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

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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)[2] which promote a step-wise management of increasingly severe asthma. Therapy consists predominantly of the use of inhalers, delivering beta$_2$-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%,[3,4] 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.[5] 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

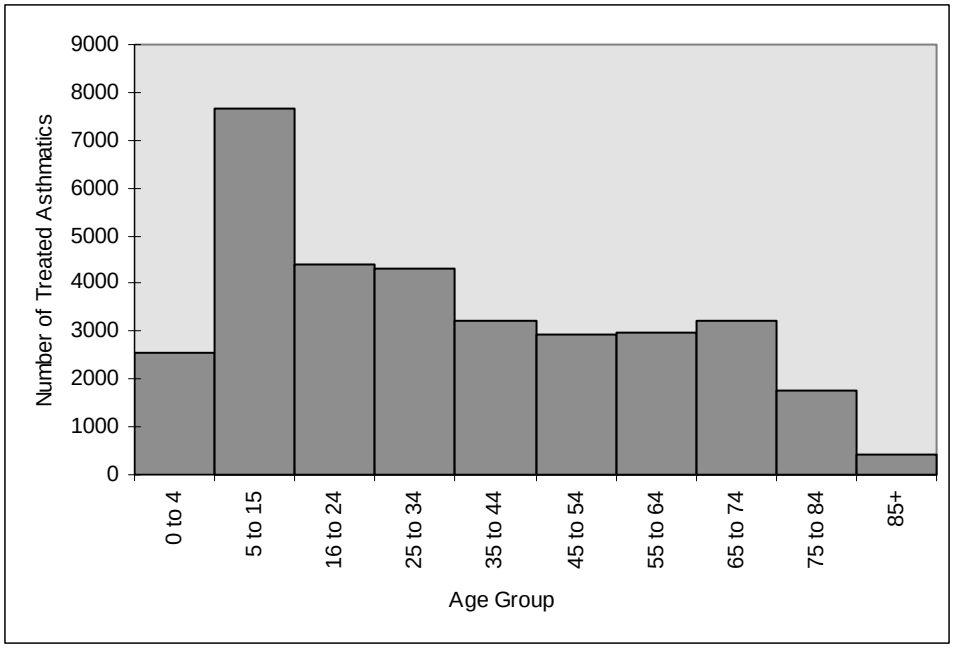
The severity of asthma has been divided into five BTS steps. The percentage of patients in each BTS step has been derived from Hoskins et al.[6] and is shown in Table 2.

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,[5,7] 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
Total Number	**2,580**	**7,679**	**23,246**

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 + 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	
Age-group	0-4 years	5-15 years	0-4 years	5-15 years	0-4 years	5-15 years
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.[9] This is currently believed to be best achieved by delivering both symptom relieving and preventative anti-inflammatory medication, typically with bronchodilators and/or corticosteriods, 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.[9] 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. [10,11,12,13]
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 corticosteriods with oral mucosa-related problems. Again this can lead to additional treatment-related costs.[14]

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.[14]

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. [15,16]

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.[17]

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.[17]

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. [17] 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.[17,9] The latest BTS Guidelines suggest the following as the most clinically appropriate asthma drug delivery systems for children under the age of 5 years.[9] These BTS guidelines are not explicitly evidenced based.

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

Age Group	*1st Choice Device*	*2nd Choice Device*	*3rd Choice Device*	*Breath-actuated*	*Dry-powder*
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 β_2-agonist but not recommended for corticosteriods

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[42]. 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.[18] 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 (ScHARR) 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 ScHARR 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 corticosteriods 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 corticosteriods 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 corticosteriods 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 ScHARR 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 corticosteriods by hand-held inhalers – review 1A

The current recommendations for prescribing in childhood asthma are based on the widely accepted British Thoracic Society guidelines[19]. 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 corticosteriods.

