Salbutamol 4 puffs a day.         |
| Step 3       | Beclomethasone 400ug four times daily +<br>Salbutamol 4 puffs a day. |
| Step 4       | Step 3 treatment + Salmeterol 50ug twice daily                       |
| Step 5       | Step 4 treatment + 5mg Prednisolone once daily                       |

The yearly costs of these drug regimens have been calculated with the use of the electronic version of the British National Formulary. The costs per step are shown in Table 5 for patients aged five years and over.

While it is very important to acknowledge that the above estimates are only approximate, they do give an order of magnitude estimate of the expenditure involved in an average health authority. Costs for children under 5 are below £100,000 per annum while costs for older children (5-15) are around £1 million per annum.

**Table 5. The expected drug costs per annum for children with chronic asthma in a health authority of 500,000 people by BTS step**

| BTS Step     | Drug cost per year per patient |            | Number in the step |            | Total Drug Costs |            |
|--------------|--------------------------------|------------|--------------------|------------|------------------|------------|
|              | 0-4 years                      | 5-15 years | 0-4 years          | 5-15 years | 0-4 years        | 5-15 years |
| Age-group    |                                |            |                    |            |                  |            |
| Below step 1 | -                              | £1.57      | 57                 | 845        | -                | £1,330     |
| Step 1       | £1.57                          | £3.14      | 1,204              | 1,536      | £1,890           | £4,820     |
| Step 2       | £42.10                         | £84.19     | 1,147              | 3,379      | £48,280          | £284,480   |
| Step 3       | £149.53                        | £299.06    | 172                | 1,459      | £25,720          | £436,330   |
| Step 4       | £323.64                        | £647.27    | 0                  | 230        | -                | £148,870   |
| Step 5       | -                              | £668.31    | -                  | 230        | -                | £153,710   |
| All Steps    |                                |            | 2,580              | 7,679      | £75,890          | £1,029,540 |

These above results for asthma drug treatment for all ages compares well with PACT-derived costs.

### 1.4 Inhaler devices for children

There are a tremendous variety of inhaler types (and pharmaceutical agents) that can be used in the management of asthma. The matrix table in appendix 1 illustrates the extent of this range. The primary objective of the treatment of children with asthma is to achieve an optimal control of the disease by reducing exacerbations, increasing lung function and limiting symptoms in order to maximise the quality of life of the individual patient.<sup>9</sup> This is currently believed to be best achieved by delivering both symptom relieving and preventative anti-inflammatory medication, typically with bronchodilators and/or corticosteroids, as directly as possible to the lungs. Inhaled aerosol therapy

has become increasingly more favoured over systemic therapy, as systemic treatment invariably carries a higher total body dose, increases the potential for adverse effects, and can take much longer to act.<sup>9</sup> The ability to provide an early, effective treatment is particularly important in children. The early control of childhood asthma can provide longer-term advantages, both in terms of improved management of the disease and reductions in the social burden of disease caused through lost school days and reduced activity levels.<sup>10,11,12,13</sup>

However, there are many factors related to the actual physical mode of delivery of asthma drugs that can work against the achievement of this goal of optimal symptom control and can strongly influence the cost-effectiveness of treatments.

Firstly, poor inhaler technique in young children, due to either poor training in using a device or indeed a mis-suited device, can reduce significantly the proportion of the dose of drug molecule that is actually inhaled, or **delivered**, and also the amount of drug **deposition** to the lung. This can mean that much higher metered doses of the drug will be needed to achieve the same clinical effect, therefore impacting on the cost-effectiveness of the drug/delivery system, or it can simply result in poor clinical management of the disease. Poor inhalation can also lead to increased side effects from drugs, particularly in the case of corticosteroids with oral mucosa-related problems. Again this can lead to additional treatment-related costs.<sup>14</sup>

Secondly, 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. Often children can find certain devices much too difficult to handle physically. Young children, in particular, have clear difficulties in achieving the co-ordination of actuation and inhalation. Such problems of poor adherence due to device-related difficulties, can often lead to higher healthcare costs in the longer term.<sup>14</sup>

Therefore, as well as selecting the most appropriate medication for children with asthma, in terms of the actual clinical properties of the drug itself, it is also vital that the selected delivery device system is that most appropriate to the child's own life-style and physical/cognitive/emotional needs.<sup>15,16</sup>

The vast majority (>90%) of childhood inhaled asthma medication is prescribed and delivered using pressurised metered dose inhalers (pMDIs). The real benefits of pMDIs lie in their relatively low cost and their ease and portability of use. However, due to the need to co-ordinate the actuation of the device with inhalation, these devices, when used alone, are not suited to children under 5 years. Typically pMDIs are combined with a **spacer device**, to aid the inhalation of the drug, ensuring a better disposition to the lung. With typical life-spans of 6-12 months, the costs of spacer devices (and face masks for younger children) are still relatively low when compared to the longer-term cost of the drug and pMDI itself, and are generally argued to be outweighed by the clinical benefits from the reduced treatment costs of stable asthma.<sup>17</sup>

Although **breath actuated** pMDIs are available, reducing the physical requirements for co-ordinated inhalation, their use in children is often hampered by the reaction of children to the sound and feel of the device as it activates.<sup>17</sup>

Newer **dry-powder inhalation systems** (DPIs) are also generally believed to improve drug deposition to the lung (around 30% of dose compared to only 10-20% with pMDIs) and as such suggest both clinical and cost benefits. The portability of DPIs compared to pMDIs + spacers is seen as an attraction, as is the increased ability to monitor closely delivered dosage. However, the relatively low strength of inhalation seen in younger children can cause problems with their use as DPI systems rely on the patients' own inhalation strength to disperse the drug.<sup>17</sup> The use of dry-powder systems is generally not advised in children under 5 years, although there may be individual cases where there is a clear justification for their use if it can be shown that the child can operate the system correctly and can receive the correct dosage to the lung.

Nebulisers are significantly more costly to operate than the other inhalation devices and thus their use is now largely reserved for the treatment of acute asthma in patients who are so severely affected that they cannot use inhaled pMDI based treatment.

Issues of device availability, clinical-effectiveness and suitability are covered in the later sections of the report and are further highlighted in the recent Drugs and Therapeutics Bulletin on asthma

devices and the revised BTS Asthma Guidelines.<sup>17,9</sup> The latest BTS Guidelines suggest the following as the most clinically appropriate asthma drug delivery systems for children under the age of 5 years.<sup>9</sup> These BTS guidelines are not explicitly evidenced based.

**Table 6. BTS Guidelines on Device Choices for Asthmatic Children Aged <6 years**

| <b>Age Group</b>    | <b>1<sup>st</sup> Choice Device</b> | <b>2<sup>nd</sup> Choice Device</b> | <b>3<sup>rd</sup> Choice Device</b> | <b>Breath-actuated</b> | <b>Dry-powder</b>   |
|---------------------|-------------------------------------|-------------------------------------|-------------------------------------|------------------------|---|
| 0-2 Years inclusive | MDI + spacer + face mask            | MDI + spacer                        | Nebuliser (rarely needed)           | Avoid                  | Avoid   |
| 3-5 Years inclusive | MDI + spacer                        | MDI + spacer + face mask            | Nebuliser (rarely needed )          | Not proven             | Possible use for $\beta_2$ -agonist but not recommended for corticosteroids |

A large number of inhaler devices exist for the treatment of asthma in children. A recent Cochrane systematic review has addressed the effectiveness of inhaler systems (i.e. wet chamber nebulisers versus metered dose inhalers with holding chambers to deliver beta2-agonist medications) for acute asthma<sup>42</sup>. Moreover there is now significant evidence to suggest that an MDI + spacer is more appropriate than nebulisers from both a clinical and cost-effective viewpoint for the treatment of asthma exacerbations in an acute setting, for both children and adults alike.<sup>18</sup> The authors could find no previous systematic review of clinical trials comparing these inhaler devices to provide an objective and unbiased appraisal of their clinical and cost effectiveness in young children with chronic asthma. The aim of this report is to examine the clinical effectiveness and cost effectiveness of inhaler systems (devices) for children, particularly young children (less than 5 years of age), with chronic asthma.

## 2.0 Methods

### 2.1 Search strategy

A search for studies was performed by the Bradford team. The search strategies for the Medline searches and results are shown in Appendix 2. Search Strategies for all the other databases are available from the reviewers. This search incorporated both hand searching (retrospective and prospective) of core journals in respiratory disease and conference abstracts (see Appendix 3), as well as electronic bibliographies (see Appendix 4).

In addition an independent following literature search was performed by the School of Health & Related Research (SchHARR) team:

- a search for systematic reviews addressing the use of inhaler devices for children with asthma
- a clinical effectiveness search to retrieve randomised controlled trials comparing inhaler devices in children with asthma
- a health economics literature search on inhaler devices in asthma
- a rapid search for relevant literature on the epidemiology of asthma in children, especially under 5 year olds

Both searches included the following databases:

- Medline
- Embase
- Science Citation Index
- Cochrane Library
- NHS CRD: DARE, NEED and HTA
- HealthSTAR
- National Research Register

From 1966 to March 2000.

Web pages were contacted for INAHTA members and other Health Technology Assessment (HTA) organisations to determine if HTA reports had been produced on this topic. The results of these two searches were used as the basis of this review.

The submissions from manufacturers and sponsors received the National Institute for Clinical Excellence were also comprehensively reviewed for relevant clinical and cost effectiveness evidence (Appendix 5).

### 2.2 Inclusion and exclusion criteria

As an initial filter, each title and abstract was checked by the SchHARR team to determine whether the study was of relevance to this report. Randomised trials were considered relevant if they compared one inhaler device with another in a population of the appropriate age group. The results of the search were compared with those already carried out by colleagues from Bradford and any relevant articles resulting were added. In vitro and ex vivo studies were excluded from this review.

#### *Types of studies*

Randomised controlled trials were considered. Studies may be laboratory or community based. Trial duration must have been for a minimum of four weeks for trials of corticosteroids otherwise any duration is considered.

#### *Types of participants*

Children (from age 2 to 16 years) with chronic, stable asthma (i.e. not during an exacerbation) diagnosed by a clinician or according to internationally accepted criteria. Children under 2 years of age were excluded due to difficult to make an accurate diagnosis of asthma in this age group. Never the less a retrospective review of all studies (without an age filter) in this review found relevant studies in the under 2 year age group.

### *Types of interventions*

Trials were considered that compared clinical outcomes of a single drug delivered by different inhaler devices. These devices were standard pMDI (with or without large volume spacer device) versus any hand-held device (reviews 1A and 1B respectively) and nebuliser versus any hand-held inhaler (review 2). Co-interventions and contamination may have occurred, but these will be recorded. Drugs considered were inhaled corticosteroids for review 1A, short-acting beta-agonists for review 1B and short-acting beta-agonists or anti-cholinergics for review 2.

### *Selection of trials:*

The results of the computerised search were independently reviewed by two reviewers (DB, FR) on the basis of a search of title, abstract and key words/MESH headings. Any potentially relevant articles were obtained in full.

The full text of potentially relevant articles was reviewed independently by the two reviewers to assess each study according to the previously written criteria. Disagreement was resolved by third party adjudication.

### *Economic evaluations*

Economic studies were considered within the report provided that they were based on a direct comparison between different inhaler devices delivering either exactly the same or comparable drugs in children under the age of 5 years. As such economic studies which used placebo controls or which compared very different forms of treatment (and as such focused on a treat vs no treat option) were excluded.

## **2.3 Data extraction strategy**

Details of each trial (intervention, duration, participants, design, quality and outcome measures) were extracted independently by the two reviewers directly into tables. Disagreement was resolved by consensus. First authors of the included studies were contacted as necessary to provide additional information or data for their studies.

## **2.4 Quality assessment strategy**

Methodological quality assessment were independently carried out by two reviewers using the Cochrane approach to assessment of allocation concealment and. All trials are scored and entered using the following principles:

Grade A: Adequate concealment

Grade B: Uncertain

Grade C: Clearly inadequate concealment

Grade D: Not used

## **2.5 Methods of analysis/synthesis**

The number of studies available for children with asthma was limited and the outcomes were numerous and not all reported fully. Therefore meta-analysis was not able to be performed and the evidence has been analysed on an individual narrative basis.



## 2.0 Results

This report gives the results of a systemic review of the evidence of effectiveness of inhaler devices available for use in non-acute childhood asthma. It is divided into three categories. Reviews 1A and 1B detail the delivery of inhaled corticosteroids and beta-2 bronchodilators respectively by comparison of a standard CFC pressurised metered dose inhaler (pMDI) with or without spacer device against CFC-free pMDI, breath actuated pMDI or dry powder inhaler (DPI). Review 2 details the delivery of beta-agonist bronchodilators by nebuliser versus any of the other devices listed above.

