Health Technology Assessment 2001; Vol. 5: No. 26

Review

Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature

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Health Technology Assessment
NHS R&D HTA Programme

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Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature

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Competing interests: none declared

Published September 2001

This report should be referenced as follows:

Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L, *et al*. Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature. *Health Technol Assess* 2001;**5**(26).

Health Technology Assessment is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE. Copies of the Executive Summaries are available from the NCCHTA website (see opposite).

NHS R&D HTA Programme

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Initially, six HTA panels (pharmaceuticals, acute sector, primary and community care, diagnostics and imaging, population screening, methodology) helped to set the research priorities for the HTA Programme. However, during the past few years there have been a number of changes in and around NHS R&D, such as the establishment of the National Institute for Clinical Excellence (NICE) and the creation of three new research programmes: Service Delivery and Organisation (SDO); New and Emerging Applications of Technology (NEAT); and the Methodology Programme.

This has meant that the HTA panels can now focus more explicitly on health technologies ('health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care) rather than settings of care. Therefore the panel structure has been redefined and replaced by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

The HTA Programme will continue to commission both primary and secondary research. The HTA Commissioning Board, supported by the National Coordinating Centre for Health Technology Assessment (NCCHTA), will consider and advise the Programme Director on the best research projects to pursue in order to address the research priorities identified by the three HTA panels.

The research reported in this monograph was funded as project number 97/23/02.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for any recommendations made by the authors.

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The editors and publisher have tried to ensure the accuracy of this report but do not accept liability for damages or losses arising from material published in this report. They would like to thank the referees for their constructive comments on the draft document.

ISSN 1366-5278

Published by Core Research, Alton, on behalf of the NCCHTA.
Printed on acid-free paper in the UK by The Basingstoke Press, Basingstoke.

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Contents

List of abbreviations

A & E	accident and emergency*
BA-pMDI	breath-actuated pMDI
BP	blood pressure
bpm	beats per minute
CFB	change from baseline*
CFC	chlorofluorocarbon (pMDI propellant)
CI	confidence interval
COPD	chronic obstructive pulmonary disease
df	degrees of freedom†
DPI	dry powder inhaler
EIA	exercise induced asthma
$FEF_{25–75\%}$	maximum expiratory flow over 25–75% of expiration
FEV_1	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
MDPI	multidose powder inhaler
NA	not applicable*
OR	odds ratio
PD_{20}	dose of challenging drug required to cause a fall in FEV_1 of 20%
PEFR	peak expiratory flow rate
pMDI	pressurised metered-dose inhaler
Raw	airways resistance
RCT	randomised controlled trial
SD	standard deviation
SEM	standard error of the mean
SGaw	specific airway conductance
SMD	standardised mean difference
$V_{max50\%}$	maximum flow at 50% of expiration (similar to $FEF_{25–75\%}$)
VTG	volume of trapped gas (a measure of small airways obstruction)
WMD	weighted mean difference

* Used only in tables
† Used only in figures

Executive summary

Background

Asthma and chronic obstructive pulmonary disease (COPD) are common diseases of the airways and lungs that have a major impact on the health of the population. The mainstay of treatment is by inhalation of medication to the site of the disease process. This can be achieved by a number of different device types, which have wide variations in costs to the health service.

A number of different inhalation devices are available. The pressurised metered-dose inhaler (pMDI) is the most commonly used and cheapest device, which may also be used in conjunction with a spacer device.

Newer chlorofluorocarbons (CFC)-free inhaler devices using hydrofluoroalkanes (HFAs) have also been developed. The drug is dissolved or suspended in the propellant under pressure. When activated, a valve system releases a metered volume of drug and propellant.

Other devices include breath-actuated pMDIs (BA-pMDI), such as Autohaler® and Easi-Breathe®. They incorporate a mechanism activated during inhalation that triggers the metered-dose inhaler.

Dry powder inhalers (DPI), such as Turbohaler®, Diskhaler®, Accuhaler® and Rotahaler®, are activated by inspiration by the patient. The powdered drug is dispersed into particles by the inspiration.

With nebulisers oxygen, compressed air, or ultrasonic power is used to break up solutions or suspensions of medication into droplets for inhalation. The aerosol is administered by mask or by a mouthpiece.

There has been no previous systematic review of the evidence of clinical effectiveness and cost-effectiveness of these different inhaler devices.

Objectives

To review systematically the clinical effectiveness and cost-effectiveness of inhaler devices in asthma and COPD.

Methods

The different aspects of inhaler devices were separated into the most clinically relevant comparisons. Methods involved systematic searching of electronic databases and bibliographies for randomised controlled trials (RCTs) and systematic reviews. Pharmaceutical companies and experts in the field were contacted for further information. Trials that met the inclusion criteria were appraised and data extraction was under-taken by one reviewer and checked by a second reviewer, with any discrepancies being resolved through agreement.

Results

In vitro characteristics versus *in vivo* testing and clinical response

There is evidence that when comparative testing is performed on inhaler devices using the same methods, there is some correlation between particle size measurements and clinical response. However, the measurements are dependent upon the methods used, and a single measure of a device in isolation is of limited value. Also, there is little data on comparing devices of different types. There is currently insufficient data to verify the ability of *in vitro* assessments to predict inhaler performance *in vivo*.

Effectiveness of metered-dose inhalers for the delivery of corticosteroids in asthma

The review of three trials in children and 21 trials in adults demonstrated no evidence to suggest clinical benefits of any other inhaler device over a pMDI in corticosteroid delivery.

Effectiveness of metered-dose inhalers for the delivery of beta-agonists in stable asthma

In children, 11 studies were reviewed, of which seven compared the Turbohaler with the pMDI. One study found a significant treatment difference in peak expiratory flow rate, although there were differences in the patients' baseline characteristics. In adults, a review of 70 studies found no demonstrable difference in the clinical bronchodilator effect of short-acting β_2-agonists

delivered by the standard pMDI compared with that produced by any other DPI, HFA-pMDI or the Autohaler device. The finding that HFA-pMDIs may reduce treatment failure and oral steroid requirement in beta-agonist delivery needs further confirmatory research in adequately randomised clinical trials.

Effectiveness of nebulisers versus metered-dose inhalers for the delivery of bronchodilators in stable asthma

In children, three included trials compared different devices with a nebuliser and demonstrated no evidence of clinical superiority of nebulisers over inhaler devices in bronchodilator delivery. A total of 23 studies in adults found equivalence for the main pulmonary outcomes and no evidence of difference in other outcomes.

Effectiveness of metered-dose inhalers for the delivery of beta-agonists in COPD

Only two studies were included in this review. No evidence of clinical difference was found in beta-agonist delivery.

Effectiveness of nebulisers versus metered-dose inhalers for the delivery of bronchodilators in COPD

Evidence from 14 trials demonstrated equivalence for the main outcomes of pulmonary function. For other outcomes there was no evidence of treatment difference in bronchodilator delivery.

Patients' ability to use metered-dose inhalers

Differences among studies and the heterogeneity of the results make it difficult to draw conclusions about inhaler technique differences between device types. The review of technique after teaching the correct technique suggests that there is no difference in patients' ability to use DPI or pMDIs.

Economic analysis

The total number of NHS prescriptions for inhaler therapy for asthma in 1998 was over 31 million, with a net ingredient cost in excess of £392 million. This economic assessment uses decision analysis to estimate the relative cost-effectiveness of inhaler devices for the delivery of bronchodilator and corticosteroid inhaled therapy. Overall, there were no differences in patient outcomes among the devices. On the assumption that the devices were clinically equivalent, pMDIs were the most cost-effective devices for asthma treatment.

Conclusions

This systematic review examined the evidence from clinical trials evaluating the clinical effectiveness of different inhaler devices in the delivery of inhaled corticosteroids and β_2-bronchodilators for patients with asthma and COPD. The evidence from the published clinical literature demonstrates no difference in clinical effectiveness between nebulisers and alternative inhaler devices compared to standard pMDI with or without a spacer device. The cost-effectiveness evidence therefore favours pMDIs (or the cheapest inhaler device) as first-line treatment in all patients with stable asthma unless other specific reasons are identified. Patients can use pMDIs as effectively as other inhaler devices as long as the correct inhalation technique is taught.

Recommendations for research

Further clinical trials are required to demonstrate any differences in the clinical effectiveness and cost-effectiveness of inhaler devices and nebulisers compared with pMDIs. These should be of sufficient statistical power and methodological rigour to demonstrate any clinical benefit. Trials should be undertaken in community settings to ensure the generalisability of results. Outcome measures should be more patient-centred and report adverse effects more completely. Reporting of data from trials should be improved.

Chapter 1
Introduction

Inhaled therapy delivering β_2-agonists and corticosteroid drugs in various doses has become accepted as the mainstay of asthma treatment.[1] In comparison with oral therapy, it allows low doses of medication to be delivered directly to the site of action in the airways, significantly reducing systemic side-effects.

A number of different inhalation devices are available. The pressurised metered-dose inhaler (pMDI) was the first inhaler device, and was introduced in 1956. It contains chlorofluorocarbons (CFCs) as a propellant. This is the most commonly used and cheapest device, which may also be used in conjunction with a spacer device. With the implementation of the 1987 Montreal Protocol and phasing out of CFCs, newer CFC-free inhaler devices using hydrofluoroalkanes (HFAs) have been developed. The drug is dissolved or suspended in the propellant under pressure. When activated, a valve system releases a metered volume of drug and propellant.

Other devices include breath-actuated pMDIs (BA-pMDIs), such as Autohaler and Easi-Breathe®. They incorporate a mechanism activated during inhalation that triggers the metered-dose inhaler. Dry powder inhalers (DPIs), such as Turbohaler®, Diskhaler®, Accuhaler® and Rotahaler®, are activated via inspiration by the patient. The powdered drug is dispersed into particles by the inspiration.

With nebulisers, either oxygen, compressed air, or ultrasonic power are used to break up solutions or suspensions of medication into droplets for inhalation. The aerosol is administered by mask or a mouthpiece.

There are a large number of inhaler devices available for the treatment of asthma and a number of factors may influence the choice of device made by clinicians and patients (*Figure 1*). These choices may have a considerable impact upon the health of individual patients and wider

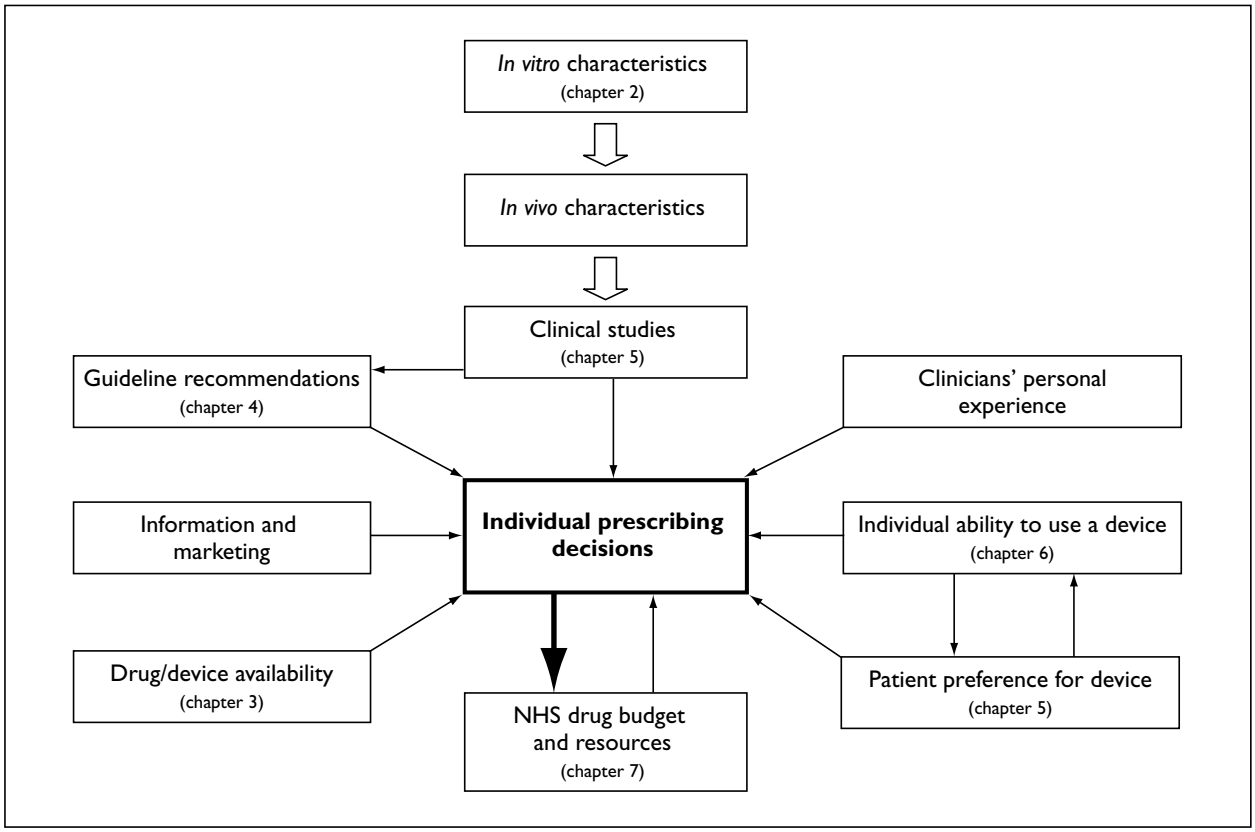


FIGURE 1 *Factors influencing the choice of device made by clinicians and patients*

healthcare costs. There are large differences in the costs of the same drug using different inhaler devices and of the drugs used in specific devices.

This report describes current practice and systematically reviews the evidence of clinical effectiveness and cost-effectiveness of inhaler devices used in the treatment of asthma. The report comprises the following sections.

- Chapter 2 is a systematic review of the literature concerning the relationship between *in vitro* characteristics of inhaler devices and clinical outcomes.
- Chapter 3 describes the relationship between the availability of the different drugs by the various inhaler device types currently available from UK manufacturers.
- Chapter 4 describes the current guideline recommendations that exist at present regarding the choice of inhaler devices.
- Chapter 5 reports the results of systematic reviews of the evidence from clinical trials comparing inhaler devices to evaluate their relative clinical effectiveness.
- Chapter 6 is a systematic review of the evidence for the ability of individual patients to use the different inhaler devices and the effect that teaching by healthcare professionals has in this respect.
- Chapter 7 is an appraisal of the economic impact of inhaler devices in asthma.
- Chapter 8 is the summary of the reviews and gives recommendations for future research.

Chapter 2

The relationship between *in vitro* characteristics of inhaler devices and clinical outcomes: a systematic review

Background

In vitro analysis is carried out to ascertain the quality of the manufactured product, and the analyses are usually conducted under strictly standardised conditions. The absolute amounts of drug leaving the inhaler and the variation in this parameter are typical *in vitro* measurements determined in the analyses. Although the analyses are done *in vitro*, it is often implied that the *in vitro* results reflect the *in vivo* situation. *In vitro* testing allows many different variables within and between inhaler systems to be assessed rapidly and comparatively cheaply, without subjecting patients to the inconvenience and hazards of *in vivo* testing. *In vivo* testing is performed to determine factors such as the pulmonary availability, clinical dose range, variability in patient response and side-effect profile. Studies[2] have shown that the amount of drug reaching the site of action determines the elicited effect (pulmonary availability).

In order to evaluate the usefulness of *in vitro* testing it is important to determine if measurements conducted using inhaler devices *in vitro* show any correlation with clinical effect in patients with asthma. This could be achieved by looking at the relationship between *in vitro* measurements and both lung deposition (measured by gamma scintigraphy or by pharmacokinetic methods) and clinical effect.

Gamma scintigraphy allows quantification of the percentage of the metered dose of drug that is deposited in the lungs. A gamma-ray emitting label is conjugated into the drug formulation and deposition of the inhaled drug is then followed by an external gamma camera.[3] Gamma scintigraphy measures deposition of the drug in the lungs rather than its uptake by the bronchi. A popular pharmacokinetic method involves the administration of charcoal in order to prevent the absorption of the swallowed drug.[4] This so-called charcoal-block method takes advantage of the fact that if the uptake of the oral and gastrointestinal portions of an inhaled drug is blocked by activated charcoal, the amount of active drug reaching the systemic circulation equals the amount of active drug absorbed over the lung membrane.[5] Thus, pharmacokinetic methods measure the absolute amount of drug taken up by the lungs.

The deposition pattern of inhaled drug in the respiratory tract is determined by a complex interaction between the device, the aerosol formulation and the patient's inhalation technique.[6] This is further complicated by the large number of spacer devices that are available for use with pMDIs.[7,8] *In vitro* (fine particle fraction) data are poor predictors of relative lung deposition from two different inhaler devices (e.g. pMDI and DPI) because they have different spray characteristics.[9] This is sometimes falsely referred to as one device having higher lung deposition than another.

Furthermore, the relationship between *in vitro* measurements (particle size), lung deposition and clinical effect often has wide ranging limits and frequent disagreements.[10] Drug delivery systems are, therefore, unique and extrapolation of lung deposition results from one delivery system to another should not be made.[4] Therefore, we searched for studies that used (commercially available) inhaler devices (excluding nebulisers) that conducted measurements both *in vitro* and *in vivo*, including clinical outcome measurements.

In order to be able to answer the original brief in a meaningful manner, we divided the original question as follows:

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

Methodology: search terms and strategy

We restricted our search to include studies that involved patients with asthma because data from healthy volunteers are known to be different[11,12] and our primary interest is in clinical effect.

Available electronic medical databases (until August 2000) were searched for (randomised controlled) studies using the following search terms:

- *in vitro* AND asthma*

AND

- inhal* OR lung OR clinical effect OR clinical efficacy OR deposition OR *in vivo* OR cascade.

The reference lists of all selected studies and review articles were checked in order to identify any further relevant citations not captured by electronic searching.

Results

The electronic search (EMBASE, MEDLINE and online respiratory journal databases) yielded 1380 citations. From this list, 46 references were selected for which copies of full text papers were obtained. Five additional references were added from bibliographic searching of relevant articles and from contact with 'experts' in the field. Therefore, of 1385 abstracts, 51 were identified as relevant by scanning the title and abstracts. We were not able to find any randomised controlled trials (RCTs) comparing hand-held inhaler devices in patients with asthma which involved *in vitro* and *in vivo* measurements as well as clinical effect measured by lung function. We were also not able to find any RCTs that studied particle size to clinical outcomes in patients with asthma using commercially available inhaler devices (e.g. Persson and Wirén[13]). Therefore, some of the relevant studies are discussed below as in a traditional narrative review.

We were able to locate one study[14] that used the pMDI (attached to a large volume spacer) containing cromolyn sodium and conducted measurements both *in vitro* (Andersen cascade impactor) and *in vivo* (scintigraphy). Results from this study showed that the fraction of cromolyn sodium generated by the pMDI show that *in vitro* estimates of the percentage of cromolyn sodium contained in particles less than 5.8 μm accurately predicted *in vivo* measurements of the deposition fraction of cromolyn sodium in the lungs of patients with asthma. The average *in vivo* estimate of the deposition fraction by scintigraphy was 11.3% ± 3.6%, which was not significantly different from the average *in vitro* estimate of the respirable fraction by the Andersen cascade impactor (11.5% ± 2.4%). Unfortunately, this study did not record any measurements of lung function.

In addition, we were able to locate two further studies[15,16] that conducted measurements *in vitro* and also included lung function measurements. The first study[15] compared two DPIs containing sodium cromoglycate and the second study[16] compared two versions of the pMDI containing salbutamol. The first study was a well-designed, randomised, double-blinded, crossover trial with double-dummy technique. The authors used a modified Andersen cascade impactor for measurements of *in vitro* deposition. A total of 16 patients with asthma were recruited into the 'clinical' *in vivo* study and their responses to an exercise challenge were studied after inhaling the study drug. The ratio of the percentage *in vitro* lung deposition between the two devices (Blacil versus Lomudal) was 2.54 (33.0% and 13.0%, respectively). The ratio of the clinical effect between the two devices (Lomudal versus Blacil) as measured by the mean percentage decrease in the maximum volume of air expired in the first second of expiration (FEV_1) and peak expiratory flow rate (PEFR) after exercise challenge was: FEV_1 = 2.0 (6%/3%) and PEFR = 2.5 (10%/4%). As predicted by the modified Andersen cascade impactor, the decrease in pulmonary function after the administration of disodium cromoglycate was smaller from the Blacil than from the Lomudal inhaler, and the magnitude and direction of the difference was very similar to that obtained *in vitro*. From these study results it seems logical that the cascade impaction test is valuable for predicting the efficacy of inhalation in these DPIs (Lomudal and Blacil) containing disodium cromoglycate.

The study by Vidgren and colleagues[16] was also a well-designed RCT. This study also used the modified Andersen cascade impactor and showed that there was very little difference *in vitro* as regards percentage lung deposition between the two pMDIs (Orion versus Glaxo): 23.0% and 19.0%, respectively. PEFR measurements conducted after patients with asthma inhaled the study medication showed no significant differences between the two pMDIs containing salbutamol, as predicted by the *in vitro* lung deposition study.

Discussion

This is a difficult area for a systematic review due to the paucity of data in patients with asthma showing a correlation among *in vitro* measurements, *in vivo* measurements and clinical outcomes for inhaler devices. From the available literature, one can assume that *in vitro* assessments of inhaler performance are important in inhaler development, quality control and for product registration purposes. However, there is currently insufficient data to verify the ability of *in vitro* assessments to predict inhaler performance *in vivo*.

Measurements of fine particle dose (defined by the amount of drug with an aerodynamic diameter less than 5 (m) by cascade impactor have shown that the measured fine particle dose *in vitro* is highly dependent on the geometry of the inlet to the impactor. It is possible to modify *in vitro* techniques so that they more closely resemble the *in vivo* situation.[17] Recent studies have shown that the fine particle dose is considerably lower when the cast of a human throat is used than when a standard glass inlet is used.[6,18] The use of such a modification also decreases the ballistic fraction of the inhaled drug[19] and more closely resembles the clinical situation.[20] Other studies[15,16,21] demonstrate that there is good correlation between *in vitro* fine particle dose and *in vivo* lung deposition when the human throat cast inlet is used for the *in vitro* measurements.

As can be seen from the studies discussed above, the correlation between *in vitro* and *in vivo* measurements are specific to the inhaler and drug combination. Therefore, data from one inhaler and drug combination should not be used to predict *in vivo* behaviour in another. In addition, the extrapolation of *in vitro* techniques to the *in vivo* situation requires an appropriate experimental system, such as an impactor using an anatomical human throat replica as the inlet.

Conclusion

Recent studies with modified *in vitro* techniques suggest that there is a relationship between *in vitro* measurements and lung deposition. This relationship is specific to the set (inhaler device and drug combination) for which the *in vitro*/*in vivo* parameters were conducted. Studies have also shown that there is a relationship between *in vitro* measurements and clinical effect measured by lung function (FEV_1 and PEFR). However, there is still an incomplete understanding of the relationship between *in vitro* techniques, particle size, aerodynamic diameter and drug mass (μg). Future study designs should take account of these factors with attention to drug mass at the mouth and the lower respiratory tract deposition in patients with asthma.

Chapter 3

The relationship between the availability of the different drugs and the various inhaler device types

Informed decisions should be based on the relative efficacy of different inhaler devices or inhaled drugs. However, in practice, these decisions are constrained by the combination of the drug and device that can be specifically prescribed. These drug/device combinations are limited by commercial availability and marketing, and on a practical level these factors are likely to have a larger impact on prescribing than the evidence of effectiveness of the individual drugs and devices.

A large number of drug/device combinations are available (*Tables 1–6*). If a particular device is preferred by a user or clinician, then this could limit which drug is prescribed and vice versa. This is particularly relevant in the area of inhaled corticosteroids, where much debate[22,23] concerns the relative merits of the 'second generation' corticosteroids, budesonide and fluticasone, over the original beclometasone. The resource implications of these choices are important given the large price differences with beclometasone available as a generic medication. Additionally, it is desirable that the range of drugs prescribed to an individual is delivered through the same or similar devices. Within the current availability of drug/device combinations this may not be possible for many patients.

If the primary decision is based on the drug to be prescribed then the devices available are shown in *Table 6*.

If the primary decision is made to opt for a DPI device, then the devices with the largest trial evidence of effectiveness and the largest market share are the Turbohaler from AstraZeneca and the Accuhaler from Allen & Hanburys. In addition to the increased cost of the DPI over the pMDI, there is further additional cost as the choice of inhaler device now necessitates using the proprietary budesonide and fluticasone respectively as the inhaled corticosteroid.

The problem is currently compounded by the phasing-out of CFC-propelled pMDIs. This is likely to restrict future choice as the manufacturers of the cheaper, less used and possibly generic products are unable or unwilling to produce a CFC-free replacement product. There may also be pressure by manufacturers to switch to the usually more expensive DPI product as a CFC-free choice. This could have considerable financial implications for the NHS. It has been estimated that annual prescribing costs alone could range from a small saving to a cost in excess of £100 million.[24]

The pharmaceutical industry markets specific products in such a way as to be advantageous to their individual situations. This is illustrated by the incomplete range of inhaler and drug types available from the major manufacturers. While there may indeed be technical and development barriers to change over to CFC-free inhalers, it will also provide an opportunity for the manufacturers to 'adjust' and re-market their product ranges.

Summary

The range of drug/device combinations is large and it is difficult for a clinician to make informed prescribing decisions about all of the possible permutations.

Prescribing decisions will be influenced by availability as well as evidence of clinical effectiveness.

TABLE 1 *Breath-actuated pressurised metered-dose inhalers*

Drug		Name of device	Company
Anti-cholinergic	Ipratropium	Atrovent® Autohaler	Boehringer Ingelheim
	Oxitropium	Oxivent® Autohaler	
Beta-agonist	Salbutamol	Aerolin® Autohaler	3M
		Salamol® Easi-Breathe	Baker Norton
		Ventolin® Easi-Breathe	Allen & Hanburys
Combination bronchodilator	Fenoterol/ipratropium	Duovent® Autohaler	Boehringer Ingelheim
Cromones	Cromoglycate	Cromogen® Easi-Breathe	Baker Norton
Corticosteroid	Beclometasone	AeroBec® Autohaler AeroBec Forte® Autohaler	3M
		Beclazone® Easi-Breathe	Baker Norton
		Becotide® Easi-Breathe Becloforte® Easi-Breathe	Allen & Hanburys

TABLE 2 Pressurised metered-dose inhalers

Drug		Name of device	Company
Anti-cholinergic	Ipratropium	Atrovent Atrovent Forte®	Boehringer Ingelheim
	Oxitropium	Oxivent	
Beta-agonists	Orciprenaline	Alupent®	Boehringer Ingelheim
	Reproterol	Bronchodil®	ASTA Medica
	Salbutamol	Asmasal Spacehaler®	Medeva
	Terbutaline	Bricanyl® Bricanyl Spacer (mini spacer)	AstraZeneca
	Fenoterol	Berotec 100™ Berotec 200™	Boehringer Ingelheim
Combination bronchodilator	Salbutamol/ipratropium Fenoterol/ipratropium	Combivent® Duovent®	Boehringer Ingelheim
Long-acting beta-agonist	Salmeterol	Serevent®	Allen & Hanburys

TABLE 3 *CFC-free pMDIs*

Drug		Name of device	Company
Bronchodilator	Salbutamol	Airomir® Salbulin®	3M
		Salamol®	Baker Norton
		Ventolin Evohaler®	Allen & Hanburys
Corticosteroid	Beclometasone	Qvar® Qvar Autohaler	3M
	Fluticasone	Evohaler	Allen & Hanburys

TABLE 4 *Dry powder inhalers*

Drug		Name of device	Company
Anti-cholinergic	Ipratropium	Atrovent Aerocaps®	Boehringer Ingelheim
Beta-agonist	Salbutamol	Asmasal Clickhaler®	Medeva
		Ventodisks®	Allen & Hanburys
		Ventolin Accuhaler	
		Ventolin Rotacaps®	
	Terbutaline	Bricanyl® Turbohaler	AstraZeneca
Long-acting beta-agonist	Eformoterol	Foradil®	Novartis
		Oxis® Turbohaler	AstraZeneca
	Salmeterol	Serevent Diskhaler Serevent Accuhaler	Allen & Hanburys
Cromones	Cromoglycate	Intal® Syncroner® (mini-spacer) Intal Spincap®	Rhône-Poulenc Rorer
Corticosteroid	Beclometasone	Asmabec® Clickhaler Asmabec Spacehaler™ 250 (built-in mini-spacer)	Medeva
		Becodisks® Becloforte Diskhaler Becotide Rotacaps	Allen & Hanburys
	Budesonide	Pulmicort® Turbohaler	AstraZeneca
	Fluticasone	Flixotide® Diskhaler Flixotide Accuhaler	Allen & Hanburys
Steroid/long-acting beta-agonist	Fluticasone + salmeterol	Seretide® 100 (Accuhaler) Seretide 250 (Accuhaler) Seretide 500 (Accuhaler)	Allen & Hanburys
	Budesonide/eformoterol	Symbicort	AstraZeneca
Steroid/bronchodilator	Salbutamol + beclometasone	Ventide® Rotacaps	Allen & Hanburys
	Ventide Paediatric Rotacaps		

TABLE 5 *Nebulised medication*

Drug		Name of device	Company
Bronchodilators	Ipratropium	Atrovent	Boehringer Ingelheim
		Ipratropium Steri-Neb®	Baker Norton
		Respontin®	Allen & Hanburys
	Salbutamol	Salamol Steri-Neb	Baker Norton
		Ventolin Nebules®	Allen & Hanburys
	Terbutaline	Bricanyl Respules®	AstraZeneca
Combination bronchodilators	Salbutamol/ipratropium Fenoterol/ipratropium	Combivent Duovent	Boehringer Ingelheim
Cromones	Cromoglycate	Cromogen Steri-Neb	Baker Norton
		Intal	Rhône-Poulenc Rorer
Corticosteroids	Budesonide	Pulmicort Respules®	AstraZeneca
	Fluticasone	Flixotide Nebules	Allen & Hanburys

TABLE 6 *Inhaler devices available for specific drugs*

For inhaled corticosteroids	
Beclometasone	Generic and proprietary pMDI BA-pMDI CFC-free pMDI DPI (Clickhaler, Diskhaler and Rotacaps)
Budesonide	pMDI DPI (Turbohaler)
Fluticasone	pMDI CFC-free pMDI Diskhaler and Accuhaler
For short-acting beta-agonist bronchodilators (salbutamol and terbutaline only illustrated)	
Salbutamol	Generic and proprietary pMDI BA-pMDI CFC-free pMDI DPI (Clickhaler, Ventodisks, Accuhaler and Rotacaps)
Terbutaline	pMDI DPI (Turbohaler)
For long-acting beta-agonist bronchodilators (eformoterol and salmeterol)	
Eformoterol	DPI (Turbohaler, Foradil®)
Salmeterol	pMDI DPI (Diskhaler, Accuhaler)

Chapter 4

A description of the current guideline recommendations regarding the choice of inhaler devices

The most commonly used guidelines in UK practice are from the British Thoracic Society.[1,25] Other national guidelines come from the National Heart, Lung and Blood Institute in North America.

A number of traditional reviews of the evidence have been published, most recently from the *Drug and Therapeutics Bulletin*.[29] Additionally, information may come to the attention of physicians or patients from other sources that are not formal guidelines but offer apparently 'expert' advice. This is illustrated by the Asthma Training Centre. The Asthma Training Centre is a national body and the following refers to a report of a trainers' workshop and a dissemination of advice for choosing inhaler devices in childhood.[26] No comment was made on the evidence base for the advice.

- ***Age 4–7 years***
  "If a patient can suck and hold his/her breath, then he/she can be given a breath actuated device, otherwise the patient should be given a metered-dose inhaler with a spacer device."

- ***Age 7–11 years***
  " ... the best device ... is the dry powder device."

- ***Age 11–17 years***
  No recommendations from pMDI, BA-pMDI or DPI.

It should be noted that in guideline recommendations, assessing the patient for a suitable device in terms of inhaler technique and teaching and rechecking of inhaler technique are often emphasised. However, in the summary versions circulated to clinicians this message is often lost.

The British Thoracic Society guidelines, 1997[1]

These were revised from guidelines originally published in 1993. These guidelines are not explicitly evidence-based. The recommendations make no reference upon which criteria inhaler device choices should be made; in favour of efficacy, cost-effectiveness, ease of use or avoidance of side-effects.

The recommendations regarding children are summarised in *Table 7*. For older children and adults there are no specific recommendations.

The National Heart, Lung and Blood Institute, USA, 1997

These guidelines were produced on the basis of expert consensus opinion (NIH 97-4051 July 1997; <www.nhlbi.nih.gov.guidelines/asthma/asthgdln.htm>). These have little direct advice regarding the choice of specific inhaler devices. In contrast to the British Thoracic Society guidelines[1] by age group, the minimum age for the prescribing of different inhaler devices was advised (*Table 8*).

Whilst it is difficult to be concise and didactic regarding the individual choice of inhaler devices, these guidelines are very broad, especially for adults.

TABLE 7 *British Thoracic Society guideline recommendations for inhaler devices for children*

Age	1st choice	2nd choice	3rd choice
1–2 + years	pMDI + spacer + face mask Note: avoid DPI and BA-pMDI	pMDI + spacer	Nebuliser
3–5 years	pMDI + spacer	pMDI + spacer + face mask	Nebuliser
	Note: BA-pMDI not proven; DPI occasionally useful for beta-agonists but 'not recommended' for corticosteroids		

TABLE 8 *The National Heart, Lung and Blood Institute guidelines for inhaler devices for children*

Device	Age
pMDI alone	> 5 years
pMDI + spacer*	> 4 years
BA-pMDI	> 5 years
DPI	May be used from 4 years but results more consistent > 5 years
Nebuliser	< 2 years or those unable to use other devices

* *Spacers are recommended for all patients on medium to high doses of inhaled corticosteroids*

Drug and Therapeutics Bulletin

These bulletins are commissioned, independent reviews produced by the Consumers' Association for Clinicians and Pharmacists. They are widely circulated to clinicians. Recently, the treatment of asthma using inhaled steroids in children[27] and adults[28] was addressed.

Device choice in children was addressed without specific recommendations.

> "The inhaler device should be one that the child and the parents prefer and that the child is able to use. An MDI with a large-volume spacer is often a reasonable first choice in children ..."
>
> "In general, administration of corticosteroid via a nebuliser has few if any advantages over an MDI plus spacer (fitted with a face-mask where necessary) ..."

The later review in adults did not address inhaler device selection at all.

The *Drug and Therapeutics Bulletin* further reviewed inhaler devices.[29] This again gave age-specific recommendations (*Table 9*).

Summary

There appears to be a lack of consensus and guidance for an individual prescriber faced with a wide range of possible inhaler devices. The current guidelines are either vague, absent, and where present, possibly contradictory. In such a vacuum, choices may become influenced by factors that are not clinically relevant or evidence-based.