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[20], MIMS[21]) or the product data sheets. There is clear evidence[22], that generally DPI devices cause more systemic side effects than pMDI (especially with large volume spacer) devices hence the guideline recommendations[19] to avoid DPIs for corticosteriod 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 oro-pharyngeal 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[23] but the selection and teaching of these subjects may not reflect usual practice. Other work by Agertoft, in a filter study in 198 children[24] 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[25]), 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[26] 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 corticosteriods to children. The comparator of Rotahaler is now rarely used and also is unsuitable for children[19] (comments as for Turbuhaler). The dosage chosen is at 1:1 but now the accepted would be for pMDI:Rotahaler to be 1:2[27, 28]. 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
Agertoft 1993 Importance of inhaler device on the effect of budesonide. *Citation:*Archives of Disease in Childhood 1993;69:130-133 (Also published as Ugeskr Laeger 1994;156:4134-4137)	*Design:* Parallel, open RCT *Device:* pMDI+ Nebuhaler vs Turbuhaler *Drug:* Budesonide *Dose:* pMDI+Nebuhaler – run-in dose Turbuhaler – half of run-in dose *Duration:* 9 weeks	*Participants:* 126 asthma patients, 87M, 39F mean age 9.2, range 4-15 241 children were screened by halving their steroid dosage. The 126 that deteriorated asthma control went forward to randomisation. *Quality:* Cochrane B	*No significant differences in:* Change from baseline of; FEV1 0.12(0.28), 0.11(0.28) litres FVC 0.13, 0.12 litres FEF25-75% 0.15, 0.12 l/sec PEFR am 11.5(30), 14.9(30) l/min symptom score; day -0.30(0.38), -0.26(0.38) night –0.15(0.30), -0.21(0.30) %falls in response to exercise of FEV1 12.3, 11.1% FVC 6.9, 6.4% FEF25-75% 27.6, 22.7% PEFR 13.0, 11.2 24hr urinary cortisol 31.5(17), 32.7(19) *Statistical difference in:* relief medication use, puffs/week 4.67, 3.83	This study supports equivalence of pMDI+Nebuhaler versus Turbuhaler at half the pMDI dose. This should not be taken to mean that the device is twice as effective. There was no difference in 24 hour urinary cortisol between the groups implying a similar delivered dose of medication. Relief medication usage is statistically different between groups but the effect is small (less than 1 extra puff/week). Ranked ahead of Edmunds 1979 due to much greater study size.
Edmunds 1979 A clinical comparison of beclomethasone dipropionate delivered by pressurised aerosol and as a powder from a Rotahaler. Implies Rotahaler supplied by Allen and Hanbury's Research Division. *Citation:*Archives of Disease of Chidhood 1979;54:233-235	*Design:* Cross-over RCT, double-blinded, double-dummy, *Device:* pMDI versus Rotahaler *Drug:* Beclomethasone *Dose:* 2puffs qds v 1capsule qds (presumed each 200ug qds) *Duration:* 2 X 1 month	*Participants:* 14 asthma patients, 7M, 7F mean age 9.7 years, range 4.8-15.1 *Quality:* Cochrane A	*No significant differences in:* PEFR am symptom free days relief salbutamol use *Significant difference in:* mean symptom scores in favour of pMDI. (p=0.04) (no further data extractable from paper) 8 patients preferred aerosol, 2 preferred Rotahaler.	Poorly presented study with no statistical results given (author states 'no significance'). Rotahaler (Rotacaps) is an unusual device to use now and would normally be considered to need twice the pMDI dosage. This study is presumed to be 1:1 dosing.

Delivery of β_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[29, 30, 31, 32, 33, 34, 35] compared pMDI with Turbuhaler. No significant difference was found in the following outcomes: FEV_1, FVC, HR, $FEF_{25-75\%}$, BP, Raw, PEFR and VTG. Ahlström et.al[35] 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[36, 37] compared pMDI with Rotahaler. No significant difference was found in the following measured outcomes: FEV_1, FVC, $FEF_{25-75\%}$, PEFR, HR, BP, drop-out rate or asthma symptom scores. In the long-term study (12 weeks) by Kemp 1989[36], the number of acute exacerbations requiring medical intervention was significantly higher in the pMDI group.

One study[38] compared HFA (CFC-free) inhalers with CFC pMDI. No difference in measured FEV_1 was found. One study compared a device called an Italseber[39] 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 $ß_2$ agonist delivery via pMDI plus spacer with $ß_2$ agonist delivery by DPI.