### 2.1 Search

Taken together, the search strategies yielded a large numbers of publications – thus from the SchHARR search alone over 2000 were initially added to the database. Around 650 were explicitly described as randomised controlled trials.

There were 79 publications that had mention of economics, but on further inspection of titles and abstracts these were narrowed down to some 17 relevant or potentially relevant articles that were retrieved.

The Bradford team's search results from the electronic search were:

Review 1A 783 – 37 full papers reviews of which 3 met inclusion criteria

Review 1B 1056 – 180 full papers reviewed of which 11 met inclusion criteria

Review 2 536 – 20 full papers reviewed of which 3 met inclusion criteria

These included children and adults.

Randomised trials were considered relevant if they compared one inhaler device with another. After this filter had been applied the following numbers trials were obtained: Review 1A - 2 trials; Review 1B - 11 trials; Review 2 - 3 trials. The numbers included in the present review were 2, 11 and 3 trials respectively.

### 2.1 Clinical Effectiveness

#### ***Delivery of corticosteroids by hand-held inhalers – review 1A***

The current recommendations for prescribing in childhood asthma are based on the widely accepted British Thoracic Society guidelines<sup>19</sup>. In the under 5s DPIs are not recommended. In the over 5s there may be a small role for DPIs but even here it is suggested that this should not be for the delivery of corticosteroids.

Two randomised controlled trials are available to address this question (see Table 7). Both compare a pMDI (with a spacer in one case) versus a dry-powder inhaler (DPI). These should be put in the context of the above guidelines.

Agertoft 1993 compares pMDI with Nebuhaler to the Turbuhaler DPI for the delivery of budesonide. Based on previous in vitro and in vivo studies it had been suggested that the Turbuhaler delivered approximately twice the dose of drug to the lungs. Therefore, this was tested in the clinical study by using a 2:1 dosing regimen between the pMDI and Turbuhaler. Overall the study does support the 2:1 dosing hypothesis, suggesting that lung deposition is equivalent. The current situation as far as prescribing advice is concerned is unclear with no explicit directions to reduce dose in common formularies (BNF<sup>20</sup>, MIMS<sup>21</sup>) or the product data sheets. There is clear evidence<sup>22</sup>, that generally DPI devices cause more systemic side effects than pMDI (especially with large volume spacer) devices hence the guideline recommendations<sup>19</sup> to avoid DPIs for corticosteroid delivery in children. However the above study shows that there is no significant difference between the compared devices in the levels of 24 hour urinary cortisol, implying a similar systemic delivery. Other potential side-effects of hoarse voice or oropharyngeal thrush were not examined in this study

The inhaler technique of the Turbuhaler must be considered especially in children, as this will have a significant bearing on efficacy. The Turbuhaler has a high internal resistance and needs a relatively high inspiratory flow of 60 litres/minute for optimal drug delivery. This may not be achievable especially in younger children even if it is assumed that the patient is taught to use

the device and this factor is known to the teacher. Studies have shown that children as young as 3 years can use a Turbuhaler efficiently<sup>23</sup> but the selection and teaching of these subjects may not reflect usual practice. Other work by Agertoft, in a filter study in 198 children<sup>24</sup> comparing pMDI+Nebuhaler vs Turbuhaler showed that in younger children within the trial, Turbuhaler drug delivery was less efficient; children 5 years and above showed drug delivery of 1:2 (as accepted in adults and the Agertoft study for children 4-15 years<sup>25</sup>), whilst children of 3 and 4 years showed drug delivery of 1:1.

In summary this large and well designed study does support the equivalence of pMDI+Nebuhaler versus Turbuhaler at half of the pMDI dose. However it does not present any evidence for advantages over the accepted place of pMDI+large volume spacer as the device of choice in childhood asthma management.

Edmunds<sup>26</sup> compares a pMDI alone to a Rotahaler and has a number of major flaws. A pMDI alone would not be a suitable device for the delivery of corticosteroids to children. The comparator of Rotahaler is now rarely used and also is unsuitable for children<sup>19</sup> (comments as for Turbuhaler). The dosage chosen is at 1:1 but now the accepted would be for pMDI:Rotahaler to be 1:2<sup>27, 28</sup>. Finally the study is under-powered.

Although both these trials included children of 5 years of less, the majority of these recruited children were of 5 years or older.

**Table 7. Details of RCTs in Children from Review 1A – Steroids by hand-held inhalers (In all tables ranked according to Cochrane quality A, B, C or D)**

| Author, year   | Methodology  | Details   | Results (all MDI, DPI, and (SD))  | Comments  |
|--|--|---|---|---|
| <p><b>Agertoft 1993</b><br/>Importance of inhaler device on the effect of budesonide.</p> <p><i>Citation:</i>Archives of Disease in Childhood 1993;69:130-133</p> <p>(Also published as Ugeskr Laeger 1994;156:4134-4137)</p>  | <p><i>Design:</i> Parallel, open RCT<br/><i>Device:</i> pMDI+ Nebuhaler vs Turbuhaler<br/><i>Drug:</i> Budesonide<br/><i>Dose:</i> pMDI+Nebuhaler – run-in dose<br/>Turbuhaler – half of run-in dose<br/><i>Duration:</i> 9 weeks</p>              | <p><i>Participants:</i> 126 asthma patients, 87M, 39F<br/>mean age 9.2, range 4-15</p> <p>241 children were screened by halving their steroid dosage. The 126 that deteriorated asthma control went forward to randomisation.</p> <p><i>Quality:</i> Cochrane B</p> | <p><i>No significant differences in:</i><br/>Change from baseline of;<br/>FEV1 0.12(0.28), 0.11(0.28) litres<br/>FVC 0.13, 0.12 litres<br/>FEF25-75% 0.15, 0.12 l/sec<br/>PEFR am 11.5(30), 14.9(30) l/min<br/>symptom score;<br/>day -0.30(0.38), -0.26(0.38)<br/>night -0.15(0.30), -0.21(0.30)<br/>%falls in response to exercise of<br/>FEV1 12.3, 11.1%<br/>FVC 6.9, 6.4%<br/>FEF25-75% 27.6, 22.7%<br/>PEFR 13.0, 11.2<br/>24hr urinary cortisol 31.5(17), 32.7(19)</p> <p><i>Statistical difference in:</i><br/>relief medication use, puffs/week<br/>4.67, 3.83</p> | <p>This study supports equivalence of pMDI+Nebuhaler versus Turbuhaler at half the pMDI dose. This should not be taken to mean that the device is twice as effective. There was no difference in 24 hour urinary cortisol between the groups implying a similar delivered dose of medication.</p> <p>Relief medication usage is statistically different between groups but the effect is small (less than 1 extra puff/week).</p> <p>Ranked ahead of Edmunds 1979 due to much greater study size.</p> |
| <p><b>Edmunds 1979</b><br/>A clinical comparison of beclomethasone dipropionate delivered by pressurised aerosol and as a powder from a Rotahaler.</p> <p>Implies Rotahaler supplied by Allen and Hanbury's Research Division.</p> <p><i>Citation:</i>Archives of Disease of Childhood 1979;54:233-235</p> | <p><i>Design:</i> Cross-over RCT, double-blinded, double-dummy,<br/><i>Device:</i> pMDI versus Rotahaler<br/><i>Drug:</i> Beclomethasone<br/><i>Dose:</i> 2puffs qds v 1capsule qds (presumed each 200ug qds)<br/><i>Duration:</i> 2 X 1 month</p> | <p><i>Participants:</i> 14 asthma patients, 7M, 7F<br/>mean age 9.7 years, range 4.8-15.1</p> <p><i>Quality:</i> Cochrane A</p>   | <p><i>No significant differences in:</i><br/>PEFR am<br/>symptom free days<br/>relief salbutamol use</p> <p><i>Significant difference in:</i><br/>mean symptom scores in favour of pMDI. (p=0.04)<br/>(no further data extractable from paper)</p> <p>8 patients preferred aerosol, 2 preferred Rotahaler.</p>  | <p>Poorly presented study with no statistical results given (author states 'no significance').</p> <p>Rotahaler (Rotacaps) is an unusual device to use now and would normally be considered to need twice the pMDI dosage. This study is presumed to be 1:1 dosing.</p>   |

### ***Delivery of $\beta_2$ agonists: pMDI vs other hand-held inhalers – Review 1B***

Eleven studies were found comparing pMDI with other inhaler devices for inhaled beta agonist drugs (see Table 8).

Seven studies<sup>29, 30, 31, 32, 33, 34, 35</sup> compared pMDI with Turbuhaler. No significant difference was found in the following outcomes: FEV<sub>1</sub>, FVC, HR, FEF<sub>25-75%</sub>, BP, Raw, PEFR and VTG. Ahlström et.al<sup>35</sup> reported significantly (p=0.046) higher morning PEFR values as opposed to the pMDI group, however the baseline evening PEFR was significantly (p=0.03) higher in the Turbuhaler group when compared to the pMDI group.

Two studies<sup>36, 37</sup> compared pMDI with Rotahaler. No significant difference was found in the following measured outcomes: FEV<sub>1</sub>, FVC, FEF<sub>25-75%</sub>, PEFR, HR, BP, drop-out rate or asthma symptom scores. In the long-term study (12 weeks) by Kemp 1989<sup>36</sup>, the number of acute exacerbations requiring medical intervention was significantly higher in the pMDI group.

One study<sup>38</sup> compared HFA (CFC-free) inhalers with CFC pMDI. No difference in measured FEV<sub>1</sub> was found. One study compared a device called an Italseber<sup>39</sup> with pMDI and found significant difference (p<0.05) in the overall mean percentage predicted PEFR over a 5 hour period after administration of bronchodilator. Attempts to find out from the authors and the Sponsor Company as to what this device is were unsuccessful.

Four of these randomised controlled trials recruited children of 5 years or less. These trials involved a total of 278 children, some of which were aged 5 years or more. The remaining three studies demonstrated no difference when comparing  $\beta_2$  agonist delivery via pMDI plus spacer with  $\beta_2$  agonist delivery by DPI.

**Table 8. Details of 11 RCTs in Children from Review 1B**

| Study Author, Year  | Methodology   | Details  | Results  | Comments  |
|---|---|--|--|---|
| <p><b>Custovic 1995</b><br/>                     Depart of Paediatrics,<br/>                     Manchester, UK.<br/>                     Also has Glaxo involvement<br/>                     Citation: J Pharm Med 5; 161-168.</p> | <p><i>Design:</i> randomised double-blind double-dummy crossover study, computer generated schedule. Histamine challenge used.<br/> <i>Device:</i> HFA-pMDI alone vs CFC-pMDI alone<br/> <i>Drug:</i> salbutamol<br/> <i>Dose:</i> 200ug (both devices)<br/> <i>Duration:</i> 30 min</p>  | <p><i>Participants:</i> 25 children, age range 6-14yrs, mean age 10yrs. Pulmonary function test performed 30min post-dose, than histamine challenge performed and FEV<sub>1</sub> measured until FEV<sub>1</sub> decreased by 20% (PD<sub>20</sub>).<br/> <i>Study quality:</i> Cochrane-A</p>   | <p><i>No significant differences in:</i><br/>                     FEV<sub>1</sub> or protection against histamine-induced bronchoconstriction as measured by PD<sub>20</sub>.<br/>                     -----<br/>                     FEV<sub>1</sub>: mean ± SD (absolute value)<br/>                     HFA: 2.24 ± 0.70<br/>                     pMDI: 2.79 ± 0.74</p>   | -   |
| <p><b>Hirsch 1997</b><br/>                     German Medical Hospital<br/>                     Citation: Resp Med, 91; 341-346</p>   | <p><i>Design:</i> randomised double-blind double-dummy parallel study, used drawing lots.<br/> <i>Device:</i> Turbuhaler vs pMDI alone<br/> <i>Drug:</i> terbutaline<br/> <i>Dose:</i> 0.5mg (both devices)<br/> <i>Duration:</i> 10 min</p>  | <p><i>Participants:</i> 118 children, age range 8-15, mean age 11.3. Pulmonary function testing done 10 min post-dose.<br/> <i>Study quality:</i> Cochrane-A</p>   | <p><i>No significant differences in:</i><br/>                     Change from baseline FEV<sub>1</sub> and FVC.<br/> <br/> <i>Significant differences in:</i> Vmax50% favouring pMDI<br/>                     -----<br/>                     FEV<sub>1</sub>: mean ± SD (absolute value)<br/>                     TH: 2.33 ± 0.76<br/>                     pMDI: 2.13 ± 0.80</p>   | -   |
| <p><b>Kemp 1989</b><br/>                     Asthma Research Centre, USA<br/>                     Citation: J Allergy Clin. Immunol 83(3); 697-702</p>  | <p><i>Design:</i> 2 separate studies reported (a) randomised double-blind double-dummy crossover study using 2 doses: 100 &amp; 200ug on separate days &amp; (b) a parallel run study using 200ug qid for 12 weeks. Used computer coded treatment.<br/> <i>Device:</i> Rotahaler vs pMDI alone<br/> <i>Drug:</i> salbutamol<br/> <i>Dose:</i> (a) 90-100 &amp; 180-200ug and study (b) 180-200ug<br/> <i>Duration:</i> (a) 360min &amp; (b) 12 weeks.</p> | <p><i>Participants:</i> (a) 30 children, mean age 9.4yrs. Lung function measured from 5 to 360min post-dose.<br/> <br/> <i>Study quality:</i> Cochrane-A<br/>                     -----<br/> <i>Participants:</i> (b) 204 (164F) children, age range 4-11, mean age 8.2yrs. Lung function measured from 5 to 480min post-dose.<br/> <br/> <i>Study quality:</i> Cochrane-A</p> | <p>Study A:<br/> <i>No significant differences in:</i><br/>                     FEV<sub>1</sub>, HR or BP.<br/> <br/>                     Study B:<br/> <i>No significant differences in:</i> FEV<sub>1</sub>, FEF<sub>25-75</sub>, FVC, PEFR, dropout rate or symptom scores.<br/> <br/> <i>Significant difference in:</i><br/>                     Number of acute exacerbations (requiring intervention): 26 (25%) in the pMDI group vs 13 (13%) Rotahaler group (p&lt;0.05).<br/>                     -----<br/>                     FEV<sub>1</sub>: mean ± SE (% change)<br/>                     Study A<br/>                     RH: 19% ± 0.18%<br/>                     pMDI: 19% ± 0.13%<br/> <br/>                     Study B<br/>                     RH: 18% ± 0.18%<br/>                     pMDI: 18% ± 0.13%</p> | <p>Analyses of baseline mean FEV<sub>1</sub> (using unpaired two-tailed t-test) showed that the pMDI group had significantly lower FEV<sub>1</sub> when compared to the RH group. This may explain the higher rate of acute exacerbations seen in the pMDI group.</p> |