TABLE 9 Drug and Therapeutics Bulletin *recommendations*

Age	1st choice	2nd choice	Comments
0–2 years	pMDI + spacer + face mask	Nebuliser	Ensure optimum spacer use; avoid 'open vent' nebulisers
3–6 years	pMDI + spacer	Nebuliser	Very few children at this age can use a dry powder inhaler adequately
6–12 years (bronchodilators)	pMDI + spacer or DPI or BA-pMDI		If using DPI or BA-pMDI, also consider pMDI + spacer for exacerbations
6–12 years (corticosteroids)	pMDI + spacer	DPI or BA-pMDI for low-dose corticosteroids only	May need to adjust dose if switching between inhalers; advise mouth-rinsing or gargling
12+ years (bronchodilators)	pMDI	DPI or BA-pMDI	Use pMDI if technique satisfactory; use large volume spacer in acute attack
12+ years (corticosteroids)	pMDI (+ spacer for moderate or high doses)	DPI or BA-pMDI for low-dose corticosteroids only	May need to adjust dose if switching between inhalers; advise mouth-rinsing or gargling
Acute asthma (all ages)	pMDI + spacer or nebuliser		Ensure optimum spacer use and appropriate dosing; written instructions for what to do in acute asthma

Chapter 5

Comparative clinical testing between different inhaler devices: five systematic reviews

A number of different inhalation devices are available, including the pMDI, the most commonly used and cheapest device that may be used in conjunction with a spacer device. Others include BA-pMDIs, such as Autohaler and Easi-Breathe, and DPIs, such as Turbohaler, Diskhaler, Accuhaler and Rotahaler. This is now further confused by the necessary introduction of HFA-propelled pMDIs (CFC-free), whose properties may well be different from the current CFC-propelled pMDIs, and how this translates into clinically important differences is important. In addition to the above hand-held inhaler devices, inhaled therapy can also be delivered by nebulisation, by air-driven or ultrasonic machines.

The following five systematic reviews were undertaken to evaluate the evidence of the clinical effectiveness of inhaler devices in the treatment of asthma and chronic obstructive pulmonary disease (COPD). The various combinations of comparison between different inhaler devices, drugs and clinical situation are of such variety that in order to produce manageable and meaningful results, reviews of the clinical evidence focused on five key areas. These areas cover the major proportion of clinical decision-making in inhaled therapy for airways disease.

- **Review A**
  This considers the delivery of the available corticosteroids (beclometasone, budesonide and fluticasone) by hand-held inhalers for the treatment of stable asthma in children and adults.

- **Review B**
  This considers the delivery of bronchodilators (β_2-agonists) by hand-held inhalers for the treatment of stable asthma in children and adults. Other bronchodilators are available (e.g. anticholinergics) but these are much less used in asthma than the former and were not considered.

For both of these reviews, studies were considered if they compared a standard pMDI inhaler, with or without a spacer device, versus one of the other types of inhaler device (DPI, CFC-free or BA-pMDI).

- **Review C**
  This considers the delivery of any short-acting bronchodilator using a nebuliser compared with any hand-held inhaler (usually a pMDI) in stable asthma in children and adults.

- **Review D**
  This considers the delivery of any short-acting bronchodilator using a standard pMDI inhaler, with or without a spacer device, compared with one of the other types of inhaler device (DPI, CFC-free or BA-pMDI) in stable COPD.

- **Review E**
  This considers the delivery of any short-acting bronchodilator using a nebuliser compared with any hand-held inhaler (usually a pMDI) in stable and acute COPD.

Methods of the reviews

Literature search strategy

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 online databases 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.

- 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)

Note: The *Lancet* and *British Medical Journal* were searched at the UK Cochrane Centre for all RCTs 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.

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

British Thoracic Society
American Thoracic Association
European Respiratory Society.

- Bibliographies of all trials are systematically searched prospectively.

The Cochrane Airways Group Register of Trials was searched using the following terms:

REVIEW A – 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 easi-breathe 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 B – bronchodilators, 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 easi-breathe OR autohaler OR cyclohaler OR rotahaler OR dry powder OR MDI OR DPI OR CFC-free OR HFA*

AND

b. salbutamol OR ventolin OR albuterol OR terbutaline OR bricanyl OR isoprenaline OR orciprenaline OR metaproterenol OR isoproterenol OR reproterenol OR fenoterol OR pirbuterol OR reproterol OR rimiterol.

REVIEW C – bronchodilators, nebuliser versus:
As (a) and (b) above

AND

c. nebuli*.

REVIEW D
As Review B above.

REVIEW E
As Review C above.

Reference lists of all available primary studies and review articles were reviewed to identify relevant citations. Authors of included RCTs were contacted if further information was required and for any other unpublished studies.

In addition, the UK headquarters of pharmaceutical companies who manufacture inhaled drugs were contacted. Details of published and unpublished studies supported by the companies were requested.

Inclusion and exclusion criteria

Types of studies

Only RCTs were considered. Studies could be laboratory- or community-based. Duration must have been a minimum of 4 weeks for trials in Review A (corticosteroids), otherwise any study duration was considered for the other four reviews.

Types of participants

Children aged 2–16 years inclusive and adults (from age 17) with chronic, stable asthma (i.e. not during an exacerbation) and patients with COPD in a stable or acute state, all diagnosed by a clinician or according to internationally accepted criteria. Children under 2 years old were specifically excluded due to the difficulty of diagnosing asthma against a less specific 'wheezing illness' in this age group.

Types of interventions

Trials were considered that compare clinical outcomes of a single drug delivered by different inhaler devices. These devices were a standard pMDI (with or without a spacer device) versus any hand-held device for Reviews A, B and D, and nebuliser versus any hand-held inhaler for Reviews C and E. Drugs considered were inhaled corticosteroids for Review A, short-acting beta-agonists for Review B and short-acting beta-agonists or anti-cholinergics for Reviews C, D and E.

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.

For all of these reviews, to avoid confounding, studies were only included if they delivered the same single drug via both of the devices compared.

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.

Quality assessment strategy

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

- Grade A: adequate concealment
- Grade B: uncertain
- Grade C: clearly inadequate concealment
- Grade D: not used.

Studies were ranked by the above grading and secondarily by study size.

Methods of analysis/synthesis

The data were combined using meta-analysis with further discussion as needed. Where insufficient data were available or meta-analysis was inappropriate, narrative review was used.

The meta-analysis was performed using the Cochrane Collaboration software program,

RevMan 4.0.4. Individual trial data were entered in terms of *n*, and mean and standard deviation for each treatment group at the end of the trial period. Individual study results were combined and weighted on the basis of using a fixed effect model (assuming that the results were distributed around a single 'true' value) where there was no statistically significant heterogeneity between the individual trial results. Alternatively, where heterogeneity did exist, a random effects model was used. This uses a more conservative approach and results in a wider interval around the point estimate.

Where results of separate trials are presented using the same units and measuring the same thing, these were combined using the weighted mean difference (WMD). The combined result remains in the original units.

Trials using different units or measuring a different although equivalent measure (e.g. change from baseline and absolute values) were combined using the standardised mean difference (SMD). Here, the mean difference (mean1 – mean2) is divided by the pooled standard deviation (giving the SMD) and these are then combined using the appropriate weighting. The results are in units of a 'standard deviation' and can be applied to data that are 'similar' to the original trial data; for example, a treatment with a benefit over a placebo of SMD 0.1 (95% confidence interval (95% CI), 0.05 to 0.15) when applied to a 'similar' group of patients (based on demographic or clinical characteristics) with a PEFR of 400 litres/minute (standard deviation (SD) 100) is equivalent to an improvement to 410 litres (95% CI, 405 to 415).

Evidence of clinical efficacy between inhaler devices in children and adults

REVIEW A: delivery of corticosteroids in stable asthma

Results in children

Three randomised controlled trials[30,31,37] are available to address this question. All compare a pMDI (with a spacer in two cases) with a DPI. Study characteristics are listed in *Table 10*. There are insufficient data to warrant meta-analysis and therefore the studies are reviewed narratively below.

The study by Adler and colleagues[30] is published in abstract form only and presents results for PEFR only. It compares the then new Clickhaler DPI with the pMDI + spacer. The ages of the children were relatively old: mean age 10.9 years, range 6–17 years. There was no statistically significant difference between the devices for morning PEFR or the other secondary efficacy end-points (undefined). The authors stated that the study had an 80% power to detect a 20-litre/minute difference in PEFR between the devices.

Agertoft and Pedersen[31] compared the pMDI + 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 the dose in common formularies[32,33] or in the product data sheets. There is clear evidence[34] that generally DPI devices cause more systemic side-effects than pMDI devices (especially with a large volume spacer), hence the guideline recommendations[1] to avoid DPIs for corticosteroid delivery in children. However, the above study[31] 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 assumed that the patient is taught to use the device and the teacher knows this factor. Studies have shown that children as young as 3 years old can use a Turbuhaler efficiently,[35] but the selection and teaching of these patients may not reflect usual practice. Other work by Agertoft and colleagues,[36] a filter study in 198 children comparing the pMDI + Nebuhaler versus Turbuhaler, showed that in younger children within the trial Turbuhaler drug delivery was less efficient: children 5 years old and above showed a drug delivery of 1:2

TABLE 10 *Review A: RCTs in children – steroids by hand-held inhalers*

Study	Methodology	Details	Results	Comments
Adler *et al.*, 1997[30] Efficacy and safety of beclometasone dipropionte delivered via a novel DPI (Clickhaler) in paediatric patients with asthma	*Design*: parallel, double-blind, double-dummy RCT *Device*: pMDI + Volumatic® vs Clickhaler *Drug*: beclometasone *Dose*: up to 400 µg/day *Duration*: 4 weeks	*Participants*: 144 asthmatic children, mean age 10.9 years, range 6–17 years *Quality*: Cochrane B	*No significant differences in*: Change in morning PEFR Other outcomes are unspecified and reported as non-significant without details	Published in abstract form only
Agertoft & Pedersen, 1993[31] Importance of inhaler device on the effect of budesonide (Also published as *Ugeskr Laeger* 1994; **156**:4134–7)	*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 (87 M, 39 F), mean age 9.2 years, range 4–15 years 241 children were screened by halving their steroid dosage; 126 who deteriorated asthma control went forward to randomisation *Quality*: Cochrane B	*No significant differences in*: Clinic: Change from baseline of: FEV_1, FVC, $FEF_{25–75\%}$ and % falls in FEV_1, FVC, $FEF_{25–75\%}$ and PEFR in response to exercise; 24 h urinary cortisol Home diary cards: PEFR (am + pm), day and night symptom score *Statistical difference in*: relief medication use, puffs/week	This study supports equivalence of pMDI + Nebuhaler versus Turbuhaler at half the pMDI dose. This should not be taken to mean that the device is twice as effective Relief medication usage is statistically different between groups but the effect is small (less than 1 extra puff/week) Ranked ahead of Edmunds and colleagues[37] due to much larger study size
Edmunds *et al.*, 1979[37] A clinical comparison of beclometasone dipropionate delivered by pressurised aerosol and as a powder from a Rotahaler	*Design*: crossover RCT, double-blinded, double-dummy *Device*: pMDI vs Rotahaler *Drug*: beclometasone *Dose*: 2 puffs q.d.s. vs 1 capsule q.d.s. (presumed each 200 µg q.d.s.) *Duration*: 2 x 1 month	*Participants*: 14 asthma patients (7 M, 7 F), mean age 9.7 years, range 4.8–15.1 years *Quality*: Cochrane A	*No significant differences in*: PEFR (am + pm), symptom-free days and relief salbutamol use *Significant difference in*: mean symptom scores in favour of pMDI ($p = 0.04$) 8 patients preferred aerosol, 2 preferred Rotahaler	Poorly presented study with no statistical results given (author states 'no significance') Rotahaler (Rotacaps) is an unusual device to use now and would normally be considered to need twice the pMDI dosage; this study is presumed to be 1:1 dosing

FVC, total volume of air expired – from maximum capacity; $FEF_{25–75\%}$, maximum expiratory flow over 25–75% of expiration

(as accepted in adults and the Agertoft and Pedersen[31] study for children aged 4–15 years old), whilst children of 3 and 4 years old showed a drug delivery of 1:1.

In summary, this large and well-designed study[31] does support the equivalence of the pMDI + Nebuhaler versus Turbuhaler at half of the pMDI dose. However, it does not present any evidence for advantages over the accepted place of the pMDI + large volume spacer as the device of choice in childhood asthma management.

A study by Edmunds and colleagues[37] compared 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[1] (comments as for Turbuhaler). The dosage chosen was at 1:1 but now the accepted dosage for the pMDI:Rotahaler would be 1:2.[38,39] Finally, the study is under-powered.

Results in adults

Description of studies

The studies include a broad range of individuals, location and types of intervention. Study characteristics are listed in *Tables 11* and *12*. All included studies have some form of drug company sponsorship such as supply of study drugs, funding or authorship. In one case, this potential conflict of interest was not declared. Duration of studies ranged from 4 to 12 weeks in a community setting

TABLE 11 *Review A: study characteristics of included studies on the delivery of steroids in asthma for pMDI versus DPI*

Study	Methodology	Details	Results	Comments
Carmichael *et al.*, 1978[54] Beclometasone dipropionate dry-powder inhalation compared with conventional aerosol in chronic asthma 'Encouragement and support' from 2 doctors of Allen & Hanburys Research Ltd	*Design*: crossover, double-blind, double-dummy *Device*: Rotahaler vs pMDI alone *Drug*: beclometasone *Dose*: 100 µg q.d.s. *Duration*: 3 x 4 weeks	*Participants*: 20 asthmatic patients (11 M, 9 F: 14 completed the study), aged 30–65 years A third arm of DPI 150 µg q.d.s. was also part of the study *Quality*: B	Clinic: FEV_1, FVC Diary card: PEFR am + pm; day and night cough, wheeze and dyspnoea; salbutamol usage; exacerbation	
Chatterjee & Butler, 1980[45] Beclometasone dipropionate in asthma: a comparison of two methods of administration One author from Glaxo-Allenbury Research and statistical support from same company	*Design*: crossover, double-blind, double-dummy *Device*: Rotahaler vs pMDI alone *Drug*: beclometasone *Dose*: 200 vs 100 µg q.d.s. *Duration*: 2 x 8 weeks	*Participants*: 70 asthmatics (65 analysed: 49 M, 16 F), median age 48 years, range 20–79 years *Quality*: B	Clinic: FEV_1, FVC; cortisol Diary card: PEFR am + pm; salbutamol; exacerbation	
Drepaul *et al.*, 1989[38] Becotide or Becodisks: a controlled study in general practice One author from Allen & Hanburys Ltd	*Design*: parallel, double-blind, double-dummy *Device*: Diskhaler vs pMDI alone *Drug*: beclometasone *Dose*: 400 vs 200 µg b.d. *Duration*: 8 weeks	*Participants*: 365 asthmatics in 78 centres (196 M, 169 F), mean age 42 years *Quality*: B	FEV_1, FVC; PEFR am + pm change from baseline; symptom score; relief medication; Candida swab	Not intention to treat, some outcomes as low as 100 in each group Statistically significant differences between groups at baseline
Engel *et al.*, 1989[47] Clinical comparison of inhaled budesonide delivered either via pMDI or Turbuhaler Possibly one author from Astra (Sweden)	*Design*: crossover, open *Device*: Turbuhaler vs pMDI alone *Drug*: budesonide *Dose*: stratified 400 or 800 µg b.d. *Duration*: 2 x 4 weeks	*Participants*: 29 asthmatics (9 entered at 400 µg b.d. and 20 at 800 µg b.d.), mean age 41 years, range 19–66 years *Quality*: B	FEV_1; PEFR am + pm; preference; exacerbation; hoarse voice	Other outcomes measured but only reported 'not significant'
Koskela *et al.*, 2000[55] Equivalence of two steroid-containing inhalers: Easyhaler multidose powder inhaler compared with conventional aerosol with large volume spacer Paper supplied by Orion Pharma by first author	*Design*: parallel, double-blind, double-dummy *Device*: Easyhaler (DPI) vs pMDI + spacer *Drug*: beclometasone *Dose*: 800 µg daily *Duration*: 8 weeks	*Participants*: 144 mild asthmatics (55 M, 89 F), mean age 43 years *Quality*: A	Clinic: FEV_1, FVC; cortisol; histamine PD_{15} Diary: PEFR am + pm, SGRQ, cough, wheeze, dyspnoea; hoarse voice, thrush; relief medication; exacerbation	

continued

TABLE 11 contd *Review A: study characteristics of included studies on the delivery of steroids in asthma for pMDI versus DPI*

Study	Methodology	Details	Results	Comments
Lal *et al*., 1980[46] Beclometasone dipropionate aerosol compared with dry powder in the treatment of asthma One author from, and materials supplied by Allen & Hanburys Research Ltd	*Design*: crossover, double-blind, double-dummy *Device*: Rotahaler vs pMDI alone *Drug*: beclometasone *Dose*: 200 vs 100 µg t.d.s. *Duration*: 2 x 4 weeks	*Participants*: 20 asthmatics (6 M, 14 F), median age 38 years, range 16–58 years *Quality*: B	FEV_1, FVC; PEFR am + pm; exacerbation; preference; *Candida*; cortisol	
Lundback *et al*., 1993[43] Evaluation of fluticasone propionate (500 µg/day) administered either as dry powder via a Diskhaler inhaler or pressurised inhaler and compared with beclometasone dipropionate (1000 µg/day) administered by pressurised inhaler Author for correspondence from Glaxo Group Research Ltd	*Design*: parallel, double-blind, double-dummy *Device*: Diskhaler vs pMDI (60% with spacer) *Drug*: fluticasone *Dose*: 500 µg daily *Duration*: 6 weeks	*Participants*: 391 asthmatics (208 M, 183 F), mean age 45 years, range 16–91 years *Quality*: B	FEV_1, FVC; PEFR am + pm; hoarse voice; *Candida*; preference; exacerbations; cortisol	Statistically significant differences between groups at baseline
Lundback *et al*., 1994[56] A comparison of fluticasone propionate when delivered by either the MDI or the Diskhaler inhaler in the treatment of mild-to-moderate asthma Author for correspondence from Glaxo Group Research Ltd	*Design*: parallel, double-blind, double-dummy *Device*: Diskhaler vs pMDI (30% with spacer) *Drug*: fluticasone *Dose*: 100 µg b.d. *Duration*: 4 weeks	*Participants*: 296 mild-to-moderate asthmatics (134 M, 162 F), median age 39 years, range 17–76 years *Quality*: B	FEV_1, FVC; PEFR am + pm; relief medication; hoarse voice, thrush; cortisol	
Morrison Smith & Gwynn, 1978[57] A clinical comparison of aerosol and powder administration of beclometasone dipropionate in asthma Allen & Hanburys Research Ltd for 'providing material' and 'numerical processing of the results'	*Design*: crossover, open *Device*: Rotahaler vs pMDI alone *Drug*: beclometasone *Dose*: 100 µg q.d.s. *Duration*: 2 x 4 weeks	*Participants*: 37 asthmatics (23 M, 14 F), mean age 14 years, range 7–25 years *Quality*: B	Symptom scores; relief medication; preference	40 patients initially included in the trial: 2 patients, aged 3 and 32, excluded for 'wide difference in age'
Nieminen & Lahdensuo, 1995[48] Inhalation treatment with budesonide in asthma: a comparison of Turbuhaler and MDI with Nebuhaler Contact with author was forwarded to Astra (Sweden); all data were held by Astra; randomisation and drug distribution was by Astra (not acknowledged in publication)	*Design*: crossover, open *Device*: Turbuhaler vs pMDI + spacer *Drug*: budesonide *Dose*: 400 µg b.d. *Duration*: 2 x 4 weeks	*Participants*: 24 patients with moderate to severe asthma (11 M, 14 F), mean age 43 years, range 20–65 years *Quality*: B	FEV_1, FVC; PEFR am + pm; symptoms; relief medication; hoarse voice; methacholine PD_{20}	

continued

TABLE 11 contd *Review A: study characteristics of included studies on the delivery of steroids in asthma for pMDI versus DPI*

Study	Methodology	Details	Results	Comments
Nieminen *et al.*, 1998[44] A new beclometasone dipropionate multi-dose powder inhaler in the treatment of bronchial asthma Two authors from Orion Pharma	*Design*: parallel, open *Device*: Easyhaler (DPI) vs pMDI + spacer *Drug*: beclometasone *Dose*: 400 µg b.d. *Duration*: 12 weeks	*Participants*: 133 asthmatics (49 M, 84 F), mean age 48 years, range 18–68 years; randomised 2:1 in favour of Easyhaler Quality: A	FEV_1, FVC; PEFR am + pm; symptom scores; exacerbation; relief medication; hoarse voice, thrush; cortisol; histamine PD_{15}	Statistically significant differences between groups at baseline
Poukkula *et al.*, 1998[58] Comparison of a multidose powder inhaler containing beclometasone dipropionate with a beclometasone dipropionate-MDI with spacer in the treatment of asthmatic patients Three authors (including corresponding author) from Orion Pharma and funded by Orion Pharma	*Design*: parallel, open *Device*: Easyhaler (DPI) vs pMDI +spacer *Drug*: beclometasone *Dose*: 500 µg b.d. *Duration*: 12 weeks	*Participants*: 144 moderate asthmatics (54 M, 94 F), mean age 46 years *Quality*: B	FEV_1, FVC; PEFR am + pm; symptom scores; exacerbation; relief medication; hoarse voice, thrush; cortisol; histamine PD_{15}	
Toogood *et al.*, 1997[59] Comparison of the antiasthmatic, oropharyngeal and systemic glucocorticoid effects of budesonide administered through a pressurised aerosol plus spacer or the Turbuhaler DPI Supported by a grant from Astra Pharm Inc	*Design*: parallel, open *Device*: Turbuhaler vs pMDI + spacer *Drug*: budesonide *Dose*: 0.4–2.4 mg/day increased each 2 weeks *Duration*: 8 weeks	*Participants*: 61 asthmatics (31 M, 30 F), mean age 54 years *Quality*: A	FEV_1, FVC; PEFR; symptom score; relief medication; cortisol	
Vidgren *et al.*, 1994a/b[41] Easyhaler powder inhaler – a new alternative in the anti-inflammatory treatment of asthma Two authors (including corresponding author) from Orion Pharma and funded by Orion Pharma	*Design*: 3-way, open, crossover *Device*: Easyhaler (DPI) vs Diskhaler vs pMDI + spacer *Drug*: beclometasone *Dose*: 800 µg daily *Duration*: 3 x 4 weeks	*Participants*: 20 asthmatics (5 M, 15 F), mean age 36 years, range 16–57 years *Quality*: A	FEV_1, FVC; PEFR am + pm; symptom scores; hoarse voice, thrush; cortisol; methacholine PD_{20}	

PD_{15}, dose of challenging drug required to cause a fall in FEV_1 of 15% (also PD_{20} etc.); SGRQ, St George's Respiratory Questionnaire

with additional laboratory assessment of lung function or blood parameters. Different inhaled steroids and different delivery devices, including different spacer devices, were used. Additionally, even between the same drug/device comparison, different studies have used a different dosage ratio.

Methodological quality of included studies

Overall, the methodological quality of the included studies was variable, with four scoring 'A' on the Cochrane scale, and the others scoring 'B' through lack of reporting of allocation concealment. Many studies did not comment on withdrawals and drop-outs, and also did not report whether intention-to-treat analysis was employed. The sample size of the studies was mixed. Of the 22 papers, eight had less than 50 participants, eight had 50–250 participants and six had more than 250 participants.

TABLE 12 *Review A: study characteristics of included studies on the delivery of steroids by CFC-free pMDIs*

Study	Methodology	Details	Results	Comments
Busse *et al.*, 1999[42] Efficacy response of inhaled beclometasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant	*Design*: 3 parallel arms, double-blind, double-dummy *Device*: HFA vs CFC pMDIs *Drug*: beclometasone *Dose*: 100, 400 and 800 µg daily arms *Duration*: 6 weeks	*Participants*: 109 asthmatics at 100 µg, 106 at 400 µg, 108 at 800 µg (117 M, 206 F) *Quality*: B	Change from baseline of FEV_1, FVC, $FEF_{25–75\%}$, PEFR, FEV_1 reversibility to beta-agonist; days free from wheeze, shortness of breath, cough or chest tightness; nights free from asthma-related symptoms; puffs of beta-agonist used per day	Estimated SD used for FEV_1 change 3 parallel arms used at each dose and 2:1 dose comparison (CFC 800 µg vs HFA 400 µg) used for total of 4 included studies
Dahl *et al.*, 1997[49] Equivalence of asthma control with new CFC-free formulation HFA-134a beclometasone dipropionate and CFC-beclometasone dipropionate Author for correspondence is from 3M	*Design*: Crossover, double-blind, double-dummy *Device*: HFA vs CFC pMDIs *Drug*: beclometasone *Dose*: between 200 and 600 µg daily at 1:1 dosing HFA:CFC *Duration*: 2 x 4 weeks	*Participants*: 68 asthmatics (59 M, 9 F), mean age 49 years *Quality*: B	Clinic: FEV_1 Diary card: PEFR, cough, wheeze, breathlessness; exacerbation; relief medication	
Damedts *et al.*, 1999[50] Switch to non-CFC-inhaled corticosteroids: a comparative efficacy study of HFA-beclometasone dipropionate and CFC-beclometasone dipropionate MDIs Author for correspondence is from 3M	*Design*: parallel, open, 3:1 randomisation, HFA:CFC *Device*: HFA vs CFC pMDIs *Drug*: beclometasone *Dose*: between 400 and 1600 µg daily; HFA treated at half CFC dose *Duration*: 8 weeks	*Participants*: 473 asthmatics (192 M, 281 F), mean age 40 years *Quality*: B	Change from baseline of PEFR, FEV and exacerbations	The primary outcome measure was PEFR. This was statistically different at baseline. Also, male/female distribution was statistically different between groups: CFC 43% and HFA 34% for males. PEFR was only extractable at 4 rather than 8 weeks (from a graph) The distribution of doses is also different: the paper describes < 500, 500–1000 and > 1000 µg groups (and the half 'equivalent' HFA dose). These three groups are distributed: CFC 54%, 41% and 5%; HFA 52%, 19%, 29%
Davies *et al.*, 1998[51] Hydrofluoroalkane-134a beclometasone dipropionate extrafine aerosol provides equivalent asthma control to chlorofluorocarbon beclometasone dipropionate at approximately half the total daily dose Author for correspondence is from 3M and the study published in a supplement sponsored by 3M	*Design*: parallel, double-blind, double-dummy *Device*: HFA vs CFC pMDIs *Drug*: beclometasone *Dose*: HFA 800 µg, CFC 1500 µg *Duration*: 12 weeks	*Participants*: 233 asthmatics (102 M, 131 F), mean age 40 years *Quality*: B	*No significant differences in*: Change from baseline of: PEFR; FEV_1; cough, wheeze, breathlessness; exacerbations; use of relief medication; oral thrush, hoarse voice	The SD estimated from graphs (unlabelled error bars) appeared unusually small (approximately 50 for PEFR and 0.15 for FEV_1) and therefore estimated values were used (90 and 0.9, respectively)

continued

TABLE 12 contd *Review A: study characteristics of included studies on the delivery of steroids by CFC-free pMDIs*

Study	Methodology	Details	Results	Comments
Gross *et al.*, 1999[52] Hydrofluoroalkane-134a beclometasone dipropionate 400 µg is as effective as chlorofluorocarbon beclometasone dipropionate 800 µg for the treatment of moderate asthma Author for correspondence is from 3M and the study was supported by a grant from 3M	*Design*: parallel, single-blind *Device*: HFA vs CFC pMDIs *Drug*: beclometasone *Dose*: 400 µg vs 800 µg daily *Duration*: 12 weeks	*Participants*: 347 moderate asthmatics (162 M, 185 F), mean age 33 years (3rd arm of 117 patients received HFA-placebo) *Quality*: B	Clinic: FEV_1 Diary: PEFR; relief medication; exacerbations; hoarse voice, oral thrush	
Jenkins, 1995[60] Clinical evaluation of CFC-free MDI Glaxo trial (in supplement to Aerosol Medicine)	*Design*: parallel, double-blind, double dummy *Device*: HFA vs CFC pMDIs *Drug*: fluticasone *Dose*: 250 µg b.d. *Duration*: 4 weeks	*Participants*: 381 mild-to-moderate asthmatics *Quality*: B	Hoarse voice, oral thrush; cortisol	Not a full paper but part of a description of data in several areas relating to development of HFA inhalers by GlaxoWellcome
Milanowski *et al.*, 1999[40] Inhaled beclometasone with non-CFC propellant (HFA 134a) is equivalent to beclometasone dipropionate-CFC for the treatment of asthma Sponsored by Norton Healthcare Ltd	*Design*: parallel, double-blind *Device*: HFA vs CFC pMDIs *Drug*: beclometasone *Dose*: study (a): 100 µg q.d.s.; study (b): 500 µg q.d.s. *Duration*: study (a): 6 weeks; study (b): 12 weeks	*Participants*: Study (a): 119 asthmatics (67 M, 52 F), mean age 38 years Study (b): 119 asthmatics (54 M, 65 F), mean age 44 years *Quality*: B	FEV_1 PEFR; oral thrush	Other outcomes measured but not reported suitably for meta-analysis

Results

A total of 784 abstracts were identified from the electronic search, of which 33 were selected for possible inclusion in the review. Six further abstracts were identified from the references in the included studies and one study, which was in press, was supplied by a pharmaceutical company in response to a request. The full text of each paper was obtained.

Papers were excluded for the following reasons (*Table 13*):

- six studies evaluated the steroid inhaler device against placebo, different inhaled steroid or mixed inhaled steroid and bronchodilator delivery
- five studies were comparisons of only one inhaler device or did not allow separate analysis of the individual devices used
- one study was a duplicate publication (acknowledged in the second journal)
- one was a review article only.

A total of 22 papers were included for this review. These described 26 studies: Milanowski and colleagues 1999a[40] and Milanowski and colleagues 1999b[40] were two separate trials and Vidgren and colleagues 1994a[41] and Vidgren and colleagues 1994b[41] were parts of a three-way crossover trial. Busse and colleagues[42] had three parallel arms and a dose comparison arm.

The studies were reviewed in three categories:

- DPI versus pMDI
- HFA-pMDI versus pMDI
- BA-pMDI versus pMDI.

Data were extracted and outcomes were combined by meta-analysis.

Dry powder inhalers versus pMDI ± spacer

A total of 14 papers[38,41,43–48,54–59] describe 15 studies (considering the three-way crossover of Vidgren and colleagues 1994a/b[41] as separate studies). In all, 15 outcomes were available for analysis with a

TABLE 13 *Review A: delivery of corticosteroids in stable asthma – exclusions*

Study	Reason for exclusion
Agertoft & Pedersen, 1994[61]	Presentation of the same data published earlier as 'Agertoft 1993'
Bjorkander *et al.*, 1982[62]	Comparison of pMDI vs pMDI + spacer only, and comparing different drugs
Gleeson & Price, 1988[63]	Investigation of a spacer only and comparison against placebo
Liljas *et al.*, 1997[64]	Economic evaluation comparing steroid and/or bronchodilator administration by pMDI vs DPI
Matthys *et al.*, 1998[65]	HFA inhaler vs placebo
Mitfessel, 1997[66]	Post-marketing surveillance; no pMDI/DPI comparison
Pauwels *et al.*, 1996[67]	Comparisons with beta-agonist and corticosteroid in the same trial
Pedersen *et al.*, 1994[68]	Review article only
Petro *et al.*, 1996[69]	Open study of Turbohaler only
Selroos & Halme, 1991[34]	Beclometasone compared with budesonide via the two devices
Shapiro *et al.*, 1988[70]	Dose ranging study of DPI only; no device comparison
Town *et al.*, 1994[71]	Autohaler vs DPI; no comparison with a standard pMDI
Uhde, 1997[72]	Post-marketing surveillance; no pMDI/DPI comparison
Vidgren *et al.*, 1995[73]	Found from citation list; only considers salbutamol delivery

range of three to 14 studies for each outcome. No outcomes other than patient preference showed any evidence of heterogeneity within the included studies. A fixed effects model was therefore used throughout.

The DPI has a statistically significant benefit in improvement of FEV_1 compared with pMDI + spacer: 0.11 litres/second (95% CI, 0.01 to 0.21); or as the SMD of FEV_1 versus pMDI combined with and without spacer: 0.12 litres/second (95% CI, 0.02 to 0.21). No benefit is shown in other comparisons (FEV_1, DPI versus pMDI without spacer, or the SMD of FEV_1 with and without spacer separately). If parallel and crossover studies are considered separately, only the SMD of FEV_1 for parallel studies of DPI versus pMDI ± spacer remains significant: 0.12 litres/second (95% CI, 0.01 to 0.22).

The DPI is statistically more effective than the pMDI + spacer in improving morning PEFR: 12.4 litres/minute (95% CI, 1.8 to 23.1); and the SMD of PEFR for the pMDI + spacer and pMDI ± spacer combined: 0.13 (95% CI, 0.03 to 0.22). These differences persist for parallel studies but not for crossover studies. These results are statistically significantly different. However, the results are within clinically acceptable differences of ± 30 litres/minute, as defined in previous studies.

Statistically significant differences were apparent in the baseline characteristics of three of the studies.[38,43,44]

Drepaul and colleagues[38] have characteristics that favour the pMDI at baseline, with a PEFR of 332 and 314 litres/minute for the pMDI and DPI groups, respectively. This is not statistically significant ($p = 0.19$), but significant differences exist for day and night symptom scores and use of relief medication ($p = 0.03$, 0.01 and 0.004 respectively), showing the pMDI group as less severe. This paper only presents results as absolute change from baseline. The more severe DPI group has greater 'room for improvement' and this method of presentation of results would tend to favour the DPI in this instance.

Lundback and colleagues[43] have a mean morning PEFR of 362 and 386 litres/minute for the pMDI and DPI groups, respectively. Even using a conservatively large estimated SD of 100 (this was not available from the paper and no reply was received from contact with the author), this is a significant difference ($p = 0.018$; two-tailed t test).

Nieminen and colleagues[44] have a mean morning PEFR of 466 and 487 litres/minute and a mean FEV_1 of 2.84 and 3.10 litres/second for the pMDI and DPI groups, respectively. This is not significant for PEFR ($p = 0.18$; two-tailed t test) but is for FEV_1 ($p = 0.05$). These latter two studies, with less severe baseline characteristics for the DPI groups, presented the results as absolute values, and again this method of result presentation favours the DPI.

Two methods were used to explore the impact of these baseline differences. First, exclusion from analysis was considered. Excluding Lundback and colleagues[43] or Nieminen and colleagues[44] from analysis results in no significant treatment effects for any of the FEV_1 or PEFR comparisons. Drepaul and colleagues,[38] presenting results as 'change from baseline', necessitates using SMD. Excluding Drepaul and colleagues[38] alone results in no significant treatment effect for the SMD of the FEV_1.

Secondly, analysis was performed using the alternative presentation of results, that is change from baseline for Lundback and colleagues[43] and Nieminen and colleagues,[44] and absolute values for Drepaul and colleagues[38] (using estimates as necessary based on the original data). No statistically significant differences were found in treatment effect for any of the comparisons of FEV_1 or PEFR. This is illustrated graphically for the SMD of FEV_1 in *Figure 2* for the original data and *Figure 3* for the alternate analysis.