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

Study Author, Year	Methodology	Details	Results	Comments
Custovic 1995 Depart of Paediatrics, Manchester, UK. Also has Glaxo involvement *Citation:* J Pharm Med 5; 161-168.	*Design:* randomised double-blind double-dummy crossover study, computer generated schedule. Histamine challenge used. *Device:* HFA-pMDI alone vs CFC-pMDI alone *Drug:* salbutamol *Dose:* 200ug (both devices) *Duration:* 30 min	*Participants:* 25 children, age range 6-14yrs, mean age 10yrs. Pulmonary function test performed 30min post-dose, than histamine challenge performed and FEV_1 measured until FEV_1 decreased by 20% (PD_{20}). *Study quality*: Cochrane-A	*No significant differences in:* FEV_1 or protection against histamine-induced bronchoconstriction as measured by PD_{20}. --- FEV_1: mean ± SD (absolute value) HFA: 2.24 ± 0.70 pMDI: 2.79 ± 0.74	-
Hirsch 1997 German Medical Hospital *Citation:* Resp Med, 91; 341-346	*Design:* randomised double-blind double-dummy parallel study, used drawing lots. *Device:* Turbuhaler vs pMDI alone *Drug:* terbutaline *Dose:* 0.5mg (both devices) *Duration:* 10 min	*Participants:* 118 children, age range 8-15, mean age 11.3. Pulmonary function testing done 10 min post-dose. *Study quality*: Cochrane-A	*No significant differences in:* Change from baseline FEV_1 and FVC. *Significant differences in:* Vmax50% favouring pMDI --- FEV_1: mean ± SD (absolute value) TH: 2.33 ± 0.76 pMDI: 2.13 ± 0.80	-
Kemp 1989 Asthma Research Centre, USA *Citation:* J Allergy Clin. Immunol 83(3); 697-702	*Design:* 2 separate studies reported (a) randomised double-blind double-dummy crossover study using 2 doses: 100 & 200ug on separate days & (b) a parallel run study using 200ug qid for 12 weeks. Used computer coded treatment. *Device:* Rotahaler vs pMDI alone *Drug:* salbutamol *Dose:* (a) 90-100 & 180-200ug and study (b) 180-200ug *Duration:* (a) 360min & (b) 12 weeks.	*Participants:* (a) 30 children, mean age 9.4yrs. Lung function measured from 5 to 360min post-dose. *Study quality*: Cochrane-A --- *Participants:* (b) 204 (164F) children, age range 4-11, mean age 8.2yrs. Lung function measured from 5 to 480min post-dose. *Study quality*: Cochrane-A	Study A: *No significant differences in:* FEV_1, HR or BP. Study B: *No significant differences in:* FEV_1, FEF_{25-75}, FVC, PEFR, dropout rate or symptom scores. *Significant difference in:* Number of acute exacerbations (requiring intervention): 26 (25%) in the pMDI group vs 13 (13%) Rotahaler group ($p<0.05$). --- FEV_1: mean ± SE (% change) Study A RH: 19% ± 0.18% pMDI: 19% ± 0.13% Study B RH: 18% ± 0.18% pMDI: 18% ± 0.13%	Analyses of baseline mean FEV_1 (using unpaired two-tailed t-test) showed that the pMDI group had significantly lower FEV_1 when compared to the RH group. This may explain the higher rate of acute exacerbations seen in the pMDI group.