| Study Author, Year   | Methodology   | Details  | Results  | Comments  |
|--|---|--|--|---|
| <p><b>Laberge 1994</b><br/> Depart of Ped. Quebec, Canada<br/> <i>Citation:</i> J Pediatr 124; 815-817</p>   | <p><i>Design:</i> randomised double-blind double-dummy crossover study, used random numbers.<br/> <i>Device:</i> Turbuhaler vs pMDI + Nebuhaler<br/> <i>Drug:</i> terbutaline<br/> <i>Dose:</i> cumulative dosing study, giving a total dose of 2.0mg within 80 min than followed by 5mg of nebulised salbutamol.</p> | <p><i>Participants:</i> 10 children, age range 3-6yrs, mean age 4.6yrs. Lung function measured 15 min after each dose of medication.<br/><br/> <i>Study quality:</i> Cochrane-A</p>  | <p><i>No significant differences in:</i> HR, BP, tremor or airways resistance.<br/> -----<br/> No FEV<sub>1</sub> reported.</p>  | -   |
| <p><b>Bronsky 1995</b><br/> Medical Research Centre, Utah. Supported by Glaxo Research Institute.<br/> <i>Citation:</i> J of Asthma 32(3); 207-214.</p>        | <p><i>Design:</i> randomised double-blind double-dummy crossover study using Latin-square treatment schedule. Exercise challenge used.<br/> <i>Device:</i> Rotahaler vs pMDI alone<br/> <i>Drug:</i> salbutamol<br/> <i>Dose:</i> pMDI-180ug vs RH-200ug<br/> <i>Duration:</i> 51 min</p>                             | <p><i>Participants:</i> 44 children, age range 4-11yrs, mean age 8yrs. Pulmonary function test performed up to 51 min after taking the drug and running on a treadmill for 6min at pre-determined target rates (85% of HR<sub>max</sub>). Study also reported 15 min post dose FEV<sub>1</sub> (i.e. pre-exercise).<br/><br/> <i>Study quality:</i> Cochrane-B</p> | <p><i>No significant differences in:</i> pre and post exercise FEV<sub>1</sub> after drug administration.<br/> -----<br/> FEV<sub>1</sub>: mean ± SD (absolute value)<br/> RH: 1.70 ± 0.44<br/> pMDI: 1.69 ± 0.41</p>  | Study used exercise challenge to show that the two devices are equally effective against EIA.                                   |
| <p><b>Chambers 1980</b><br/> Christchurch Hospital, NZ. Boehringer Ingelheim provided the trial materials.<br/> <i>Citation:</i> Arch Dis Child 55; 73-74.</p> | <p><i>Design:</i> randomised double-blind double-dummy crossover study.<br/> <i>Device:</i> Italseber vs pMDI<br/> <i>Drug:</i> fenoterol<br/> <i>Dose:</i> 200ug (both devices)<br/> <i>Duration:</i> 5 hours</p>  | <p><i>Participants:</i> 13 children (7F), age range 6-12yrs, mean age 8.7yrs. PEFR test performed up to 5 hours post-dose.<br/><br/> <i>Study quality:</i> Cochrane-B</p>  | <p><i>Significant differences in:</i> Overall mean %predicted PEFR over 5 hours duration post bronchodilator (p&lt;0.05) using two-way ANOVA favouring DPI.<br/> -----<br/> PEFR: mean ± SD (% change)<br/> IS: 42.5% ± 22.52%<br/> pMDI: 48.75% ± 18.19%</p>  | Device does not appear to be in current use. Unable to determine further details after contact with author and sponsor company. |
| <p><b>Hultquist 1989</b><br/> AstraZeneca, Sweden<br/> <i>Citation:</i> Allergy, 44; 467-470</p>   | <p><i>Design:</i> randomised double-blind double-dummy crossover study.<br/> <i>Device:</i> Turbuhaler vs pMDI alone<br/> <i>Drug:</i> terbutaline<br/> <i>Dose:</i> 0.5mg + prn (both devices)<br/> <i>Duration:</i> 2 weeks</p>   | <p><i>Participants:</i> 57 children, age range 6-18, mean age 11. PEFR was measured 10 min post-dose.<br/><br/> <i>Study quality:</i> Cochrane-B</p>   | <p><i>No significant differences in:</i> PEFR (morning &amp; evening) and symptom scores.<br/><br/> <i>Significant differences in:</i> preference for device where more children preferred the Turbuhaler (49%) than the pMDI (23%).<br/> -----<br/> PEFR morning: mean, no errors reported (absolute values )<br/> TH: 357<br/> pMDI: 357<br/><br/> PEFR: evening: mean, no errors reported<br/> TH: 362<br/> pMDI: 362</p> | -   |

| Study Author, Year   | Methodology  | Details   | Results   | Comments   |
|--|--|---|---|--|
| <b>Razzouk 1999</b><br>AstraZeneca, Sweden<br>Citation: Int J Pharma 180; 169-175          | <i>Design:</i> randomised double-blind double-dummy crossover study.<br><i>Device:</i> Turbuhaler vs pMDI alone<br><i>Drug:</i> salbutamol<br><i>Dose:</i> 100ug (both devices)<br><i>Duration:</i> 240 min  | <i>Participants:</i> 40 children, (9F), age range 6-12, mean age 9.<br>Pulmonary function testing performed from 15-240min post-dose.<br><br><i>Study quality:</i> Cochrane-B   | <i>No significant differences in:</i> Geometric means of mean FEV <sub>1</sub> and FEV <sub>1max</sub> .<br>Study also used Turbuhaler 50ug vs Turbuhaler 100ug & pMDI 100ug, showing no significant differences.<br>-----<br>FEV <sub>1</sub> : mean ± SD (absolute value)<br>TH: 1.82 ± 0.41<br>pMDI: 1.84 ± 0.43   | -  |
| <b>Svenonius 1994</b><br>Astra Draco AB, Lund Sweden<br>Citation: Allergy 49; 408-412      | <i>Design:</i> randomised double-blind double-dummy crossover study. Exercise challenge used.<br><i>Device:</i> Turbuhaler vs pMDI alone<br><i>Drug:</i> terbutaline<br><i>Dose:</i> 1mg (both devices)<br><i>Duration:</i> 15 min   | <i>Participants:</i> 12 children (2F), age range 9-17, mean age 13.8. Lung function measured before exercise than given the drug and measured again up to 15 min post-dose to observe reversibility of EIA.<br><br><i>Study quality:</i> Cochrane-B | <i>No significant differences in:</i> FEV <sub>1</sub> and VTG,<br>-----<br>FEV <sub>1</sub> : mean ± SD (absolute value)<br>TH: 3.04 ± 1.03<br>pMDI: 2.93 ± 0.93   | -  |
| <b>Fuglsang, 1989</b><br>AstraZeneca, Sweden<br>Citation: Pediatric Pulmonology 7; 112-115 | <i>Design:</i> single-blinded double-dummy crossover study, used computer generated schedule.<br><i>Device:</i> Turbuhaler vs pMDI alone<br><i>Drug:</i> terbutaline<br><i>Dose:</i> 2.0mg (both devices)<br><i>Duration:</i> cumulative dosing study, giving a total dose of 2.0mg within 80 min. | <i>Participants:</i> 13 children (3F), age range 7-15yrs, mean age 10.5yrs. Pulmonary function testing done 15 min post-dose.<br><br><i>Study quality:</i> Cochrane-B   | <i>No significant differences in:</i> FEV <sub>1</sub> , FEF <sub>25-75%</sub> , PEFR or FVC.<br><br><i>Significant differences in:</i> Heart rate (HR) when using pMDI but not with Turbuhaler. More children complained of tremor in the pMDI (7) group than in the Turbuhaler group (0).<br>-----<br>FEV <sub>1</sub> : mean ± SD (% change)<br>TH: 62% ± 23.00%<br>pMDI: 60% ± 25.67% | -  |
| <b>Ahlström 1989</b><br>Sweden, Medical Hospital.<br>Citation: Allergy 44; 515-518         | <i>Design:</i> open randomised crossover study<br><i>Device:</i> Turbuhaler vs MDI + Nebuhaler<br><i>Drug:</i> terbutaline<br><i>Dose:</i> 0.5mg qid (both devices)<br><i>Duration:</i> 14 days  | <i>Participants:</i> 21 children (7F), age range 2-5yrs, mean age 3.9yrs. PEFR measured 15 min after drug administration.<br><br><i>Study quality:</i> Cochrane-B   | <i>No significant difference in:</i> day or night symptom scores, day or night side effects or additional use of beta-2 medication.<br><br><i>Significant difference in:</i> morning PEFR favouring Turbuhaler over pMDI + Nebuhaler. (p=0.046)<br>-----<br>PEFR actual values not reported.  | PEFR result to be treated with caution as evening baseline PEFR was significantly (p=0.03) higher in the Turbuhaler group. |

## ***Delivery of $\beta_2$ agonists or anticholinergics by nebuliser – review 2***

Three randomised controlled trials are available in stable asthmatic children 2 years or older. Two compare pMDI+spacer and one a Rotahaler DPI versus nebuliser (see Table 9).

The term nebuliser is poorly defined and in clinical practice various types are used (often interchangeably) such as ultrasonic, and compressor or air/oxygen driven. Drug delivery characteristics may well be different between such systems<sup>40</sup>. Dosing recommendations and clinical studies may not make distinctions.

In any study of hand-held inhalers versus nebulisers the choice of dosages to be studied is critical. Nebulisers deliver a lower fraction of the prescribed dose than pMDI+spacer; approximately 10% versus 20-30%<sup>28, 41</sup> and therefore larger doses are prescribed. In addition recommended doses via nebuliser are for acute severe attacks and doses tend to reflect this. In contrast, recommended doses of pMDI will be more conservative<sup>20, 21</sup>. Comparison of standard doses may not be justified and would therefore favour nebuliser. This problem was overcome in the systematic review 'Comparison of holding chambers and nebulisers for beta-agonists in acute asthma'<sup>42</sup> by only considering studies that titrated doses to clinical response. The ratio of pMDI to nebuliser dose in the included studies was between 1:4 to 1:6. Recommended doses for salbutamol for symptomatic relief are 200ug by pMDI and 2.5 or 5mg by nebuliser<sup>20, 21</sup>, giving ratios of 1:12.5 or 1:25. To summarise, drug delivery and clinical response shows that pMDI+spacer delivers 2 to 6 times the dose of a nebuliser, but nebuliser dosages are recommended at 12.5 to 25 times the dose. Blackhall<sup>43</sup> is a cumulative dose response study allowing various doses to be considered. At a 'standard' relief dosage of pMDI Terbutaline 500ug (2 puffs) there was no statistical difference to 4mg nebulised although the direction of effect did favour the latter. At 1mg pMDI (4 puffs) again there was no statistical difference but the direction of effect favoured pMDI. Pierce<sup>44</sup>, of 4 weeks duration for each treatment period and set in the home. Dose was adjusted for body weight and at pMDI:nebuliser ratio of 1:4. There were no differences in any measures of lung function or patient reported symptom scores.