Use of additional relief medication as SMD shows a treatment effect in favour of DPI versus pMDI with and without spacer combined: –0.15 (95% CI, –0.26 to –0.03). As described above,

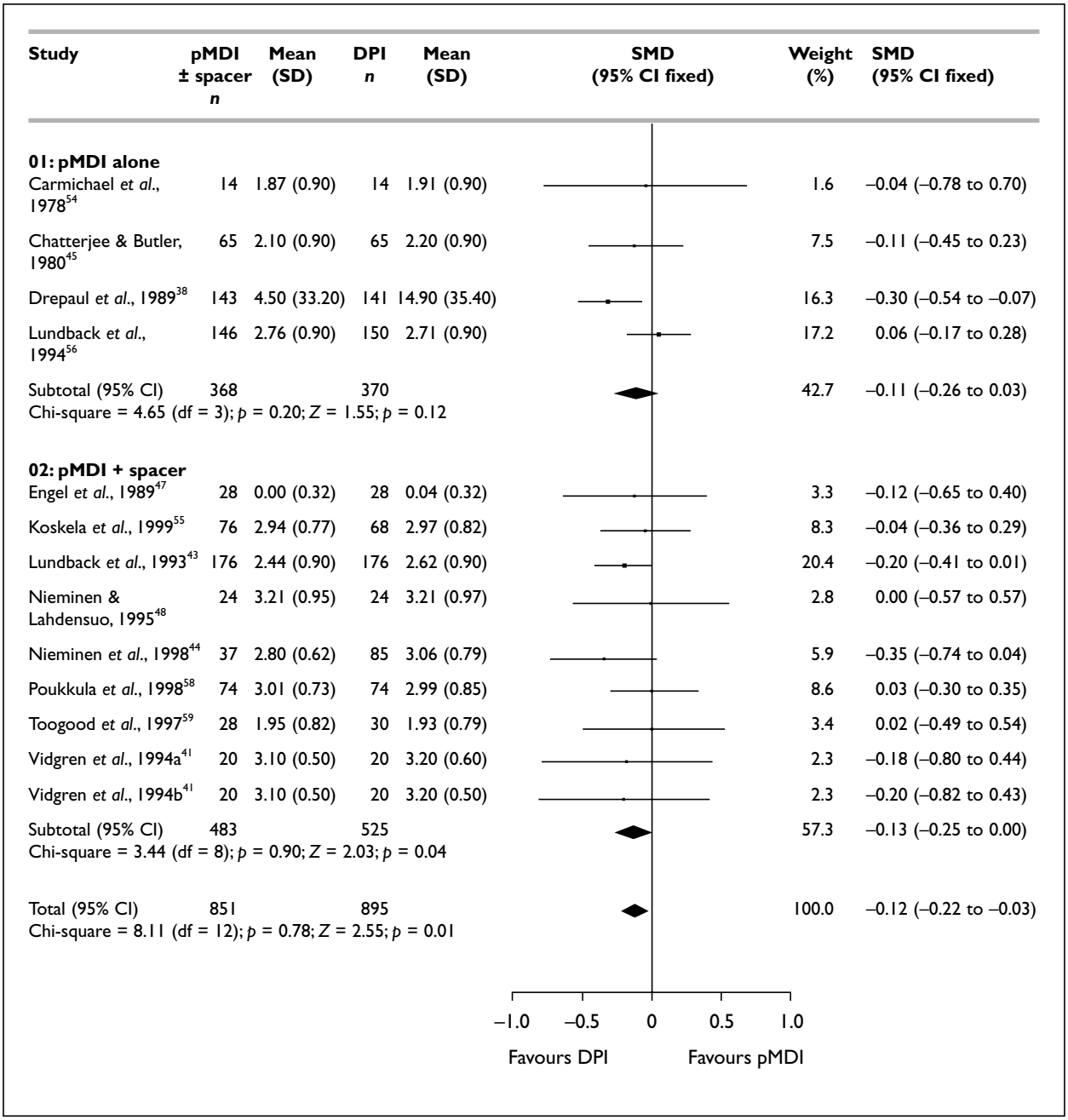


FIGURE 2 *Dry powder devices versus pMDI ± spacer: SMD of FEV_1 – original analysis*

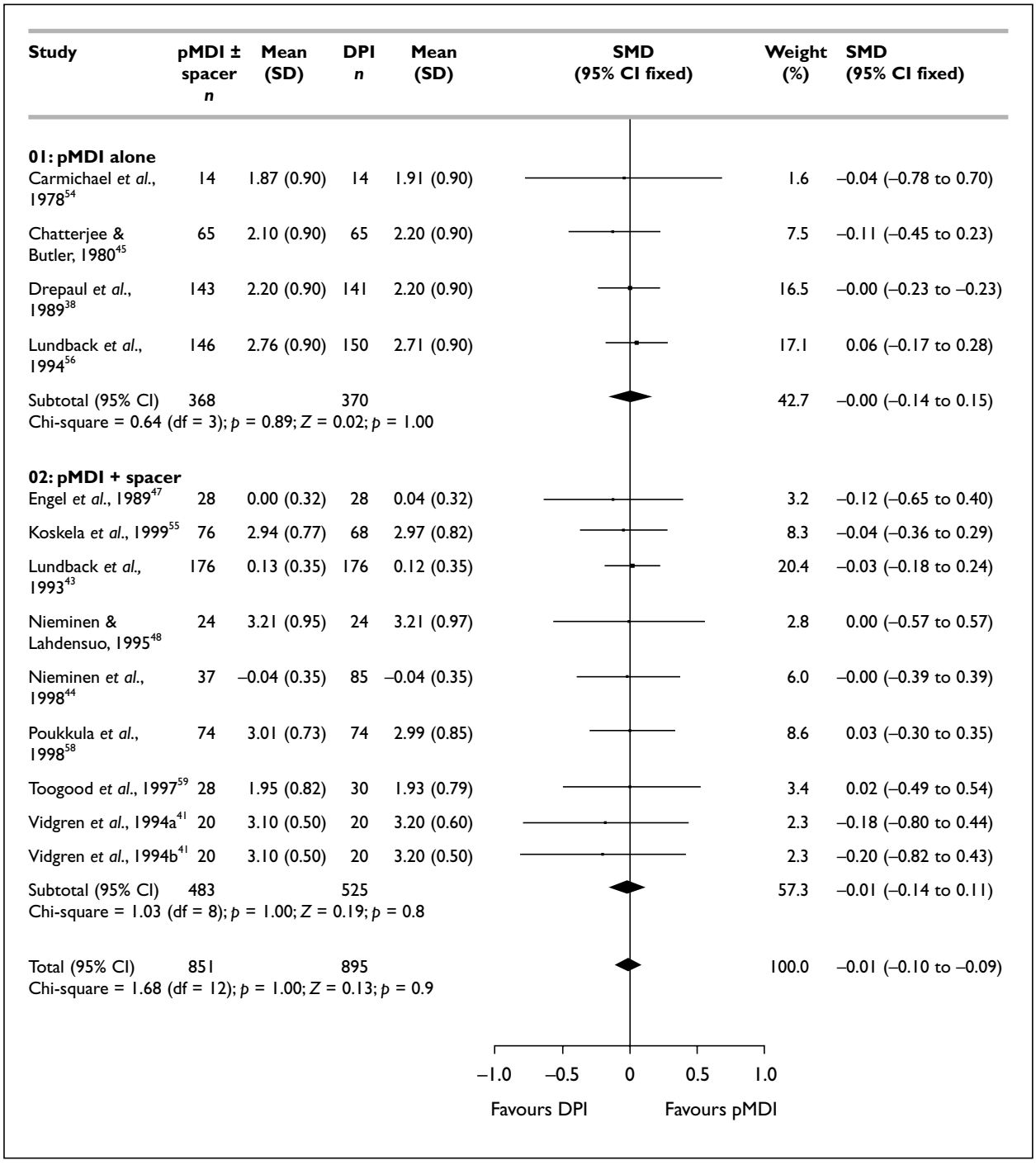


FIGURE 3 *Dry powder devices versus pMDI ± spacer: SMD of FEV_1 – alternative analysis*

Drepaul and colleagues[38] showed a statistically significant baseline difference between the groups ($p = 0.004$) in favour of the pMDI, and this outcome was analysed in terms of change from baseline. If an estimate is made for absolute values and these are included, there is no significant treatment effect.

Other important outcomes analysed show no significant treatment effects for DPI versus pMDI ± spacer. Overall symptom score: SMD 0.03 (95% CI, –0.10 to 0.17); exacerbation numbers: relative risk (RR) 0.91 (95% CI, 0.55 to 1.51); cortisol levels: 8.6 nmol/litre (95% CI, –45 to 62); provocation testing with histamine or methacholine, PD_{15} or PD_{20}: 101 mg (95% CI, –165 to 368); occurrence of hoarse voice or oral thrush: RR 1.04 (95% CI, 0.83 to 1.29) and RR 1.19 (95% CI, 0.84 to 1.70), respectively. These results are for all DPI versus pMDI ± spacer but also hold true for the pMDI

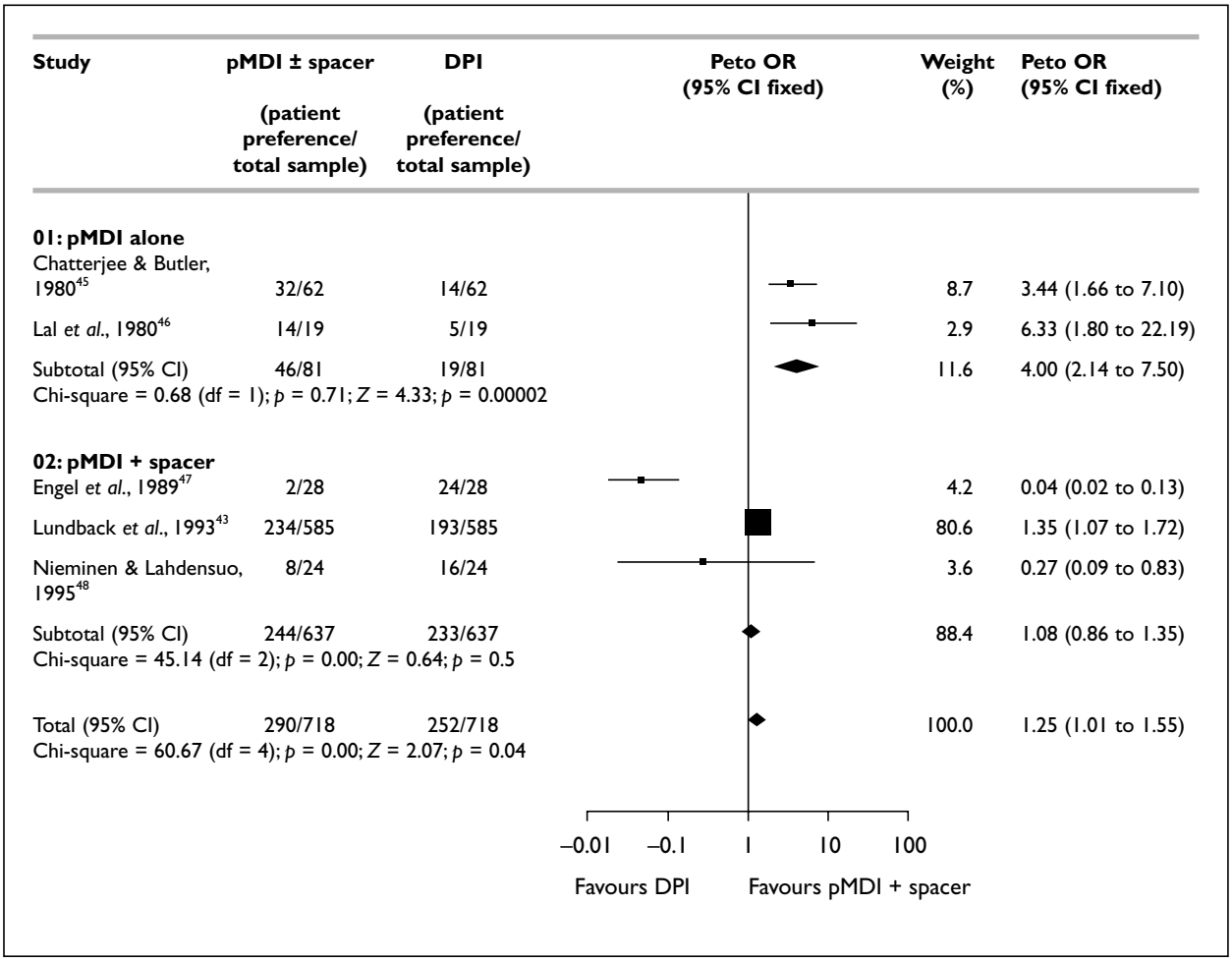


FIGURE 4 *Dry powder devices versus pMDI ± spacer: patient preference – DPI versus pMDI*

with and the pMDI without spacer or considering crossover and parallel studies separately.

Patient preference for a DPI over pMDI shows marked heterogeneity, which is demonstrated best graphically (*Figure 4*).

The heterogeneity is largely explained by examination of the DPI type within each study. Chatterjee and Butler[45] and Lal and colleagues[46] used a Rotahaler, which was statistically significantly less preferred than the pMDI alone, and of 81 patients 19 preferred the Rotahaler and 46 preferred the pMDI. Engel and colleagues[47] and Nieminen and Lahdensuo[48] used the Turbuhaler, which was significantly preferred to the pMDI, and of 52 patients 40 preferred the Turbuhaler and 10 preferred the pMDI. Lundback and colleagues[43] used a Diskhaler, which showed no overall preference, and of 585 patients 193 preferred the Diskhaler and 234 preferred the pMDI. Patient preference, as assessed within such studies, needs to be viewed with some caution as there is much scope for bias. It should also be noted that, with the exception of Lundback and colleagues,[43] the numbers assessed are small.

Individual DPI devices may be different within the group and combined analysis may not be appropriate. Analysing FEV_1, PEFR or hoarse voice (other outcomes do not have enough data to warrant subgroup analysis) by the different types of DPI (Rotahaler, Turbuhaler, Diskhaler and Easyhaler®) does not, however, show any significant differences in treatment effect or any evidence of heterogeneity.

HFA (CFC-free)-pMDI versus CFC-pMDI

A total of 11 studies are available[40,42,49–52,60] (Milanowski and colleagues 1999a/b[40] are two separate dose studies within one paper; Busse and colleagues[42] had three parallel arms of which two were combined to produce a dose comparison). In all, ten studies have data for FEV_1 and morning PEFR; seven have data for use of relief medication; six have data for oral thrush; and three have data

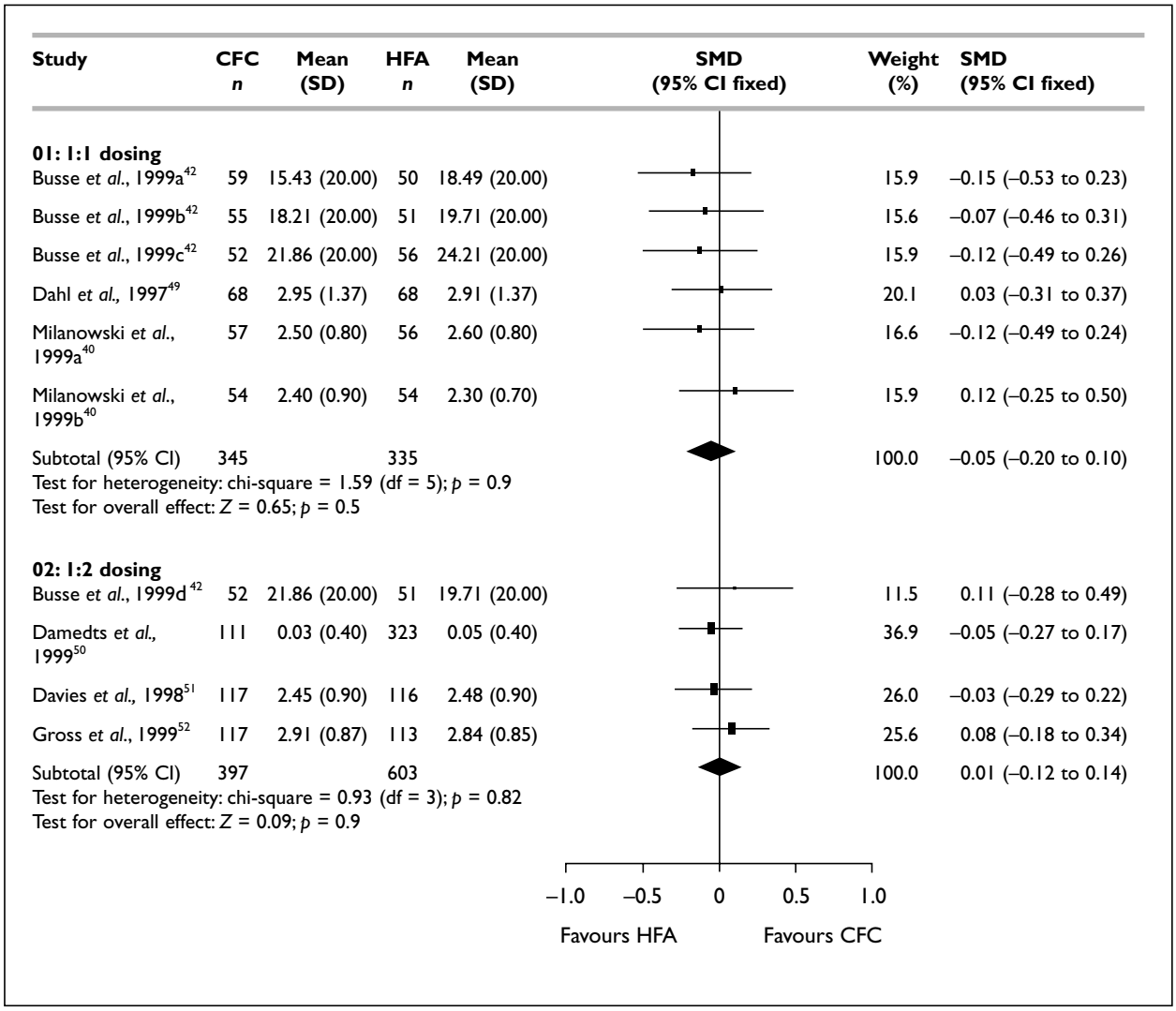


FIGURE 5 *Beclometasone HFA versus CFC inhalers: SMD of FEV_1 – 1:1 and 1:2 dosing treatment effects*

for hoarse voice and exacerbations. The studies are predominantly comparing beclometasone: ten of the 11 studies used this drug and the remaining study used fluticasone. Only one trial[49] is of cross-over design and there is no evidence of statistical heterogeneity for all trials or considering parallel versus crossover design, and therefore a fixed effects model was used throughout and the results below relate to the parallel/crossover totals.

Three of these studies[40,49] use a 1:1 dosing schedule between HFA and CFC inhalers whilst Damedts and colleagues,[50] Davies and colleagues[51] and Gross and colleagues[52] use a 1:2 dosing schedule. Busse and colleagues[42] use three different dose parallel arms at 1:2 dosing and also allow analysis at 1:1 dosing. Using 1:1 and 1:2 dosing as subgroups, analysis shows no significant difference in treatment effects for any outcome, or any difference between the two dosage ratios. For the SMD of FEV_1 the results are –0.05 (95% CI, –0.20 to 0.10) and 0.01 (95% CI, –0.12 to 0.14) for 1:1 and 1:2 dosing respectively (*Figure 5*). For the SMD of PEFR the results are 0.02 (95% CI, –0.13 to 0.17) and –0.09 (95% CI, –0.22 to 0.04) for 1:1 and 1:2 dosing respectively. For the SMD for the use of additional relief medication the results are –0.13 (95% CI, –0.31 to 0.05) and 0.05 (95% CI, –0.12 to 0.21) for 1:1 and 1:2 dosing respectively.

Adverse events (oral thrush and hoarse voice) show no difference between treatments but owing to the low incidences, 80/701 (of which 63/236 are from the high-dose Milanowski and colleagues' 1999b[40] study) and 27/843 cases respectively, the CIs are very wide. Oral thrush: RR 0.79 (95% CI, 0.57 to 1.10) and 0.51 (95% CI, 0.05 to 5.56) for 1:1 and 1:2 dosing, respectively; hoarse voice: RR 1.22 (95% CI, 0.54 to 2.79) available for 1:2 dosing only.

BA-pMDI versus pMDI
Only one study[53] using such a device was identified and included. This used an 'equivalence model' design (that the 90% CI for the difference between the inhalers falls completely within the reference device (pMDI) mean response interval –20% to + 20%). Using this method, clinic and home pulmonary function, symptom scores and relief medication usage showed equivalence. Using the data within a usual treatment effect with 95% CI, again there were no significant differences. It should be noted that the power calculations are different (requiring less numbers) for the former 'equivalence' design of trial.

Discussion

The findings suggest that for measures of pulmonary function, symptom scores, exacerbation rates and adverse effects such as hoarse voice, oral thrush and effects on the hypothalamic-adrenal axis (at least as evidenced by serum cortisol), there is no difference in clinical efficacy between a pMDI with or without spacer and a DPI, or between a pMDI and a CFC-free (HFA) pMDI in adults for the delivery of corticosteroids. Although in the case of DPI versus pMDI statistically significant differences are present, these are either within clinically equivalent limits, and/or the differences are not apparent once baseline characteristics are taken into account. For pMDI versus BA-pMDI the evidence is limited to one study.

A strength of the analyses produced in this review is the narrowness of the CIs produced either side of no overall treatment effect. A common method of design for showing equivalence is to show that the new treatment is ± 20% of the reference treatment or that the 90% CI lies entirely within predefined clinically acceptable limits for equivalence. Alternatively, the 90% CI of the two treatments are shown to overlap.

Limitations of the analysis are related to a number of factors. All of the studies in this review had some degree of commercial sponsorship. Research teams may not therefore have been in a position of equipoise, and potential biases in the conduct and reporting of results are important to consider. Certain potentially biasing factors are discussed immediately below.

Measuring change in parallel studies
The results of many tests of pulmonary function can be presented in various ways: predominantly as absolute values or as a change from baseline (may be absolute or relative). This may be a source of bias. In the DPI versus pMDI comparison, three studies had statistically significant differences at baseline. As discussed in the 'Results' section (page 24), the choice of measurement used was critical to the outcome of not only the individual studies but also the meta-analysis.

Crossover versus parallel design
A recognised problem in combining trials for meta-analysis is that of the difference between crossover and parallel trials. The distribution in the included studies is ten crossover and 15 parallel. Of the ten crossover studies none describes a washout period between the arms, and this may have introduced bias, especially for inhaled corticosteroids which have a long duration of action. Five of the ten studies did describe tests for carry-over effect or combination within an analysis of variance model but no statistically significant effects were stated. Also, the meta-analysis within the RevMan 4.0.4 program can only treat data if it were unpaired or parallel. The analysis was therefore performed separately for crossover and parallel studies. Sensitivity analysis shows no difference between the SMD of FEV_1 treatment effect of crossover and parallel studies (–0.06; 95% CI, –0.22 to 0.11 and –0.07; 95% CI, –0.15 to 0.02, respectively) and no differences were found in individual comparisons and outcomes as detailed in the 'Results' section. First arm data only can be used as a parallel trial but this was not available in any papers. Crossover data can be analysed with appropriate weighting if a measure of error can be supplied or derived for the change of individual patient response. Whilst the study may be analysed for paired data, in almost all cases the error presented relates to group mean data.

Doses used
Although it has been difficult to demonstrate clinically, inhaled corticosteroids will have a dose–response curve, albeit shallow.[28] Dose selection for a study may have an important role in the ability of a trial to detect differences between inhaler devices, should they exist. The majority of asthmatic patients require relatively low doses of inhaled steroids to maintain good health (approximately 200–800 µg of beclometasone daily, that is low to moderate doses on Step 2 of the British Thoracic Society asthma guidelines[1]).
In the 20 adult studies with set dosage regimes, the distribution was (assuming fluticasone as twice the equivalent dose of budesonide or beclometasone): 400 µg daily, six studies; 600 µg daily, four studies; 800 µg daily, five studies; 1000 µg daily or greater, five studies. The doses used tend not to reflect usual clinical practice and using high doses at the top of the dose–response curve

may bias towards underestimating or missing a treatment difference, if one exists. Doses used also need to be considered in the context of disease severity discussed below.

Disease severity
The less severe the disease, the less medication is needed and potential improvements in pulmonary function and symptoms from baseline will be smaller. Clinical trials will tend to recruit patients with more stable and less severe disease, as shown by the low numbers of exacerbations (69 cases from 2065 patients) in the studies that even report numbers, and the very low mean symptom scores or use of additional relief medication, usually less than two puffs/day. In studies reporting FEV_1 at baseline, the mean FEV_1 was 2.60 litres (SD 0.42). Seven of the ten trials reporting a severity grade of asthma at baseline were mild or mild to moderate. Overall, the study populations appear to have relatively mild asthma. Whilst this probably reflects 'usual' disease in the general population, it will tend towards not showing a treatment effect between inhaler devices, should one exist (type II error).

Duration
Inhaled corticosteroids have a long duration of action and may take weeks to months to reach a plateau of effect. The British Thoracic Society asthma guidelines1 suggest titrating doses at intervals of 1–3 months. The longest study is of 12 weeks duration; 11 studies are of 4 weeks duration; seven of 6–9 weeks duration; and five of 12 weeks duration. As the duration becomes shorter, there is an increasing risk of missing a treatment difference, if one exists, because the treatment may have failed to reach its maximum effect.

HFA:CFC dose ratio
Many of the individual studies appear to have adequate design and power to show equivalence. However, when, as above, the studies are analysed as subgroups based on the HFA:CFC dose ratio being 1:1 or 1:2, then there is no significant difference seen between the two groups (*Figure 5*). Each group of studies (and subsequently marketing and prescribing recommendations) claims that their dose ratio is the correct one. This current analysis is unable to distinguish between them. Indeed, Dahl and colleagues[49] at 1:1 and Damedts and colleagues,[50] Davies and colleagues[51] and Gross and colleagues[52] at 1:2 dosing are the same preparation from the same company. On a practical level, a prescription for HFA beclometasone 400 µg daily can be dispensed as either of two 'equivalent' preparations. However, one will be accompanied by advice that it is twice as potent as the other. Under ideal clinical practice this should not make too much difference because doses will be titrated to individual response. In the transfer from CFC to HFA inhalers there is potential for significant confusion.

REVIEW B: delivery of ß$_2$-agonist bronchodilators from the pMDI versus other inhaler devices in stable asthma

Results in children
A total of 11 studies[74–84] were found comparing the pMDI with other inhaler devices for inhaled beta-agonist drugs. Characteristics are detailed in *Table 14*.

Seven studies[74–80] compared the pMDI with the Turbuhaler. No significant difference was found in the following outcomes: FEV_1, FVC, HR, $FEF_{25–75\%}$, BP, Raw (airways resistance), PEFR and VTG. Ahlström and colleagues[80] reported significantly ($p = 0.046$) higher morning PEFR values in comparison with the pMDI group; however, the baseline evening PEFR was significantly ($p = 0.03$) higher in the Turbuhaler group compared with the pMDI group.

Two studies[81,82] compared the pMDI with the Rotahaler. No significant difference was found in the following measured outcomes: FEV_1, FVC, $FEF_{25–75\%}$, PEFR, HR, BP, dropout rate or asthma symptom scores. In the long-term study[81] (12 weeks), the number of acute exacerbations requiring medical intervention was significantly higher in the pMDI group.

One study[83] compared HFA (CFC-free) inhalers with the CFC-pMDI. No difference in measured FEV_1 was found. One study[84] compared a device called an Italseber with the pMDI and found a significant difference ($p < 0.05$) in the overall mean percentage predicted PEFR over a 5-hour period after administration of a bronchodilator. Attempts to find out what this device is from the authors and the sponsor company were unsuccessful.

The above-mentioned studies (*Table 14*)[74–84] were at a 1:1 dosing schedule. The drug deposition review[39] reported the following ranges for lung deposition: pMDI alone, 10–20%; pMDI + spacer, 20–30%; Rotahaler, 10%; Turbuhaler, 20–35%. Prescribing recommendations[32,33] for salbutamol

TABLE 14 *Review B: details of 11 RCTs in children*

Study	Methodology	Details	Results	Comments
Ahlström *et al.*, 1989[80] Medical Hospital, Sweden	*Design*: open, randomised, crossover study *Device*: Turbuhaler vs MDI + Nebuhaler *Drug*: terbutaline *Dose*: 0.5 mg q.d.s. (both devices) *Duration*: 14 days	*Participants*: 21 children (7 F), age range 2–5 years, mean age 3.9 years PEFR measured 15 minutes 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 β_2 medication *Significant difference in*: Morning PEFR favouring Turbuhaler over pMDI + Nebuhaler (p = 0.046)	PEFR result to be treated with caution as evening baseline PEFR was significantly (p = 0.03) higher in the Turbuhaler group
Bronsky *et al.*, 1995[82] Medical Research Centre, Utah Supported by Glaxo Research Institute	*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 180 µg vs Rotahaler 200 µg *Duration*: 51 minutes	*Participants*: 44 children, age range 4–11 years, mean age 8 years Pulmonary function test performed up to 51 minutes after taking the drug and running on a treadmill for 6 minutes at pre-determined target rates (85% of HRmax). Study also reported 15 minutes post-dose FEV_1 (i.e. pre-exercise) *Study quality*: Cochrane B	*No significant differences in*: Pre- and post-exercise FEV_1 after drug administration	Study used exercise challenge to show that the two devices are equally effective against EIA
Chambers *et al.*, 1980[84] Christchurch Hospital, New Zealand	*Design*: randomised, double-blind, double-dummy, crossover study *Device*: Italseber® vs pMDI *Drug*: fenoterol *Dose*: 200 µg (both devices) *Duration*: 5 h	*Participants*: 13 children (7 F), age range 6–12 years, mean age 8.7 years PEFR test performed up to 5 h post-dose *Study quality*: Cochrane B	*Significant differences in*: Overall mean % predicted PEFR of over 5 h in duration post-bronchodilator (p < 0.05) using 2-way ANOVA favouring DPI	Device does not appear to be in current use; unable to determine further details after contact with author and sponsor company
Custovic *et al.*, 1995[83] Department of Paediatrics, Manchester, UK; also has involvement with Glaxo 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*: 200 µg (both devices) *Duration*: 30 minutes	*Participants*: 25 children, age range 6–14 years, mean age 10 years Pulmonary function test performed 30 minutes 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}	

continued

TABLE 14 contd *Review B: details of 11 RCTs in children*

Study	Methodology	Details	Results	Comments
Fuglsang & Pedersen, 1989[79] AstraZeneca, Sweden	*Design*: single-blind, double-dummy, crossover study; used computer-generated schedule *Device*: Turbuhaler vs pMDI alone *Drug*: terbutaline *Dose*: 2.0 mg (both devices) *Duration*: cumulative dosing study, giving a total dose of 2.0 mg within 80 minutes	*Participants*: 13 children (3 F), age range 7–15 years, mean age 10.5 years Pulmonary function testing done 15 minutes post-dose *Study quality*: Cochrane B	*No significant differences in*: FEV_1, $FEF_{25–75\%}$, PEFR or FVC *Significant differences in*: HR when using pMDI but not with Turbuhaler. More children complained of tremor in the pMDI group (7) than in the Turbuhaler group (0)	
Hirsch *et al.*, 1997[74] German Medical Hospital	*Design*: randomised, double-blind, double-dummy, parallel study, used drawing lots *Device*: Turbuhaler vs pMDI alone *Drug*: terbutaline *Dose*: 0.5 mg (both devices) *Duration*: 10 minutes	*Participants*: 118 children, age range 8–15 years, mean age 11.3 years Pulmonary function testing done 10 minutes post-dose *Study quality*: Cochrane A	*No significant differences in*: Change from baseline FEV_1 and FVC *Significant differences in*: $V_{max50\%}$ favouring pMDI	
Hultquist *et al.*, 1989[76] AstraZeneca, Sweden	*Design*: randomised, double-blind, double-dummy, crossover study *Device*: Turbuhaler vs pMDI alone *Drug*: terbutaline *Dose*: 0.5 mg + prn (both devices) *Duration*: 2 weeks	*Participants*: 57 children, age range 6–18 years, mean age 11 years PEFR was measured 10 minutes post-dose *Study quality*: Cochrane B	*No significant differences in*: PEFR (am and pm) and symptom scores *Significant differences in*: Preference for device where more children preferred the Turbuhaler (49%) than the pMDI (23%)	

continued

TABLE 14 contd *Review B: details of 11 RCTs in children*

Study	Methodology	Details	Results	Comments
Kemp *et al.*, 1989[81] Asthma Research Centre, USA	*Design*: 2 separate studies reported (a) randomised, double-blind, double-dummy, crossover study using 2 doses: 100 and 200 µg on separate days; and (b) a parallel run study using 200 µg q.d.s. for 12 weeks; used computer-coded treatment *Device*: Rotahaler vs pMDI alone *Drug*: salbutamol *Dose*: (a) 90–100 µg and 180–200 µg; and (b) 180–200 µg *Duration*: (a) 360 minutes and (b) 12 weeks	*Participants*: (a) 30 children, mean age 9.4 years Lung function measured from 5 to 360 minutes post-dose *Study quality*: Cochrane A *Participants*: (b) 204 (164 F) children, age range 4–11 years, mean age 8.2 years Lung function measured from 5 to 480 minutes post-dose *Study quality*: Cochrane A	(a) *No significant differences in*: FEV_1, HR or BP (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%) in the Rotahaler group ($p < 0.05$)	Analyses of baseline mean FEV_1 (using unpaired two-tailed *t* test) showed that the pMDI group had significantly lower FEV_1 when compared to the Rotahaler group. This may explain the higher rate of acute exacerbations seen in the pMDI group
Laberge *et al.*, 1994[75] Department of Pediatrics, Quebec, Canada	*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 2.0 mg within 80 minutes then followed by 5 mg of nebulised salbutamol	*Participants*: 10 children, age range 3–6 years, mean age 4.6 years Lung function measured 15 minutes after each dose of medication *Study quality*: Cochrane A	*No significant differences in*: HR, BP, tremor or airways resistance	
Razzouk *et al.*, 1999[77] AstraZeneca, Sweden	*Design*: randomised, double-blind, double-dummy, crossover study *Device*: Turbuhaler vs pMDI alone *Drug*: salbutamol *Dose*: 100 µg (both devices) *Duration*: 240 minutes	*Participants*: 40 children (9 F), age range 6–12 years, mean age 9 years Pulmonary function testing performed from 15 to 240 minutes post-dose *Study quality*: Cochrane B	*No significant differences in*: Geometric means of mean FEV_1 and FEV_{1max} Study also used Turbuhaler 50 µg vs Turbuhaler 100 µg and pMDI 100 µg, showing no significant differences	

continued

TABLE 14 contd *Review B: details of 11 RCTs in children*

Study	Methodology	Details	Results	Comments
Svenonius *et al.*, 1994[78] Astra Draco AB, Lund, Sweden	*Design*: randomised, double-blind, double-dummy, crossover study; exercise challenge used *Device*: Turbuhaler vs pMDI alone *Drug*: terbutaline *Dose*: 1 mg (both devices) *Duration*: 15 minutes	*Participants*: 12 children (2 F), age range 9–17 years, mean age 13.8 years Lung function measured before exercise then drug administered and measured again up to 15 minutes post-dose to observe reversibility of EIA *Study quality*: Cochrane B	*No significant differences in*: FEV_1 and VTG	

EIA, exercise-induced asthma; HR, heart rate; ANOVA, analysis of variance; $V_{max50\%}$, maximum flow at 50% of expiration (similar to $FEF_{25-75\%}$); BP, blood pressure; VTG, volume of trapped gas – a measure of small airways obstruction

suggest 100–200 µg by pMDI and 200–400 µg by the Rotahaler; for terbutaline, 250–500 µg by pMDI and 500 µg by Turbuhaler. Therefore, the above 1:1 dosing studies would tend to favour the Turbu-haler over the pMDI and may disadvantage the Rotahaler when compared with the pMDI.