Study Author, Year	Methodology	Details	Results	Comments
Laberge 1994 Depart of Ped. Quebec, Canada *Citation:* J Pediatr 124; 815-817	*Design:* randomised double-blind double-dummy crossover study, used random numbers. *Device:* Turbuhaler vs pMDI + Nebuhaler *Drug:* terbutaline *Dose:* cumulative dosing study, giving a total dose of 2.0mg within 80 min than followed by 5mg of nebulised salbutamol.	*Participants:* 10 children, age range 3-6yrs, mean age 4.6yrs. Lung function measured 15 min after each dose of medication. *Study quality*: Cochrane-A	*No significant differences in:* HR, BP, tremor or airways resistance. ---------- No FEV_1 reported.	-
Bronsky 1995 Medical Research Centre, Utah. Supported by Glaxo Research Institute. *Citation:* J of Asthma 32(3); 207-214.	*Design:* randomised double-blind double-dummy crossover study using, Latin-square treatment schedule. Exercise challenge used. *Device:* Rotahaler vs pMDI alone *Drug:* salbutamol *Dose:* pMDI-180ug vs RH-200ug *Duration:* 51 min	*Participants:* 44 children, age range 4-11yrs, 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_{max}). Study also reported 15 min post dose FEV_1 (i.e. pre-exercise). *Study quality*: Cochrane-B	*No significant differences in:* pre and post exercise FEV_1 after drug administration. ---------- FEV_1: mean ± SD (absolute value) RH: 1.70 ± 0.44 pMDI: 1.69 ± 0.41	Study used exercise challenge to show that the two devices are equally effective against EIA.
Chambers 1980 Christchurch Hospital, NZ. Boehringer Ingelheim provided the trial materials. *Citation:* Arch Dis Child 55; 73-74.	*Design:* randomised double-blind double-dummy crossover study. *Device:* Italseber vs pMDI *Drug:* fenoterol *Dose:* 200ug (both devices) *Duration:* 5 hours	*Participants:* 13 children (7F), age range 6-12yrs, mean age 8.7yrs. PEFR test performed up to 5 hours post-dose. *Study quality*: Cochrane-B	*Significant differences in:* Overall mean %predicted PEFR over 5 hours duration post bronchodilator ($p<0.05$) using two-way ANOVA favouring DPI. ---------- PEFR: mean ± SD (% change) IS: 42.5% ± 22.52% pMDI: 48.75% ± 18.19%	Device does not appear to be in current use. Unable to determine further details after contact with author and sponsor company.
Hultquist 1989 AstraZeneca, Sweden *Citation:* Allergy, 44; 467-470	*Design:* randomised double-blind double-dummy crossover study. *Device:* Turbuhaler vs pMDI alone *Drug:* terbutaline *Dose:* 0.5mg + prn (both devices) *Duration:* 2 weeks	*Participants:* 57 children, age range 6-18, mean age 11. PEFR was measured 10 min post-dose. *Study quality*: Cochrane-B	*No significant differences in:* PEFR (morning & evening) and symptom scores. *Significant differences in:* preference for device where more children preferred the Turbuhaler (49%) than the pMDI (23%). ---------- PEFR morning: mean, no errors reported (absolute values) TH: 357 pMDI: 357 PEFR: evening: mean, no errors reported TH: 362 pMDI: 362	-