Grimwood<sup>45</sup> compares a Rotahaler DPI to a nebuliser. As previously discussed this is not a clinically valid comparison, especially in children. As stated in the narrative to review 1A, the study Rotahaler dose of salbutamol 400ug is probably equivalent to 200ug by pMDI (2 puffs). This is compared to 4mg by nebuliser. No statistical difference was found.

In summary, three trials totalling 51 subjects demonstrated no evidence of clinical superiority of nebulisers over other inhaler devices. Again, most of these children in these trials, were aged 5 years or older.



**Table 9. Details of RCTs in Children from Review 2 – bronchodilators by nebuliser versus hand-held inhalers**

| Author, year   | Methodology   | Details   | Results (all MDI, nebuliser, and (SD))  | Comments   |
|--|---|---|---|--|
| <p><b>Blackhall 1987</b><br/>A dose response study of inhaled terbutaline administered via Nebuhaler or nebuliser to asthmatic children</p> <p>Financial support from Astra Pharmaceuticals, Australia<br/><i>Citation:</i>Eur J Respir Dis 1987;71:96-101</p> | <p><i>Design:</i> Cross-over, open, dose response RCT<br/><i>Device:</i> pMDI+Nebuhaler vs Nebuliser<br/><i>Drug:</i> terbutaline.<br/><i>Dose:</i> pMDI 0.5+0.5+1+2mg<br/>Nebuliser 1+1+2+4mg<br/><i>Duration:</i> 2 X 1 day</p>                   | <p><i>Participants:</i>12 asthmatic children, 6M, 6F aged 5-10<br/><i>Quality:</i> Cochrane A</p>   | <p><i>No significant differences in:</i><br/>Increase in FEV1 0.38(0.08), 0.48(0.15) litres<br/>absolute pulse 97(13.0), 97(8.7) (pMDI 0.5mg and nebulised 4mg used)</p> <p>The log dose-response curves were parallel.</p>   | <p>Children of this age are suggested to be prescribed 250-500ug by pMDI and 3-5mg by nebuliser (British National Formulary). At these doses there is a non-significant difference in favour of nebuliser for FEV1. If the comparison is 1mg vs 4mg then the non-significant difference favours pMDI+spacer.</p> |
| <p><b>Grimwood 1981</b><br/>Salbutamol: tablets, inhalational powder, or nebuliser?</p> <p>Allen and Hanbury's NZ supplied placebo tablets and capsules.</p> <p><i>Citation:</i>BMJ 1981;282;105-106</p>   | <p><i>Design:</i> 3 way cross-over RCT, double-blinded, double-dummy.<br/><i>Device:</i> Rotahaler vs nebuliser vs oral tablet.<br/><i>Drug:</i> Salbutamol<br/><i>Dose:</i> 400ug v 4mg v 4mg<br/><i>Duration:</i> 3 X 4 hours (separate days)</p> | <p><i>Participants:</i> 17 'severe' asthmatic children, 7M, 10F mean age 7.2, range 4-12.</p> <p><i>Quality:</i> Cochrane B</p>                               | <p><i>No significant difference in:</i><br/>%improvement in PEFR<br/>15 min; 73(49), 98(82)%<br/>45 min; 78(66), 110(88)</p>  | <p>There appears to be a trend in favour of the nebuliser. However, Rotahaler would not be a valid comparison for most children. Salbutamol 400ug by Rotahaler is probably equivalent to 200ug by pMDI.</p>  |
| <p><b>Pierce 1992</b><br/>Nebuhaler versus wet aerosol for domiciliary bronchodilator therapy.</p> <p>One author was an employee of Astra Pharmaceuticals, Australia</p> <p><i>Citation:</i>The Medical Journal of Australia 1992;156:771-774</p>              | <p><i>Design:</i> Cross-over RCT, open<br/><i>Device:</i> pMDI+Nebuhaler versus nebuliser<br/><i>Drug:</i> Terbutaline<br/><i>Dose:</i> pMDI 0.25mg/5kg<br/>Nebuliser 1mg/5kg<br/><i>Duration:</i> 2 X 4 weeks</p>                                  | <p><i>Participants:</i> 22 asthmatic children, 11M, 11F mean age 9.9</p> <p>32 adults presented separately in the study</p> <p><i>Quality:</i> Cochrane B</p> | <p><i>No significant differences in:</i><br/>FEV1 1.61(0.54), 1.74(0.61) litres<br/>FVC 2.14(0.79), 2.28(0.84) litres<br/>PEFR pm 289(80), 299(79) l/min (presumed printing error on PEFR am; 227(82), 292(78)<br/>symptom scores;<br/>wheeze 0.62(0.55), 0.67(0.53)<br/>cough 0.93(0.85), 0.77(0.57)<br/>dyspnoea 0.80(0.75), 0.75(0.69)<br/>sleep disturbance 0.64(0.74), 0.51(0.48)</p> <p>11 preferred pMDI and 10 the nebuliser.</p> | <p>This study set in the home over 4 weeks showed equivalence of pMDI+spacer versus nebuliser.<br/>Of note, in the adult part of the same study, adults preferred nebuliser 23 to 11, despite again equivalent clinical response.</p>  |

## 2.3 Cost Effectiveness

The purpose of this section of the report is to summarise the health economic evidence related to comparisons of different inhalation device types, in the treatment of children with asthma. Observed differences in the effectiveness of drug delivery between inhaler systems, even when of the same general type, mean that the specific mode of delivery will potentially influence the overall clinical effectiveness of a specific asthma drug. As such the cost-effectiveness of drug treatments for asthma can be heavily influenced by both the drug molecule itself and the device selected to deliver the drug.<sup>18,15</sup>

In reality, it is genuinely difficult to consider the cost-effectiveness of an asthma drug and delivery device separately. It is also arguably more difficult to measure clinical effects in children than in adults. Such difficulties have resulted in a general lack of published cost-effectiveness, or cost-utility, analyses that have focused specifically on the relative economic benefits of different drug delivery mechanisms in young children.

The vast majority of the published cost-effectiveness and cost-utility studies, on the treatment of asthma in children, focus exclusively on an assessment of the clinical safety and efficacy when comparing drug therapy against a placebo-based treatment alternative (Table 10). In this sense such studies certainly help support the case for early drug therapy for children with asthma using both corticosteroids and  $\beta_2$ -agonists, but they do not help to differentiate in any way between the different delivery mechanisms themselves.<sup>15</sup>

The economic studies listed in Table 10 are certainly not exhaustive, but they are generally seen as the most commonly referenced studies in this area. They are provided here to allow a more complete view to be taken of health economics that relate to the treatment of children with asthma. However, they have no real relevance in terms of the specific research questions related to inhaler devices themselves.

**Table 10. Placebo controlled studies of asthma treatment in children with asthma**

| Reference                             | Year | Study Type | Subjects and Treatment              | Results                                     |
|---------------------------------------|------|------------|-------------------------------------|---|
| Northfield et al <sup>46</sup>        | 1991 | CEA        | Inhaled $\beta^2$ -agonist / N=1133 | Short-term benefits                         |
| Rutten-van Molken et al <sup>47</sup> | 1993 | CEA        | Inhaled corticosteroids / N=116     | Good cost-effectiveness                     |
| Connet et al <sup>48</sup>            | 1993 | CEA        | Inhaled corticosteroids / N=40      | Reductions in non-steroid costs             |
| Campbell et al <sup>49</sup>          | 1993 | CEA        | Inhaled corticosteroids / N=556     | Low-dose corticosteroids was cost effective |
| Perera et al <sup>50</sup>            | 1995 | CUA        | Inhaled corticosteroids / N=86      | Good cost-utility values / treatment costs  |
| Booth et al <sup>51</sup>             | 1996 | CEA        | Inhaled corticosteroids / N=225     | Good cost-effectiveness values              |
| Lord et al <sup>52</sup>              | 1999 | CEA        | Inhaled anticholinergics/N=376      | Good cost-effectiveness                     |

(CEA = cost effectiveness analysis)

The investigation of the health-economic arguments underpinning differences between drug delivery systems undoubtedly depends greatly on the availability of good quality clinical comparative studies. The previous sections of this report already highlight the fact that for children under the age of 5 years, the availability of such randomised trial evidence is extremely limited. Despite the existence of good cost-effectiveness evidence supporting the introduction of the drug treatments themselves, there remains very little, if any, real formal economic appraisals of the different asthma drug delivery systems.

The literature search and inspection of the industry submissions, identified only two published economic papers that had formally included any evaluation of the cost-effectiveness of inhaler devices in children with asthma under the age of 5 years. The first paper by Liljas *et al.* considered the economic comparison of different spacer devices with pMDIs. The second paper by Dewar *et al.* considered the economic benefits of pMDIs against nebulisers for acute asthma. We found no economic evidence related to the use of breath-actuated or dry-powder devices.

One of the best, and most recent, articles to review the relative cost-effectiveness data on asthma drug delivery systems is that of Massie et al (1997).<sup>53</sup> This article discusses the potential cost

advantages of the various device types and helps to provide at least some conceptual framework within which to consider the current economic evidence. The remainder of this section considers the identified economic evidence in more detail, along with data from company submissions, using three types of possible health economic comparisons that are likely to be of most interest in informing the debate around the effective management of asthma in children under 6 years of age.

***The relative cost-effectiveness of pMDI + spacer compared with Dry Powder Inhalers (DPIs) and Breath Actuated MDIs.***

The following lists the main breath actuated and dry powder systems currently available in the UK.

| <b><i>Breath Actuated MDIs</i></b> | <b><i>Dry Powder Inhalers (DPIs)</i></b> |
|------------------------------------|--|
| Autohaler                          | Turbohaler                               |
| Maxair                             | Diskhaler                                |
| Easi-breathe                       | Accuhaler                                |
|                                    | Rotahaler                                |
|                                    | Spinhaler                                |

The majority of the clinical data related to dry-powder systems is restricted to either comparisons between different DPIs themselves<sup>54</sup> (not covered by this report), or comparisons against pMDIs + spacers (see review 1A and 1B). Such clinical comparisons against pMDIs + spacers are generally based on the use of  $\beta_2$ -agonists, and typically use the Turbohaler or Rotahaler DPIs as references. These studies tend to be conducted in older children, and as such they do not represent under 6s explicitly. However, the general message from such studies appears to be one of equivalent efficacy, when both devices are operated correctly at equivalent dosage ratios.

There were no clinical studies identified in the under 6 years age group which compared MDI + spacer with any breath actuated device. The use of breath-actuated devices is not generally indicated by current treatment guidelines and there are no published economic data supporting their use.

The overall message related to choice between breath-operated devices and pMDIs + spacers seems to be that, given the assumption of equal efficacy when operated correctly, the most cost-effective device would be the least cost option (i.e. a cost minimisation situation).

***The relative cost-effectiveness of different spacer devices used alongside pMDIs in the delivery of corticosteroids and/or bronchodilators***

Published and unpublished data was identified regarding the relative cost-effectiveness of different spacer devices used alongside pMDIs in the delivery of corticosteroids and/or bronchodilators in the treatment of chronic asthma in children. The issue of the effectiveness and cost effectiveness of spacers will be dealt with in the later HTA report<sup>1</sup>.

## **4.0 Conclusion**

A plethora of different devices have been introduced to aid inhaled drug delivery in asthmatic patients. The large number of devices and competing claims of manufacturers/sponsors has resulted in considerable confusion over the best choice of device in clinical practice.

This report presents the effectiveness and cost effectiveness of inhaler systems in children (particularly young, i.e. less than 5 years, children) with chronic asthma.

### **4.1 Clinical Effectiveness**

This systematic review identified a small number of trials of variable quality and limited follow up that have been published comparing inhaler devices in childhood asthma. Only a small proportion of these studies have recruited children under the age of five years. Validation of the search strategy was carried out by SchARR and by comparison with submissions from the pharmaceutical industry, and the authors are confident that all available published evidence was included.

The review of trial evidence demonstrates little or no additional clinical benefit of nebulisers and other commercial inhaler devices over a simple pMDI (with or without spacers) for children with chronic asthma. Prescribing choices will therefore be governed by specific individual need, the likelihood of good compliance and cost.

### **4.2 Cost Effectiveness**

There is a wide range in the costs of inhaler devices. Few, cost-effectiveness studies were identified that make any direct comparison between asthma inhalers. No economic comparison of pMDI + spacers against any breath operated device was found. The use of DPI systems may provide an improved  $\beta_2$ -agonist management in some children who are physically and cognitively capable of using such a device correctly. Industry submissions reflected this paucity of health economic evidence.