Results in adults

All of the studies included in this review were of good quality, with most scoring at least a 'B' grade or higher when using the Cochrane allocation concealment grading and greater than '3' when using the Jadad[85] five-point scoring system for study quality. Four of the included studies[86–89] were reported as abstracts and were therefore devoid of substantial details for critical appraisal. Many of the included studies were designed as comparative trials with null hypothesis of bioequivalence (equal efficacy).

The electronic search yielded 1123 citations: 33 references were found in EMBASE, MEDLINE, CINAHL and online respiratory journal databases; 1063 citations came from the Airways Group register. Additionally, 27 references were added from bibliographic searching of relevant articles and electronic databases listing clinical trials. Of a total of 1123 abstracts, 180 were identified as comparing the pMDI with a DPI or a CFC-free or HFA-pMDI. Two reviewers agreed that 180 of these abstracts were potentially suitable for inclusion. On scanning the full text of the 180 studies, the first reviewer excluded 66 of the studies (reasons explained in 'Characteristics of excluded studies', *Table 15*). Of the remaining 114 studies, 24 were excluded by at least two reviewers and 81 studies were included in the review (with nine studies being duplicate publications of studies already included). Characteristics of all excluded and included studies can be found in *Tables 15* and *16*.

The result for each outcome measured is reported as overall effects of the pMDI versus each hand-held inhaler device separately.

The outcome measures that were not significantly different ($p \geq 0.05$) are presented in *Table 17*. An example of a non-significant meta-view analysis (Forrest plot: when the overall weighted mean value 'black diamond' crosses the line of no effect) is shown in *Figure 6*.

In summary, most of outcomes in this review were not significantly different when the standard pMDI was compared with any of the DPI or HFA-pMDI devices. These non-significant outcomes included: FEV_1, FVC, PEFR, AUC-FEV_1, BP, symptoms, bronchial hyperreactivity, systemic bioavailability, inhaled steroid requirement, serum K+ and β_2-agonist bronchodilator usage.

Significant differences ($p \leq 0.05$) in the absence of heterogeneity were found in the following outcome measures.

Rotahaler

Two long-term crossover studies[90,91] reporting preference for inhaler device showed that patients preferred the pMDI more than three times more frequently when compared with the Rotahaler: odds ratio (OR) 3.45 (95% CI, 1.67 to 7.13; $p = 0.0008$). When data from these two long-term studies were combined with those from a short-term crossover study[92] it showed

Text continues on page 63

TABLE 15 *Review B: characteristics of excluded studies*

Study	Reason for exclusion
Agertoft & Pedersen, 1994[122]	Study used budesonide and not a bronchodilator
Avital & Springer, 1995[123]	Salbutamol vs placebo using pMDI with Babyhaler® and face mask measured against methacholine-induced bronchoconstriction
Battistini *et al*., 1997[124]	Comparison of Autohaler vs MDI with either AeroChamber®, Babyhaler or Volumatic spacer
Becker *et al*., 1985[125]	Comparison of pMDI vs pMDI with a tube spacer
Biddiscombe *et al.,* 1993[126]	Not a RCT; an *in vivo* study to test the *in vitro* 'Andersen MKII cascade impactor' method
Bloomfield *et al*., 1979[127]	Comparison was with and without a tube spacer using pMDI
Bollert *et al*., 1997[128]	Study did not use a β_2-agonist, but used ipratropium bromide
Booth, 1999[129]	UK, National Research Register database, but listed investigator has no knowledge of study and therefore no study details could be obtained
Borgstrom & Newman, 1993[130]	Study used healthy volunteers instead of patients with asthma
Burgess *et al*., 1993[131]	Study on spacer comparisons: pMDI + 700 ml Volumatic vs pMDI + 1500 ml plastic bottle
Campbell *et al*., 1995[132]	Study in acute patients en route to hospital via ambulance
Cavagni *et al.,* 1993[133]	Comparison of MDI vs MDI with a jet disposable spacer
Chambers *et al.,* 1980[84]	Device (Italseber) is not a commonly known device; further details could not be obtained from the contact author/sponsor company
Chhabra, 1987[134]	Bioavailability/bioequivalence comparison between 2 generic pMDIs
Chipps *et al*., 1992[135]	MDI canister fitted with a Gentlehaler® (actuator) vs MDI with aerochamber spacer
Cissik *et al*., 1986[136]	Study did not compare the same drug(s) with the same system of delivery
Clark & Lipworth, 1996[137]	Study used healthy volunteers instead of patients with asthma
Cordero, 1987[138]	Spacer comparison using terbutaline MDI with or without an extension tube
Crimi *et al*., 1989[139]	Comparison of MDI vs MDI with InspiRase® spacer device; study also used clenbuterol
Cunningham & Crain, 1994[140]	Study of spacer effectiveness: pMDI vs pMDI with spacer
Dawson, 1985[141]	Study compared a DPI against another (Rotahaler vs Inhalator®)
Deenstra *et al*., 1988[142]	Study comparison was a DPI vs DPI, no pMDI involved
Donateo *et al.,* 1996[143]	Comparison of MDI vs MDI with jet spacer
Donnell *et al*., 1995[144]	Study carried out a comparison between propellants not between devices: HFA-placebo vs CFC-placebo vs HFA-salbutamol
Dubus *et al*., 1997[145]	Comparison of 5 spacers with pMDI (AeroChamber vs Aeroscopic® vs Babyhaler with a face mask vs Nebuhaler vs Volumatic)
Fuglsang & Pedersen, 1988[146]	Spacer comparisons: pMDI vs pMDI with spacer vs pMDI with Nebuhaler vs placebo
Fuller, 1986[147]	Spacer comparisons: pMDI vs pMDI with AeroChamber vs pMDI with spacer
Gioulekas *et al*., 1996[148]	No pMDI used: study compared Turbuhaler vs Rotahaler
GlaxoWellcome & Allen & Hanburys[149]	Poor quality response from company regarding providing data; therefore study was excluded as no data could be obtained after repeated requests
Gomm *et al*., 1980[150]	Study of spacer effectiveness: pMDI vs pMDI with tube spacer
Green & Price, 1991[151]	Comparison was with and without a Volumatic spacer using pMDI
Gunawardena *et al*., 1997[152]	Study compared large volume spacer (Volumatic) vs small volume spacer (Spacehaler) using pMDI
Haahtela *et al*., 1998[153]	Comparison of 2 DPIs: Easyhaler vs Diskhaler

continued

TABLE 15 contd *Review B: characteristics of excluded studies*

Study	Reason for exclusion
Harrison *et al.*, 1996[154]	Study did not use any bronchodilator drugs: it was a study of pMDIs containing CFC vs HFA-134a without any drugs inside canister
Harvey & Williams, 1992[155]	Patient allocation not randomised and patients not clearly diagnosed as having asthma
Haworth, 1996[156]	Not an RCT, but a retrospective analysis of written and computerised patient information
Herer, 1993[157]	Study presented data as a percentage of predicted value, the only study that presented data in such a manner; was also only a published abstract and missing other relevant data
Hidinger & Park, 1981[158]	Study of spacer effectiveness: pMDI vs pMDI with tube spacer
Hidinger & Kjellman,1984[159]	pMDI vs pMDI with collapsible spacer (750 ml)
Hidinger & Dorow, 1984[160]	Study of spacer effectiveness: pMDI vs pMDI with 750 ml spacer
Hindle *et al.*, 1995[161]	Study used healthy volunteers instead of patients with asthma
Hindle *et al.*, 1997[162]	Study used healthy volunteers instead of patients with asthma
Jenkins, 1995[60]	Not a clinical trial but a review of trials
Kaiser *et al.*, 1994[163]	Not a RCT, but an observational study also used pirbuterol acetate as the bronchodilator
Kerac *et al.*, 1998[164]	Comparison of MDI vs MDI with Volumatic spacer vs MDI with bottle spacer
Kishida *et al.*, 1993[165]	MDI with or without spacer or extension tube
Kraemer *et al.*, 1985[166]	MDI with a 750 ml Volumatic spacer or 80 ml spacer and vs nebuliser
Lahdensuo & Muittari, 1986[167]	Only partially randomised – the pMDI not randomised: all patients got pMDI on day 1; DPI vs DPI (placebo) arm randomised
Langaker & Hidinger, 1982[168]	pMDI vs pMDI with a tube extension
Laurikainen *et al.*, 1997[169]	DPI (Easyhaler) vs another DPI, no pMDI involved in the study
Lee & Evans, 1987[170]	3-way spacer comparison: pMDI with InspiRase vs pMDI with aerochamber vs pMDI with aerosol bag
Liljas *et al.*, 1997[64]	Combined used of salbutamol and budesonide using MDI vs Turbuhaler
Lindsay *et al.*, 1994[171]	Two different drugs compared: terbutaline in Turbuhaler vs salbutamol in pMDI
Lipworth & Clark, 1997[172]	Study employed healthy volunteers, not patients with asthma
Lipworth, 1999[173]	Study employed healthy volunteers, not patients with asthma
Mahadewsingh *et al.*, 1996[174]	No pMDI used in study comparisons: study used Turbuhaler vs Diskhaler vs Rotahaler
Malmstrom *et al.*, 1999[175]	Easyhaler compared against a pMDI in children but the study was open and not randomised
Morice *et al.,* 2000[176]	Not a RCT, design more suitable to cohort (both retrospective and prospective) study
Mortensen *et al.*, 1991[177]	Study on mucociliary clearance and all patients inhaled nebulised albumin labelled with technetium-99m and isotonic saline
Muittari & Ahonen, 1979[178]	Not randomised, all patients received pMDI then they all received DPI
Nelson & Loffert, 1994[179]	Comparison of spacers (Optihaler and AeroChamber) vs pMDI with spacer
Newman *et al.*, 1998[180]	Study employed healthy volunteers, not patients with asthma
Nimmo *et al.*, 1993[181]	Study used 2 different drugs (albuterol and terbutaline) in 2 DPIs (Turbuhaler and Diskhaler) then retrospectively compared with patients' previous use of MDIs
O'Reilly *et al.,* 1986[182]	Comparison of pMDI with or without a conical spacer
Oliver *et al.*, 1982[183]	Study of spacer effectiveness: pMDI vs pMDI with tube spacer
Pauwels *et al.,* 1984[184]	pMDI vs pMDI with a tube extension
Pauwels *et al.*, 1996[67]	Study used 2 different steroids and beta-agonist with both the Turbuhaler and pMDI Turbuhaler (budesonide and terbutaline) vs pMDI (short-acting β_2 and beclometasone dipropionate)

continued

TABLE 15 contd *Review B: characteristics of excluded studies*

Study	Reason for exclusion
Pedersen, 1983[185]	Comparison of spacer vs no spacer using pMDI
Pedersen, 1985[186]	Different drugs used in the 2 devices: Rotahaler (salbutamol) vs pMDI + tube spacer (terbutaline)
Rachelefsky *et al.,* 1986[187]	Study of spacer effectiveness: pMDI vs pMDI with tube spacer
Rivlin *et al.,* 1984[188]	Study of spacer effectiveness: pMDI vs pMDI with 750 ml spacer and also vs nebuliser
Rogers & Ganderton, 1995[189]	Not an RCT, but consensus statement from a workshop of the British Association for Lung Research
Rymsa *et al.,* 1998[190]	Study compared the MAGhaler® with patients' usual device (and not specifically a pMDI)
Schecker *et al*., 1993[191]	Pirbuterol acetate (Maxair) used as the bronchodilator in Autohaler vs MDI, not one of the drugs used in our search criteria
Selroos *et al*., 1996[39]	Not an RCT, but a review of the comparative clinical studies where 2 or more delivery devices have been used
Serra *et al*., 1996[192]	Different bronchodilators and dosage used in the 2 groups compared: salbutamol (Group A) vs terbutaline (Group B)
Sly *et al*., 1988[193]	Study of spacer effectiveness with the use of placebo: pMDI (salbutamol) with AeroChamber vs pMDI (placebo) with AeroChamber
Stenius-Aarniala *et al*., 1993[194]	Study of spacer effectiveness: Salbuvent vs Volumatic vs Rondo® spacer (new spacer)
Terzano & Mannino, 1996[195]	*In vitro* study, which uses a device that simulates human inspiratory patterns; comparison between pMDI and Autohaler
Vazquez-Aceves *et al.,* 1995[196]	Comparison of pMDI with an AeroChamber and another spacer device
Vervloet *et al*., 1994[197]	Two different drugs used Maxair Autohaler (pirbuterol) vs Ventodisks (salbutamol sulphate)
Vidgren *et al*., 1990[89]	Study used healthy volunteers and involved a DPI (Chiesi®) vs the Rotahaler
Vidgren *et al*., 1994[41]	Deposition study comparing (99mTc-labelled salbutamol) Easyhaler vs pMDI, unblinded and not randomised
Vidgren *et al*., 1995[73]	Not a RCT, but a review on Easyhaler device
Vilsvik *et al*., 1991[198]	Study used different drugs and doses with the inhaler devices: Turbuhaler (terbutaline 0.5 mg) vs MDI (salbutamol 0.2 mg)
Waterhouse *et al*., 1993[199]	Study used healthy volunteers instead of patients with asthma
Waterhouse *et al.,* 1995[200]	Study used healthy volunteers instead of patients with asthma
Wong & Hargreave, 1993[201]	Not a RCT, but a narrative review on clinical equivalence of generic inhaler devices
Wong *et al.,* 1995[202]	MDI vs MDI with 750 ml spacer vs MDI with 1.5 litre bottle
Wong *et al*., 1998[203]	Study was designed to observe the effect against methacholine bronchoconstriction
Xuan *et al*., 1989[204]	Study of spacer effectiveness: pMDI vs pMDI with 750 ml spacer

TABLE 16 *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
3M Health Care[205]	*Design*: open-labelled, randomised, parallel, age-stratified study – long term *Device*: HFA-134a pMDI vs pMDI *Drug*: salbutamol *Dose*: 100 µg per actuation (both devices) *Duration*: 4 weeks	63 children, aged 4–11 years (15 were 4–7 years/48 were 8–11 years) with at least a 6-month history of asthma and using an inhaled beta-agonist were enrolled FEV_1 of > 50% was predicted; reversibility greater than 12% to bronchodilator	Patients randomly assigned to receive either HFA-132a salbutamol or standard Ventolin pMDI; 2 inhalations, q.d.s. for 4 weeks	*Testing*: pulmonary function tests before and over a 6-h period after 2 puffs of study medication at the end of the 4-week period; study data also measured and provided for 1–2 weeks of study duration *Variables*: all FEV_1 values, PEFR (am + pm), asthma disability scores, β_2 usage, sleep disturbances	All study details provided by 3M Health Care, UK Cochrane Allocation = B
Ahlström *et al.*, 1989[80]	*Design*: open-labelled, randomised, crossover study – long term *Device*: Turbuhaler vs pMDI + Nebuhaler *Drug*: terbutaline *Dose*: 0.5 mg t.d.s. (both devices) *Duration*: 14 days	26 children initially but 5 withdrawn (2 due to poor compliance, 1 irregular budesonide use, 2 had exacerbations). Data presented for 21 children (7 F), age range 2–5 years, mean age 3.9 years, duration of asthma 1–4 years (mean 2.7 years). All other treatments kept constant during study except for the intervention	Patients randomly assigned to receive either Bricanyl Turbuhaler (0.5 mg/dose, 1 inhalation t.d.s.) or Bricanyl pMDI + nebuhaler spacer (0.25 mg/dose, 2 inhalations t.d.s.). Each treatment lasted for 14 days and then crossed over for another 14 days with other treatment arm	*Testing*: PEFR measured 15 minutes after drug (bronchodilator) administration *Variables*: day and night symptom scores, day and night side-effects or additional use of β_2 medication and PEFR	*Potential bias*: during the pMDI + Nebuhaler arm 2 inhalations t.d.s. was used as opposed to 1 inhalation t.d.s. for the Turbuhaler arm Cochrane Allocation = B
Andersen *et al.*, 1998[206]	Methacholine challenge used *Design*: double-blind, double-dummy, randomised, crossover study – short term *Device*: Turbuhaler vs pMDI *Drug*: terbutaline *Dose*: 1 mg (both devices) – Turbuhaler: 2 x 0.5 mg; pMDI: 4 x 0.25 mg *Duration*: 1 day x 2	16 adults (11 F), mean age 27 years, range 18–39 years, with asthma defined by American Thoracic Society criteria FEV_1 of > 88% predicted Only patients who had a sufficient hyper-responsiveness to methacholine challenge were recruited (PC30 < 9.6 mg/ml of methacholine)	All patients were challenged with a double dose of the last concentration of methacholine determined on screening day. If FEV_1 decreased by 20% or more, patients were randomly assigned to receive either terbutaline via the Turbuhaler or pMDI (1 mg). Spirometry was performed at 5, 15, and 30 minutes after study treatment was administered	*Testing*: spirometry performed after methacholine challenge and study treatment *Variables*: FEV_1, FVC, PIF, $FEF_{25\%}$, $FEF_{50\%}$, $FEF_{75\%}$, PEF	Potential bias: during the pMDI period 4 inhalations were used as opposed to 2 inhalations during the Turbuhaler period Cochrane Allocation = B

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Bleecker *et al.*, 1998[207]	*Design*: double-blind, double-dummy, randomised, parallel study – long term (3-way study also included a placebo HFA arm) *Device*: HFA-134a pMDI *Drug*: salbutamol *Dose*: 90 µg per actuation *Duration*: 12 weeks	379 adults (231 F), mean age 36 years (SD: 12), with asthma defined by objective criteria FEV_1 of between 40% and 80% predicted; 15% reversibility in FEV_1	Patients randomly assigned to receive either HFA-132a salbutamol, standard Ventolin pMDI or placebo HFA; 2 inhalations q.d.s. for 12 weeks. Patients eligible for study entry after screening evaluation underwent a 7-day run-in period	*Testing*: pulmonary function tests before and over a 6-h period after 2 puffs of study medication at the end of the 12-week period. Study data also measured and provided (as graphs) for weeks 0, 4 and 8 of study duration *Variables*: FEV_1, FEV_1-AUC, inhaled steroid usage	Parallel study, therefore data entered separately from crossover studies. Study was published in 5 different journals in different forms Cochrane Allocation = B
Bondesson *et al.*, 1998[96]	*Design*: open-labelled, randomised, crossover study – cumulative dosing *Device*: Turbuhaler *Drug*: salbutamol *Dose*: total 1600 µg in 12 minutes (100, 100, 200, 400 and 800) *Duration*: 25 minutes after last dose	12 adults (3 F), mean age 59 years, range: 47–68 years FEV_1 of > 50% predicted (range: 36–79); mean reversibility 20% (range: 15–26) 7 patients were former smokers, 4 current and 1 never smoked	Patients randomly assigned to receive salbutamol from the Turbohaler or pMDI; total dose delivered from each device was 1600 µg Washout = 24 h	*Testing*: spirometry done 25 minutes post-dose, all other measurements 15 minutes after dose *Variables*: FEV_1, tremor, serum potassium, adverse events and HR	Author reply: randomisation/allocation by computer. Author did not provide requested spirometry data values Cochrane Allocation = A
Borgstrom *et al.*, 1996[2]	*Design*: randomised, double-blind, double-dummy, 4-way crossover study *Device*: Turbuhaler *Drug*: terbutaline *Dose*: single doses of 0.25 mg and 0.5 mg per actuation *Duration*: 360 minutes	13 (9 M) patients, mean age 36 years, range 18–50 years Mean FEV_1 of > 59% predicted (range 39–72%); mean FEV_1 reversibility 15 minutes after inhalation of 1 mg terbutaline via Turbuhaler was 34% (range 20–59%)	Patients received on 4 different study days via Bricanyl pMDI or Bricanyl Turbuhaler 0.25 or 0.50 mg terbutaline as a single dose. Activated charcoal (30 g) was given to all patients before and up to 2 h after drug inhalation as an oral slurry to block gastrointestinal uptake of swallowed drug Washout = 24 h	*Testing*: spirometry was done 15 minutes onwards after drug dose but only mean over the total 360-minute study period was reported *Variables*: FEV_1, FVC, $FEF_{25\%}$, $FEF_{50\%}$, PEF, SGaw, AUC-FEV_1, deposition	Author reply: randomisation/allocation by computer Cochrane Allocation = A

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Boye, 1983[92]	*Design*: randomised crossover study *Device*: Rotahaler *Drug*: fenoterol *Dose*: 200 µg per actuation *Duration*: 1–5 h	20 adults (8 F) with mean age 51, range 20–69, with reversible airways disease FEV_1/PEF bronchodilator reversibility of 15%	Patients initially given 200 µg of fenoterol with spirometry over 1 h later followed by PEFR at home 5 h later Patients were also given 200 µg x 3 twice daily for 4 days with measurements of PEFR at home Washout not reported	*Testing*: spirometry was done before and 1, 5, 10, 30 and 60 minutes after a single 200 µg dose but only PEF graph shown with no SEM or SD *Variables*: PEFR, VC, FEV_1 and preference for device –only abstractable results that could be used	No reply to correspondence, from author to date Cochrane Allocation = B
Bronsky *et al.*, 1987[208]	*Design*: randomised, double-blind, double-dummy, parallel study *Device*: Rotahaler *Drug*: salbutamol *Dose*: 200 µg/puff from Rotahaler, but 180 µg/puff from pMDI *Duration*: 6 h	231 adults patients (Rotahaler: 115; pMDI: 116) with asthma were recruited FEV_1 of ≤ 80% predicted; FEV_1 bronchodilator reversibility was 15%, 15 minutes after 262 µg of isoproterenol	Patients were given either salbutamol through the Rotahaler or pMDI; lung functions were measured at 30 minutes and every hour for 6 h	Testing: spirometry done 30 minutes post-dose than every hour for 6 h Variables: FEV_1, $FEF_{25–75\%}$, FVC. PEFR and treatment failure reported after 12 weeks of device use. Only mean over 6 h reported for FEV_1, FVC and $FEF_{25–75\%}$, but none useful as no SD or SEM reported	Allocation of patients to treatment according to randomly generated codes Cochrane Allocation = A
Bronsky *et al.*, 1995[82]	*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 180 µg vs Rotahaler 200 µg *Duration*: 51 minutes	44 children, age range 4–11 years, mean age 8 years FEV_1 of < 70% predicted after bronchodilators have been held for 8 h; FEV_1 bronchodilator reversibility was 15%, 15 minutes after inhalation of puffs from a beta-adrenergic bronchodilator	Pulmonary function test performed up to 51 minutes after taking the drug and running on a treadmill for 6 minutes at pre-determined target rates (85% of HR_{max}); study also reported 15 minutes post-dose FEV_1 (i.e. pre-exercise)	Pre- and post-exercise FEV_1 after drug administration (i.e. before any exercise challenge)	Cochrane Allocation = B

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Bronsky *et al.*, 1999[101]	*Design*: randomised, double-blinded, parallel study *Device*: HFA-134a pMDI *Drug*: salbutamol *Dose*: 2 puffs b.d. for 12 weeks (exact dose not reported for with device) *Duration*: 12 weeks	51 adult patients (29 F) with asthma, mean age 35 and 39 years, range 18–65 years FEV_1 of ≤ 80% predicted; = 15% increase in FEV_1 30 minutes after 200 µg of CFC-salbutamol from DPI	All patients were initially optimised for 12 weeks on standard CFC-pMDI, then 24 patients were assigned to HFA-pMDI for another 12 weeks while 27 remained on CFC-pMDI. Pulmonary function test reported as peak percentage change was carried out 2 h post-dose and AUC until termination of effect (i.e. FEV_1 fell to 15% above baseline)	FEV_1, treatment failures, oral steroid use, AUC-FEV_1, symptoms	Cochrane Allocation = B
Chapman *et al.*, 1997[110]	Different doses used in devices *Design*: randomised, double-blind, crossover study *Device*: Turbuhaler *Drug*: salbutamol *Dose*: 200 µg in Turbuhaler; 100 µg in pMDI; both treatments given q.d.s. for 2 weeks each *Duration*: 2 weeks	37 adults (18 F), mean age 39 years FEV_1 ≥ 50% predicted; 15% or greater increase in FEV_1 after 200 µg salbutamol from pMDI	Total study duration was 4 weeks; 1 week run-in followed by 2 weeks treatment and 1 week of washout in between	PEFR, FEV_1 (measured 15 minutes post-dose), preference, β_2 use and symptoms	Cochrane Allocation = B
Cohen *et al.*, 1999[86]	*Design*: randomised, double-blind, parallel study *Device*: HFA-134a pMDI *Drug*: salbutamol *Dose*: 180 µg per actuation *Duration*: 12 weeks	Patients with asthma aged 12 years old FEV_1 between 50% and 80% was predicted; increase in FEV_1 of = 15% after salbutamol	180 µg salbutamol used prn from either the HFA-134 pMDI or standard pMDI for 12 weeks	Study measurements done at day 1, and weeks 6 and 12 were FEV_1, AUC-FEV_1, PEFR am + pm, symptoms, nocturnal awakenings and exacerbations	Study reported as abstract with no useful data for review. Further information requested from author Cochrane Allocation = B

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Croner *et al.*, 1980[113]	*Design*: randomised, double-blind, crossover study *Device*: Rotahaler *Drug*: salbutamol *Dose*: 0.1 mg/puff in pMDI and 0.2 mg/puff in Rotahaler; 3–6 puffs of each/day prn *Duration*: 4 weeks	43 children (11 F), age range 3–16 years, mean 9.6 years	Children inhaled salbutamol 3–6 times a day as required from either a Rotahaler or pMDI for weeks. Daily pulmonary function measured with an air flow meter 10 minutes after drug dose	PEFR, preference, symptoms, additional β_2 use and inhaled steroid use	Coding was used for treatment allocation and was not unblinded until the trial was completed Cochrane Allocation = A
Custovic *et al.*, 1995[83]	*Design*: randomised, double-blind, double-dummy, crossover study *Device*: HFA-pMDI *Drug*: salbutamol *Dose*: 200 µg (both devices) *Duration*: 30 minutes	25 children (9 F), age range 6–14 years, mean age 10 years FEV_1 > 50% predicted; PD_{20} of < 3.91 µmol	Pulmonary function measured was performed 30 minutes post-dose, then histamine challenge was performed and FEV_1 measured until FEV_1 decreased by 20% (PD_{20}). Data used was before histamine challenge	FEV_1 and protection against histamine-induced broncho-constriction as measured by PD_{20}	Allocation of treatment was predetermined according to a sequence of continuous patient randomisation numbers that were generated by computer Cochrane Allocation = A
Dirksen & Groth, 1983[103]	*Design*: randomised, double-blind, double-dummy, crossover study *Device*: Spinhaler® *Drug*: fenoterol *Dose*: total dose 400 µg (both devices) *Duration*: 100 minutes (25 minutes x 4)	9 adults (8 F), age range 27–65 years, mean age 47 years Mean FEV_1 of 54% predicted (range 42–71); FEV_1 reversibility of = 15%, 15 minutes after 0.2 mg fenoterol from the pMDI	Study measurements were done 20 minutes after taking each cumulative dose in the following sequence: 0.05 mg + 0.05 mg + 0.1 mg + 0.2 mg	Pulse rate, tremor, FVC, FEV_1, $FEV_{1\%}$, maximum voluntary ventilation, FEF, forced mid-expiratory flow, side-effects	Cochrane Allocation = B

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Dockhorn *et al.*, 1995[209]	*Design*: randomised, double-blind, double-dummy, 6-way crossover study *Device*: HFA-pMDI *Drug*: salbutamol *Dose*: 100/200 µg (both devices) *Duration*: 480 minutes	26 non-smoking adult patients (6 F) with stable asthma, mean age 28 years, range 18–50 years	Mean FEV_1 of 68.7% was predicted; FEV_1 reversibility = 20% within 30 minutes after inhalation of 200 µg of salbutamol from CFC-pMDI	Pulmonary function measurements done after single-dose of 100 µg salbutamol at 10–480 minutes post-dose	AUC, time of onset, duration of effect, FEV_1, adverse effects, rescue β_2 use, BP, PR Cochrane Allocation = B
Dockhorn *et al.*, 1997[210]	*Design*: randomised, single-blinded, 4-way crossover study *Device*: HFA-134a pMDI *Drug*: salbutamol *Dose*: 2 puffs (both devices), exact dose not mentioned *Duration*: 90 minutes	20 (7 F) adults with stable asthma, mean age 23.9 years, range 14–43 years FEV_1 of 89.6% predicted (SD 9.3). Patients had to have demonstrated exercise-induced asthma measured by decrease in FEV_1 of 20% but < 50% after exercise	Standardised exercise was performed 30 minutes after study drug administration and study measurements were performed from 5 to 90 minutes post-exercise. Exercise was on a treadmill with speed and incline adjusted to reach 80–90% maximum HR (220 bpm – age in years), for 8–10 minutes Washout = between 2 and 7 days	Spirometry, HR, ECG, BP	Cochrane Allocation = B
Duncan *et al.*, 1977[99]	*Design*: randomised, double-blinded, double-dummy, crossover study *Device*: Spinhaler *Drug*: salbutamol *Dose*: 200 µg *Duration*: 300 minutes	20 adult patients (5 F) with stable asthma, mean age 59 years, range 13–72 years FEV_1 reversibility of = 20% after 0.5% salbutamol by intermittent positive-pressure ventilation	Pulmonary function measured at 15 and 30 minutes, and at 30-minutes intervals until 300 minutes post-dose from inhaler device	FEV_1, FVC, HR, side-effects	Author reply: Latin-square design used and computer-generated coding used for allocation concealment Cochrane Allocation = A

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Ekstrom *et al.*, 1995[97]	*Design*: open, randomised, 2-way crossover study *Device*: Turbuhaler *Drug*: terbutaline *Dose*: total dose 4 mg *Duration*: 180 minutes (6 x 30 minutes)	31 (13 F) adults with stable asthma (average duration 16 years), mean age 46 years, range 18–69 years FEV_1 of 65% was predicted (range 41–99 years); FEV_1 reversibility =15% after 0.5 mg terbutaline from Turbuhaler 2 patients were current smokers, 15 former and 14 never smoked	Cumulative doses every 30 minutes (as 0.125, 0.125, 0.25, 0.5, 1.0 and 2.0 mg) given by either Turbuhaler or pMDI. Study measurements were done 25 minutes after each cumulative dose Washout = 20 h	FEV_1, $FEF_{25–75\%}$, FVC, PEFR, tremor, serum potassium, PR, BP	Author reply: allocation concealment and randomisation by computer-generated codes Cochrane Allocation = A
Fuglsang & Pedersen, 1989[79]	*Design*: single-blinded, double-dummy, crossover study; used computer-generated schedule *Device*: Turbuhaler *Drug*: terbutaline *Dose*: 2.0 mg (both devices) *Duration*: cumulative dosing study, giving a total dose of 2.0 mg within 80 minutes	13 children (3 F) with stable asthma, mean age 10.5 years, range 7–15 years 20% reversibility in FEV_1 after inhalation of 0.5 mg of terbutaline	Pulmonary function testing done 15 minutes post-dose. Initial dose in the 2 groups was different as it was impossible to produce a Turbuhaler that could deliver 0.125 mg terbutaline but it was considered important to have a response below 0.025 mg; therefore 0.125 mg terbutaline was delivered from the pMDI only (total dose: pMDI = 1.875 mg; Turbuhaler = 2 mg). Cumulative doses were administered every 20 minutes	FEV_1, $FEF_{25–75\%}$, PEFR or FVC, HR, tremor, symptoms, adverse effects	Author reply: computer-generated randomisation code was used for allocation of treatment Cochrane Allocation = A
Geoffroy *et al.*, 1999[211]	*Design*: randomised, double-blinded, double-dummy, 5-way crossover study *Device*: Spiros® *Drug*: salbutamol *Dose*: 90 and 180 µg *Duration*: 360 minutes	60 adults enrolled (27 F), mean age 29.7 years (SD 10.5), range 18–65 years; 44 patients completed the study FEV_1 of 59% was predicted; FEV_1 reversibility = 15%, 30 minutes after inhalation of 90 µg salbutamol from pMDI	Study measurements done from 10 to 360 minutes post-dose. Blood samples were also obtained and ECG performed at 30, 60 and 120 minutes. FEV_1 on second study day had to be between 85% and 115% of study day 1 Washout = 24 h < 14 days	FEV_1, FVC, $FEF_{25–75\%}$, PEFR, BP, HR, serum potassium, ECG	Author reply: random allocation of patient to treatment sequence Cochrane Allocation = A

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Giannini *et al.*, 2000[212]	Methacholine challenge used in study *Design*: double-blind, double-dummy, randomised, crossover study *Device*: Autohaler vs pMDI + Volumatic *Drug*: salbutamol *Dose*: 100 µg (both devices) *Duration*: until PD_{20} reached	18 adults (8 F), mean age 40 (SD 18) years, range 19–72 years, with stable moderate asthma Patients had to have a baseline fall in FEV_1 of 20% after methacholine challenge	15 minutes after 100 µg of salbutamol was administered methacholine challenge began until PD_{20} was reached. Challenge was done every 2 minutes from 0.04 mg to 0.32 mg of cumulative doses Washout = 1 week	FEV_1, PD_{20}	Cochrane Allocation = B
Golish *et al.*, 1998[107]	Different doses used in devices *Design*: randomised, double-blind, double-dummy, 3-way crossover study *Device*: Rotahaler vs pMDI + InspiEase® spacer device *Drug*: salbutamol *Dose*: Rotahaler 400 µg vs pMDI 180 µg *Duration*: 360 minutes	20 adult patients (13 F) with stable asthma, mean age 40.9 (SD 14.2) years $FEV_1 \leq 80\%$ predicted when inhaled β_2-agonists withheld for 6 h and FEV_1 15% 15 minutes after inhalation of salbutamol via pMDI + spacer FEV_1 of 50.7% was predicted (SD 15.9)	Study measurements done from 15 to 360 minutes post-dose; study also had third arm that was pMDI alone; this arm data were not used Washout = 24 h	FEV_1, BP, HR, symptoms	Cochrane Allocation = B
Haahtela *et al.*, 1994[213]	*Design*: open-labelled, randomised, 3-way crossover study *Device*: Easyhaler *Drug*: salbutamol *Dose*: total dose 720 µg *Duration*: 2 h (30 minutes x 4)	20 adult patients (9 F), mean age 50 years, age range 23–66 years FEV_1 of 65% predicted; all patients had FEV_1 reversibility of = 15% after 200 µg salbutamol During study days, FEV_1 variation had to be less than 20% and on entry FEV_1 % predicted had to be < 85%	Four doses of salbutamol administered every 30 minutes: 90, 90, 180 and 360. Study measurements were done 20 minutes after each cumulative dose	FEV_1, FVC, PEFR, BP, HR, adverse events	Cochrane Allocation = B