Study Author, Year	Methodology	Details	Results	Comments
Razzouk 1999 AstraZeneca, Sweden *Citation:* Int J Pharma 180; 169-175	*Design:* randomised double-blind double-dummy crossover study. *Device:* Turbuhaler vs pMDI alone *Drug:* salbutamol *Dose:* 100ug (both devices) *Duration:* 240 min	*Participants:* 40 children, (9F), age range 6-12, mean age 9. Pulmonary function testing performed from 15-240min post-dose. *Study quality*: Cochrane-B	*No significant differences in:* Geometric means of mean FEV_1 and $FEV_{1\ max}$. Study also used Turbuhaler 50ug vs Turbuhaler 100ug & pMDI 100ug, showing no significant differences. --- FEV_1: mean ± SD (absolute value) TH: 1.82 ± 0.41 pMDI: 1.84 ± 0.43	-
Svenonius 1994 Astra Draco AB, Lund Sweden *Citation:* Allergy 49; 408-412	*Design:* randomised double-blind double-dummy crossover study. Exercise challenge used. *Device:* Turbuhaler vs pMDI alone *Drug:* terbutaline *Dose:* 1mg (both devices) *Duration:* 15 min	*Participants:* 12 children (2F), age range 9-17, mean age 13.8. Lung function measured before exercise than given the drug and measured again up to 15 min post-dose to observe reversibility of EIA. *Study quality*: Cochrane-B	*No significant differences in:* FEV_1 and VTG, --- FEV_1: mean ± SD (absolute value) TH: 3.04 ± 1.03 pMDI: 2.93 ± 0.93	-
Fuglsang, 1989 AstraZeneca, Sweden *Citation:* Pediatric Pulmonology 7; 112-115	*Design:* single-blinded double-dummy crossover study, used computer generated schedule. *Device:* Turbuhaler vs pMDI alone *Drug:* terbutaline *Dose:* 2.0mg (both devices) *Duration:* cumulative dosing study, giving a total dose of 2.0mg within 80 min.	*Participants:* 13 children (3F), age range 7-15yrs, mean age 10.5yrs. Pulmonary function testing done 15 min post-dose. *Study quality*: Cochrane-B	*No significant differences in:* FEV_1, $FEF_{25-75\%}$, PEFR or FVC. *Significant differences in:* Heart rate (HR) when using pMDI but not with Turbuhaler. More children complained of tremor in the pMDI (7) group than in the Turbuhaler group (0). --- FEV_1: mean ± SD (% change) TH: 62% ± 23.00% pMDI: 60% ± 25.67%	-
Ahlström 1989 Sweden, Medical Hospital. *Citation:* Allergy 44; 515-518	*Design:* open randomised crossover study *Device:* Turbuhaler vs MDI + Nebuhaler *Drug:* terbutaline *Dose:* 0.5mg qid (both devices) *Duration:* 14 days	*Participants:* 21 children (7F), age range 2-5yrs, mean age 3.9yrs. PEFR measured 15 min after drug administration. *Study quality*: Cochrane-B	*No significant difference in:* day or night symptom scores, day or night side effects or additional use of beta-2 medication. *Significant difference in:* morning PEFR favouring Turbuhaler over pMDI + Nebuhaler. (p=0.046) --- PEFR 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 β_2 agonists or antichiolingerics 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[40]. 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%[28, 41] 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[20, 21]. 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'[42] 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[20, 21], 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[43] 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[44], 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[45] 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
Blackhall 1987 A dose response study of inhaled terbutaline administered via Nebuhaler or nebuliser to asthmatic children Financial support from Astra Pharmaceuticals, Australia *Citation:*Eur J Respir Dis 1987;71:96-101	*Design:* Cross-over, open, dose response RCT *Device:* pMDI+Nebuhaler vs Nebuliser *Drug:* terbutaline. *Dose:* pMDI 0.5+0.5+1+2mg Nebuliser 1+1+2+4mg *Duration:* 2 X 1 day	*Participants:*12 asthmatic children, 6M, 6F aged 5-10 *Quality:* Cochrane A	*No significant differences in:* Increase in FEV1 0.38(0.08), 0.48(0.15) litres absolute pulse 97(13.0), 97(8.7) (pMDI 0.5mg and nebulised 4mg used) The log dose-response curves were parallel.	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.
Grimwood 1981 Salbutamol: tablets, inhalational powder, or nebuliser? Allen and Hanbury's NZ supplied placebo tablets and capsules. *Citation:*BMJ 1981;282;105-106	*Design:* 3 way cross-over RCT, double-blinded, double-dummy. *Device:* Rotahaler vs nebuliser vs oral tablet. *Drug:* Salbutamol *Dose:* 400ug v 4mg v 4mg *Duration:* 3 X 4 hours (separate days)	*Participants:* 17 'severe' asthmatic children, 7M, 10F mean age 7.2, range 4-12. *Quality:* Cochrane B	*No significant difference in:* %improvement in PEFR 15 min; 73(49), 98(82)% 45 min; 78(66), 110(88)	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.
Pierce 1992 Nebuhaler versus wet aerosol for domiciliary bronchodilator therapy. One author was an employee of Astra Pharmaceuticals, Australia *Citation:*The Medical Journal of Australia 1992;156:771-774	*Design:* Cross-over RCT, open *Device:* pMDI+Nebuhaler versus nebuliser *Drug:* Terbutaline *Dose:* pMDI 0.25mg/5kg Nebuliser 1mg/5kg *Duration:* 2 X 4 weeks	*Participants:* 22 asthmatic children, 11M, 11F mean age 9.9 32 adults presented separately in the study *Quality:* Cochrane B	*No significant differences in:* FEV1 1.61(0.54), 1.74(0.61) litres FVC 2.14(0.79), 2.28(0.84) litres PEFR pm 289(80), 299(79) l/min (presumed printing error on PEFR am; 227(82), 292(78) symptom scores; wheeze 0.62(0.55), 0.67(0.53) cough 0.93(0.85), 0.77(0.57) dyspnoea 0.80(0.75), 0.75(0.69) sleep disturbance 0.64(0.74), 0.51(0.48) 11 preferred pMDI and 10 the nebuliser.	This study set in the home over 4 weeks showed equivalence of pMDI+spacer versus nebuliser. Of note, in the adult part of the same study, adults preferred nebuliser 23 to 11, despite again equivalent clinical response.