Given the lack of effectiveness and cost effectiveness data in this area, and taking on board the existing clinical guidelines, the use of pMDI and spacers (with face masks where indicated) appears optimal in terms of both clinical and economic outcomes. The use of more expensive spacer devices should be actively considered and subjected to more rigorous pharmacoeconomic study. The wider consideration of indirect costs, including those of lost time from work due to child care and one off purchases (such as bedding, heating etc), and issues of quality of life issues such as time off from school, poor sleep quality, distress with symptoms and the overall effect of asthma on the ability to play and socialise should all play a role in assessing the economic benefits of new asthma treatments.

### **4.3 Further Research**

An NHS R&D HTA programme funded review of the impact of inhaler devices in asthmatics of all ages is currently under way and is expected to be published in August 2000<sup>1</sup>.

**Author Contributions:**

NP coordinated the SchARR contribution to the report and wrote, in collaboration, with SB the section on cost effectiveness. JW coordinated the Bradford contribution to the report and wrote the section on clinical effectiveness, in collaboration, with DB and FR. RT took overall editorial responsibility for the report.

**Conflicts of interest:**

None.

## 5.0 References

1. *The clinical and cost-effectiveness of inhaler devices in asthma and COPD: four systematic reviews of the research findings.* John Wright, Clinical Epidemiology Dept, Bradford Hospitals, NHS R&D HTA funded project. Report due to be published May 2000
2. British Thoracic Society. Guidelines on Asthma Management,
3. *Thorax* 1997; 52: Suppl 1.
4. The Department of Health. Health Survey for England 1996. London, The Stationery Office.
5. European Community Respiratory Health Survey Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey. *Eur Respir J* 1996; 9: 687-695.
6. Key Health Statistics from General Practice 1996. Series MB6 no 1 ONS
7. Hoskins G, Smith B, Neville R, et al. The Tayside Asthma Management Initiative. *Health Bull* 1998; 56: 586-591.
8. Key Population and Vital Statistics 1994 VS no 21 PP1 no 17 ONS.
9. Anonymous The British guidelines on asthma management 1995 review and position statement - introduction. *THORAX* 1997; **52**:S1-S21.
10. Lenney W. The burden of paediatric asthma. *Pediatric Pulmonology* 1997;13-16.
11. Silverman M, Pedersen S, Martinez F. Early intervention in childhood asthma. *European Respiratory Journal* 1998; **12**:1-2.
12. Pedersen S. Clinical issues in paediatric asthma. *Respiratory Medicine* 1997; **91**:40-41.
13. Pedersen S. What are the goals of treating paediatric asthma? *Pediatric Pulmonology* 1997;22-26.
14. Bisgaard H. Future options for aerosol delivery to children. *Allergy* 1999; **54** Suppl **49**:97-103.
15. McKenzie L. Economic evaluation in asthma care : methodological issues in measuring costs and outcomes and a review of recent studies. 1997; **4/97**:(Abstract)
16. Anonymous. Inhaler devices for asthma. *Drugs and Therapeutics Bulletin* 2000; **38**:9-14.
17. Amirav I, Newhouse MT. Metered-dose inhaler accessory devices in acute asthma -efficacy and comparison with nebulizers: a literature review. *Archives of Pediatrics & Adolescent Medicine* 1997; **151**:876-882.
18. Buxton MJ. The economics of asthma - An introduction. *EUR RESPIR REV* 1996; **6**:105-107.
19. BTS (British Thoracic Society). The British guidelines on asthma management. *Thorax* 1997; **52** Suppl **1**:S1-S21

20. BNF (British National Formulary)  
*Publication of British Medical Association and Royal Pharmaceutical Society*
21. MIMS (Monthly Index of Medical Specialities)  
*Haymarket Publishing Services Ltd*
22. Selroos O, Halme M. Effect of a Volumatic spacer and mouth rinsing on systemic absorption of inhaled corticosteroids from a metered dose inhaler and a dry powder inhaler.  
*Thorax 1991;46:891-894*
23. Stahl E, Ribeiro LB, Sandahl G. Dose response to inhaled terbutaline powder and peak inspiratory flow through Turbuhaler® in children with mild to moderate asthma.  
*Pediatr Pulmonol 1996;22:106-10*
24. Agertoft L, Nikander K, Pedersen S. Drug delivery to various age groups of children from two different inhalers.  
*Am J Respir Crit Care Med 1997; 155 (4 pt 2): A972*
25. Agertoft L, Pedersen S. Importance of the inhalation device on the effect of Budesonide.  
*Archives of Disease in Childhood 1993;69:130-133*
26. Edmunds AT, McKenzie S, Tooley M, Godfrey S. A clinical comparison of beclomethasone dipropionate by pressurised aerosol and as a powder from a Rotaher.  
*Archives of Disease in Childhood 1979;54:233-235*
27. Drepaul BA, Payler DK et al. Becotide or Becodisks? A controlled trial in General Practice *Clinical Trials Journal 1989;26;5:335-344*
28. Selroos O. Pietinalho A. Riska H. Delivery devices for inhaled asthma medication. Clinical implications of differences in effectiveness.  
*Clinical Immunotherapeutics. 1996;6(4):273-299*
29. Hirsch T, Peter-Kern M, Koch R, Leupold W. Influence of inspiratory capacity on bronchodilation via Turbuhaler or pressurized metered-dose inhaler in asthmatic children.  
*Respiratory Medicine 1997;91:341-346.*
30. Laberge S, Spier S, Drblik SP, Turgeon JP. Comparison of inhaled terbutaline administered by either the turbuhaler dry powder or a metered-dose inhaler with spacer in preschool children with asthma. *Journal of Pediatrics 1994;124(5):815-817.*
31. Hultquist C, Ahlstrom H, Kjellman NM, Malmqvist LA, Svenonius E, Melin S. A double-blind comparison between a new multi-dose powder inhaler (turbuhaler) and metered dose inhaler in children with asthma.  
*Allergy 1989;44:467-470.*
32. Razzouk H, dos Santos L, Giudicelli J, Queiros M, Chieira M, Castro A, et al. A comparison of the bronchodilatory effect of 50 and 100 ug salbutamol via turbuhaler and 100 ug salbutamol via pressurized metered dose inhaler in children with stable asthma.  
*International Journal of Pharmaceutics 1999;180:169-175.*
33. Svenonius E, Arborelius M, Wiberg R, Stahl E, Svenonius M. A comparison of

terbutaline inhaled by turbuhaler and by a chlorofluorocarbon (CFC) inhaler in children with exercise-induced asthma. *Allergy* 1994;**49**:408-412.

34. Fuglsang G, Pedersen S. Comparison of a new multidose powder inhaler with a pressurized aerosol in children with asthma. *Pediatric Pulmonology* 1989;**7**:112-115.
35. Ahlström H, Svenonius E, Svensson M. Treatment of asthma in pre-school children with inhalation of terbutaline in turbuhaler compared with nebuhaler. *Allergy* 1989;**44**(7): 515-518.
36. Kemp JP, Furukawa CT, Bronsky EA, Grossman J, Lemanske RF, Mansfield LE, et al. Albuterol treatment for children with asthma: a comparison of inhaled powder and aerosol. *Journal of Allergy and Clinical Immunology* 1989;**83**(3):697-702.
37. Bronsky EA, Spector SL, Pearlman DS, et al. Albuterol aerosol versus albuterol Rotacaps in exercise-induced bronchospasm in children. *Journal of Asthma* 1995;**32**: 207-214.
38. Custovic A, Taggart SC, Stuart A, Robinson A, Woodcock A. Efficacy of a new non-ozone depleting formulation for salbutamol. *Journal of Pharmacological Medicine* 1995;**5**:161-168.
39. Chambers S, Dunbar J, Taylor B. Inhaled powder compared with aerosol administration of fenoterol in asthmatic children. *Archives of Diseases in Childhood* 1980;**55**: 73-74.
40. BTS NPG (Nebuliser Project Group of the BTS Standards of Care Committee) *Thorax* 1997; **52**(Suppl 2): S1-S106
41. Zainudin BMZ et al. Comparison of bronchodilator responses and deposition patterns of salbutamol inhaled from a pressurised metered dose inhaler, as a dry powder, and as a nebulised solution *Thorax* 1990;**45**:469-473
42. Cates CJ. Comparison of holding chambers and nebulisers for beta-agonists in acute asthma. In: *Airways Module of The Cochrane Database of Systematic Reviews. Available in The Cochrane Library [database on disk and CDROM]. The Cochrane Collaboration; 2000, Issue 1. Oxford: Update Software. Updated quarterly.*
43. Blackhall MI. A dose response study of inhaled terbutaline administered via Nebuhaler or nebuliser to asthmatic children. *European Journal of Respiratory Disease* 1987;**71**:96-101
44. Pierce RJ, McDonald CF et al. Nebuhaler versus wet aerosol for domiciliary bronchodilator therapy. *The Medical Journal of Australia* 1992;**156**:771-774
45. Grimwood K, Johnson-Barrett JJ, Taylor B. Salbutamol: tablets, inhalational powder, or nebuliser? *British Medical Journal* 1981;**282**:105-106
46. Northfield M, Patel RK, Richardson A, Taylor MD, Richardson PDI. Life-style changes in mild asthma during intermittent symptom-related use of terbutaline inhaled via turbuhaler. *Current Medical Research And Opinion* 1991;**12**:441-449.



47. Ruttenvanmolken MPMH, Vandoorslaer EKA, Jansen MCC, Vanessenzandvliet EE, Rutten FFH. Cost-effectiveness of inhaled corticosteroid plus bronchodilator therapy versus bronchodilator monotherapy in children with asthma. *Pharmacoeconomics* 1993;**4**:257-270.
48. Connett GJ, Warde C, Wooler E, Lenney W. Use of budesonide in severe asthmatics aged 1-3 years. *Archives of Disease in Childhood* 1993;**69**:351-355 IS-.
49. Campbell LM, Simpson RJ, Turbitt ML, Richardson PDI. A comparison of the cost effectiveness of budesonide 400 mu g/day and 800 mu g/day in the management of mild-to-moderate asthma in general practice. *BR J MED ECON* 1993;**6**:67-74.
50. Perera BJ. Efficacy and cost effectiveness of inhaled steroids in asthma in a developing country. *Archives of Disease in Childhood* 1995;**72**:312-5; discussion 315-.
51. Booth PC, Wells NEJ, Morrison AK. A comparison of the cost effectiveness of alternative prophylactic therapies in childhood asthma. *Pharmacoeconomics* 1996;**10**:262-268.
52. Lord J, Ducharme FM, Stamp RJ, Littlejohns P, Churchill R. Cost effectiveness analysis of inhaled anticholinergics for acute childhood and adolescent asthma. *British Medical Journal* 1999;**319**:1470-1471.
53. Massie RJ, Mellis CM. The economic aspects of drug delivery in asthma. *Pharmacoeconomics* 1997;**11**:398-407.
54. Williams J, Richards KA. Ease of handling and clinical efficacy of fluticasone propionate Accuhaler/Diskus registered inhaler compared with the Turbohaler registered inhaler in paediatric patients. *BR J CLIN PRACT* 1997;**51**:147-153.
55. Bisgaard H. Drug delivery from inhaler devices. *BR MED J* 1996;**313**:895-896.
56. Liljas B, Bisgaard H. The economic impact of the use of different inhalation devices in childhood asthma. *British Journal of Medical Economics* 1997;**11**:113-119.
57. Bowton DL, Goldsmith WM, Haponik EF. Substitution of metered-dose inhalers for hand-held nebulizers -success and cost savings in a large, acute-care hospital. *CHEST* 1992;**101**:305-308.
58. Idris AH, Mcdermott MF, Raucci JC, Morrabel A, Mcgorray S, Hendeles L. Emergency department treatment of severe asthma - metered-dose inhaler plus holding chamber is equivalent in effectiveness to nebulizer. *CHEST* 1993;**103**:665-672.
59. Gibson PG, Wlodarczyk JH, Borgas T. Drug delivery in asthma: A comparison of spacers with a jet nebuliser. *AUST NEW ZEALAND J MED* 1995;**25**:324-329.
60. Tenholder MF, Bryson MJ, Whitlock WL. A model for conversion from small volume nebulizer to metered dose inhaler aerosol therapy. *CHEST* 1992;**101**:634-637.