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Harris & Rothwell, 1981[214]	*Design*: randomised, double-blind, double-dummy, crossover study *Device*: Rotahaler or Spinhaler *Drug*: fenoterol *Dose*: 200 µg *Duration*: 60 minutes	11 adults (5 F), age range 16–66 years FEV_1 reversibility of = 20% after standard sympathomimetic aerosol On study days variation in lung function was less than 10%	On study days 200 µg fenoterol was administered from either device in a double-blinded fashion. Study measurements were done 5, 15, 30 and 60 minutes post-dose Patients studied on 2 occasions not more than 1 week apart	FEV_1, PR	Study included but no data used as in non-extractable form. No reply from author to date Cochrane Allocation = B
Hartley *et al.*, 1977[215]	*Design*: randomised, double-blind, double-dummy, crossover study *Device*: Rotahaler *Drug*: salbutamol *Dose*: 200 µg *Duration*: 240 minutes	10 patients (6 F) with asthma, age range 21–52 years Patients were admitted to hospital with severe attacks and studied in hospital (prior to discharge) when stable, over 5 days FEV_1 reversibility was = 15% following 200 µg salbutamol from pMDI	Each morning baseline PEFR, PR and BP were measured until stable, then patient was given 50, 100, 200 or 400 µg salbutamol from Rotahaler or 200 µg from the pMDI. Study measurements were made from 10 minutes post-dose to 240 minutes	PEFR, PR, BP	Data were extracted from graph, but no SD was provided in graph for % increase in PEFR. Double Latin-square design was used for treatment allocation and was double-blinded Cochrane Allocation = A
Hartley *et al.*, 1979[90]	*Design*: double-blinded, crossover study (not mentioned if randomised) *Device*: Rotahaler *Drug*: salbutamol *Dose*: 200 µg *Duration*: 3 months	38 adult patients (25 F) completed the study (mean duration of asthma 18.8 years), mean age 47 years, range 22–76 years FEV_1 reversibility was = 15% after salbutamol Patients without a good pMDI technique were not entered into the study	200 µg salbutamol was taken for 3 months each using both devices in a double-blind fashion. Per puff the pMDI delivered 100 µg and the Rotahaler delivered 200 µg. Patients completed daily diary cards and made PEFR recordings	Diary cards, PEFR, FEV_1, preference, symptoms, additional β_2 usage, rescue steroid use, wheeze	Cochrane Allocation = B

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Hawksworth *et al.*, 1999[87]	*Design*: randomised, double-blind, crossover study *Device*: HFA-134a pMDI *Drug*: salbutamol *Dose*: 200 µg per actuation *Duration*: 60 minutes	24 adult patients with a history of exercise-induced asthma, age range 19–45 years, mean 27 years FEV_1 = 65% predicted and fall in FEV_1 = 20% post-exercise	Single doses study drug administered 30 minutes prior to a 6-minute exercise test Washout = 24 h	FEV_1 measured 15 minutes pre-dosing, 5 minutes pre-exercise and at regular intervals for 60 minutes post 6-minute exercise test The maximum % fall in FEV_1 post-exercise compared to the pre-exercise value reported	Study was published as an abstract only Cochrane Allocation = B
Hetzel and Clark, 1977[105]	*Design*: open-labelled, randomised, crossover study *Device*: Rotahaler *Drug*: salbutamol *Dose*: total dose 1500 µg *Duration*: 60 minutes	17 patients, mean age 44 years, range 23–68 years, with stable asthma and good inhaler technique FEV_1 reversibility was ≥ 15% 14 patients were studied in this cumulative dosing study Baseline FEV_1 could not vary by 15% on the 2 study days	Single dose of 100 µg salbutamol was given initially; study measurements were made from 2 to 15 minutes, then 200, 400 and 800 µg given followed by readings at 5 and 15 minutes after each cumulative dose	FEV_1, FVC, pulse rate. Acute exacerbations data were obtained from long-term (1 month) study, since there were 3 different studies in this trial	Study mentions that the order of treatment was altered in consecutive patients, so a grade of 'C' is allocated to this study for concealment, after discussion with JWr FEV_1 (SD) values obtained from graph Cochrane Allocation = C
Hirsch *et al.*, 1997[74]	*Design*: randomised, double-blind, double-dummy, parallel study; used drawing lots *Device*: Turbuhaler vs pMDI alone *Drug*: terbutaline *Dose*: 0.5 mg (both devices) *Duration*: 10 minutes	118 children, age range 8–15 years, mean age 11.3 years FEV_1 was < 70% predicted	Pulmonary function testing done 10 minutes post-dose	Change from baseline FEV_1, FVC and $V_{max50\%}$	Author reply used drawing lots for allocation concealment and provided further details on the process of double-blinding Cochrane Allocation = A

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Hultquist *et al.*, 1989[76]	*Design*: randomised, double-blind, double-dummy, crossover study *Device*: Turbuhaler vs pMDI alone *Drug*: terbutaline *Dose*: 0.5 mg + prn (both devices) *Duration*: 2 weeks	57 children (14 F), age range 6–18 years, mean age 11 years All patients had bronchial reversibility of 15% and were well trained in using the pMDI	Multicentre study involving 5 centres; 1-week run-in followed by 2 weeks treatment from each inhaler device. PEFR was measured 10 minutes post-dose	PEFR (am + pm), symptom scores and preference for device	Cochrane Allocation = B
Jackson *et al.*, 1994[216]	*Design*: randomised, single-blinded, double-dummy, crossover study *Device*: Turbuhaler vs pMDI alone *Drug*: terbutaline *Dose*: 0.25 mg (both devices) *Duration*: 45 minutes	10 adults (7 F), mean age 42 years, range 19–66 years, with highly reactive airways were selected, defined as provocative concentration of methacholine producing a 20% fall in FEV_1 ≤ 0.2 mg/ml and a diurnal variation of PEFR of 15%	Patients inhaled 0.25 mg terbutaline via each device and SGaw was measured at 10-sec intervals for 2 minutes, then at intervals until 45 minutes Washout = at least 2 days	SGaw, Raw, thoracic gas volume, AUC	Author reply: randomisation using blocks of 6 for the treatment sequence Cochrane Allocation = B
Johnsen & Weeke, 1988[98]	*Design*: open-labelled, randomised, crossover study *Device*: Turbuhaler *Drug*: terbutaline *Dose*: total dose 4 mg (both devices) *Duration*: 180 minutes (30 minutes x 6)	9 adults (4 F), mean age 30 years, range 20–46 years, with stable asthma (duration of 2–34 years) Greater than 15% differences between baseline FEV_1 values were not allowed. FEV_1 reversibility of at least 20% after either 0.5 mg terbutaline or 0.2 mg salbutamol	Cumulative doses were given to patients every 30 minutes and study measurements were done 5 and 20 minutes after each inhaled dose Mean washout period = 6 days (range 2–9 days)	FEV_1, FVC, HR, tremor, PIF, forced inspiratory volume, forced inspiratory vital capacity, forced inspiratory flow	FEV_1, FVC, HR, tremor and all SDs obtained from graphs Cochrane Allocation = B

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Kemp *et al.*, 1989[81]	*Design*: 2 separate studies reported: (a) randomised, double-blind, double-dummy, crossover study using 2 doses (100 and 200 µg on separate days); (b) a parallel run study using 200 µg q.d.s. for 12 weeks. Used computer-coded treatment *Device*: Rotahaler vs pMDI alone *Drug*: salbutamol *Dose*: (a) 90–100 µg and 180–200 µg; (b) 180–200 µg *Duration*: (a) 360 minutes; (b) 12 weeks	(a) 30 children, mean age 9.4 years (b) 204 (164 F) children, age range 4–11 years, mean age 8.2 years	*Participants*: (a) lung function measured from 5 to 360 minutes post-dose *Participants*: (b) lung function measured from 5 to 480 minutes post-dose	Only data from 12 week (Study b) entered into RevMan Study (a): FEV_1, HR and BP Study (b): FEV_1, $FEF_{25-75\%}$, FVC, PEFR, dropout rate or symptom scores. Number of acute exacerbations (requiring intervention)	SD for FEV_1 estimated from range provided. Study used Latin-square design for allocation of treatment and was double-blinded Cochrane Allocation = A
Kemp *et al.*, 1997[217]	*Design*: randomised, partially-blinded, double-dummy, 3-way crossover study *Device*: Rotahaler *Drug*: salbutamol *Dose*: Rotahaler 200 µg/ pMDI 180 µg *Duration*: 300 minutes	12 (6 F) mild-to-moderate asthma patients, mean age 23.5 years (SD 8.1), range 12–36 years FEV_1 of 71.1% (SD 5.7) predicted. Baseline FEV_1 could not vary more than 12% on any study day. FEV_1 reversibility of 20% at 20 minutes after 2 puffs of Ventolin via pMDI	Each patient was given 2 inhalations of 90 µg/ inhalation of salbutamol from the pMDI and on another day 2 inhalations of 100 µg/inhalation from a Rotahaler. Study measurements were done 15–300 minutes after each single dose Washout = between 3 and 8 days	FEV_{1max}, FEV_1, FVC, $FEF_{25-75\%}$, PEFR, serum potassium, AUC, duration, onset, blood glucose, ECG, tremor, side-effects	FEV_1 (SD) abstracted from graph Cochrane Allocation = B
Kiviranta, 1985[91]	*Design*: randomised, double-blinded, double-dummy, crossover study *Device*: Rotahaler *Drug*: fenoterol *Dose*: 0.2–0.4 mg 2–4 times daily *Duration*: 4 weeks	20 adults (11 F), mean age 35 years, range 18–57 years, mean asthma duration 11 years (range 1–43); 9 patients were mild, 10 were moderate and 1 was severe Mean PEFR was 430 litres/minute (SD 109) with 15% increase after bronchodilator	Run-in period lasted for a week, then the patients were randomised to receive fenoterol by either Rotahaler or pMDI for another 2 weeks	Diary of symptoms, PEFR 30 minutes post-dose	Cochrane Allocation = B

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Kleerup *et al.*, 1996[218]	*Design*: randomised, single-blinded, 2-way crossover study *Device*: HFA-134a pMDI *Drug*: salbutamol *Dose*: total dose 1440 µg (90 x 16) *Duration*: 150 minutes (30 minutes x 5)	24 adults (5 F), mean age 35.4 years (SD 11.7), range 18–57 years, with stable asthma for at least 12 months Mean % predicted FEV_1 was 68.2% (SD 10.9); mean FEV_1 reversibility after inhalation of 2 puffs of salbutamol from pMDI was 30.8% (SD 10.9); baseline FEV_1 was not allowed to vary greater than 15% between study days	Patients received 1, 1, 2, 4 and 8 (18 total) inhalations from each device at 30-minute intervals. Study measurements were made following each cumulative dose. Washout = between 24 h and 8 days	HR, BP, serum potassium, spirometry	Block randomisation in groups of 8 used for treatment allocation Cochrane Allocation = B
Kou *et al.*, 1998[219]	*Design*: randomised, double-blinded, double-dummy, crossover study *Device*: Diskhaler *Drug*: salbutamol *Dose*: 200 µg (both devices) *Duration*: 10–15 minutes post-dose	12 Chinese patients (8 F), age range 2–60 years PEFR or FEV_1 reversibility of 15% after salbutamol challenge	Patients inhaled 200 µg of salbutamol from either a Diskhaler or pMDI. Study measurements were done 10–15 minutes post-dose from each device	PEFR, side-effects	Treatment allocation according to balanced Latin-square and randomised protocol Cochrane Allocation = B
Laberge *et al.*, 1994[220]	*Design*: randomised, double-blind, double-dummy, crossover study *Device*: Turbuhaler vs pMDI + Nebuhaler *Drug*: terbutaline *Dose*: total dose of 2.0 mg within 80 minutes then 20 minutes later followed by 5 mg of nebulised salbutamol	10 children, age range 3–6 years, mean age 4.6 years All patients had reversibility of 30% in airway resistance after inhalation of 2.5 mg nebulised salbutamol	Lung function measured 15 minutes after each dose of medication	HR, BP, tremor and airways resistance; Raw (SD) obtained from graph	Authors reply on allocation concealment, used random numbers table for allocation of treatment Cochrane Allocation = A

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Langley *et al.*, 1998[88]	*Design*: randomised, double-blind, double-dummy, crossover study *Device*: HFA 134a pMDI *Drug*: salbutamol *Dose*: single dosing study (100 µg and 200 µg) *Duration*: 6 h	63 adult patients, age range 13–63 years, mean age 36 years FEV_1 between 50% and 85% predicted and = 15% increase in FEV_1 after 200 µg salbutamol	Single doses of 100/200 µg salbutamol administered through HFA-134a pMDI or standard pMDI Washout = not reported	FEV_1 measured prior to dosing and at intervals until 6 h post-dosing. Mean over 6 h reported for peak FEV_1 and AUC-FEV_1	Study published only as an abstract in journal Cochrane Allocation = B
Latimer *et al.*, 1982[221]	*Design*: randomised, double-blind, double-dummy, crossover study *Device*: Rotahaler *Drug*: salbutamol *Dose*: 200 µg *Duration*: 4 h	10 adult patients (5 F), mean age 59.5 years, range 32–74 years FEV_1 reversibility = 20% 15 minutes after inhaling 200 µg salbutamol from pMDI; baseline FEV_1 could not vary by 10% between study days – if it did, visit was rescheduled	Patients were given study medication from the inhaler devices; study measurements were done every 15 minutes for the first hour then every 30 minutes for 4 h	FEV_1, VC, AUC, pulse, BP, tremor	Block design was used for randomisation and treatment allocation Cochrane Allocation = B
Lofdahl *et al.*, 1997[104]	2 trials were included in study but only study 1 used in RevMan as it had the same doses in both devices *Design*: randomised, double-blind, double-dummy, crossover study *Device*: Turbuhaler *Drug*: salbutamol *Dose*: 200 µg *Duration*: 6 h	12 adults patients (5 F), mean age 50 years, range 24–68 years; all patients had asthma duration of 10 years (range 3–24); 3 were current smokers, 6 were former and 3 never Mean % predicted FEV_1 was 71% (range 46–109), mean FEV_1 reversibility was 24% (range 15–40) 15 minutes after inhalation of 200 µg of salbutamol from pMDI; between study days baseline FEV_1 was not allowed to vary by more than 15% – if it did, the visit was rescheduled	Patients were given salbutamol on separated days from the Turbuhaler at 50, 100 and 200 µg and the pMDI dose was 2 x 100 µg, therefore the 200 µg dose data were used Study measurements were done before and 20 minutes to 6 h post-dose	FEV_1, FVC, adverse effects, tremor, serum potassium, ECG	Author reply: all requested data provided, allocation concealment was blind and used Latin-square for randomisation method Cochrane Allocation = A

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Maesen *et al.*, 1986[222]	*Design*: randomised, double-blind, double-dummy, crossover study *Device*: Aerohaler® *Drug*: ipratropium bromide *Dose*: 40 µg *Duration*: 360 minutes	20 adult patients (6 F), mean age 46.7 years (SD 16.7), age range 21–60 years, with stable asthma All had an initial FEV_1 of at least 1 litre to ≤ 70% predicted; on study days baseline FEV_1 could not vary by more than 15%; all patients showed FEV_1 reversibility of = 15% after 40 µg ipratropium bromide 60 minutes after inhalation	All patients received study drug from either the MDI or Aerohaler Study measurements were performed 5 minutes before and 15, 30, 60, 120, 180, 300 and 360 minutes post-dose and 15 minutes after additional fenoterol; at the end of each study day and 6 h post-dose each patient received 400 µg of fenoterol via the pMDI Data point was not included in RevMan	FEV_1, FVC, PEF, $FEF_{25\%}$, $FEF_{50\%}$, $FEF_{75\%}$, $FEF_{25-75\%}$	Study included but no data used from the trial as data are in non-extractable form; no reply from author to date Cochrane Allocation = B
Mathieu *et al.*, 1992[108]	Different doses in devices and study also used methacholine challenge *Design*: open-labelled, randomised, parallel, age-stratified study *Device*: Diskhaler *Drug*: salbutamol *Dose*: pMDI 200 µg/ Diskhaler 400 µg *Duration*: 30 minutes	12 adults (6 F) with stable asthma who met the American Thoracic Society criteria for asthma All had baseline FEV_1 ≥ 80% predicted	Each patient inhaled methacholine aerosol, in progressively doubled concentrations until FEV_1 decreased by 20% or more. Each patient then inhaled either 200 µg salbutamol from the pMDI or 400 µg from the Diskhaler Washout = at least 24 h but < 1 week	FEV_1, FVC, functional residual capacity, measured continuously for 30 minutes	
Mellen *et al.*, 1999[223]	Design: randomised, double-blinded, double-dummy, crossover study Device: Turbuhaler Drug: salbutamol *Dose*: total dose 3200 µg (both devices) *Duration*: 180 minutes (6 x 30 minutes)	24 adult patients (11 F), mean age 48 years, range 21–68 years; 7 ex-smokers, 2 current smokers FEV_1 reversibility over baseline was = 15% 15 minutes post-dose	Each patient received salbutamol in a cumulative fashion at 30-minute intervals. The doses were 200, 200, 400, 800 and 1600 µg. The nominal dose per actuation was 100 µg from both devices. Study measurements were made 20–25 minutes post-study for each cumulative study dose Washout = 2–10 days	FEV_1, serum potassium, AUC, HR, BP	Cochrane Allocation = B

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Morice *et al.*, 1996[224]	*Design*: randomised, double-blinded, double-dummy, crossover study *Device*: DPI of undefined type *Drug*: salbutamol *Dose*: total dose 400 µg *Duration*: 240 minutes post-dose	62 adult patients with 15% and = 200 ml reversibility in FEV_1	2 trials were done short-term (240 minutes post-dose) and a long-term 4-week study; only the short-term study provided enough data to be included into RevMan. Salbutamol was administered to each patient as 100, 100 and 200 µg; lung function measured until 240 minutes	FEV_1, FVC	FEV_1 (SD) obtained from published graphs Cochrane Allocation = B
Nelson *et al.*, 1999[225]	*Design*: randomised, double-blind, double-dummy, parallel study *Device*: Spiros *Drug*: salbutamol *Dose*: 2 puffs 4 times daily from each device (Spiros 108 µg/puff and pMDI 90 µg/puff) *Duration*: 12 weeks	283 adult patients were enrolled (97 Spiros group (60 F), 92 pMDI group (45 F), 94 placebo group); 240 completed the study; mean age 34.2 and 34.6 years (SD 13.4 and 15.4) Mean FEV_1 of 64% (SD 11.4) and 64% (SD 10.3) predicted; mean FEV_1 reversibility was 20.7 (SD 7.4) and 19.9 (SD 8.0)	2 puffs 4 times daily from each inhaler device for 12 weeks. Schedule visits at weeks 4, 8 and 12 for assessment; end of week 12 the study treatment was administered and FEV_1 measured for 360 minutes (no SD reported)	FEV_1, PEFR, exacerbations, β_2 use, symptoms, adverse effects and treatment failures	Cochrane Allocation = B
Newhouse *et al.*, 1999[226]	*Design*: randomised, double-blinded, double-dummy, 5-way crossover study *Device*: Clickhaler *Drug*: salbutamol *Dose*: 200 µg (both devices) *Duration*: 240 minutes post-dose	16 adult patients (4 F), mean age 57.3 years (SD 18), with stable asthma enrolled over 12 months Resting FEV_1 of 40–80% predicted and a minimum of 15% increase in FEV_1 after 200 µg salbutamol using a pMDI; mean predicted FEV_1 was 60% (SD 9) and mean FEV_1 increase after salbutamol was 25% (SD 9.33); variation of FEV_1 on study days was not allowed to be more than 15%	Salbutamol 200 µg was administered from either device, and study measurements were done from 15 to 240 minutes post-dose	FEV_1, FVC, MEF, $FEF_{25–75\%}$, respiratory rate, pulse rate, tremor, BP	Cochrane Allocation = B

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Newman & Clarke, 1993[227]	*Design*: randomised, crossover study *Device*: Gentlehaler *Drug*: salbutamol *Dose*: 100 µg radio-labelled (both devices) *Duration*: 60 minutes	10 adult patients (3 F), age range 24–78 years Mean predicted FEV_1 was 52% (range 20–97); FEV_1 reversibility was 15% after 200 µg of salbutamol from a pMDI; baseline FEV_1 could not vary by more than 15% on study days	Each patient inhaled 100 µg-labelled salbutamol from each device and a gamma X-ray was taken, then 15, 30 and 60 minutes of spirometry was done. Data for measurements at 15 minutes were used in RevMan (as it was the first point of measure post-dose) Washout = 48 h	FEV_1, FVC, maximal mid-expiratory flow rate, lung deposition, PEFR	Cochrane Allocation = B
Nieminen *et al.*, 1994[228]	*Design*: randomised, double-blind, crossover study *Device*: Easyhaler *Drug*: salbutamol *Dose*: Easyhaler 180 µg and pMDI 200 µg *Duration*: 360 minutes	21 adult patients (11 F), mean age 51 years, range 20–73 years, with stable asthma (mean asthma duration of 16 years); 5 patients had mild asthma, 9 moderate and 5 severe Mean predicted FEV_1 was 64% (range 29–97); all patients showed 15% increase in baseline FEV_1; variation in FEV_1 was not allowed to be greater than 15% on study days – if it was, the visit was rescheduled	Each patient received salbutamol from either device. Two inhalations were received from the pMDI (total 200 µg) and one from the Easyhaler (180 µg). Study measurements were done from 15 to 360 minutes post-dose	FEV_1, FVC, BP, HR, PEFR, AUC	Author reply: all requested data provided Cochrane Allocation = A
O'Callaghan *et al.*, 1997[229]	*Design*: 2-way, crossover design study *Device*: Clickhaler *Drug*: salbutamol *Dose*: 100 µg *Duration*: 2 h	85 children, mean age 11.4 years (SD 2.9) with mild-to-moderate asthma All patients had reversibility of FEV_1 of 15% to β_2-agonist	2 trials were included in the study but only data from the short-term study were used as the 4-week study was open and non-comparative	FEV_1, FVC, PEFR	Study included but no data used from the trial as data are in non-extractable form; no reply from author to date Cochrane Allocation = B

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Osterman *et al.*, 1989[230]	*Design*: open-labelled, randomised, crossover, study *Device*: Turbuhaler *Drug*: terbutaline *Dose*: 100 µg per actuation *Duration*: 4 weeks	23 adults with stable asthma, but 19 (15 F) completed the study, mean age 46 years (range 20–66 years) and mean duration of asthma was 17 years (range 2–35 years) FEV_1 reversibility of 15% after inhalation of terbutaline (or equivalent medication); baseline FEV_1 was 1 litre	2 treatment periods each lasting 2 weeks during which patients inhaled 0.5 mg terbutaline 4 times daily from either device. Extra inhalations were permitted but patients were required to record this on the diary card. Patients recorded their PEFR at home 15 minutes post-dose	PEFR, adverse effects, treatment failures, preference	Cochrane Allocation = B
Osterman *et al.*, 1991[95]	*Design*: open-labelled, randomised, parallel study *Device*: Turbuhaler *Drug*: terbutaline *Dose*: 0.5 mg 4 times daily *Duration*: 6 weeks	258 patients recruited: 177 in Turbuhaler group and 81 in pMDI group; 160 and 77 respectively completed the study; mean age 47–48 years, range 17–77 years (mean duration of asthma 15–16 years; range 1–60) Mean FEV_1 reversibility 26–27% (range 15–79)	Run-in period of 2 weeks followed by 6 weeks of treatment with either device. pMDI was 2 x 0.25 mg q.d.s. and Turbuhaler 1 x 0.50 mg q.d.s. Extra inhalations were allowed but patients had to record usage in diary cards along with other study measurements	Symptoms (4-point scale), PEFR, additional β_2 usage, treatment failures	Cochrane Allocation = B
Parameswaran *et al.*, 1999[231]	Study used methacholine challenge *Design*: randomised, double-blind, double-dummy, crossover study *Device*: HFA-pMDI *Drug*: salbutamol *Dose*: 100, 200 and 400 µg *Duration*: Until PC_{20} reached	18 adult (11 F) patients, mean age 31 years, range 19–53 years Baseline FEV_1 of 92% was predicted; FEV_1 was not allowed to vary by more than 10% on study days	Baseline PC_{20} was determined after 200 µg salbutamol from the pMDI. On study days patients were given either 100, 200 or 400 µg salbutamol from either device and methacholine challenge started 10 minutes later until PC_{20} was reached. PR and BP were measured 5 minutes after inhalation. Adverse effects to methacholine were noted on a 3-point Likert scale	PC_{20}, FEV_1, BP, HR, respiratory rate	Treatment allocation sequence was determined by 8 x 8 Latin square Cochrane Allocation = A

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Persson *et al.*, 1988[232]	*Design*: open-labelled, randomised, crossover study *Device*: Turbuhaler *Drug*: terbutaline *Dose*: total dose 4 mg *Duration*: 150 minutes (5 x 30 minutes)	13 adult patients (7 F), mean age 39 years, range 20–59 years, with stable asthma and 20% increase in FEV_1 and an absolute FEV_1 70% of predicted after inhalation of 0.5 mg terbutaline via pMDI; baseline FEV_1 was not allowed to vary by more than 15% between study days	Each patient received cumulative doses of terbutaline every 30 minutes (0.25, 0.25, 0.5, 1.0 and 2.0) from either device; study measurements were done 20–25 minutes after each cumulative dose	FEV_1, tremor, AUC, FVC, peak inspiratory flow rate, forced inspiratory vital capacity	Author reply randomised in blocks of 4; FEV_1 (SD) abstracted from graph Cochrane Allocation = B
Pover *et al.*, 1988[109]	Different doses used in device *Design*: randomised, double-blind, double-dummy, crossover study *Device*: Diskhaler *Drug*: salbutamol *Dose*: Diskhaler 400 µg/ pMDI 200 µg *Duration*: 240 minutes	42 adult patients (26 F), age range 16–75 years All patients had FEV_1 reversibility of 15% following 200 µg salbutamol; patients whose baseline FEV_1 was < 0.5 litres were excluded; baseline FEV_1 on study days could not vary by more than 10%	Each patient received either 400 µg salbutamol from the Diskhaler or 200 µg from the pMDI; FEV_1 measurements were done from 5 to 240 minutes post-dose. The 30-minute timepoint data were entered into RevMan	FEV_1, AUC	FEV_1 (SD) abstracted from graph Cochrane Allocation = B
Ramsdell *et al.*, 1998[233]	*Design*: randomised, single-blinded, 2-way, crossover study *Device*: HFA-134a pMDI *Drug*: salbutamol *Dose*: total dose 1440 µg *Duration*: 120 minutes	22 adult patients, mean age 32.8 years (SD 11.9), with at least a 12-month history of asthma FEV_1 between 40% and 80% predicted and FEV_1 reversibility of 15% 30 minutes after inhaling 2 inhalations of pirbuterol acetate via Maxair®; FEV_1 was required to be between 35% and 85% predicted between each study day and not vary by 15% from baseline	Patients self-administered (under supervision) the study treatments at 30-minute intervals; after each cumulative dose study measurements were performed Washout = 48 h to 8 days	FEV_1, ECG, serum potassium, HR, BP	SDs, FEV_1, HR, serum potassium and BP abstracted from graphs Cochrane Allocation = B

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Ramsdell *et al.*, 1999[100]	*Design*: open-labelled, randomised, parallel study *Device*: HFA-134a pMDI *Drug*: salbutamol *Dose*: two puffs b.d. (strength or dose/puff not mentioned) *Duration*: 12 months	469 adult stable asthma patients (337 HFA and 132 CFC), mean age 34 years (SD 14) (100 F in both groups) Severity – mild: 30/26 HFA/CFC; moderate: 41/42 HFA/CFC; severe: 29/33 HFA/CFC group Predicted FEV_1 was 69% (SD 18) in HFA group and 66% (SD 17) in CFC group; FEV_0 reversibility was = 15% within 30 minutes of using a short-acting beta-agonist	Patients inhaled 2 puffs twice a day for 12 months from either device and additional puffs were allowed in required. Clinic visit for study measurements were done at 0, 3, 6, 9 and 12 months. At each clinic visit patients self-administered 2 puffs of the study drugs and study measurements were done up to 6 h post-dose	FEV_1, adverse effects, treatment failure, exacerbations, oral steroid requirement, AUC, duration, onset	Allocation of treatment was randomised and randomisation was done in blocks of 12, with 2 patients receiving HFA-pMDI for every 1 patient receiving CFC-pMDI Cochrane Allocation = A
Razzouk *et al.*, 1999[77]	*Design*: randomised, double-blind, double-dummy, 4-way, crossover study *Device*: Turbuhaler *Drug*: salbutamol *Dose*: 100 µg (both devices) *Duration*: 240 minutes	40 children (9 F), age range 6–12 years, mean age 9 years (mean duration of asthma 7 years, range 2–12) Mean FEV_1 predicted was 80% 30 minutes after inhaling 200 µg salbutamol from a pMDI (range 61–109), mean FEV_1 reversibility 20 (range 9–45)	Study performed in 2 centres in France and 5 centres in Portugal. 37 patients received 50 µg via Turbuhaler, 37 received 100 µg via Turbuhaler, 38 received 100 µg via pMDI and 40 patients received placebo. Pulmonary function testing was performed from 15 to 240 minutes post-dose Washout = 20 h and < 14 days	FEV_1, FEV_{1max}, adverse effects – but not separated by group	Author reply used sealed envelopes for allocation concealment Cochrane Allocation = A
Ruffin *et al.*, 1995[234]	*Design*: randomised, single-blinded, 4-way, crossover study *Device*: HFA-134a pMDI *Drug*: salbutamol *Dose*: total dose 1920 µg (16 x 120 µg salbutamol sulphate) *Duration*: 150 minutes (5 x 30 minutes)	24 adults patients (16 F), mean age 40 years (SD 12.4) Mean predicted FEV_1 was 65% (SD 13.6), mean FEV_1 reversibility 28.8 (SD 10.4) after 240 µg salbutamol	All patients inhaled cumulative doses of salbutamol from each device as 1, 1, 2, 4 and 8 puffs every 30 minutes Washout = 1–8 days	FEV_1, FVC, serum potassium, pulse rate, BP	Email and fax replies from author on allocation concealment, treatment generated before start of study, codes used for canisters Cochrane Allocation = A

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Salorinne & Siren, 1983[235]	*Design*: randomised, double-blind, double-dummy, crossover study *Device*: Rotahaler *Drug*: fenoterol *Dose*: 0.2 mg *Duration*: 360 minutes	10 adults patients (3 F) with moderate-to-severe asthma, mean age 49 years, range 19–70 years Mean FEV_1 predicted was 51% (range 32–78); FEV_1 reversibility was 15% after 0.4 mg rimiterol	Patients inhaled single doses of 0.2 mg fenoterol from either device and study measurements were done from 10 to 360 minutes post-dose Washout = least 24 h	FEV_1, PEFR, FVC, MEF_{50}, AUC	Cochrane Allocation = B
Selroos *et al.*, 1994[112]	Different dose used in devices *Design*: randomised, double-blinded, double-dummy, cross-over (re author reply) study *Device*: Turbuhaler vs pMDI + 750 ml nebuhaler spacer *Drug*: terbutaline *Dose*: Turbuhaler 1 mg vs pMDI 1 mg *Duration*: 15 minutes post-dose	15 adult patients (10 F), mean age 45.9 years (SD 13.7) < 10% improvement in FEV_1 after 0.4 mg salbutamol or 1 mg terbutaline	Patients received terbutaline from either device on separate days and study measurements were done 15 minutes post-dose	FEV_1	Author reply: randomisation was done in block of 4 and the study was of crossover design Cochrane Allocation = B
Seppala *et al.*, 1998[94]	*Design*: randomised, double-blind, double-dummy, crossover study *Device*: MDPI vs pMDI + 270 ml spacer *Drug*: salbutamol *Dose*: 100 µg (both devices) *Duration*: 360 minutes	41 non-smoking adult patients (17 F) with stable asthma, mean age 43.6 years (SD 14.9, range 20–69) Mean FEV_1 predicted was 58.1% (SD 9.9; range 35–70); mean FEV_1 reversibility was 39.2 (SD 18.9) 20 minutes after 200 µg of salbutamol from a pMDI	Patients inhaled study drugs from either device and study measurements were done from 10 to 360 minutes post-dose Washout = 24 h	FEV_1, Raw, BP, HR, AUC, adverse effects, preference	Cochrane Allocation = B

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Seppala *et al.*, 1998[236]	Study used methacholine challenge *Design*: randomised, double-blind, double-dummy, crossover study *Device*: MDPI vs pMDI + Volumatic spacer *Drug*: salbutamol *Dose*: 100 µg *Duration*: until PD_{20}-FEV_1 was reached	26 adult patients (20 F), mean age 43.3 years (SD 13.9, range 19–64) FEV_1 predicted was 79.9% (SD 11.2, range 60–100); baseline FEV_1 on each study day had to be between 60% and 90% predicted	Patients were given 100 µg salbutamol from either device and 30 minutes later methacholine challenge was started in cumulative doses every 5 minutes (18, 36, 71, 110, 180, 360, 530, 890, 1600 and 2300 µg) and FEV_1 was measured every 3–4 minutes after each dose. Methacholine challenge continued until FEV_1 decreased by 20% compared to baseline (PD_{20}) Washout = 24 h but < 2 weeks	FEV_1, BP, HR, ECG, adverse effects, PD_{20}-FEV_1	Cochrane Allocation = B
Silvasti *et al.*, 1993[237]	*Design*: randomised, double-blind, double-dummy, crossover study *Device*: Easyhaler *Drug*: salbutamol *Dose*: 180 µg (both devices) *Duration*: 360 minutes	23 adult patients (8 F), mean age 49.3 years (SD 13.1), mean duration of asthma 12 years (SD 14.6); severity - mild: 4, moderate: 9, severe: 2, very severe: 3 All patients showed = 15% in FEV_1 after inhalation of 200 µg of salbutamol; variation of < 15% on study days in FEV_1 was required – if it was greater, the visit was rescheduled	A single dose of 180 µg salbutamol was delivered to all patients from either device on separate days and study measurements were done until 360 minutes post-dose; 30-minute data points were entered into RevMan Washout between study days = 1 week	PEFR, FVC, FEV_1, AUC-Raw, FEV_{1max}, adverse effects	Cochrane Allocation = B
Svedmyr *et al.*, 1982[93]	*Design*: open-labelled, randomised, crossover study *Device*: Rotahaler *Drug*: salbutamol *Dose*: total dose 4.2 mg *Duration*: 150 minutes (5 x 30 minutes)	7 adult patients (2 F) with asthma, mean age 51.29 years (SD 11.94), mean duration of asthma 11.14 years (SD 10.16) All patients showed FEV_1 reversibility to 1.25 mg terbutaline of between 20% and 50%	Starting dose for both the devices was not the same as the pMDI had an initial dose of 100 µg and none for the Rotahaler. Rotahaler dose began at 200 µg	FEV_1, FVC, HR	Cochrane Allocation = B