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.[18,15]

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 corticosteriods and β_2-agonists, but they do not help to differentiate in any way between the different delivery mechanisms themselves.[15]

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 [46]	1991	CEA	Inhaled β^2-agonist / N=1133	Short-term benefits
Rutten-van Molken et al [47]	1993	CEA	Inhaled corticosteriods / N=116	Good cost-effectiveness
Connet et al [48]	1993	CEA	Inhaled corticosteriods / N=40	Reductions in non-steroid costs
Campbell et al [49]	1993	CEA	Inhaled corticosteriods / N=556	Low-dose corticosteriods was cost effective
Perera et al [50]	1995	CUA	Inhaled corticosteriods / N=86	Good cost-utility values / treatment costs
Booth et al [51]	1996	CEA	Inhaled corticosteriods / N=225	Good cost-effectiveness values
Lord et al [52]	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-acutated 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).[53] 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.

Breath Acutated MDIs	***Dry Powder Inhalers (DPIs)***
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 [54] (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 β_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 corticosteriods 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 corticosteriods 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[1].

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 than5 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 recruit 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 β_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[1].

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.

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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 *2.36 (40mcg bd)** 1.77 (20mcg tds)	
		Atrovent Forte		40mcg x 200	6.22	Age < 6 yrs No dosing information	
	Oxitropium	Oxivent	BI	100mcg x 200	6.69	Not evaluated in children	
$Beta_2$-agonists	Orciprenaline	Alupent	BI	750mcg x 300	2.66	Age < 6 yrs 50p (750mcg bd)	
	Reproterol	Bronchodil	ASTA Medica	500mcg x 400	7.01	Age < 6 yrs No dosing information	
	Salbutamol	Asmasal Spacehaler	Medeva	100mcg x 200	5.43	2.28 - 3.04 (100mcg tds –qds) *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
		Bricanyl spacer		250mcg x 400	7.21	2.02 (250mcg qds or 500mcg bd)	Collapsible delivery system
	Fenoterol	Berotec 100	BI	100mcg x 200	2.36	Age < 6 yrs	
		Berotec 200		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 brochodilator	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 No dosing information	
Long acting beta$_2$-agonists	Salmeterol	Serevent	A & H	25mcg x 120	28.60	Age > 4yrs 26.69 (50mcg bd)	Volumatic - 2.75
'Cromones'	Cromoglycate	Intal	RPR	5mg x 112	19.09	19.09 (5mg qds)	
		Intal Syncroner		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 Syncroner		2mg, 112 x 2	85.95	No dosing information	With integral spacer device
Inhaled cortico-steroids	Beclomethasone	Asmabec Spacehaler	Medeva	50mcg x 200	5.43		With vortex generating actuator
				100mcg x 200	10.32	2.89 (100mcg bd) 5.78 (200mcg bd)	
		Asmabec Spacehaler 250		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) 4.61 (200mcg bd)	
				200mcg x 200	15.68	4.39 (200mcg bd)	
		Beclazone 250		250mcg x 200	18.02	Not indicated for children	
		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) 5.78 (200mcg bd)	
				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 18.02		Integral compact spacer device
		Filair	3M	50mcg x 200	4.14		
				100mcg x 200	7.87	2.20 (100mcg bd) 4.41 (100mcg qds) *4.41 (200mcg bd)***	
		Filair Forte		250mcg x 200	17.21	Not recom-mended 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 5.46 (50mcg bd) 10.92 (100mcg bd)	
				125mcg x 120	22.86	Not suitable for use in children	
				250mcg x 120	38.86		
Combination	Cromoglycate/ salbutamol	Aerocrom Syncroner	Castlemead	1mg/ 100mcg x 200	34.42	Not recom-mended 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/ 100mcg bd) 3.04 (100mcg/ 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
$Beta_2$-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 No dosage data available *2.20 (50mcg bd),* *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 *5.26 (40mcg bd)** 3.94 (20mcg tds)	