61. Raimondi AC, Schottlender J, Lombardi D, Molino NA. Treatment of acute severe asthma with inhaled albuterol delivered via jet nebulizer, metered dose inhaler with spacer, or dry powder. *CHEST* 1997;**112**:24-28.
62. Orens DK, Kester L, Fergus LC, Stoller JK. Cost impact of metered dose inhalers vs small volume nebulizers in hospitalized patients: The Cleveland Clinic experience. *RESPIR CARE* 1991;**38**:1099-1104.
63. Mandelberg A, Chen E, Noviski N, Priel IE. Nebulized wet aerosol treatment in emergency department - Is it essential? Comparison with large spacer device for metered-dose inhaler. *CHEST* 1997;**112**:1501-1505.
64. Bailey R, Weingarten S, Lewis M, Mohsenifar Z. Impact of clinical pathways and practice guidelines on the management of acute exacerbations of bronchial asthma. *CHEST* 1998;**113**:28-33.
65. Ackerman AD. Continuous nebulization of inhaled beta-agonists for status asthmaticus in children: a cost-effective therapeutic advance? [editorial]. *Critical Care Medicine* 1993;**21**:1422-1424.
66. Cates CJ. Comparison of holding chambers and nebulisers for beta-agonists in acute asthma. 2000;(Abstract)
67. Chou KJ, Cunningham SJ, Crain EF. Metered-dose inhalers with spacers vs nebulizers for pediatric asthma. *Archives of Pediatrics & Adolescent Medicine* 1995;**149**:201-205.
68. Dewar AL, Stewart A, Cogswell JJ, Connett GJ. A randomised controlled trial to assess the relative benefits of large volume spacers and nebulisers to treat acute asthma in hospital. *Archives of Disease in Childhood* 1999;**80**:421-423.





**Appendix 1. Asthma devices currently marketed in UK**  
**[Thanks to 3M for their assistance in compiling this table]**

***pMDI***

| Drug class                  | Approved name | Brand/ product name | Company     | Pack size    | Cost per pack         | Cost for 28 days treatment                          | Spacer device                              |
|-----------------------------|---------------|---------------------|-------------|--------------|-----------------------|---|--|
| Anti-cholinergic            | Ipratropium   | Atrovent            | BI          | 20mcg x 200  | 4.21                  | Age < 6 yrs<br>2.36 (40mcg bd)*<br>1.77 (20mcg tds) |  |
|                             |               | Atrovent Forte      |             | 40mcg x 200  | 6.22                  | Age < 6 yrs<br>No dosing information                |  |
|                             | Oxitropium    | Oxivent             | BI          | 100mcg x 200 | 6.69                  | Not evaluated in children                           |  |
| Beta <sub>2</sub> -agonists | Orciprenaline | Alupent             | BI          | 750mcg x 300 | 2.66                  | Age < 6 yrs<br>50p (750mcg bd)                      |  |
|                             | Reproterol    | Bronchodil          | ASTA Medica | 500mcg x 400 | 7.01                  | Age < 6 yrs<br>No dosing information                |  |
|                             | Salbutamol    | Asmasal Spacehaler  | Medeva      | 100mcg x 200 | 5.43                  | 2.28 - 3.04 (100mcg tds -qds)<br>3.04 (200mcg bd)** | With vortex generating actuator            |
|                             | Terbutaline   | Bricanyl            | AstraZeneca | 250mcg x 400 | 5.31                  | 1.49 (250mcg qds or 500mcg bd)                      | Nebuhaler (with/ without face mask) - 4.28 |
|                             |               |                     |             | 250mcg x 400 | 7.21                  | 2.02 (250mcg qds or 500mcg bd)                      | Collapsible delivery system                |
|                             | Fenoterol     | Berotec             | BI          | 100mcg x 200 | 2.36                  | Age < 6 yrs   |  |
| 200mcg x 200                |               |                     |             | 2.78         | No dosing information |   |  |

| Drug class                              | Approved name           | Brand/ product name | Company      | Pack size           | Cost per pack | Cost for 28 days treatment                | Spacer device                   |
|---|-------------------------|---------------------|--------------|---------------------|---------------|---|---------------------------------|
| Combination bronchodilator              | Salbutamol/ ipratropium | Combivent           | BI           | 100mcg/ 20mcg x 200 | 6.45          | No experience of use in children < 12 yrs |                                 |
|   | Fenoterol/ ipratropium  | Duovent             | BI           | 100mcg/ 40mcg x 200 | 5.38          | Age < 6 yrs<br>No dosing information      |                                 |
| Long acting beta <sub>2</sub> -agonists | Salmeterol              | Serevent            | A & H        | 25mcg x 120         | 28.60         | Age > 4yrs<br>26.69 (50mcg bd)            | Volumatic - 2.75                |
| 'Cromones'                              | Cromoglycate            | Intal               | RPR          | 5mg x 112           | 19.09         | 19.09 (5mg qds)                           |                                 |
|   |                         | Intal Synchroner    |              | 5mg, 112 x 2        | 37.97         | 18.99 (5mg qds)                           | With integral spacer device     |
|   |                         | Intal Fisonair      |              | 5mg x 112           | 22.06         | 22.06 (5mg qds)                           | 700ml chamber spacer device     |
|   |                         | Cromogen            | Baker Norton | 5mg x 112           | 15.30         | 15.30 (5mg qds)                           |                                 |
|   | Nedocromil              | Tilade              | Pantheon     | 2mg, 56 x 2         | 42.98         | Age < 6 yrs                               |                                 |
|   |                         | Tilade Synchroner   |              | 2mg, 112 x 2        | 85.95         | No dosing information                     | With integral spacer device     |
| Inhaled corticosteroids                 | Beclomethasone          | Asmabec Spacehaler  | Medeva       | 50mcg x 200         | 5.43          |   | With vortex generating actuator |
|   |                         |                     |              | 100mcg x 200        | 10.32         | 2.89 (100mcg bd)<br>5.78 (200mcg bd)      |                                 |
|   |                         |                     |              | 250mcg x 200        | 23.10         | Not indicated for children                |                                 |
|   | Beclazone               | Baker Norton        |              | 50mcg x 200         | 4.34          |   |                                 |
|   |                         |                     |              | 100mcg x 200        | 8.24          | 2.31 (100mcg bd)<br>4.61 (200mcg bd)      |                                 |
|   |                         |                     |              | 200mcg x 200        | 15.68         | 4.39 (200mcg bd)                          |                                 |
|   |                         |                     |              | 250mcg x 200        | 18.02         | Not indicated for children                |                                 |
|   | Beclazone 250           |                     |              |                     |               |   |                                 |
| Becotide                                | A & H                   |                     | 50mcg x 200  | 5.43                |               | Volumatic - 2.75                          |                                 |

| Drug class   | Approved name            | Brand/ product name | Company      | Pack size         | Cost per pack  | Cost for 28 days treatment                         | Spacer device   |   |
|--------------|--------------------------|---------------------|--------------|-------------------|----------------|--|---|---|
|              |                          |                     |              | 100mcg x 200      | 10.32          | 2.89 (100mcg bd)<br>5.78 (200mcg bd)               | Integral compact spacer device                          |   |
|              |                          |                     |              | 200mcg x 200      | 19.61          | Not suitable for children                          |   |   |
|              |                          | Becloforte          |              | 250mcg x 200      | 23.10          | Not indicated for children                         |   |   |
|              |                          | Becloforte Integra  |              | 250mcg x 200      | 23.10<br>18.02 |  |   |   |
|              |                          | Filair              |              | 3M                | 50mcg x 200    | 4.14   |   |   |
|              |                          |                     |              |                   | 100mcg x 200   | 7.87   |   | 2.20 (100mcg bd)<br>4.41 (100mcg qds)<br>4.41 ( 200mcg bd)*** |
|              | Filair Forte             |                     | 250mcg x 200 |                   | 17.21          | Not recommended for children                       |   |   |
|              | Budesonide               | Pulmicort Aerosol   | AstraZeneca  | 200mcg x 200      | 19.00          | 5.32 (200mcg bd)                                   | Collapsible spacer delivery system, or Nebuhaler – 4.28 |   |
|              |                          | Pulmicort LS        |              | 50mcg x 200       | 6.66           | 3.73 (100mcg bd)                                   |   |   |
|              | Fluticasone              | Flixotide           | A & H        | 25mcg x 120       | 6.86           |  | Volumatic – 2.75  |   |
|              |                          |                     |              | 50mcg x 120       | 5.85           | Age > 4yrs<br>5.46 (50mcg bd)<br>10.92 (100mcg bd) |   |   |
|              |                          |                     |              | 125mcg x 120      | 22.86          | Not suitable for use in children                   |   |   |
| 250mcg x 120 |                          |                     |              | 38.86             |                |  |   |   |
| Combination  | Cromoglycate/ salbutamol | Aerocrom Synchroner | Castlemead   | 1mg/ 100mcg x 200 | 34.42          | Not recommended for children                       | With integral spacer device                             |   |
|              |                          | Aerocrom inhaler    |              | 1mg/ 100mcg x 200 | 34.42          |  |   |   |

| Drug class | Approved name              | Brand/ product name | Company | Pack size           | Cost per pack | Cost for 28 days treatment                                | Spacer device    |
|------------|----------------------------|---------------------|---------|---------------------|---------------|---|------------------|
|            | Beclomethasone/ salbutamol | Ventide             | A & H   | 50mcg/ 100mcg x 200 | 5.42          | 1.52 (50mcg/<br>100mcg bd)<br>3.04 (100mcg/<br>200mcg bd) | Volumatic – 2.75 |

- Notes:**
- \* tds is the licensed dosage frequency, not bd; dose and cost shown for comparative purposes only
  - \*\* 100mcg tds – qds is the licensed dose for this product; 200mcg bd dose and cost shown for comparative purposes only
  - \*\*\* 100mcg bd - qds is the recommended dose; 200mcg bd dose and cost shown for comparative purposes only



## pMDIs – CFC free

| Drug class                 | Approved name  | Brand/ product name | Company | Pack size    | Cost per pack | Cost for 28 days treatment  | Spacer device  |
|----------------------------|----------------|---------------------|---------|--------------|---------------|---|--|
| Beta <sub>2</sub> -agonist | Salbutamol     | Airomir             | 3M      | 100mcg x 200 | 1.97          | 1.10 (200mcg bd)  | Aerochamber – standard version 4.28, masked version 7.14 |
|                            |                | Salbulin            | 3M      | 100mcg x 200 | 1.97          | 1.10 (200mcg bd)  | Aerochamber – standard version 4.28, masked version 7.14 |
|                            |                | Ventolin Evohaler   | A & H   | 100mcg x 200 | 2.30          | 1.29 ( 200mcg bd)   | Volumatic – 2.75   |
| Inhaled cortico-steroids   | Beclomethasone | Qvar                | 3M      | 50mcg x 200  | 7.87          | Age < 12 yrs<br>No dosage data available<br>2.20 (50mcg bd),<br>4.82 (100mcg bd)* | Aerochamber – standard version 4.28, masked version 7.14 |
|                            |                |                     |         | 100mcg x 200 | 17.21         |   |  |
|                            | Fluticasone    | Flixotide Evohaler  | A & H   | 125mcg x 120 | 22.86         | Not suitable for use in children  | Volumatic – 2.75   |
|                            |                |                     |         | 250mcg x 120 | 38.86         |   |  |

**Notes:** \*dosages and costs shown for comparative purposes only

## pMDIs - breath actuated

| Drug class                 | Approved name          | Brand/ product name   | Company      | Pack size           | Cost per pack | Cost for 28 days treatment                         | Spacer device                            |
|----------------------------|------------------------|-----------------------|--------------|---------------------|---------------|--|--|
| Anti-cholinergic           | Ipratropium            | Atrovent Autohaler    | BI           | 20mcg x 200         | 9.39          | Age < 6yrs<br>5.26 (40mcg bd)*<br>3.94 (20mcg tds) |  |
|                            | Oxitropium             | Oxivent Autohaler     | BI           | 100mcg x 200        | 15.72         | Not evaluated in children                          |  |
| Beta <sub>2</sub> -agonist | Salbutamol             | Aerolin Autohaler     | 3M           | 100mcg x 200        | 10.04         | 5.62 (200mcg bd)                                   |  |
|                            |                        | Ventolin Easi-Breathe | A & H        | 100mcg x 200        | 6.30          | 3.53 (200mcg bd)                                   |  |
| Combination                | Fenoterol/ ipratropium | Duovent Autohaler     | BI           | 100mcg/ 40mcg x 200 | 10.57         | Age < 6 yrs<br>No dosing information               |  |
| 'Cromone'                  | Cromoglycate           | Cromogen Easi-Breathe | Baker Norton | 5mg x 112           | 13.91         | 13.91 (5mg qds)                                    |  |
| Inhaled corticosteroids    | Beclomethasone         | Aerobec Autohaler     | 3M           | 50mcg x 200         | 10.51         |  |  |
|                            |                        |                       |              | 100mcg x 200        | 12.89         | 3.61 (100mcg bd)<br>7.22 (200mcg bd)               |  |
|                            |                        |                       |              | 250mcg x 200        | 23.97         | Not recommended for children                       |  |
|                            |                        | Becotide Easi-Breathe | A & H        | 50mcg x 200         | 4.34          |  | Can be used with Optimiser spacer device |
|                            |                        |                       |              | 100mcg x 200        | 8.24          | 2.31 (100mcg bd)<br>4.61 (200mcg bd)               |  |
|                            |                        |                       |              | 250mcg x 200        | 18.02         | Not recommended for children                       |  |