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Svenonius *et al.*, 1994[78]	Exercise challenge used in study *Design*: randomised, double-blind, double-dummy, crossover study *Device*: Turbuhaler *Drug*: terbutaline *Dose*: 1 mg (both devices) *Duration*: 15 minutes post-dose	12 children (2 F), mean age 13.8 years, range 9–17, mean duration of asthma 12 years, range 8–15 years Patients were selected if FEV_1 decreased by = 15% after a 6-minute exercise test; this fall in FEV_1 could not vary by more than 5% on study days	Lung function was measured before treadmill exercise then the drug was administered and measured again 4–15 minutes post-dose to observe reversibility of EIA; terbutaline dose per puffs was 0.5 mg for the Turbuhaler and 0.25 for the pMDI 15-minute data point was used in RevMan	FEV_1 and VTG	Cochrane Allocation = B
Taggart *et al.*, 1995[238]	*Design*: double-blind, double-dummy, crossover study (not mentioned if randomised but implied in paper) *Device*: HFA-pMDI + Volumatic spacer vs pMDI + Volumatic spacer *Drug*: salbutamol *Dose*: 200 µg (100 x 2 from both devices) *Duration*: 30 minutes post-dose	24 non-smoking adult patients (14 F), mean age 37 years Baseline FEV_1 was allowed to vary by more than 15%	Patients were given two puffs from either device; using a Volumatic spacer lung function measurements were done 30 minutes later and histamine challenge was started. Only used data at 30 minutes post-dose (pre-histamine challenge) in RevMan Washout = < 24 h < 7 days	FEV_1, FVC	Cochrane Allocation = B
Tammivaara *et al.*, 1997[239]	*Design*: open-labelled, randomised, parallel study *Device*: MDPI *Drug*: salbutamol *Dose*: 200 µg twice daily *Duration*: 12 weeks	115 adults patients (70 F), who showed an improvement in FEV_1 or PEFR of 15% after inhalation of 200 µg salbutamol; 2 patients were excluded therefore analysis was based on 113 patients (MDPI = 77/pMDI = 36, mean age 49 years (SD 13)/49 years (SD 14); mean duration of asthma 8.4 years (SD 8.6)/9.4 years (SD 9.9); predicted FEV_1 of 82.5% (SD 18.2)/74.4% (SD 20.8))	There was a run-in period of 2 weeks followed by 12 weeks of treatment period. 2 puffs twice daily were delivered from each device for 12 weeks (both devices were 100 µg/puff). Additional relief medication was allowed with a second inhaler of the same type in each group. Study measurements were noted daily by patients. 30-minute post-dose data were entered into RevMan, but 15 minutes post-dose for PEFR	PEFR, FVC, FEV_1, treatment failures, preference, additional β_2 use, adverse effects, symptoms	Author reply: treatment allocation was randomly done using computer-generated codes Cochrane Allocation = A

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Thompson, 1995[111]	Different dose was used in the devices *Design*: randomised, single-blind, double-dummy, 4-way, cross-over study *Device*: HFA-134a pMDI *Drug*: salbutamol *Dose*: HFA 8 puffs vs pMDI 16 puffs (strength/dose not specified) *Duration*: 150 minutes (5 x 30 minutes)	24 adult patients, aged 18–65 years with at least a 12-month history of asthma All patients had FEV_1 reversibility of 15%	During study days patients received consecutive doses of 1, 1, 2, 4 and 8 inhalations of salbutamol from either device at 30-minute intervals Washout = between 1 and 8 days between study days	FEV_1, $FEF_{25–75\%}$	Cochrane Allocation = B
Tinkelman *et al.*, 1998[240]	*Design*: randomised, double-blind, double-dummy, parallel study *Device*: HFA-134a pMDI *Drug*: salbutamol *Dose*: 2 puffs q.d.s. from both inhalers (dose not specified) *Duration*: 12 weeks	565 adults patients were entered into the study from 33 sites across USA (HFA = 193, pMDI = 186, placebo = 186); 29 patients were discontinued from the study All patients were aged between 18 and 65 years, with at least a 12-month history of asthma All patients had a FEV_1 of 40–80% predicted and at least 15% increase in FEV_1 30 minutes after inhaling 200 µg salbutamol from a Rotahaler Patients were recruited if they demonstrated a satisfactory technique in the use of pMDI	Randomisation was stratified so at least half the patients in each group were taking inhaled corticosteroids. 7-day run-in with usual medication was used. All patients took 2 puffs from 2 inhalers 4 times a day for 12 weeks and could also use rescue medication from a Rotahaler as required	Rescue β_2 usage, PEFR, symptoms, exacerbations, side-effects, HR, BP, complete blood count, treatment failure	PEFR, symptoms, rescue medication usage and SDs obtained from graphs Cochrane Allocation = B

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Tukiainen & Terho, 1985[241]	Different doses used in devices *Design*: randomised, double-blind, double-dummy, crossover study *Device*: Rotahaler *Drug*: salbutamol *Dose*: Rotahaler 400 µg vs pMDI 200 µg *Duration*: 120 minutes	22 adult hospital in-patients with stabilised asthma, mean age 63 years (19 F) All patients were admitted to hospital for worsening asthma and when stabilised were included in the study	On consecutive mornings the patients inhaled 2 puffs from the pMDI (100 µg/puff) followed 2 minutes later by 1 capsule from the Rotahaler (400 µg/capsule). Study measurements were done before and 5, 15, 30, 60 and 120 minutes post-dose. The 30-minute time point data were entered into RevMan. All drugs were inhaled at the same time each morning	PEFR, BP, HR	PEFR and SD were extracted from the graph Cochrane Allocation = B
Vidgren *et al.*, 1995[73]	*Design*: randomised, double-blind, double-dummy, cross-over study *Device*: Easyhaler *Drug*: salbutamol *Dose*: 100 µg (both devices) *Duration*: 240 minutes post-dose	40 adult patients (15 F), mean duration of asthma 9 years (range 1–33 years), with 15% improvement in FEV_1 or PEFR after inhaling 0.2 mg salbutamol Mean baseline FEV_1 of 58.8% was predicted. Variation between study days in baseline FEV_1 could not be more than 15% – if variation was greater visit was rescheduled	All patients received single doses of salbutamol at the same time on test days from either device and study measurements were done from 15 to 240 minutes post-dose	BP, HR, FEV_1, PEFR, AUC, FVC, preference, adverse effects	Cochrane Allocation = B
Villiger & Schwarz, 1990[242]	*Design*: open-labelled, randomised, crossover study *Device*: Turbuhaler *Drug*: salbutamol *Dose*: 500 µg (both devices) *Duration*: 360 minutes	10 adult patients with stable asthma entered the study	All patients received 1 puff (500 µg) from either the Turbuhaler or 2 puffs (500 µg) from the pMDI. Study measurements were done from 15 to 360 minutes post-dose	Side-effects, FEV, VC	Abstract only Cochrane Allocation = B

continued

TABLE 16 contd *Review B: characteristics of included studies*

Study	Methods	Participants	Interventions	Outcomes	Notes
Waterhouse *et al.*, 1992[243]	*Design*: randomised, double-blind, double-dummy, 2-way, crossover study *Device*: Autohaler *Drug*: salbutamol *Dose*: 200 µg (both devices) *Duration*: 240 minutes	25 adult hospital outpatients with stable asthma (pMDI = 6 F; Autohaler = 5 F), mean age 60.5 years (SD 9.6)/51.3 years (SD 13.3) All patients had FEV_1 of < 75% predicted and an increase of 15% 50 minutes after 200 µg salbutamol FEV_1 was predicted of 40% (17) and 43% (15)	Single dose of 200 µg was administered from either device and study measurements done from 5 to 240 minutes post-dose	FEV_1, FVC, PEFR	FEV_1, FVC, PEFR and SDs extracted from graphs Cochrane Allocation = B
Zainudin *et al.*, 1990[244]	*Design*: randomised, double-blind, double-dummy, 2-way, crossover study *Device*: Rotahaler *Drug*: salbutamol *Dose*: 400 µg (both devices) *Duration*: 60 minutes	9 adult patients (6 F), aged 20–68 years, asthma duration 10–60 years FEV_1 improved by 15% after 200 µg salbutamol via pMDI; mean baseline FEV_1 was 55%	All patients inhaled technetium-labelled salbutamol, from either pMDI, Rotahaler or nebuliser, and study measurements were done 60 minutes post-dose Washout = 3 days	PEFR, FEV_1, FVC, lung deposition using gamma camera	Cochrane Allocation = B

PIF, peak inspiratory flow; PEF, peak expiratory flow; AUC, area under the curve; SGaw, specific airway conductance; SEM, standard error of the mean; VC, vital capacity; MEF, maximum expiratory flow; MEF_{50}, MEF at 50%; MDPI, multidose powder inhaler

that patients still preferred the pMDI almost three times more frequently than the Rotahaler: OR 2.96 (95% CI, 1.58 to 5.56; $p = 0.0007$) (*Figure 7*).

Pulse rate reported by a cumulative dosing crossover study[93] as absolute change from baseline showed that it was lower by 5.5 beats per minute (bpm) when using the Rotahaler device: WMD 5.50 (95% CI, 0.96 to 10.04; $p = 0.02$).

Multi-dose powder inhaler

Inhaler preference reported as dichotomous data by one short-term crossover study[94] showed that patients preferred the MDPI more than three times more frequently than the pMDI: OR 0.37 (95% CI, 0.15 to 0.93; $p = 0.04$).

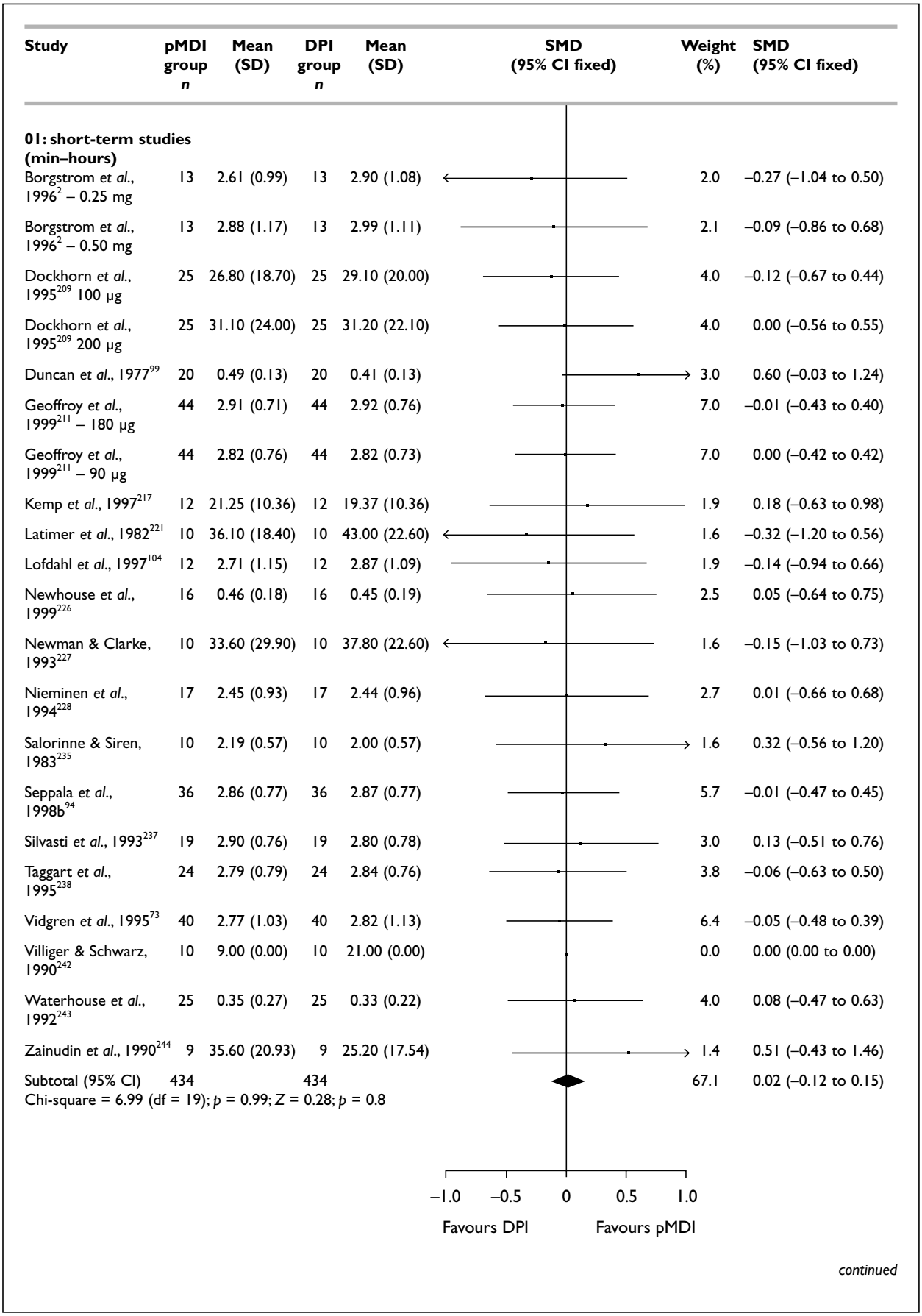
Turbuhaler

Inhaler preference reported by one long-term parallel study[95] showed that the odds of patients preferring the pMDI were three times smaller when compared with the Turbuhaler: OR 0.37 (95% CI, 0.22 to 0.65; $p = 0.0005$).

Pulse rate reported by two cumulative dosing crossover studies[96,97] as absolute mean values at the end of the study period showed that it was lower with pMDI use when compared to the Turbuhaler: WMD 4.34 (95% CI, 1.17 to 7.52; $p = 0.007$). Pulse rate was also reported by another cumulative dosing study,[98] but with data reported as absolute change from baseline, showed that it was lower by 10 bpm when using the pMDI: WMD 10.5 (95% CI, 4.49 to 16.51; $p = 0.0006$). When these three studies[96–98]

TABLE 17 *Non-significant outcomes from included studies*

Crossover studies		Parallel studies		Challenge studies		Different dose studies	
Device	**Outcomes**	**Device**	**Outcomes**	**Device**	**Outcomes**	**Device**	**Outcomes**
Turbuhaler	FEV_1, FVC, PEFR, AUC-FEV_1, BP, adverse effects, treatment failure	DPI or HFA-pMDI	FEV_1, FVC, PEFR, AUC-FEV_1, β_2 use, symptom scores, exacerbations, adverse effects, preference, inhaled steroid requirement	DPI or HFA-pMDI	FEV_1, FVC	DPI or HFA-pMDI	FEV_1, FVC, PEFR, preference, symptoms
Diskhaler	PEFR, adverse effects						
HFA-pMDI	FEV_1, FVC, exacerbations, adverse effects, treatment failures, AUC-FEV_1, pulse rate, BP, serum K+, inhaled steroid requirement						
Rotahaler	FEV_1, FVC, PEFR, AUC-FEV_1, adverse effects, exacerbations						
Spiros	FEV_1, FVC, AUC-FEV_1, adverse effects, exacerbations						
Easyhaler	FEV_1, FVC, PEFR, AUC-FEV_1, pulse rate, BP, adverse effects						
MDPI	FEV_1, FVC, PEFR, AUC-FEV_1, adverse effects						
Clickhaler	FEV_1, adverse effects						
Gentlehaler	FEV_1, FVC, PEFR						
Autohaler	FEV_1, FVC, PEFR						



continued

FIGURE 6 *The pMDI versus all other hand-held inhaler devices: example of a non-significant meta-view result (combined using SMD)*

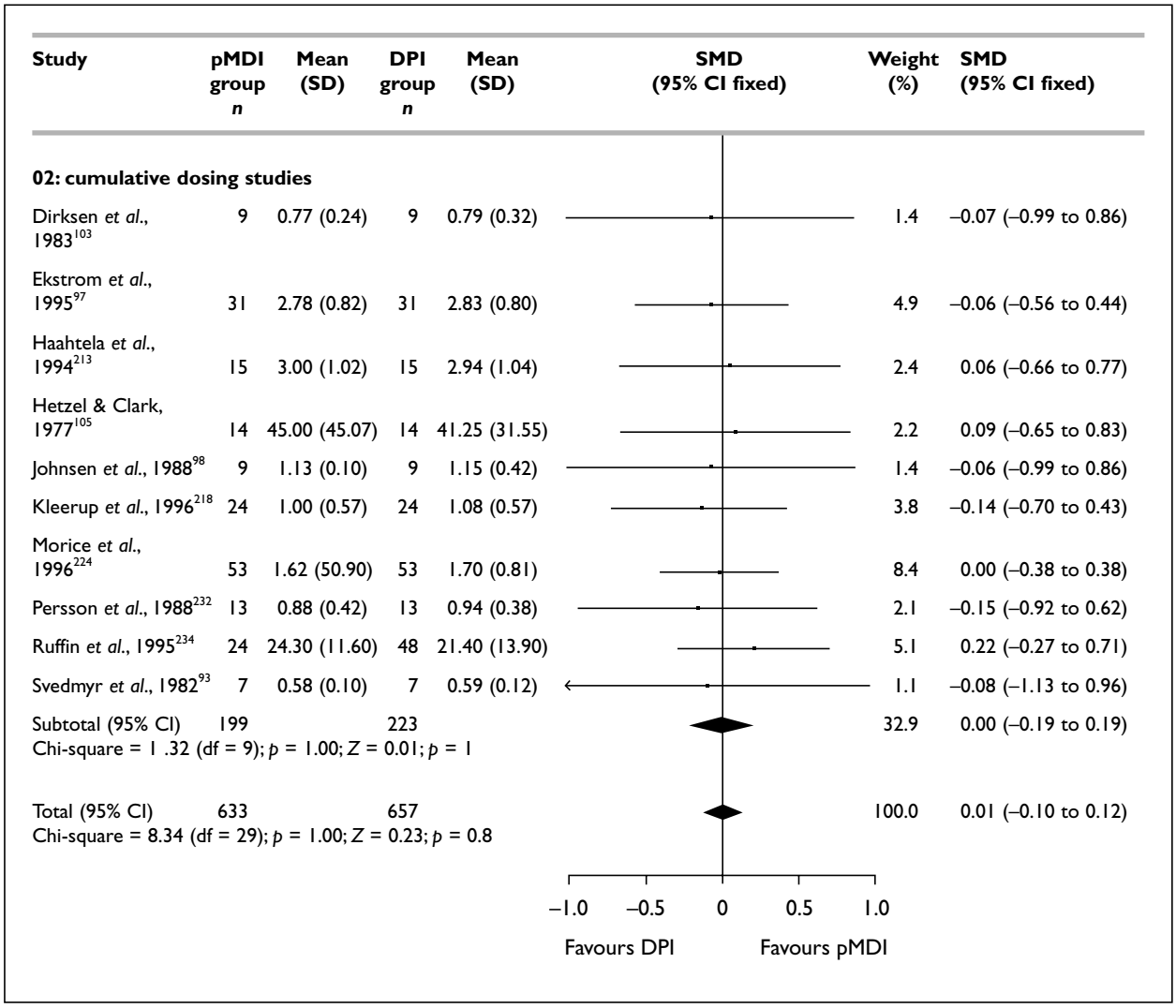


FIGURE 6 contd *The pMDI versus all other hand-held inhaler devices: example of a non-significant meta-view result (combined using SMD)*

were combined using SMD, the overall pulse rate was significantly lower with pMDI use when compared to the Turbuhaler: SMD 0.44 (95% CI, 0.05 to 0.84; $p = 0.03$) (*Figure 8*).

Spinhaler

Lung function (FEV_1 and FVC) reported as absolute change from baseline by one short-term crossover study[99] using 40 patients showed that FEV_1 increased by 80 ml with the use of the pMDI when compared to the Spinhaler. FVC, also reported by the same study as absolute change from baseline, showed that it increased by 260 ml with the use of the pMDI when compared to the Spinhaler. Both these lung function parameters were reported as mean change from baseline over 300 minutes after administration of a bronchodilator.

HFA-pMDI

Two long-term parallel studies,[100,101] both using HFA-pMDIs, reported treatment failure/study dropout as dichotomous data in 519 patients (156 in the pMDI group and 363 in the HFA-pMDI group). One study[100] combined the results of two separate studies (a and b). There was selective randomisation in study 'a' and the possible introduction of bias.

The long-term use of the HFA-pMDI containing salbutamol significantly reduced the risk of patients dropping out or failing treatment when compared to the pMDI: RR 0.40 (95% CI, 0.17 to 0.94; $p = 0.034$) (*Figure 9*).

These same two studies[100,101] using HFA-pMDIs also reported the number of patients requiring oral steroids during the study period. Use of the HFA-pMDI containing salbutamol significantly reduced (halved) the number of patients requiring treatment with short courses of oral steroids: OR 0.56 (95% CI, 0.36 to 0.87; $p = 0.010$) (*Figure 10*).

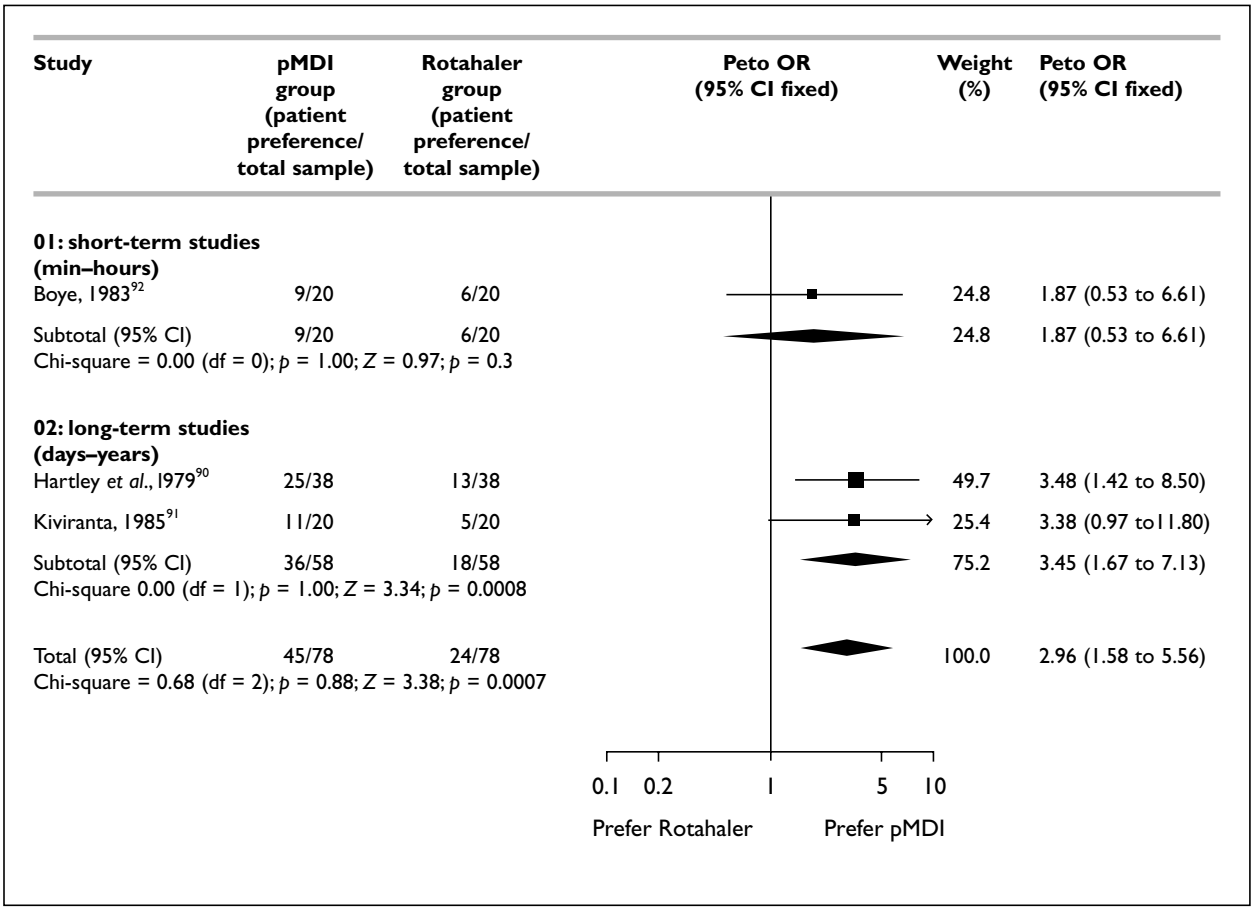


FIGURE 7 *Preference for the Rotahaler inhaler device: pMDI versus Rotahaler (combined using SMD)*

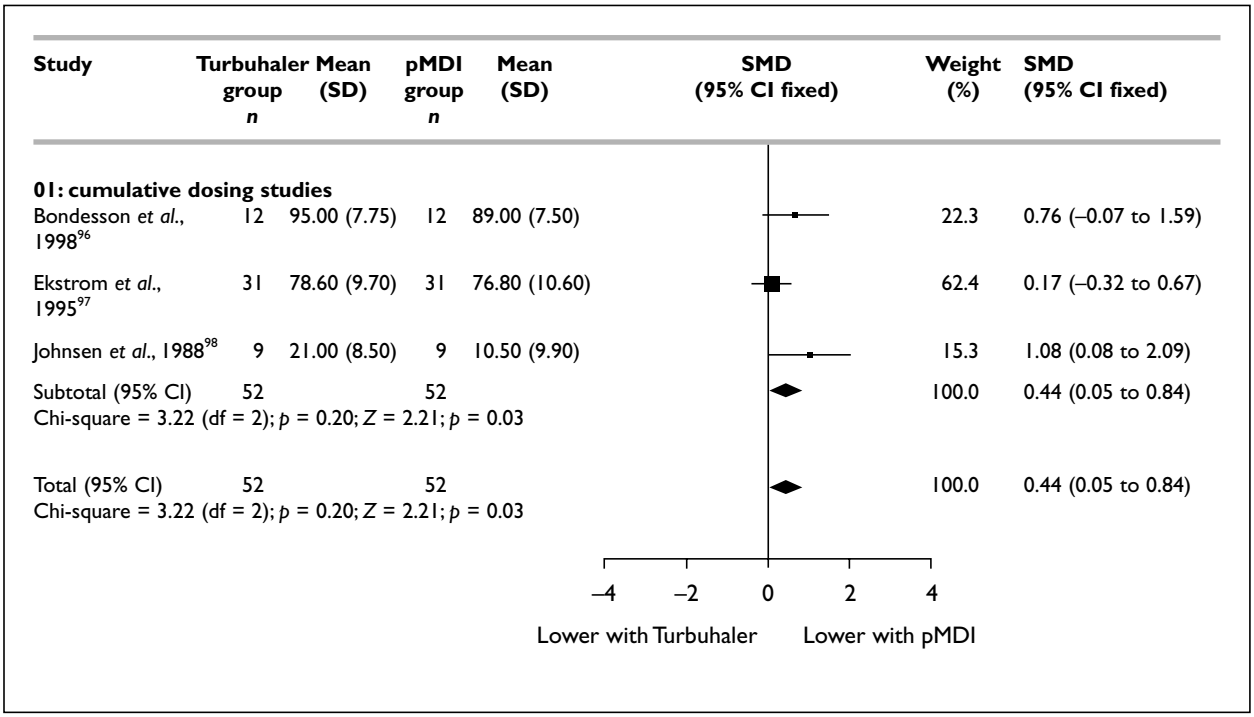


FIGURE 8 *Pulse rate: pMDI versus Turbuhaler (combined using SMD)*

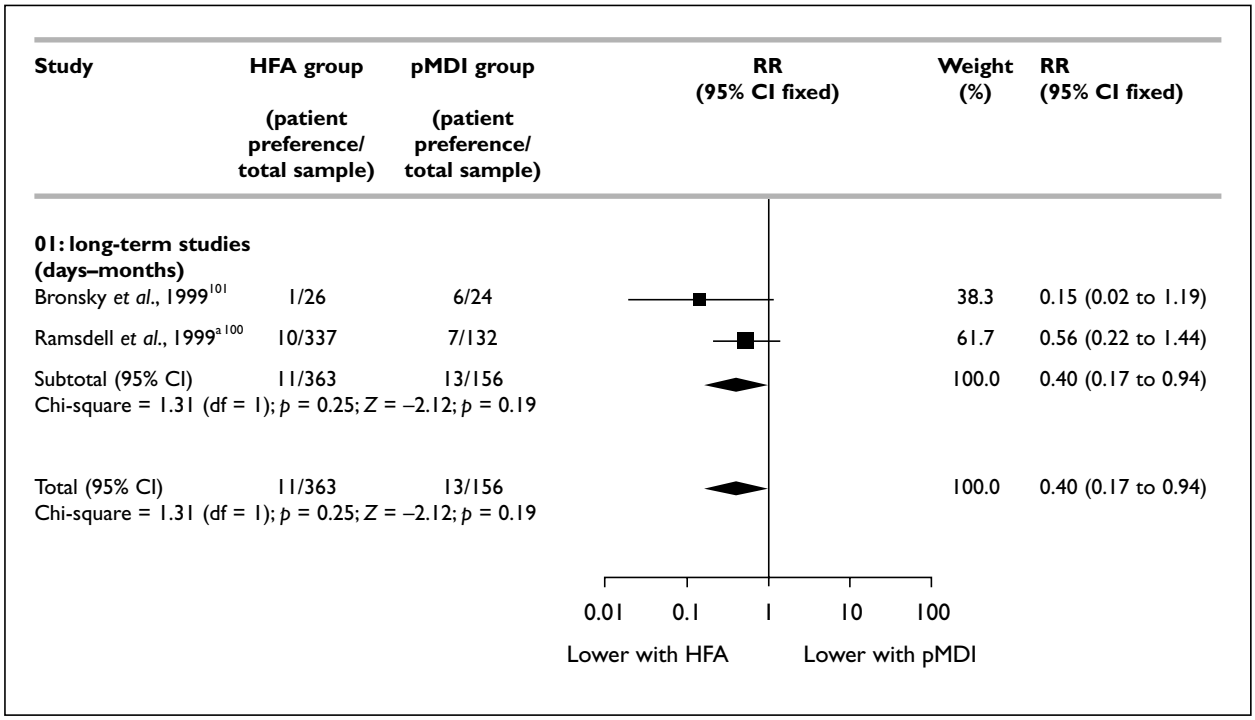


FIGURE 9 *Treatment failure meta-view for the pMDI versus DPI or HFA (% change from baseline) from parallel design studies*

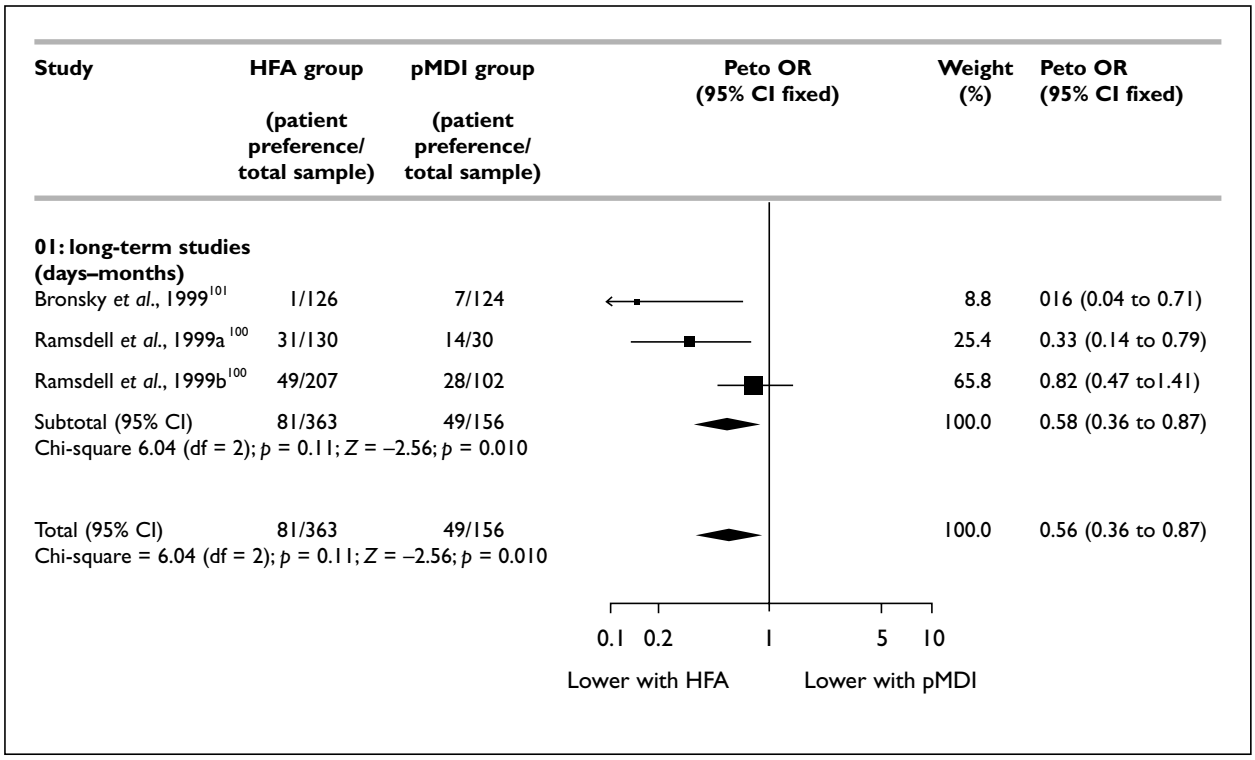


FIGURE 10 *Oral steroid requirement: pMDI versus DPI or HFA (% change from baseline) from parallel design studies*

Exclusion of Ramsdell and colleagues'[100] study 'a' because of inadequate randomisation renders both results non-significant.

The use of inhaled corticosteroids was reported in the Bronsky and colleagues'[101] study, which was reported to be similar in both study groups (54% for the HFA-pMDI and 48% for the pMDI). The Ramsdell and colleagues'[100] study did not report use of inhaled steroids during the study period.

No data were available from the included studies for the following outcome measures: quality of life, patient compliance, nocturnal awakening and days off work or school.

Discussion

A possible pitfall in Review B is the inclusion of crossover studies and the presence of carry-over effects leading to an underestimation of the real difference between treatments.[102] In the crossover studies included (e.g. Dirksen and Groth,[103] Ekstrom and colleagues,[97] Lofdahl and colleagues,[104] Hetzel and Clark,[105] Johnsen and Weeke[98]), treatment with short-acting β_2-agonists did not seem to alter (the second arm) pre-bronchodilator respiratory function (FEV_1). If pre-bronchodilator lung function did differ by greater than 10–15% from baseline, then patients were excluded from the study or the second arm visit was rescheduled. This suggests that carry-over effects are unlikely to have occurred in most of the included studies, despite their crossover design and since most studies did have a washout period.

Another possible pitfall is that this meta-analysis was conducted using crossover studies and all included studies were analysed as if they were parallel studies. It is known[106] that these two study designs (crossover and parallel) give identical results if the response to the two treatments in the same individual is completely unrelated, but parallel analysis may lead to decreased statistical power when compared to paired analysis if the response to the two treatments is positively correlated (i.e. if patients improving during bronchodilator treatment with one device are also likely to improve during treatment with another device). This is the case in Review B, since patients were responsive to both inhaler devices in all studies, as both comparative groups in all included crossover studies contained active treatment. None of the studies reported the correlation among the responses to the inhaler devices used and the majority of the studies did not provide any variance data either. Therefore, in comparison with a paired analysis, we cannot exclude that our analysis underestimated the statistical significance of the observed differences.

A major problem and potential weakness of this review has been the inaccessibility of data on outcomes known to have been measured (but unreported), and data not presented in a form that can be combined in meta-analysis. This may be a confounding factor in the results and thus the conclusions. In particular, if pharmaceutical companies provided data from their large studies it could have appreciably added to this review.

Non-significant findings

Overall

Meta-analysis of the data available from 81 RCTs included in this systematic review found no statistically significant ($p > 0.05$) differences in patients who had stable asthma when the standard pMDI was compared with any of the other ten hand-held inhaler devices (Turbuhaler, Diskhaler, HFA-pMDI, Rotahaler, Spiros, Easyhaler, MDPI, Clickhaler, Gentlehaler and Autohaler) for the following parameters: pulmonary lung function, asthma symptoms, use of additional relief medication, inhaled steroid requirement, acute exacerbation, BP, bronchial hyperreactivity and systemic bioavailability.