	Oxitropium	Oxivent Autohaler	BI	100mcg x 200	15.72	Not evaluated in children	
$Beta_2$-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 No dosing information	
'Cromone'	Cromoglycate	Cromogen Easi-Breathe	Baker Norton	5mg x 112	13.91	13.91 (5mg qds)	
Inhaled cortico-steroids	Beclomethasone	Aerobec Autohaler	3M	50mcg x 200	10.51		
				100mcg x 200	12.89	3.61 (100mcg bd) 7.22 (200mcg bd)	
		Aerobec Forte Autohaler		250mcg x 200	23.97	Not recom-mended 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) 4.61 (200mcg bd)	
		Becloforte Easi-Breathe		250mcg x 200	18.02	Not recom-mended 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
$Beta_2$-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 *2.20 (50mcg bd)* *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
$Beta_2$-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) 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) 9.33 (200mcg qds)
		Ventolin Rotacaps (Rotahaler 78p)	A & H	200mcg x 112	5.33	2.67 (200mcg bd) 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) 7.06 (500mcg qds)
Long acting $beta_2$-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 $\geq$ 4 yrs 29.40 (50mcg bd)
		Serevent Accuhaler	A & H	50mcg x 60	28.60	Age $\geq$ 4 yrs 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 Cortico-steroids	Beclomethasone	Asmabec Clickhaler	Medeva	50mcg x 200	7.18	
				100mcg x 200	10.55	2.95 (100mcg bd) 5.91(200mcg bd)
				250mcg x 100	13.24	No dosing information/ 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 recommended dose for children
		Becloforte Diskhaler	A & H	400mcg, 14 x 8	39.13	Not indicated for children
		Becotide Rotacaps (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 recommended dose for children
	Budesonide	Pulmicort Turbohaler	AstraZeneca	100mcg x 200	18.50	5.18 (100mcg bd)
				200mcg x 100	18.50	5.18 (200mcg od) 10.36 (200mcg bd)
				400mcg x 50	18.50	10.36 (400mcg od)
	Fluticasone	Flixotide Accuhaler	A & H	50mcg x 60	6.86	Age $\geq$ 4 yrs 6.40 (50mcg bd)
				100mcg x 60	9.60	Age $\geq$ 4 yrs 8.96 (100mcg bd)
				250mcg x 60	22.86	Not suitable for use in 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 7.66 (50mcg bd)
				100mcg, 14 x 4	12.23	Age ≥ 4 yrs 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) 12.68 (200mcg/ 100mcg qds)
	Salmeterol/ fluticasone	Seretide 100 Accuhaler	A & H	50mcg/ 100mcg x 60	33.54	Age > 4 yrs 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 Not recommended Age 3 – 14 yrs 28.64 (100mcg tds)
				250mcg/ ml, 2ml x 20	8.00	Age < 3 yrs Not recommended Age 3 – 14 yrs 33.60 (500mcg tds) 22.40 (500mcg bd)
		Ipratropium Steri-Neb	Baker Norton	250mcg/ ml, 1ml x 20	5.13	Age 3 –14 yrs 21.55 (100mcg tds)
				250mcg/ ml, 2ml x 20	5.99	Age 3 – 14 yrs 25.16 (500mcg tds) 16.77 (500mcg bd)
		Respontin	A & H	250mcg/ ml, 1ml x 20	5.45	Age 3 – 14 yrs 22.89 (100mcg tds)
				250mcg/ ml, 2ml x 20	6.40	Age 3 – 14 yrs 26.88 (500mcg tds) 17.92 (500mcg bd)
$Beta_2$-agonists	Salbutamol	Salamol Steri-Neb	Baker Norton	2.5mg/ 2.5ml, x 20	2.74	Age > 18 mnths 15.34 (2.5mg qds)
				5mg/ 2.5ml, x 20	5.47	Age > 18 mnths 15.32 (5mg bd)
		Ventolin Nebules	A & H	2.5mg/ 2.5ml x 20	3.38	Age > 18 mnths 18.93 (2.5mg qds)
				5mg/ 2.5ml x 20	6.90	Age > 18 mnths 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	Bricanyl Respules	AstraZeneca	5mg/ 2ml x 20	3.67	10.28 (5mg bd) 20.55 (5mg qds)
		Bricanyl Respirator Solution	AstraZeneca	10mg/ ml, 20ml x 1	2.64	3.70 (5mg bd) 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 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 89.60 (0.5mg bd)
				1mg/ 2mlx 20	44.64	Age 3 mnths – 12 yrs 124.99 (1mg bd)
	Fluticasone	Flixotide Nebules	A & H	0.5mg/ 2ml x 10	10.04	Age < 16yrs Not recommended
				2mg/ 2ml x 10	40.16	

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$.tw.	1140
12	(mdi or mdis).tw.	825
13	pmdi$.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 nebuhaler OR aerochamber* OR fisonair OR extension OR spacing device OR inspirease OR Accuhaler OR Diskhaler OR Turbohaler OR Turbuhaler 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 Inglheim Ltd.
- Glaxo Wellcome
- 3M Health Care Ltd.
- Norton Healthcare
- Yamanouchi Pharma Ltd

Glossary

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