**Notes:** \* tds is the licensed dosage frequency, not bd; dose and cost shown for comparative purposes only

## pMDI – CFC free, breath actuated

| Drug class                 | Approved name  | Brand/ product name | Company | Pack size    | Cost per pack | Cost for 28 days treatment                                       |
|----------------------------|----------------|---------------------|---------|--------------|---------------|--|
| Beta <sub>2</sub> -agonist | Salbutamol     | Airomir Autohaler   | 3M      | 100mcg x 200 | 6.02          | 3.37 (200mcg bd)   |
| Inhaled cortico-steroids   | Beclomethasone | Qvar Autohaler      | 3M      | 50mcg x 200  | 7.87          | Age < 12 yrs   |
|                            |                |                     |         | 100mcg x 200 | 17.21         | No dosage data available<br>2.20 (50mcg bd)<br>4.82 (100mcg bd)* |

**Notes:** \*dosages and costs shown for comparative purposes only

## DPI (breath actuated)

| Drug class                              | Approved name       | Brand/ product name               | Company      | Pack size      | Cost per pack                                 | Cost for 28 days treatment                    |
|---|---------------------|-----------------------------------|--------------|----------------|---|---|
| Anti-cholinergic                        | Ipratropium         | Atrovent Aerocaps                 | BI           | 40mcg x 100    | 10.53   | Not recommended for children < 12 yrs         |
| Beta <sub>2</sub> -agonists             | Salbutamol          | Asmasal Clickhaler                | Medeva       | 95mcg x 200    | 6.32  | 3.54 (2 puffs bd)                             |
|   |                     | Ventodisks for Diskhaler          | A & H        | 200mcg, 14 x 8 | 5.89  | 2.94 (200mcg bd)<br>5.89 (200mcg qds)         |
|   |                     |                                   |              | 400mcg, 14 x 8 | 10.30   | 400mcg is not a recommended dose for children |
|   |                     | Ventolin Accuhaler                | A & H        | 200mcg x 60    | 5.00  | 4.67 (200mcg bd)<br>9.33 (200mcg qds)         |
|   |                     | Ventolin Rotacaps (Rotahaler 78p) | A & H        | 200mcg x 112   | 5.33  | 2.67 (200mcg bd)<br>5.33 (200mcg qds)         |
|   | 400mcg x 112        |                                   |              | 9.01           | 400mcg is not a recommended dose for children |   |
| Terbutaline                             | Bricanyl Turbohaler | AstraZeneca                       | 500mcg x 100 | 6.30           | 3.53 (500mcg bd)<br>7.06 (500mcg qds)         |   |
| Long acting beta <sub>2</sub> -agonists | Eformoterol         | Foradil                           | Geigy        | 12mcg, 14 x 4  | 24.00   | Not recommended for children < 18 yrs         |
|   |                     | Oxis Turbohaler                   | AstraZeneca  | 6mcg x 60      | 24.80   | Use in children has not been documented       |
|   | 12mcg x 60          |                                   |              | 24.80          |   |   |
|   | Salmeterol          | Serevent Diskhaler                | A & H        | 50mcg, 14 x 4  | 29.40   | Age ≥ 4 yrs<br>29.40 (50mcg bd)               |
| Serevent Accuhaler                      |                     | A & H                             | 50mcg x 60   | 28.60          | Age ≥ 4 yrs<br>26.69 (50mcg bd)               |   |
| 'Cromones'                              | Cromoglycate        | Intal Spincaps                    | RPR          | 20mg x 112     | 16.60   | 16.60 (20mg qds)                              |

| Drug class              | Approved name  | Brand/ product name                  | Company     | Pack size      | Cost per pack                                       | Cost for 28 days treatment                          |
|-------------------------|----------------|--------------------------------------|-------------|----------------|---|---|
|                         |                | (Spinhaler 2.08)                     |             |                |   |   |
| Inhaled Corticosteroids | Beclomethasone | Asmabec Clickhaler                   | Medeva      | 50mcg x 200    | 7.18  |   |
|                         |                |                                      |             | 100mcg x 200   | 10.55   | 2.95 (100mcg bd)<br>5.91(200mcg bd)                 |
|                         |                |                                      |             | 250mcg x 100   | 13.24   | No dosing information/<br>recommendation            |
|                         |                | Becodisks for Diskhaler              | A & H       | 100mcg, 14 x 8 | 10.42   | 5.21 (100mcg bd)                                    |
|                         |                |                                      |             | 200mcg, 14 x 8 | 20.33   | 10.17 (200mcg bd)                                   |
|                         |                |                                      |             | 400mcg, 7 x 8  | 20.33   | 400mcg is not a<br>recommended dose for<br>children |
|                         |                | Becloforte Diskhaler                 | A & H       | 400mcg, 14 x 8 | 39.13   | Not indicated for<br>children                       |
|                         |                | Becotide Rotacaps<br>(Rotahaler 78p) | A & H       | 100mcg x 112   | 8.47  | 8.47 (100mcg bd)                                    |
|                         |                |                                      |             | 200mcg x 112   | 16.07   | 16.07 (200mcg bd)                                   |
|                         | 400mcg x 112   |                                      |             | 30.54          | 400mcg is not a<br>recommended dose for<br>children |   |
|                         | Budesonide     | Pulmicort Turbohaler                 | AstraZeneca | 100mcg x 200   | 18.50   | 5.18 (100mcg bd)                                    |
|                         |                |                                      |             | 200mcg x 100   | 18.50   | 5.18 (200mcg od)<br>10.36 (200mcg bd)               |
|                         |                |                                      |             | 400mcg x 50    | 18.50   | 10.36 (400mcg od)                                   |
|                         | Fluticasone    | Flixotide Accuhaler                  | A & H       | 50mcg x 60     | 6.86  | Age ≥ 4 yrs<br>6.40 (50mcg bd)                      |
|                         |                |                                      |             | 100mcg x 60    | 9.60  | Age ≥ 4 yrs<br>8.96 (100mcg bd)                     |
| 250mcg x 60             |                |                                      |             | 22.86          | Not suitable for use in<br>children                 |   |
| 500mcg x 60             |                |                                      |             | 38.86          |   |   |

| Drug class  | Approved name              | Brand/ product name                             | Company | Pack size            | Cost per pack | Cost for 28 days treatment                             |
|-------------|----------------------------|---|---------|----------------------|---------------|--|
|             |                            | Flixotide Diskhaler                             | A & H   | 50mcg, 14 x 4        | 7.66          | Age ≥ 4 yrs<br>7.66 (50mcg bd)                         |
|             |                            |   |         | 100mcg, 14 x 4       | 12.23         | Age ≥ 4 yrs<br>12.23 (100mcg bd)                       |
|             |                            |   |         | 250mcg, 14 x 4       | 23.66         | Not suitable for use in children                       |
|             |                            |   |         | 500mcg, 14 x 4       | 39.66         |  |
| Combination | Salbutamol/ beclomethasone | Ventide Rotacaps                                | A & H   | 400mcg/ 200mcg x 112 | 23.01         | Use Paediatric Rotacaps                                |
|             |                            | Ventide Paediatric Rotacaps for Rotahaler (78p) |         | 200mcg/ 100mcg x 112 | 12.68         | 6.34 (200mcg/ 100mcg bd)<br>12.68 (200mcg/ 100mcg qds) |
|             | Salmeterol/ fluticasone    | Seretide 100 Accuhaler                          | A & H   | 50mcg/ 100mcg x 60   | 33.54         | Age > 4 yrs<br>31.30 (50mcg/ 100mcg bd)                |
|             |                            | Seretide 250 Accuhaler                          |         | 50mcg/ 250mcg x 60   | 39.41         | Not suitable for use in children                       |
|             |                            | Seretide 500 Accuhaler                          |         | 50mcg/ 500mcg x 60   | 66.98         |  |

## Nebulised preparations

| Drug class                                    | Approved name | Brand/ product name         | Company      | Pack size                    | Cost per pack      | Cost for 28 days treatment  |                                   |                                     |
|---|---------------|-----------------------------|--------------|------------------------------|--------------------|---|-----------------------------------|-------------------------------------|
| Anti-Cholinergic                              | Ipratropium   | Atrovent UDV                | BI           | 250mcg/ ml, 1ml x 20         | 6.82               | Age < 3 yrs<br>Not recommended<br>Age 3 – 14 yrs<br>28.64 (100mcg tds)                      |                                   |                                     |
|   |               |                             |              | 250mcg/ ml, 2ml x 20         | 8.00               | Age < 3 yrs<br>Not recommended<br>Age 3 – 14 yrs<br>33.60 (500mcg tds)<br>22.40 (500mcg bd) |                                   |                                     |
|   |               | Ipratropium Steri-Neb       | Baker Norton | 250mcg/ ml, 1ml x 20         | 5.13               | Age 3 –14 yrs<br>21.55 (100mcg tds)   |                                   |                                     |
|   |               |                             |              | 250mcg/ ml, 2ml x 20         | 5.99               | Age 3 – 14 yrs<br>25.16 (500mcg tds)<br>16.77 (500mcg bd)                                   |                                   |                                     |
|   |               | Respontin                   | A & H        | 250mcg/ ml, 1ml x 20         | 5.45               | Age 3 – 14 yrs<br>22.89 (100mcg tds)  |                                   |                                     |
|   |               |                             |              | 250mcg/ ml, 2ml x 20         | 6.40               | Age 3 – 14 yrs<br>26.88 (500mcg tds)<br>17.92 (500mcg bd)                                   |                                   |                                     |
|   |               | Beta <sub>2</sub> -agonists | Salbutamol   | Salamol Steri-Neb            | Baker Norton       | 2.5mg/ 2.5ml, x 20  | 2.74                              | Age > 18 mnths<br>15.34 (2.5mg qds) |
|   |               |                             |              |                              |                    | 5mg/ 2.5ml, x 20  | 5.47                              | Age > 18 mnths<br>15.32 (5mg bd)    |
| Ventolin Nebules                              | A & H         |                             |              | 2.5mg/ 2.5ml x 20            | 3.38               | Age > 18 mnths<br>18.93 (2.5mg qds)   |                                   |                                     |
|   |               |                             |              | 5mg/ 2.5ml x 20              | 6.90               | Age > 18 mnths<br>19.32 (5mg bd)  |                                   |                                     |
| Ventolin Respirator Solution (Hospitals only) | A & H         |                             |              | 5mg/ ml, 20ml x 1            | 2.44               | 6.83 (2.5mg qds, or 5mg bd)   |                                   |                                     |
| Terbutaline                                   | AstraZeneca   |                             |              | Bricanyl Respules            | 5mg/ 2ml x 20      | 3.67  | 10.28 (5mg bd)<br>20.55 (5mg qds) |                                     |
|   |               |                             |              | Bricanyl Respirator Solution | 10mg/ ml, 20ml x 1 | 2.64  | 3.70 (5mg bd)<br>7.39 (5mg qds)   |                                     |

| Drug class               | Approved name           | Brand/ product name      | Company      | Pack size                          | Cost per pack | Cost for 28 days treatment                     |
|--------------------------|-------------------------|--------------------------|--------------|------------------------------------|---------------|--|
| Combination              | Salbutamol/ ipratropium | Combivent UDV            | BI           | 2.5mg/500mcg per 2.5ml, 2.5ml x 60 | 33.00         | Not recommended for children                   |
|                          | Fenoterol/ ipratropium  | Duovent UDV              | BI           | 1.25mg/ 500mcg per 4ml, 4ml x 20   | 11.00         | Age < 14 yrs<br>No dosage information provided |
| 'Cromones'               | Cromoglycate            | Cromogen Steri-Neb       | Baker Norton | 10mg/ ml, 2ml x 60                 | 11.58         | 21.62 (20mg qds)                               |
|                          |                         | Intal Nebuliser Solution | RPR          | 10mg/ ml, 2ml x 60                 | 20.45         | 38.17 (20mg qds)                               |
| Inhaled cortico-Steroids | Budesonide              | Pulmicort Respules       | AstraZeneca  | 0.5mg/ 2ml x 20                    | 32.00         | Age 3 mnths – 12 yrs<br>89.60 (0.5mg bd)       |
|                          |                         |                          |              | 1mg/ 2ml x 20                      | 44.64         | Age 3 mnths – 12 yrs<br>124.99 (1mg bd)        |
|                          | Fluticasone             | Flixotide Nebules        | A & H        | 0.5mg/ 2ml x 10                    | 10.04         | Age < 16yrs                                    |
|                          |                         |                          |              | 2mg/ 2ml x 10                      | 40.16         | Not recommended                                |