Studies with different doses

Regardless of the inhaler device being used, studies using 2:1 or greater dosing[107–112] did not provide results that were different from 1:1 dosing studies, except in one study with children[113] where daily PEFR was significantly higher (when using a 2:1 dosing schedule) in the group with the Rotahaler device.

Significant findings

Overall

This review has reported significant differences between the pMDI and the Turbuhaler, HFA-pMDI, Rotahaler, Spinhaler and MDPI for the following outcome measures: patient preference, pulse rate, oral steroid requirement and treatment failure.

Rotahaler

In most of the trials where it showed that patients preferred the pMDI to the DPI, the DPI involved was the Rotahaler device. Three crossover studies in adults (one short-term,[92] and two long-term studies[90,91]) showed that the odds of patients preferring the pMDI were three times higher compared to the Rotahaler device.

Turbuhaler
Three crossover studies in adults[96–98] showed that the pulse rate was significantly lower with the pMDI compared to the Turbuhaler. This decrease was in the order of 4–10 bpm. This lower pulse rate seen with the use of the pMDI would imply lower systemic absorption of the inhaled dose from the pMDI. This finding is in agreement with a previously published study,[2] which showed that the percentage pulmonary deposition of inhaled drug is lower with the use of the pMDI when compared to the Turbuhaler (8.3% and 22.0%, respectively, after a nominal dose of 0.5 mg terbutaline). Owing to the short half-life of β_2-agonist bronchodilators, the unwanted effects of a higher pulse rate with the use of any DPI device would be short-lived.

HFA-pMDI
More patients dropped-out of the study when they were in the pMDI group (13/156) than in the HFA-pMDI group (11/363). These two studies[100,101] have shown that regular daily use of the HFA-pMDI containing salbutamol significantly reduces the dropout rate or treatment failure. However, the 12-month study[100] has also shown that the bronchoprotective effects of salbutamol (from both the HFA-pMDI and standard pMDI) is significantly reduced with regular long-term use of salbutamol. This decrease in bronchodilator efficacy was shown by significant decreases at 12 months in AUC-FEV_1, duration of bronchodilator effect and peak percentage change in FEV_1, when compared with baseline values. There is disagreement on whether long-term regular use versus as-required use of short-acting β_2-bronchodilators reduces its effectiveness. Decreased bronchodilator effectiveness with regular long-term use is supported by some studies[114–118] but not by others.[119–121]

The requirement for oral steroids was significantly reduced with the use of the HFA-pMDI containing salbutamol, although the incidence of acute exacerbations was similar to pMDI. This was seen in the mean overall result from two long-term parallel studies.[100,101]

Caution should be taken over the findings that HFA-pMDIs reduce treatment failure and oral steroid requirements. The Ramsdell and colleagues[100] study was inadequately randomised. Exclusion of this data from the analysis renders the overall result for treatment failure non-significant. Further adequately randomised studies using as-required salbutamol are required to confirm these findings.

Summary
A plethora of different devices is available for the delivery of inhaled drugs in patients with asthma. This, and the competing claims of pharmaceutical companies, often makes it difficult for prescribers to choose the best device for different patients and circumstances. Although the standard pMDI has drawbacks for some patients (e.g. the very young, physically impaired or elderly people), it remains a suitable delivery system for β_2-agonist therapy for many patients and is convenient and inexpensive. This is reinforced by the findings of this review, which was not able to demonstrate any differences in the clinical bronchodilator effect of short-acting β_2-agonists delivered by the standard pMDI or that produced by a any other DPI, HFA-pMDI or the Autohaler device.

REVIEW C: ß$_2$-agonists for stable asthma – hand-held inhalers versus nebulisers

Results in children
Three RCTs were available in stable asthmatic children 2 years or older. Two compare the pMDI + spacer and one a Rotahaler DPI versus nebuliser. Characteristics are detailed in *Table 18*.

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.[245] 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 the pMDI + spacer – approximately 10% versus 20–30%[39,244] – and therefore larger doses are prescribed. In addition, recommended doses via a nebuliser are for acute severe attacks and doses tend to reflect this. In contrast, recommended doses via pMDI will be more conservative.[32,33] Comparison of standard doses may not be justified and would therefore favour a nebuliser. This problem was overcome in the systematic review 'Comparison of holding chambers and nebulisers for beta-agonists in acute asthma'[246] by only considering studies that titrated doses to clinical response. The ratio of pMDI: nebuliser dose in the included studies was between 1:4 and 1:6. Recommended doses for salbutamol for symptomatic relief are 200 µg by pMDI and 2.5 mg or 5 mg by nebuliser,[32,33] giving ratios of 1:12.5 or 1:25. To summarise, drug delivery and clinical response

TABLE 18 *Review C: details of RCTs in children – bronchodilators by nebuliser versus hand-held inhalers*

Study	Methodology	Details	Results	Comments
Blackhall, 1987[247] A dose–response study of inhaled terbutaline administered via Nebuhaler or nebuliser to asthmatic children Financial support from Astra Pharmaceuticals, Australia	*Design*: crossover, open, dose–response RCT *Device*: pMDI + Nebuhaler vs nebuliser *Drug*: terbutaline *Dose*: pMDI, 0.5 + 0.5 + 1 + 2 mg; nebuliser, 1 + 1 + 2 + 4 mg *Duration*: 2 x 1 day	*Participants*: 12 asthmatic children (6 M, 6 F), aged 5–10 years *Quality*: Cochrane A	*No significant differences in*: Increase in FEV_1 and absolute pulse between pMDI 0.5/1 mg and nebulised 4 mg The log dose–response curves were parallel	It is suggested that children of this age are prescribed 250–500 µg by pMDI and 3–5 mg by nebuliser (*British National Formulary*). At these doses there is a non-significant difference in favour of nebuliser for FEV_1. If the comparison is 1 mg vs 4 mg then the non-significant difference favours pMDI + spacer
Grimwood *et al.*, 1981[249] Salbutamol: tablets, inhalational powder, or nebuliser? Allen and Hanburys (NZ) supplied placebo tablets and capsules	*Design*: 3-way, crossover RCT, double-blinded, double-dummy *Device*: Rotahaler vs nebuliser vs oral tablet *Drug*: salbutamol *Dose*: 400 µg vs 4 mg vs 4 mg *Duration*: 3 x 4 h (separate days)	*Participants*: 17 'severe' asthmatic children (7 M, 10 F), mean age 7.2, range 4–12 years *Quality*: Cochrane B	*No significant difference in*: % improvement in PEFR	There appears to be a trend in favour of the nebuliser. However, Rotahaler would not be a valid comparison for most children. Salbutamol 400 µg by Rotahaler is probably equivalent to 200 µg by pMDI
Pierce *et al.*, 1992[248] Nebuhaler versus wet aerosol for domiciliary bronchodilator therapy One author was an employee of Astra Pharmaceuticals, Australia	*Design*: crossover RCT, open *Device*: pMDI + Nebuhaler vs nebuliser *Drug*: terbutaline *Dose*: pMDI, 0.25 mg/5 kg; nebuliser, 1 mg/5 kg *Duration*: 2 x 4 weeks	*Participants*: 22 asthmatic children (11 M, 11 F), mean age 9.9 years 32 adults presented separately in the study *Quality*: Cochrane B	*No significant differences in*: Clinic FEV_1 and FVC and home PEFR (am + pm), symptom scores and sleep disturbance and device preference 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 the nebuliser (23 to 11), again despite an equivalent clinical response

shows that the pMDI + spacer delivers two to six times the dose of a nebuliser, but nebuliser dosages are recommended at 12.5 to 25 times the dose.

Blackhall[247] is a cumulative dose–response study allowing various doses to be considered. At a 'standard' relief dosage of pMDI terbutaline 500 µg (two puffs), there was no statistical difference to 4 mg by nebuliser, although the direction of effect did favour the latter. At 1 mg pMDI (four puffs), again there was no statistical difference but the direction of effect favoured the pMDI.

Pierce and colleagues' study[248] was of 4 weeks' duration for each treatment period and set in the home. Dose was adjusted for body weight and at a pMDI:nebuliser ratio of 1:4. There were no differences in any measures of lung function or patient-reported symptom scores.

Grimwood and colleagues[249] 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 A (page 19), the study Rotahaler dose of salbutamol 400 µg is probably equivalent to 200 µg by pMDI (two puffs). This is compared to 4 mg by nebuliser. No statistical difference was found.

In summary, three trials totalling 51 individuals demonstrated no evidence of clinical superiority of nebulisers over other inhaler devices.

Results in adults

Description of studies

The studies included a broad range of individuals, location and types of comparison. Details are summarised in *Table 19*. Four included studies have drug company involvement through supply of study drugs, funding or authorship. The duration of the studies was usually short (hours) in 14 of the 16 studies. Two studies were in the community setting over 2–4 weeks. Different bronchodilators and delivery devices including different spacer devices were used. Additionally, even between the same drug/device comparison, different studies used a different dosage ratio.

Methodological quality of included studies

Overall, the methodological quality of the included studies was poor: all studies were of Cochrane grade 'B' (due to lack of description of allocation concealment). Nine of the 16 study designs were of open design. Many studies did not comment on withdrawals and dropouts, and also did not report whether intention-to-treat analysis was employed. The sample size of individual studies was small: the largest included 38 adults with the remainder including between seven and 22 participants. All studies were of a crossover design.

In all, 527 abstracts were identified from the electronic search, of which 20 were selected for possible inclusion in the review. Six further abstracts were identified from the references in the included studies. The full text of each paper was obtained. Nine papers were excluded for the following reasons (*Table 20*): three studies were non-clinical (histamine provocation or lung deposition); two were studies in patients with acute asthma; two were observational studies only; one compared different spacer devices; and one had no extractable data and the author was untraceable.

A total of 16 papers were included for Review C, yielding 21 included studies due to Rochat and colleagues 1983a/b[250] being separate studies within the same paper and Cissik and colleagues 1986a/b/c,[136] Pedersen and Bundgaard 1983a/b,[251] and Zainudin and colleagues 1990a/b[244] describing multiple device/drug comparisons within a multi-way crossover design.

The results for each outcome were analysed using the delivery device type (pMDI alone, pMDI + spacer or DPI) as subgroups. The results were combined because there was no evidence of heterogeneity, and also a fixed effect model was used throughout.

Throughout the results, negative figures favour the nebuliser. For the SMD of FEV_1 there was no statistically significant difference in the treatment effect of nebuliser versus pMDI alone: –0.05 (95% CI, –0.37 to 0.26); pMDI + spacer: –0.13 (95% CI, –0.38 to 0.13); DPI: –0.05 (95% CI, –0.69 to 0.59); or combined: –0.09 (95% CI, –0.28 to 0.10). Converting this to a clinically meaningful absolute value using typical group data of a FEV_1 of 2 litres and SD 0.9, this equates to 85 ml (95% CI ± 170 ml) in favour of the nebuliser.

For the SMD of PEFR the results are similar, with values of pMDI alone of 0.55 (95% CI, –0.4 to 1.49); pMDI + spacer: –0.13 (95% CI, –0.53 to 0.28); DPI: –0.22 (95% CI, –0.76 to 0.33); or combined: –0.08 (95% CI, –0.39 to 0.22). For typical data of PEFR 250 litres/minute and SD 80, this equates to 6 litres/minute (95% CI, ± 25 litres/minute) in favour of the nebuliser.

No statistically significant treatment differences were demonstrated in other outcomes, but the number of studies contributing data was small: use of additional relief medication, symptom score and patient preference for device was one study each; FEF and SGaw was four studies each. The limits of precision around the point estimate of no treatment effect are large and cannot exclude a clinically significant effect.

Discussion

Combining the included studies in a meta-analysis supports the findings of the individual studies. The individual studies are of small sample size and the nature of the patients recruited (severe and chronic asthmatics) leads to wide estimates of error (SEM) for the pulmonary function outcome measures. Therefore, the trials have low statistical power to detect possible treatment differences. The results of the meta-analysis do, however, produce narrow enough confidence intervals of no overall treatment effect, such that each end of the error range is within clinically equivalent limits, at least for the primary outcomes of the studies, namely PEFR and FEV_1.

Potential weaknesses of the analysis come from a number of sources concerning the design of the trials, the outcome measures available and publication bias. They are discussed individually below.

Doses of drugs used

In any study of hand-held inhalers versus nebulisers the choice of dosages to be studied is critical. Bronchodilators, whether nebulised or via MDI,

TABLE 19 *Review C: included trials – nebulisers versus hand-held inhalers in adults*

Study	Methodology	Details	Results	Comments
Christensson *et al.*, 1981[253] Salbutamol inhalation in chronic asthma brochiale: dose aerosol vs jet nebuliser	*Design*: crossover, open trial *Device*: pMDI alone vs jet nebuliser *Drug*: salbutamol *Dose*: 300 µg vs 5 mg *Duration*: 2 x 1 day	*Participants*: 20 asthmatics (8 M, 12 F), mean age 52 years, range 22–68 years *Quality*: B	FEV_1, FVC (CFB)	
Cissik *et al.*, 1986a,b,c[136] Double-blind crossover of five medications and two delivery methods in stable asthma	*Design*: 10-way crossover, double-blind *Device*: pMDI alone vs nebuliser *Drug*: (a) isoetharine; (b) isoproterenol; (c) metaproterenol *Dose*: (a) 680 µg vs 0.5 mg; (b) 500 µg vs 0.5 mg; (c) 1300 mg vs 3 mg *Duration*: 10 x 1 day	*Participants*: 10 asthmatics (4 M, 6 F), aged 25–59 years 3 drugs x 2 devices analysable *Quality*: B	FEV_1, $FEF_{25–75\%}$, PEF (% improvement)	
Gervais & Begin, 1987[254] Bronchodilatation with a metered-dose inhaler plus an extension, using tidal breathing vs jet nebulisation	*Design*: crossover, at least patient blinded *Device*: pMDI + aero-chamber vs jet nebuliser *Drug*: salbutamol *Dose*: 200 µg vs 2.5 mg *Duration*: 2 x 1 day	*Participants*: 10 asthmatics (3 M, 7 F), mean age 39 years, range 21–61 years *Quality*: B	FEV_1, FVC, maximal mid-expiratory flow rate (% improvement)	
Gomm *et al.*, 1983[255] Dose-response comparison of ipratropium bromide from metered-dose inhaler and by jet nebulisation	*Design*: crossover, open *Device*: pMDI alone vs jet nebuliser *Drug*: ipratropium bromide *Dose*: pMDI, 18 + 18 + 36 µg; nebuliser, 9 + 9 + 18 + 36 µg *Duration*: 2 x 1 day	*Participants*: 10 moderate asthmatics (6 M, 4 F), age range 20–67 years Doses given at 30-minute intervals, 36 vs 72 µg analysed *Quality*: B	FEV_1, FVC, PEFR, SGaw (absolute)	Unusual method of nebulisation; 2 minutes of nebulisation assumed that 0.44 of 5 ml emitted (by prior experiment) and concentration of the solution adjusted to deliver the desired dose
Laursen *et al.*, 1983[256] Comparison of a 750 ml spacer and a nebuliser in domiciliary treatment of severe chronic asthma with terbutaline One author from Astra Draco, Sweden	*Design*: 4-way crossover, double-blind *Device*: pMDI + Nebuhaler vs nebuliser *Drug*: terbutaline *Dose*: 1.5 mg vs 5 mg q.d.s. *Duration*: 4 x 1 week	*Participants*: 12 severe asthmatics (3 M, 9 F) (7 completed the trial), mean age 53 years, range 36–62 years 4-way crossover included 2 arms of placebo *Quality*: B	PEFR (absolute)	

continued

TABLE 19 contd *Review C: included trials – nebulisers versus hand-held inhalers in adults*

Study	Methodology	Details	Results	Comments
Madsen *et al.*, 1982[257] Cumulative dose–response study comparing terbutaline pressurised aerosol administered via a pear-shaped spacer and terbutaline via a nebulised solution	*Design*: crossover, open *Device*: pMDI + spacer vs nebuliser *Drug*: terbutaline *Dose*: 500 µg vs 5 mg *Duration*: 2 x 1 day	*Participants*: 13 asthmatics (11 M, 2 F), mean age 47 years, range 30–60 years *Quality*: B	FEV_1, $FEF_{75\%}$, change in FEV_1	
O'Reilly *et al.*, 1983[258] Pressurised aerosol with conical spacer is an effective alternative to nebuliser in chronic stable asthma	*Design*: 3-way crossover, open *Device*: pMDI + spacer vs nebuliser *Drug*: terbutaline *Dose*: 1.5 mg vs 7.5 mg *Duration*: 3 x 1 day	*Participants*: 9 asthmatics, age range 24–56 years 3rd arm vs positive pressure ventilation also performed *Quality*: B	FEV_1, FVC, $\dot{V}30$ (absolute)	
Pedersen & Bundgaard, 1983[251] Comparative efficacy of different methods of nebulising terbutaline	*Design*: crossover, open *Device*: (a) pMDI alone vs nebuliser; (b) pMDI + spacer vs nebuliser *Drug*: terbutaline *Dose*: 1 mg pMDI vs 4 mg nebuliser *Duration*: 5 x 1 day	*Participants*: 15 asthmatics (8 M, 7 F), mean age 36 years, range 2–58 years Other 2 arms vs nebuliser and positive pressure ventilation at 1 mg *Quality*: B	FEV_1, $\dot{V}50$, $\dot{V}75$–85 (CFB)	
Prior *et al.*, 1982[259] High-dose inhaled terbutaline in the management of chronic severe asthma: comparison of wet nebulisation and tube-spacer delivery Acknowledged help from Astra	*Design*: crossover, open *Device*: pMDI + spacer *Drug*: terbutaline *Dose*: 4 mg *Duration*: 2 x 2 weeks	*Participants*: 8 severe asthmatics (4 M, 4 F), mean age 60 years, range 5–67 years *Quality*: B	PEFR, am and pm symptom scores	PEFR taken pre-bronchodilator
Rochat *et al.*, 1983a[250] Inhalation of beta-agonists: comparison of six inhaler devices	*Design*: crossover *Device*: pMDI alone vs nebuliser *Drug*: salbutamol *Dose*: 600 µg vs 1.25 mg *Duration*: 2 x 1 day	*Participants*: 15 asthmatics *Quality*: B	FEV_1, SGaw (absolute)	1 of 4 trials in a single paper
Rochat *et al.*, 1983b[250] Inhalation of beta-agonists: comparison of six inhaler devices	*Design*: crossover *Device*: Rotahaler *Drug*: salbutamol *Dose*: 400 µg vs 1.25 mg *Duration*: 2 x 1 day	*Participants*: 10 asthmatics *Quality*: B	FEV_1, SGaw (absolute)	1 of 4 trials in a single paper

continued

TABLE 19 contd *Review C: included trials – nebulisers versus hand-held inhalers in adults*

Study	Methodology	Details	Results	Comments
Shim & Williams, 1984[260] Effect of bronchodilator therapy administered by canister versus jet nebuliser	*Design*: crossover, double-blind, double-dummy *Device*: pMDI alone vs nebuliser *Drug*: metaproterenol *Dose*: 1.95 mg vs 15 mg *Duration*: 2 x 1 day	*Participants*: 13 *Quality*: B	FEV_1, FVC	
Stauder & Hidinger, 1983[261] Terbutaline aerosol from a metered dose inhaler with a 750ml spacer or as a nebulised solution Author from Astra	*Design*: crossover, open *Device*: pMDI + spacer vs nebuliser *Drug*: terbutaline *Dose*: 1 mg vs 4 mg *Duration*: 2 x 1 day	*Participants*: 52 asthmatics, mean age 52 years, range 20–71 years *Quality*: B	FEV_1, FVC, forced mid-expiratory flow, R_{os} (absolute and CFB)	
Watanabe *et al*., 1981[252] Bronchodilator effects of nebulised fenoterol: a comparison with isoproterenol Supported by grant from Boehringer Ingelheim	*Design*: 7-way crossover, open (double-blind to dose/placebo in nebuliser) *Device*: pMDI alone vs BA-nebuliser *Drug*: fenoterol *Dose*: 400 µg vs 0.5, 1.0, 1.5, 2.0, 2.5 mg *Duration*: 7 x 1 day	*Participants*: 15 mild to severe asthmatics (9 M, 7 F), mean age 40 years, range 17–62 years *Quality*: B	FEV_1, $FEF_{25-75\%}$, FVC, SGaw (% CFB)	BA-nebuliser used Dosing study, 5 nebuliser doses, 1 pMDI dose and nebuliser placebo on 7 separate days
Zainudin *et al*., 1990[244] Comparison of bronchodilator responses and deposition patterns of salbutamol inhaled from a pMDI as a dry powder and as a nebulised solution	*Design*: crossover, open *Device*: (a) pMDI alone vs (b) Rotahaler (both versus nebuliser via mouthpiece) *Drug*: salbutamol *Dose*: all 400 µg *Duration*: 3 x 1 day	*Participants*: 9 asthmatics, age range 20–68 years *Quality*: B	FEV_1, FVC and PEFR; improvement from baseline	Nebuliser via mouthpiece

CFB, change from baseline; $\dot{V}30, \dot{V}50, \dot{V}75–85$, flow at 30, 50, 75–85%; R_{os}, oscillatory resistance (airways resistance)

TABLE 20 *Excluded papers for Review C*

Study	Reason for exclusion
Blake *et al*., 1992[262]	'Non-clinical', histamine provocation in mild asthmatics
Gibson *et al*., 1995[263]	'Non-clinical', histamine provocation in stable asthmatics
Morrone *et al*., 1990[264]	No data extractable, unable to obtain further details
Music *et al*., 1990[265]	Comparison between spacer types only added to pMDI
O'Driscoll *et al*., 1992[266]	Not a RCT; all treatment was pMDI followed by nebuliser
O'Driscoll & Bernstein, 1996[267]	Long-term follow-up of nebuliser users; observational study only with no direct comparison between pMDI and nebuliser
Shaughnessy & Slawson, 1996[268]	Acute asthma in emergency room only was studied
Wildhaber *et al*., 1999[269]	Lung deposition study only, with no clinical outcomes

have a dose–response curve. The choice of doses used for the particular devices compared may have a significant effect upon the outcome of a trial.

If both devices compared use too high a dose (at the top or flat part of the dose–response curve), then both will achieve near maximal clinical response and no difference in treatment effect will be demonstrable (risk of a type II error).

Alternatively, if the dose chosen for each device is not matched, and by necessity it is likely to be different between nebuliser and MDI, then there is the possibility that any treatment differences will reflect the dose prescribed rather than differences in efficacy of the device. If relative dose matching is achieved (by a pre-study dose-ranging study or selecting the dose to be analysed from part of a dose–response study), then, by definition, there will be no difference in treatment effect. This was avoided in the current analysis because if a choice of doses were available, then the clinically prescribed dose (those indicated in drug company data sheets and formularies, e.g. salbutamol 200 µg by pMDI and 2.5–5 mg by nebuliser or equivalent for other bronchodilators) was used. This would, however, tend to bias towards a nebuliser. This is because nebulisers deliver a lower fraction of the prescribed dose than the pMDI + spacer – approximately 10% versus 20–30%[39,244] – and therefore larger doses need to be prescribed to compensate. This problem was overcome in a systematic review of the pMDI + spacer versus nebuliser for acute asthma[246] by only considering studies that titrated doses to clinical response. This showed that the nebuliser dose needed to be four to six times the pMDI dose. To summarise, drug delivery and clinical response shows that the pMDI + spacer delivers two to six times the dose of a nebuliser, but nebuliser dosages are recommended at 12.5–25 times the dose. A wide range of dose ratios was used in the included trials between the MDIs and nebulisers: 1:1–1:16.6.

In order to explore dose-equivalence between devices, an analysis using subgroups of dosage ratios greater than 1:6, 1:6–1:4 and less than 1:4 was performed. These ratios were chosen based on the lung deposition and clinical response data above. For this analysis, Watanabe and colleagues[252] and Zainudin and colleagues 1990a/b[244] were excluded because they used breath-coordinated nebulisers, which are likely to have very different dosage equivalence to MDIs compared with more usual 'open' nebulisers. The above subgroups had treatment effects of –0.23 (95% CI, –0.57 to 0.11); –0.03 (95% CI, –0.35 to 0.29); and –0.03 (95% CI, –0.4 to 0.33), respectively. The direction of the effect is as expected, that is a greater effect in favour of the nebuliser with dose ratios less than or equal to 1:4, but this does not reach statistical significance.

Despite this, combining all treatment doses using different hand-held inhalers and nebulisers does not result in any statistical heterogeneity.

Publication bias

If it considered the 'general wisdom' that nebulised medication is superior to MDI (there needs to be some strong justification in the mind of the prescriber given the additional costs and time), then studies showing 'equivalence', as is predominantly the case, would, in effect, be 'positive' findings and subject to publication bias. However, this is unlikely to be the case because no studies demonstrating the benefit of nebulised over MDI therapy are available.

Crossover design

All of the included trials are of crossover design. Whilst this avoids the problem of combining data from crossover with parallel designed trials, there may be some loss of statistical power in using the paired data from crossover trials within the RevMan program as two separate 'parallel arms'. The primary studies generally used a paired *t* test for significance between the groups. However, despite this the resulting outcome measures do achieve meaningfully narrow 95% CIs of treatment effect.

Study setting

Only three of the 19 studies used the treatments in the domiciliary setting (2–4 weeks). The remainder were assessing the treatment response over a matter of a few hours within a laboratory or clinic to a single dose or several cumulative doses of a bronchodilator. This raises the question of generalisability to the clinical setting. However, there is no statistically significant difference between the results from each setting (but the data in the domiciliary setting are limited in amount).

Statistical sensitivity of the studies

None of the studies individually had statistical power to detect differences in treatment effect of 'near equivalent' treatments, even using paired data. This is due to a number of factors. The number of participants in each trial was small: one trial consisted of 38, the remainder were in the range seven to 22. The treatments compared are all active and efficacious and therefore the

outcome is one of relative efficacy and the differences are small in comparison to measures of error, for example the typical SD for FEV_1 is 0.8 litres. This limitation is partly overcome by the performance of a meta-analysis. For the more completely reported FEV_1 and PEFR, 19 and nine respectively of the 23 studies reporting usable data, this results in clinically narrow enough confidence intervals to be useful. However, for other outcomes such as symptom scores or lesser used measures of pulmonary function, then the lack of statistical power cannot be overcome and there may have been a failure to detect a treatment difference (type II error). No trial described any pre-trial power calculations.

Outcome measures used
The population of asthmatics using a long-term nebuliser will tend to be more severe and have greater disability from their chronic disease. Although the commonest measures of pulmonary function (FEV_1 and PEFR) are widely reported, they may not reflect the most sensitive or specific measure of disease severity in these patients. Almost by definition, bronchodilators are used for 'symptomatic relief' on an as-required basis defined by the patient. Symptom scores are used in only three out of 23 studies, although of the domiciliary studies only, this is two of the three studies reporting data. Furthermore, given the chronic and disabling nature of severe asthma, there should be some measures of quality of life or health status included in the assessment.

The results of this review show that for measures of pulmonary function (FEV_1 and PEFR) and other clinical outcomes, there is no clinical benefit of using nebulised medication in addition to or as an alternative to the pMDI with or without spacer or a DPI in stable asthma.

REVIEW D: bronchodilators for stable and acute COPD – pMDI versus other hand-held inhalers

Description of studies
Only two studies were included in this review.[270,271] Data for the Ikeda and colleagues[270] study was reported before and 15–240 minutes after study drug administration, but only the 30-minute data were used because these were the closest match to the data reported by the only other study (Formgren and colleagues[271]) that reported data at 40 minutes after study drug administration. This would allow us to sensibly combine the two results together using SMD. Formgren and colleagues'[271] study reported data as absolute change from baseline and Ikeda and colleagues[270] reported data as absolute mean value at the end of the study, and therefore data were combined using SMD. Both studies were of crossover design and involved many study arms with adequate washout periods between each arm. As a result, data from the different doses used in each of the studies were reported separately, as was the use of spacer devices. Further details of the two studies are given in *Table 21*: 'Characteristics of included studies: Review D' (page 79).

Methodological quality of included studies
The two included studies in this review were of good quality designs: Ikeda and colleagues' trial[270] scored 'A' (for Cochrane quality) and Formgren and colleagues' trial[271] scored 'B'. Both studies scored '5' when the Jadad scale[85] was used, indicating that both studies were of high methodological quality.

Results
From the search of the Cochrane Airways Group register, 1565 abstracts were identified for possible inclusion in the review. Eight abstracts were selected by two reviewers as possibly being appropriate for inclusion in the review and five abstracts were obtained from bibliographies of retrieved articles. Therefore, a total of 13 full text papers were retrieved for possible inclusion. After reading the full text of these 13 studies, eight were excluded as not appropriate, a further three were excluded on methodological grounds and the remaining two were included in the review. Reasons for exclusion of the 11 studies are listed in *Table 22*: 'Characteristics of excluded studies: Review D'.

Data abstracted from the two included studies provided the following non-significant results.

Turbuhaler
The following outcome measures were not statistically significant: FEV_1, FVC, residual volume, SGaw, treatment failures and adverse effects.

Rotahaler
The following outcome measures were not statistically significant: FEV_1, AUC-FEV_1, FVC, pulse rate, systolic BP, diastolic BP, treatment failures and adverse effects.

The outcome measures were not significantly different whether a high or a low dose of medication was used or whether a spacer device was used with the pMDI. When the data from the two included studies were combined using SMD, there still were no significant differences.

TABLE 21 *Characteristics of included studies: Review D*

Study	Methods	Participants	Interventions	Outcomes	Notes
Formgren *et al.*, 1994[271] 1.0 mg + 2.5 mg	*Design*: randomised, double-blind, double-dummy, crossover, Latin-square design *Device*: Turbuhaler vs pMDI with Nebuhaler spacer for higher dose *Drug*: terbutaline *Dose*: 1.0 mg + 2.5 mg *Duration*: 40 minutes	15 hospitalised adult patients (4 F) in stable phase of their disease without recent exacerbations and medication unchanged in weeks. All patients were ex-smokers and upon admission all patients demonstrated a ≥ 15% response in FVC and/or a decrease in residual volume without increase (< 15%) in FEV_1 after inhalation of a β_2-agonist (4 x 0.1 mg salbutamol or 4 x 0.25 mg terbutaline). COPD diagnoses was based on clinical history, X-ray, spirometry and body plethysmography after a run-in period of 1 week. Mean age 61 years (SD 9, range 44–72 years), mean % predicted FEV_1 = 35.6% (range 23–48 years), mean disease duration 11.6 years (range 1–42 years). Mean basal FEV_1 over the 5 study days for all patients did not vary outside 1.0–1.1 litres	4 treatments regimes: Turbuhaler-terbutaline 1 mg; pMDI (CFC)-terbutaline (no spacer) 1 mg; Turbuhaler-terbutaline 2.5 mg + 2.5 mg pMDI (CFC)-terbutaline with nebuhaler spacer 2.5 mg. A 1-week run-in period was used, during which PEFR was measured 5 times a day and patients were included in the study if their diurnal PEF variation did not exceed 15%. Interval of at least 48 h between treatments for washout. Study measurements were made before and 10–40 minutes after study drug administration	FEV_1, FVC, residual volume and SGaw. Results presented and entered into RevMan were 40 minutes post bronchodilator. Treatment failures and adverse events were discussed in text	2 different doses were used in study (separated by 48-h washout); therefore separated as 2 references for ease of data entry into RevMan software Cochrane Allocation = B
Ikeda *et al.*, 1999[270] 200 µg + 1000 µg	*Design*: randomised, double-blind, double-dummy, crossover design *Device*: Rotahaler vs pMDI with InspirEase spacer device (750 ml) *Drug*: salbutamol *Dose*: 1000 µg *Duration*: 240 minutes	10 patients (all M) with stable COPD recruited from outpatient chest clinic. No exacerbations in the last 3 months and no treatment with oral bronchodilators, theophylline and oral or inhaled corticosteroids during the preceding 4 weeks. Mean (SD): age 67 (4) years (range 62–73); FEV_1 1.56 (0.32) litres = 60% predicted (range 1.12–2.17); smoking pack year history 52 (21) (range 20–100), with no current smokers	Salbutamol 0.2 mg and 1 mg via Rotahaler or pMDI (CFC)-salbutamol with InspirEase spacer. There were also nebuliser arms in the study. Each treatment regime consisted of the administration of 5 capsules via Rotahaler, 10 puffs via the pMDI and approximately 2 ml solution via the nebuliser (interval of at least 2–4 days between treatments). The dose of 200 µg via the Rotahaler was administered as 1 active 200 µg capsule and 4 matching placebos, that of 200 µg via the pMDI was administered as 2 puffs of active (100 µg/puff) drug and 8 puffs of placebo	Spirometry was performed before and 15, 30, 60, 90, 120 and 240 minutes post bronchodilator but only FEV_{1max} and AUC-FEV_1 were reported. Treatment failures and adverse events mentioned in text	2 doses used in study, therefore separated as 2 references for ease of data entry into RevMan All medication and treatment sequence was coded in advance and the codes not revealed until all patients had completed the protocols. Author reply provided further information and data Cochrane Allocation = B

TABLE 22 *Characteristics of excluded studies: Review D*

Study	Reason for exclusion
Bellamy & Hutchison, 1981[272]	Comparison was against a placebo aerosol inhaler
Cushley *et al.*, 1983[273]	Study compared: MDI vs MDI + spacer vs a mini-nebuliser
Gimeno *et al.*, 1988[274]	Study includes patients with asthma, chronic bronchitis and emphysema. The author grouped all patients together and referred to them all as having COPD; no separate data was provided for each of the groups
Harvey & Williams, 1992[155]	Patient allocation not randomised and patients not clearly diagnosed as having COPD
Iversen *et al.*, 1999[275]	Study compared terbutaline Turbuhaler against placebo Turbuhaler
Larsen *et al.*, 1998[276]	Study used a new type of micro-nebuliser (piezoelectric) device vs pMDI with both delivering 100 µg per puff. Study also had mixed populations of participants (asthma = 39, COPD = 9)
Mutterlein *et al.*, 1990[277]	Comparison of DPI vs DPI (no pMDI involved) using the Ingelheim M inhalator
Petersen & Petersen, 1983[278]	Author included mixed population (both asthmatic and COPD patients in study) and data not presented separately
Van der Palen *et al.*, 1995[279]	Not a RCT. Study set out to test the differences between inhaler techniques with 4 different devices (pMDI, Turbuhaler, Diskhaler and Rotahaler)
Van der Palen *et al.*, 1998[280]	Study compared DPI against DPI (Diskus/Accuhaler vs Turbuhaler). Study also had both asthma and COPD patients
Wetterlin *et al.*, 1988[281]	Not a RCT; a qualitative review on the working aspects of the Turbuhaler

Data were not available for the following outcomes measures: quality of life measures, symptom scores, use of additional relief medication, use of inhaled or oral steroid requirement, severity of disease, days off work, compliance, patient preference, systemic bio-availability, subsidiary physiological measures (e.g. 6- or 12-minute walks, arterial blood gases) and acute exacerbations.

Discussion

A comprehensive search strategy was developed for this review. Every effort was made to identify all of the relevant studies. No study was excluded due to language. While several attempts were made to identify unpublished work, it is still possible that some studies have been missed. However, the small number of eligible studies was not due to restricted selection criteria, but rather to the absence of identified RCTs evaluating inhaler devices (pMDIs and DPIs) containing bronchodilators in COPD.