### **Notes on tables**

*Costs and pack sizes based on MIMS, May 2000; costs apply to refills where these are available.*

*Generic preparations are not included.*

Where appropriate (based on manufacturers' licensed doses\*), comparative costs are available for:

**pMDI** salbutamol 200mcg bd versus **pMDI** terbutaline 500mcg bd

**pMDI** beclomethasone/ budesonide 100-200 mcg bd versus **CFC free pMDI** beclomethasone 50-100mcg bd

**pMDI** beclomethasone/ budesonide 100-200 mcg bd versus **pMDI** fluticasone 50-100mcg bd



*A broader range of costs and dosages is provided for inhaled corticosteroids; in clinical practice the dosage should be adjusted up or down according to response, specific device characteristics, and manufacturers' prescribing advice.*

\* SEE ALSO the notes attached to each table for extra information on licensed dosages

*Where an age is specified, such as < 6yrs or > 4yrs, the table reflects the actual wording used in the UK prescribing information. In a number of instances there may be no dosage information for children of a particular age, indicating that this is not a licensed use and/or that the product has not been evaluated in this age group.*

**Abbreviations used:** od (once daily), bd (twice daily), tds (three time daily), qds (four times daily)

BI (Boehringer Ingelheim), A & H (Allen and Hanburys), RPR (Rhone-Poulenc Rorer)



## Appendix 2. Medline search strategy

Database: Medline <1966 to Present>

Search Strategy (You Saved Citations 1 From Set 88):

|    |  |        |
|----|--|--------|
| 1  | Administration, inhalation/                                  | 8945   |
| 2  | "Nebulizers and vaporizers"/                                 | 917    |
| 3  | exp Equipment design/  | 37619  |
| 4  | exp Filtration/  | 19606  |
| 5  | exp Aerosols/  | 23000  |
| 6  | is.fs.   | 218730 |
| 7  | aerosols.rw.   | 8224   |
| 8  | powders.rw.  | 1988   |
| 9  | nebuliz\$.tw.  | 2602   |
| 10 | nebulis\$.tw.  | 710    |
| 11 | meter\$ dose\$ inhal\$.tw.                                   | 1140   |
| 12 | (mdi or mdis).tw.  | 825    |
| 13 | pmidi\$.tw.  | 66     |
| 14 | spacer\$.tw.   | 5356   |
| 15 | holding chamber\$.tw.  | 50     |
| 16 | powder inhal\$.tw.   | 281    |
| 17 | inhal\$ suspen\$.tw.   | 14     |
| 18 | jet.tw.  | 4195   |
| 19 | autohaler.tw.  | 26     |
| 20 | easi breathe.tw.   | 3      |
| 21 | integra.tw.  | 34     |
| 22 | fisonair.tw.   | 5      |
| 23 | aerochamber.tw.  | 66     |
| 24 | aeroscopic.tw.   | 1      |
| 25 | nebuhaler.tw.  | 78     |
| 26 | spacehaler.tw.   | 2      |
| 27 | syncroner.tw.  | 2      |
| 28 | airomir.tw.  | 10     |
| 29 | evohaler.tw.   | 0      |
| 30 | qvar.tw.   | 5      |
| 31 | nebuchamber.tw.  | 6      |
| 32 | babyhaler.tw.  | 19     |
| 33 | volumatic.tw.  | 52     |
| 34 | rotahaler.tw.  | 55     |
| 35 | spinhaler.tw.  | 52     |
| 36 | diskhaler.tw.  | 79     |
| 37 | accuhaler.tw.  | 12     |
| 38 | turbohaler.tw.   | 45     |
| 39 | turbuhaler.tw.   | 176    |
| 40 | clickhaler.tw.   | 1      |
| 41 | diskus.tw.   | 19     |
| 42 | sidestream.tw.   | 270    |
| 43 | ventstream.tw.   | 6      |
| 44 | lc plus.tw.  | 6      |
| 45 | lc star.tw.  | 1      |
| 46 | halo lite.tw.  | 0      |
| 47 | aerobec.tw.  | 1      |
| 48 | aerolizer.tw.  | 3      |
| 49 | pari baby.tw.  | 1      |
| 50 | pari ll.tw.  | 6      |
| 51 | or/1-50  | 294079 |
| 52 | exp Asthma/  | 50211  |
| 53 | Child, preschool/  | 432286 |
| 54 | Child/   | 728617 |
| 55 | exp infant/  | 520951 |
| 56 | 53 or 55   | 724767 |
| 57 | 54 not 56  | 383627 |
| 58 | 51 and 52 and 56   | 930    |
| 59 | 51 and 52 and 57   | 1063   |
| 60 | Economics/   | 5335   |
| 61 | exp "Costs and cost analysis"/                               | 60778  |
| 62 | Economic value of life/                                      | 524    |
| 63 | exp Economics, hospital/                                     | 6847   |
| 64 | exp Economics, medical/                                      | 7180   |
| 65 | Economics, nursing/  | 3453   |
| 66 | exp models, economic/  | 1110   |
| 67 | Economics, pharmaceutical/                                   | 372    |
| 68 | exp "Fees and charges"/                                      | 10417  |
| 69 | exp Budgets/   | 3069   |
| 70 | ec.fs.   | 91376  |
| 71 | (cost or costs or costed or costly or costing\$.tw.          | 76419  |
| 72 | (economic\$ or pharmacoeconomic\$ or price\$ or pricing).tw. | 38752  |
| 73 | or/60-72   | 191816 |
| 74 | clinical trial.pt.   | 266720 |

|    |                             |         |
|----|-----------------------------|---------|
| 75 | meta\$.pt.                  | 4271    |
| 76 | review.pt.                  | 708669  |
| 77 | guideline.pt.               | 6739    |
| 78 | or/74-77                    | 979061  |
| 79 | exp Review literature/      | 887     |
| 80 | exp Clinical trials/        | 109614  |
| 81 | Meta-analysis/              | 2999    |
| 82 | exp Guidelines/             | 12520   |
| 83 | Health planning guidelines/ | 620     |
| 84 | or/60-83                    | 1168794 |
| 85 | 58 and 84                   | 402     |
| 86 | 59 and 84                   | 518     |
| 87 | limit 85 to yr=1980-2000    | 366     |
| 88 | limit 86 to yr=1980-2000    | 450     |

### **Appendix 3. Hand searched journal and conferences proceedings**

- 1) Systematic hand searching (retrospective and prospective) of core journals in respiratory disease.

The journals that have been/are being searched are:

Journal of Allergy and Clinical Immunology (1980 to present)

American Review of Respiratory Disease (1970 to present)

Annals of Allergy (1980 to present)

Thorax (1980 to present)

Allergy (1980 to present)

Journal of Asthma (1983 to present)

Respiration (1980 to present)

European Journal of Clinical Pharmacology (1980 to present)

British Journal of Diseases of the Chest (1980 to 1988)

Archives of Disease in Childhood (1980 to present)

Clinical Allergy (1980 to 1988)

Clinical and Experimental Allergy ((1989 to present)

Respiratory Medicine (1989 to present)

European Respiratory Review (1992 to present)

Canadian Respiratory Journal (1994 to present)

Pediatric Pulmonology (1985 to present)

NB: The Lancet and British Medical Journal are being searched at the UK Cochrane Centre for all randomised controlled trials and their MEDLINE entry coded as an RCT. All relevant RCTs Asthma/COPD/Bronchiectasis/Sleep apnoea will be captured for the specialised register as they appear on MEDLINE.

- 2) A search of the proceedings of the following societies from 1980 - :

British Thoracic Society

American Thoracic Association

European Respiratory Society

#### **Appendix 4. Electronic bibliographic strategy (Bradford group)**

The Cochrane Airways Group Register of Trials was used to search for published evidence. It includes the following:

The MEDLINE (Ovid) database, produced by the National Library of Medicine, and the EMBASE database, supplied by BIDS (Bath Information and Data Services), were searched in the following manner and the references downloaded onto a regularly updated Apple Macintosh-based ProCite database:

##### *A. Initial inclusive general search*

i) For asthma in MEDLINE the following search terms were used:

Asthma (MeSH)

Asthma - Exercise Induced (MeSH)

Status Asthmaticus (MeSH)

ii) For asthma in EMBASE the following search term was used:

Asthma (title, keywords, abstract)

iii) For bronchiolitis in MEDLINE the following search term was used:

Bronchiolitis (explosion term) (MeSH)

iv) For bronchiolitis in EMBASE the following search term was used:

Bronchiolitis (title, keywords, abstract)

v) For wheezing in MEDLINE the following search term was used:

Respiratory sounds (MeSH)

vi) For wheezing in EMBASE the following search term was used:

Wheez\* - asthma (title, keywords, abstract)

Note: "-" is equivalent to minus

*B. RCT identification was performed on each of these ProCite databases using the search term: placebo\* OR trial\* OR random\* OR single blind OR single-blind OR double blind OR double-blind OR controlled study OR comparative study*

*C. For each diagnosis, RCTs identified from MEDLINE and EMBASE were combined with RCTs identified from CINAHL (Ovid) and duplicates removed.*

i. For asthma in CINAHL the following search terms were used:

Asthma (MeSH)

Asthma - Exercise Induced (MeSH)

Status Asthmaticus (MeSH)

*D. The register generated from the on-line databases has identified over 500 journals with RCTs in asthma.*

The performance of this electronic register has been and continues to be compared with the level of RCT recovery through hand searches.

4. Bibliographies of all trials are systematically searched prospectively.

The above register is searched using the following terms:

Review 1A Corticosteroids, pMDI versus.....

a) inhaler OR spacer\* OR holding chamber OR volumatic OR neбуhaler OR aerochamber\* OR fisonair OR extension OR spacing device OR inspirease OR Accuhaler OR Diskhaler OR Turbohaler OR Turбуhaler OR Easibreathe OR Autohaler OR Rotahaler OR dry powder OR MDI OR DPI OR CFC-free OR HFA\*.

AND

b) steroids OR glucocorticoids OR corticosteroids OR beclomethasone OR budesonide OR fluticasone OR triamcinolone OR flunisolide OR Becotide OR Becloforte OR Pulmicort OR Flixotide

Review 1B Bronchodilators, pMDI versus.....

a) As a) above

AND

b) salbutamol OR ventolin OR albuterol OR terbutaline OR Bricanyl OR Formoterol OR Isoprenaline OR orciprenaline OR Ipratropium OR Oxitropium OR metaproterenol OR isoproterenol OR reproterenol OR fenoterol OR pirbuterol OR reproterol OR rimiterol

Review 2 Bronchodilators, nebuliser versus.....

As a) and b) above

AND

c) nebuli\*

Reference lists of all available primary studies and review articles were reviewed to identify relevant citations. Authors of included RCTs were contacted for any other unpublished studies. In addition, before the NICE report was commissioned, the UK headquarters of pharmaceutical companies who manufacture inhaled drugs were contacted. Details of published and unpublished studies supported by the companies were requested.

## **Appendix 5. Manufacturer/sponsor submissions received by the National Institute for Clinical Excellence**

- AstraZeneca
- Aventis Pharma (formerly Rhône-Poulenc Rorer)
- Boehringer Ingelheim Ltd.
- Glaxo Wellcome
- 3M Health Care Ltd.
- Norton Healthcare
- Yamanouchi Pharma Ltd



## Glossary

|                          |   |
|--------------------------|---|
| <b>BP</b>                | Blood pressure  |
| <b>CFC</b>               | Chloroflourocarbon (pMDI propellant)  |
| <b>DPI</b>               | Dry powder inhaler  |
| <b>EIA</b>               | Exercise induced asthma   |
| <b>FEF 25-75%</b>        | Maximum expiratory flow over 25 to 75% of expiration                          |
| <b>FEV1</b><br>capacity) | Maximum volume of air expired in the first second of expiration (from maximum |
| <b>FVC</b>               | Maximum total volume of air expired (from maximum capacity)                   |
| <b>HFA</b>               | Hydrofluoroalkane (CFC propellant replacement)                                |
| <b>HR</b>                | Heart rate  |
| <b>PD20</b>              | Dose of challenging drug required to cause a fall in FEV1 of 20%              |
| <b>PEFR</b>              | Peak expiratory flow rate   |
| <b>pMDI</b>              | Pressurised metered dose inhaler  |
| <b>Raw</b>               | Airways resistance  |
| <b>Vmax50%</b>           | Maximum flow at 50% of expiration (similar to FEF25-75%)                      |
| <b>VTG</b>               | Volume of trapped gas (a measure small airways obstruction)                   |