Owing to the very small number of studies included in this review, it is not possible to draw any conclusions on the use of inhaler devices containing bronchodilators in COPD.

Summary

Owing to the small number of studies, no conclusions can be drawn regarding the implications this review would have in clinical practice. There needs to be further well-designed RCTs examining the role of bronchodilators in COPD in order to be able to define the role of inhaler devices containing bronchodilators in COPD.

REVIEW E: bronchodilators for stable and acute COPD – hand-held inhalers versus nebulisers

The included studies[260,270,282–292] covered a broad range of individuals, location and types of comparison. Characteristics are detailed in *Table 23*. All but four of the included studies had drug company involvement through supply of study drugs, funding or authorship. The studies were usually response studies over a period of hours (10 of the 13 studies), although four of the 13 studies were in the domiciliary setting over 2 weeks and in each treatment arm. Two studies were hospital-based in acute exacerbation of COPD. Different bronchodilators and different delivery devices, including different spacer devices, were used. Additionally, even between the same drug/device comparison, different studies used a different dosage ratio.

Overall, the methodological quality of the included studies was poor, with all studies rating Cochrane grade 'B' for allocation concealment. Most studies did not comment on withdrawals and dropouts or did not report whether intention-to-treat analysis was employed. The sample size of individual studies was small, with two trials of 40 and 47 patients, whilst the remaining 11 trials ranged from seven to 28 patients. All but one study was of a crossover design.

TABLE 23 *Characteristics of included studies: Review E*

Study	Methodology	Details	Results	Comments
Allen *et al.*, 1988[282] Nebuhaler or nebuliser for high dose bronchodilator therapy in chronic bronchitis: a comparison Financial support from Astra Pharmaceuticals	*Design*: crossover, open trial *Device*: pMDI + spacer vs jet nebuliser *Drug*: terbutaline *Dose*: 10 mg vs 10 mg *Duration*: 2 x 2 weeks	*Participants*: 13 patients (8 M, 5 F), mean age 64.5 years, range 46–71 years *Quality*: B	FEV_1, FVC (CFB); cough, wheeze, phlegm, breathlessness; relief medication	
Berry *et al.*, 1989[283] Nebuliser vs spacer for bronchodilator delivery in patients hospitalised for acute exacerbations of COPD Grant and materials supplied by Schering Ph	*Design*: crossover, double-blind, double-dummy *Device*: pMDI + spacer vs nebuliser *Drug*: salbutamol *Dose*: 0.36 mg vs 2.5 mg *Duration*: 2 x 1 day	*Participants*: 20 patients (all M), mean age 67.9 years, range 60–91 years *Quality*: B	FEV_1, FVC, Borg score	
Gross *et al.*, 1989[284] Dose–response to ipratropium as a nebulised solution in patients with chronic obstructive pulmonary disease (a 3-centre study) Grant from Boehringer Ingelheim	*Design*: crossover, double-blind, double-dummy *Device*: pMDI alone vs jet nebuliser *Drug*: ipratropium bromide *Dose*: 40 µg vs 400 µg *Duration*: 7 x 1 day	*Participants*: 47 patients (35 M, 12 F), median age 58 years, range 31–65 years Other nebuliser dosages also available in paper *Quality*: B	FEV_1	
Hansen, 1989[285] Terbutaline as powder inhalation from Bricanyl Turbuhaler compared to terbutaline as nebuliser solution in severe chronic airways obstruction Part funded by Draco, Denmark	*Design*: crossover, open *Device*: Turbuhaler vs jet nebuliser *Drug*: terbutaline *Dose*: 2 mg vs 5 mg *Duration*: 2 x 1 day	*Participants*: 22 patients (12 M, 10 F), mean age 69.5 years Study performed in patients' home *Quality*: B	FEV_1, FVC	
Hansen *et al.*, 1994[286] Terbutaline inhalations by the Turbuhaler as replacement for domiciliary nebuliser therapy in severe chronic obstructive pulmonary disease An author and part funding from Astra, Denmark	*Design*: crossover, double-blind, double-dummy *Device*: Turbuhaler vs nebuliser *Drug*: terbutaline *Dose*: 2.5 mg vs 5 mg *Duration*: 2 x 2 weeks	*Participants*: 40 patients (25 completed: 9 M, 16 F), mean age 60 years, range 54–81 years Domiciliary study *Quality*: B	PEFR (CFB), preference, exacerbation	
Hansen & Andersen, 1995[287] Salbutamol powder inhaled from the Diskhaler compared to salbutamol as nebuliser solution in severe chronic airways obstruction Part funding from Glaxo UK	*Design*: crossover, double-blind, double-dummy *Device*: Diskhaler vs jet nebuliser *Drug*: salbutamol *Dose*: 1.6 mg vs 2.5 mg *Duration*: 2 x 1 day	*Participants*: 28 patients (11 M, 17 F), mean age 67 years (range 53–82 years) *Quality*: B	FEV_1 (CFB), symptoms (absolute), preference	

continued

TABLE 23 contd *Characteristics of included studies: Review E*

Study	Methodology	Details	Results	Comments
Higgins *et al.*, 1987[288] Changes in blood gas levels after Nebuhaler and nebuliser administration of terbutaline in severe chronic airway obstruction Financial support from Astra	*Design*: crossover, double-blind, double-dummy *Device*: pMDI + spacer vs nebuliser *Drug*: terbutaline *Dose*: 4 mg vs 4 mg *Duration*: 2 x 4 h	*Participants*: 20 patients, mean age 70 years *Quality*: B	FEV_1 (absolute)	
Ikeda *et al.*, 1999[270] Comparison of the bronchodilator effects of salbutamol via a MDI with spacer, a dry-powder inhaler and a jet-nebuliser in patients with chronic obstructive pulmonary disease Materials supplied by Glaxo	*Design*: 3-way crossover, double-blind, double-dummy *Device*: (a) pMDI + spacer vs nebuliser; (b) Rotahaler vs nebuliser *Drug*: salbutamol *Dose*: 200 µg MDI vs 1 mg nebuliser *Duration*: 7 x 1 day	*Participants*: 10 patients (all M), mean age 67.2 years, range 62–73 years *Quality*: B	Max FEV_1 increase, AUC-FEV_1	
Jenkins *et al.*, 1987[289] Comparison of domiciliary nebulised salbutamol and salbutamol from a MDI in stable chronic airflow limitation Generous funding from Allen & Hanburys	*Design*: 4-period crossover, double-blind, double-dummy *Device*: pMDI + spacer vs nebuliser *Drug*: salbutamol *Dose*: pMDI, mean 316 µg q.d.s.; nebuliser, mean 3.8 mg q.d.s *Duration*: 4 x 2 weeks	*Participants*: 19 severe airflow limitation (12 M, 7 F), mean age 63.4 years, range 32–78 years 4-period crossover: 2 periods on each treatment. Dose was decided by individual titration to maximum response pre-study *Quality*: B	PEFR, FEV_1, FVC, relief medication	
Maguire *et al.*, 1991[290] Comparison of hand-held nebuliser with metered dose inhaler–spacer combination in acute obstructive pulmonary disease	*Design*: crossover, open *Device*: pMDI + spacer vs nebuliser *Drug*: metaproterenol *Dose*: 1.3 mg vs 15 mg *Duration*: 6 h	*Participants*: 7 hospitalised COPD patients (1 patient enrolled twice – 1 month apart) Part of a study including asthmatics; results presented separately in paper *Quality*: B	FEV_1, FVC, $FEF_{25–75\%}$	
Mestitz *et al.*, 1989[291] Comparison of outpatient nebulised vs metered dose inhaler terbutaline in chronic airflow obstruction	*Design*: crossover, double-blind, double-dummy *Device*: pMDI alone vs nebuliser *Drug*: terbutaline *Dose*: 1.25 mg vs 2.5 mg *Duration*: 2 x 2 weeks	*Participants*: 18 stable patients (17 M, 1 F), mean age 67.5 years, range 62–75 years *Quality*: B	FEV_1, VC, 6 minute walk distance; wheeze, cough, dyspnoea, sleep, sputum; relief medication, preference	Some asthma patients included. Only 1 had never smoked. Elderly and low reversibility, therefore for practical purposes considered to be COPD

continued

TABLE 23 contd *Characteristics of included studies: Review E*

Study	Methodology	Details	Results	Comments
Shim & Williams, 1984[260] Effect of bronchodilator therapy administered by canister versus jet nebuliser	*Design*: crossover, double-blind, double-dummy *Device*: pMDI alone vs nebuliser *Drug*: metaproterenol *Dose*: 1.95 mg vs 15 mg *Duration*: 2 x 1 day	*Participants*: 13 *Quality*: B	FEV_1, FVC	
Turner *et al.*, 1988[292] Equivalence of continuous flow nebuliser and metered-dose inhaler with reservoir bag for treatment of acute airflow obstruction	*Design*: parallel, double-dummy *Device*: pMDI + spacer vs nebuliser + mouthpiece *Drug*: metaproterenol *Dose*: 1.95 mg vs 15 mg *Duration*: 2 x 90 minutes	*Participants*: 22 acute COPD (15 M, 7 F), mean age 56 years Separate results presented for asthma within paper *Quality*: B	FEV_1, respiratory rate, Borg score	

Papers were excluded for the following reasons (*Table 24*): one was a review article; one was a mixed population of asthma and COPD with no extractable data; and the remaining two were not trials of nebuliser versus a hand-held inhaler.

The results for each outcome were analysed using the delivery device type (pMDI alone, pMDI + spacer or DPI) as subgroups. The results were combined because there was no evidence of heterogeneity and also therefore a fixed effect model was used throughout.

For the SMD of FEV_1, all 13 studies contribute data and there was no statistically significant difference in treatment effect of nebuliser versus pMDI alone: –0.10 (95% CI, –0.39 to 0.20); pMDI + spacer: –0.02 (95% CI, –0.33 to 0.30); DPI: 0.15 (95% CI, –0.15 to 0.45) or combined: 0.01 (95% CI, –0.17 to 0.18). Converting this to a clinically meaningful absolute value using typical group data of FEV_1 0.8 litres and SD 0.3 litres, this equates to 3 ml (95% CI, ± 50 ml) in favour of the MDI. For absolute FEV_1 the results are similar, although only nine studies contribute data; the subgroup total is 3 ml (95% CI, ± 67 ml).

All other outcomes show no statistically significant effects but these outcomes are infrequently reported, range from one to four studies and the CIs are wide around no treatment effect and therefore are not clinically useful.

Further subgroup analysis and sensitivity testing has not been performed. If the 'worst case scenario' is explored of putting all the studies favouring the nebuliser in one subgroup and all the studies favouring the MDI in another subgroup, then neither shows any statistically significant treatment effect and therefore no statistical difference from each other. This is displayed graphically in *Figure 11*.

Discussion

The results of Review E show that for an objective measure of pulmonary function (FEV_1) there is no clinical benefit of using nebulised medication in addition to or as an alternative to a pMDI, with or without spacer, or a DPI in stable or exacerbation of COPD. There is less data available for other

TABLE 24 *Excluded studies: Review E*

Study	Reason for exclusion
Assoufi & Hodson, 1989[293]	Mixed population of asthma/COPD and no extractable data
Lu, 1997[294]	Review article
Nisar *et al.*, 1990[295]	Not a RCT; pMDI followed by nebulised salbutamol
O'Driscoll *et al.*, 1990[296]	No direct comparison between nebuliser and pMDI (comparing laboratory nebuliser response to domiciliary response)

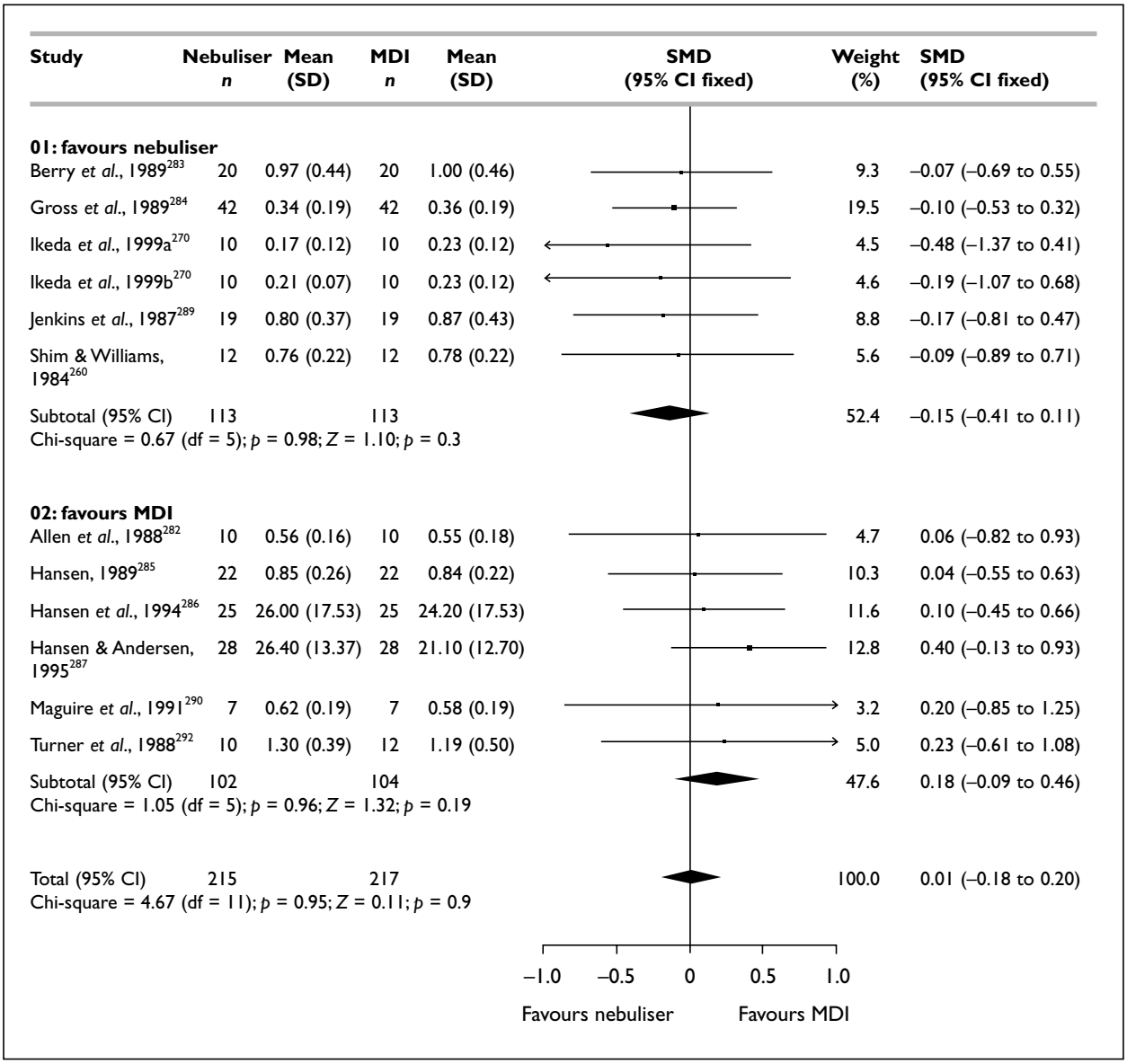


FIGURE 11 *Nebuliser versus MDI ± spacer: SMD of FEV_1 – worst case scenario*

measures of disease such as PEFR or symptom scores but it also shows no benefit of nebulised medication over MDI. However, the confidence interval for these outcomes is wide and may encompass treatment effects that are considered clinically significant.

Combining these studies in a meta-analysis supports the findings of the individual studies. The individual studies are of small sample size and the nature of the patients recruited (severe patients with COPD) leads to wide estimates of error (SEM) for the pulmonary function outcome measures. Therefore, the trials are of low statistical power to detect possible treatment differences. The results of the meta-analysis do, however, produce narrow enough confidence intervals of no overall treatment effect for FEV_1, so that each end of the error range is within clinically equivalent limits.

Weaknesses of the analysis come from a number of sources concerning the design of the trials, the outcome measures available and publication bias. They are discussed individually below.

Publication bias

If it considered the 'general wisdom' that nebulised medication is superior to the MDI (there needs to be some strong justification in the mind of the prescriber given the additional costs and time), then studies showing 'equivalence', as is predominantly the case, would in effect be 'positive' findings and subject to publication

bias. However, this is unlikely to be the case as no studies are available demonstrating the benefit of nebulised therapy over MDI therapy.

Crossover design
All but one of the included trials are of crossover design. Whilst this largely avoids the problem of combining data from crossover with parallel designed trials, there may be some loss of statistical power in using the paired data from crossover trials as two separate 'parallel arms' within the RevMan program. The primary studies generally used a paired *t* test for significance between the groups. Unfortunately, the results were not usually presented with an exact *p*-value or with error estimates relating to the individual patient responses, and therefore it was not possible to analyse using the correct weighting for crossover studies. Despite this the resulting outcome measure of FEV_1 and the SMD of FEV_1 do achieve meaningfully narrow 95% CIs around no treatment effect difference.

Study setting
Four of the 13 studies used the treatments in the domiciliary setting (all were for 2 weeks in each treatment arm). The remainder were assessing the treatment response over a matter of a few hours within a laboratory or clinic to a single dose or several cumulative doses of a bronchodilator. This raises the question of generalisability to the clinical setting. However, there is no statistically significant difference between the results from each setting.

Doses of drugs used
Bronchodilators, whether nebulised or via a MDI, have a dose–response curve. The choice of dose used for a particular device may have a significant effect upon the outcome of a trial. If both devices compared use too high a dose (at the top or flat part of the dose–response curve), then both will achieve near maximal clinical response and no difference in treatment effect will be demonstrable. Alternatively, if the dose chosen for each device is not matched, and by necessity it is likely to be different between the nebuliser and the MDI, then there is a likelihood that any treatment differences will reflect the dose prescribed rather than differences in efficacy of the device. If relative dose matching is achieved (by a pre-study dose-ranging study or by selecting the dose to be analysed from part of a dose– response study), then, by definition, there will be no difference in treatment effect. This was avoided in the current analysis because if a choice of doses were available, then the clinically prescribed dose (from drug data sheets or formularies) was used. Despite this, combining all treatment doses used does not result in any statistical heterogeneity.

Statistical sensitivity of the studies
None of the studies individually had the statistical power to detect differences in the treatment effect of 'near equivalent' treatments – even using paired data. This is due to a number of factors. The number of participants in each trial was small: two trials were of 40 and 47 patients, with the remainder in the range of seven to 28 patients. The treatments compared are all active and efficacious and therefore the outcome is one of relative efficacy and the differences are small in comparison with measures of error, for example the typical SD for FEV_1 is 0.4 litres. This limitation is partly overcome by the performance of a meta-analysis. For the completely reported FEV_1 this results in clinically narrow enough confidence intervals to be useful. However, for other outcomes, such as symptom scores or lesser used measures of pulmonary function, then the lack of statistical power cannot be overcome and there may have been a failure to detect a treatment difference (type II error). No trial described any pre-trial power calculations.

Outcome measures used
The population of patients with COPD using a long-term nebuliser will tend to be more severe and have greater disability from their chronic disease. Although one of the commonest measures of pulmonary function (FEV_1) is widely reported in the studies, it may not reflect the most sensitive or specific measure of disease severity in these patients. Indeed, it is rarely used in the clinical setting to guide treatment or assess the individual patient. Almost by definition, bronchodilators are used for 'symptomatic relief' on an as-required basis defined by the patient. Symptom scores are used in only two out of 13 studies, and for COPD there is no standardised or validated scoring system. Furthermore, given the chronic and disabling nature of severe COPD, there should be some measures of quality of life or health status included in the assessment.

Nebulised therapy for COPD is in widespread use. However, there is no evidence from the published clinical literature to suggest that there is any clinical benefit over a standard pMDI + spacer, although a higher than usual dose may be needed. If the clinical response is equivalent then the disadvantages of a nebuliser (increased cost of delivery device and drug, increased time taken for administration, poor mobility due to size, weight and the usual need for a mains electricity supply) become more important.

Chapter 6

The ability of individual patients to use the different inhaler devices: a systematic review

The clinical effectiveness of inhaler devices depends on more than just the devices themselves. Clinical benefit will also depend on the ability of the patient to use the device and on their compliance. Patient technique is a multifaceted process that will encompass an individual's previous experiences, education, abilities and teaching of technique with a specific device. These different factors may interact to various degrees with the different types of inhaler device to influence eventual technique and compliance.

A common assumption is that patients use pMDI devices inadequately. This is often referred to in studies comparing a new device to a pMDI. Of the 15 studies of DPI or BA-pMDI versus pMDI in Review A, chapter 5, nine referenced studies showing poor pMDI technique and the others commented on pMDI technique difficulties without citation. Review articles and editorials may similarly cite such data on poor pMDI technique.[297] Indeed, the British Thoracic Society asthma guidelines[1] comment, "Many patients are unable to use MDIs correctly ... addition of a spacer device will reduce co-ordination problems." The implication is that patients used other devices more effectively, although comparative data to support this is not cited.

The systematic review of the clinical evidence in chapter 5 supports the equivalence of clinical efficacy between inhaler device types. Secondary factors therefore need to be considered in making informed prescribing decisions, for example patient compliance and technique. A systematic review and analysis was undertaken to appraise the evidence regarding the inhaler technique of the different inhaler devices available.

Criteria for considering studies for this review

Types of studies

RCTs were the 'gold standard' for the analysis. Preliminary searching revealed few randomised trials. In addition to RCTs, non-RCTs and 'before and after' teaching type were also considered. Trials could be of any duration and in any setting. Any cross-sectional data of inhaler technique from any other source were also considered.

Types of participants

Participants over 2 years old with asthma or COPD diagnosed by a physician or according to the relevant accepted criteria were included. Analysis was undertaken separately for children and adults.

Types of interventions

Trials were considered that compared inhaler technique and/or clinical outcomes after educational interventions/programmes about inhaler technique by healthcare professionals. The control group was 'standard care' defined by the investigators or no teaching.

Types of outcome measures

These included:

- inhaler technique score
- numbers with good/satisfactory/poor inhaler technique
- measures of lung function, for example PEFR, FEV_1
- symptom scores
- relief medication usage
- exacerbation rates.

Search strategy for identification of studies

The Cochrane Airways Group and Cochrane Consumers & Communication Review Group databases as well as EMBASE, MEDLINE and CINAHL were searched using:

a. inhal* OR device*
AND
b. teach* OR instruct* OR educat*
AND
c. technique* OR skill*

The reference lists of included studies were also reviewed for potentially relevant articles.

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 previously written criteria. Disagreement was resolved by third party adjudication.

Quality assessment

Where appropriate, methodological quality assessment was performed independently by two reviewers. The Cochrane approach to assessment of allocation concealment was used:

Grade A: adequate concealment
Grade B: uncertain
Grade C: clearly inadequate concealment
Grade D: not used.

Data extraction

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. The data were then entered into RevMan 4.0.4 for analysis.

Statistical considerations

Trials were combined for meta-analysis using RevMan 4.0.4. Dichotomous outcomes such as numbers of patients with ideal technique/no mistakes were assessed using RR (with 95% CI) and, where possible, the number-needed-to-treat. Data from continuous outcomes were analysed as WMD (with 95% CI), or SMD if different scales were used. Subgroup analysis was carried out on age, disease severity, inhaler device and teaching method. For each outcome, the null hypothesis that there is no heterogeneity between trials was tested. Sensitivity tests were used to investigate any possible heterogeneity in the size of the measured response attributable to the subgroups identified above and due to study quality. Funnel plots were constructed for each primary outcome measure to test for possible publication bias.

Results

The data on inhaler technique were analysed in three main categories.

- 'Baseline' technique was considered as a measure of usual or current practice. Such data came from one-off audits or cross-sections of inhaler technique, and from the 'baseline' data from interventional studies, of RCTs or 'before and after' type.
- 'Post intervention' technique was considered as a measure of the potential achievable with good/best practice (i.e. that achieved at the end of interventional studies, of randomised controlled or before and after type). The combining of both types of study is justified because it is an absolute measure used post study intervention and is not relative to a baseline as immediately below.
- Also, the actual effect of teaching on inhaler technique was analysed as the improvement compared with controls (in the case of RCTs) or compared with before teaching (in the case of before and after studies).

Details of included studies are given in *Tables 25–27*. *Table 25* gives details of the RCTs on teaching of inhaler technique. *Tables 26* and *27* give more brief details on before and after and cross-sectional data studies, respectively.

The principal outcomes used were 'ideal' inhaler technique and a score out of a total number of steps. The 'ideal' outcome is dichotomous and was defined in various ways within the studies but most commonly as all of the inhaler steps performed correctly, but also as all 'essential' steps performed correctly or as one out of several qualitative grades, for example perfect, adequate or poor. Technique scores are continuous variables, that is the number of steps performed correctly out of the total number of steps. The number and definition of steps varied between studies and between inhaler device types within studies. So, within the meta-analysis, these scores are combined using a SMD. This is the difference between interventions standardised by dividing by the pooled SD.

Baseline technique data

A total of 28 studies were available, with data from one-off audits and from the 'baseline' data from interventional studies.

For the outcome of 'ideal' inhaler technique score, that is no mistakes on whatever scoring system was used, then 53% (95% CI, 50% to 57%) of patients using a DPI had maximum scores compared with 23% (95% CI, 22% to 24%) using a pMDI alone and 57% (95% CI, 53% to 60%) using a pMDI with spacer. The results can be seen graphically in *Figure 12*. This illustrates well the heterogeneity and also, as the studies are ranked in year order, it can be seen that there is no improvement in practice with time.

TABLE 25 *Included RCTs*

Study	Methodology	Details	Results (SD)	Comments
Heringa *et al.*, 1987[299] The effect of a structured education programme on knowledge and psychomotor skills of patients using beclometasone dipropionate aerosol for steroid dependant asthma	*Design*: randomised, blinded assessment *Interventions*: structured education programme; one-to-one teaching and demonstration, 2 x 20 minutes; control group encouraged to read package insert *Device*: pMDI alone *Duration*: retested at 4 weeks	*Participants*: 35 males enrolled: 26 completed and were analysed; mean age 60 years, range 49–69 years; recruited from established clinic, and beclometasone requiring *Scoring system*: 11-point scale *Study quality*: Cochrane B	*Significant differences in*: Technique score change from baseline: education, n = 13, 2.1 (0.8); control, n = 13, 0.2 (0.5); p = 0.05 'Within education group' improvement (paired t test) score 7.2 (0.7) to 9.2 (0.6) p = 0.019	Based on the given 'p'-values, the quoted SD values are in fact SEM No mention of validation or source of scoring system Dropouts, 9 of 35 patients, not analysed or commented upon
Hughes *et al.*, 1991[300] Controlled trial of a home and ambulatory programme for asthmatic children	*Design*: pseudo-randomised (alternate allocation) *Interventions*: structured education programme, 4 x 3 monthly visits; control group, routine primary and clinic care *Device*: pMDI and DPI *Duration*: final assessment 2 years after enrolment (1 year after education finished)	*Participants*: 95 children (86 completed and analysed), mean age 9.7 years (60 M, 35 F); recruited from asthma clinic with established diagnosis *Scoring system*: rated good, fair or poor. Good – shook canister, inhaled to total lung capacity, good coordination, held breath, re-shook before second actuation (5 points) *Study quality*: Cochrane C	*Significant differences in*: Numbers with 'good' technique at 12 months: education 36/38; control 15/27 p = 0.0005 At 24 months: education 29/31; control 18/29 p = 0.008	
Lirsac & Braunstein, 1991[301] A randomised assessment of 2 methods of using aerosols (translation)	*Design*: randomised, 3-arm parallel trial *Interventions*: information card vs video film education vs video film and personal education plus use of a spacer if necessary *Device*: pMDI (+ spacer) *Duration*: assessed at 2 weeks	*Participants*: 45 asthmatics with poor inhalation technique; mean age 40 years, range 10–71 years *Scoring system*: 4-point scale *Study quality*: Cochrane B	*No significant differences in*: Scores between card, n = 14, score 3.14 (0.86); video, n = 14, score 3.57 (0.51) Or numbers all correct card 6/14; video 8/14 *Significant differences in*: Baseline FEV_1 (paired t test) for video and video/education groups ($p < 0.001$ and $p < 0.02$)	The study uses video + personal instruction as the control; this analysis uses the information card as the control arm FEV_1 also measured Video/education group not used for the RCT comparison as the device also changed from baseline
Mulloy *et al.*, 1996[302] A 1-year prospective audit of an asthma education programme in an outpatient setting	*Design*: randomised, 3-parallel trial; blinded assessment of technique *Interventions*: verbal and video education asthma nurse specialist *Device*: pMDI (+ spacer) *Duration*: 1-year follow-up	*Participants*: 60 asthmatics; mean age 28.5 years, range 10–71 years; recruited as 'new attendees' or those within the clinic who had not previously seen the asthma nurse *Scoring system*: 7-point scale (not described) *Study quality*: Cochrane B	*Significant differences in*: Scores at 1 and 12 months: control 5.5 (1.1) and 5.3 (2.19); education 6.5 (1.64) and 6.5 (0.55)	*Marked dropout rate*: control, n = 30, 28, 21; intervention, n = 30, 18, 12 At baseline, 1 month, 12 months The study p-values refer to within group changes (paired t test) despite the parallel design. Further analysis does still show between group (unpaired t test) significant differences

continued

TABLE 25 contd *Included RCTs*

Study	Methodology	Details	Results (SD)	Comments
Owens-Harrison *et al.*, 1996[303] Evaluation of education provided by a pharmacist to hospitalised patients who use MDI	*Design*: randomised, parallel trial *Interventions*: verbal and video education, total 30 minutes by pharmacist *Device*: pMDI *Duration*: 2 days	*Participants*: 74 COPD patients; mean age 67 years; 74 of 87 patients had less than maximum score and were randomised *Scoring system*: 8-point scale (references given) *Study quality*: Cochrane B	*Significant differences in*: Scores immediately and at 2/3 days: control, 4.24 (1.64) and 4.47 (1.72); education 7.49 (1.04) and 6.86 (1.73)	
Rydman *et al.*, 1999[304] Evaluating the outcome of 2 teaching methods of BA-inhaler in an inner city asthma clinic	*Design*: randomised, parallel trial *Interventions*: verbal instruction and demonstration; control had written instruction *Device*: pMDI and BA-pMDI *Duration*: between 8 and 20 weeks	*Participants*: 68 asthmatics in clinic longer than 6 months (60 completed); mean age 46 years *Scoring system*: pMDI 8-point; BA-pMDI 9-point (references cited) *Study quality*: Cochrane B	Unusual statistical analysis in the paper (each patient scored as 0 for any mistake or 1 for no mistakes, the group mean score was used). No difference claimed between groups Control, n = 28, score 0.83 (0.37), i.e. 23/28 patients all correct; education, n = 32, score 0.96 (0.17), i.e. 31/32 all correct p = 0.06 (apparently using a t test on skewed data)	FEV_1 measured pre- and post-study but not described in the methods Only the BA-pMDI was assessed as an RCT pMDI can be analysed as 'before and after'
Self *et al.*, 1983[305] The value of demonstration and role of the pharmacist in teaching the correct use of pressurised bronchodilators	*Design*: randomised, 3-way parallel trial *Interventions*: (a) personal instruction from pharmacist; (b) in-house educational video Controls had written instruction sheet *Device*: pMDI *Duration*: between 1 and 16 weeks	*Participants*: 29 mild asthmatics from allergy clinic; mean age 29 years (9 M, 20 F) *Scoring system*: 10-point scale (not stated); 2 actuations scored, total possible score 20 *Study quality*: Cochrane B	*Significant differences in*: Immediate scores between control and either education: control, n = 10, score 10.7 (4.5); personal, n = 9, score 16.8 (4.1); video, n = 10, score 16.9 (5.0)	The same person doing the teaching was immediately scoring the resultant inhaler technique
Tullio & Corsen, 1987[306] Effect of pharmacist counselling on ambulatory patients' use of aerosolised bronchodilators	*Design*: pseudo-randomised, parallel trial *Interventions*: personal instruction from pharmacist; controls had manufacturer's leaflet *Device*: pMDI *Duration*: mean follow-up of 2.5 months	*Participants*: 29 mild-to-moderate asthma or COPD in clinic and newly requiring an inhaler, mean age 60 years *Scoring system*: 11-point *Study quality*: Cochrane C	*Significant differences in*: Scores: control, n = 10, 7.1 (1.8); education, n = 9, 10.1 (1.0) *and* % change in FEV_1: control, 5.2 (1.0); education, 18.5 (1.5)	FEV_1 measured 'Randomisation' was by a different service for each of 2 clinics

continued

TABLE 25 contd *Included RCTs*

Study	Methodology	Details	Results (SD)	Comments
Van der Palen *et al.*, 1997[298] Evaluation of the long-term effectiveness of three instruction modes for inhaling medicines	*Design*: randomised, 4-way parallel trial; blinded assessment of technique *Interventions*: (a) personal tuition; pulmonary function technician, until no errors; (b) video to take home; (c) group; led by specialist nurse, average 45 minutes *Device*: pMDI/DPI *Duration*: up to 9 months	*Participants*: 152 COPD patients (148 completed); all COPD patients in the clinic who had used an inhaler for more than 1 month were approached *Scoring system*: Total ('essential') steps pMDI 8 (3)-point; Diskhaler 8 (2)-point; Rotahaler 10 (3)-point; Turbuhaler 8 (3)-point *Study quality*: Cochrane B	*Significant differences in*: Numbers with all 'essential' steps correct: control, 16/33; personal, 28/37; video, 30/40; group, 37/38 Score (as % correct of all steps): control, 74; personal, 90; video, 91; group, 93	Estimated SD used for the technique scores
Verver *et al.*, 1996[307] Effects of instruction by practice assistants on inhaler technique and respiratory symptoms of patients. A controlled, randomised video-taped intervention study	*Design*: randomised, parallel trial; blinded assessment *Interventions*: personal instruction from pharmacist; controls had manufacturer's leaflet *Device*: DPI *Duration*: mean follow-up of 2.5 months	*Participants*: 48 patients with asthma or COPD recruited from practice records of those using a DPI; 46% of patients invited chose to enrol; mean age 53 years, range 15–85 years *Scoring system*: 9-point; consensus view of the Netherlands Asthma Foundation *Study quality*: Cochrane C	*Significant differences in*: Inhaler scores: education, n = 25; score 6.56 (1.0) control, n = 23; score 5.91 (1.2) *No significant differences in*: All steps correct: education 5/25; group 2/23	Symptom score also measured The study analysis for technique score uses before and after or 'within group' change to arrive at p = 0.01 (paired t test) Alternative analysis between groups at the end of study remains significant, p = 0.046 (unpaired t test)
Wilson *et al.*, 1993[308] A controlled trial of 2 forms of self-management education for adults with asthma	*Design*: randomised, 4-arm parallel trial *Interventions*: (a) structured, small group, nurse-led programme; 4 x 90-minute sessions; (b) individually tailored, nurse-led programme; 5 x 45 minutes; (c) control, no education; (d) control with workbook education (not used in the current analysis) *Device*: pMDI *Duration*: 1 year	*Participants*: 323 mild-to-moderate asthmatics recruited from clinic (278 completed); 52% of those eligible entered *Scoring system*: 8-point (source cited and items listed) *Study quality*: Cochrane B	*Significant differences in*: Inhaler scores at 1 year: group, n = 66, score 7.48 (0.86); individual, n = 66, score 7.27 (0.89); control, n = 63, score 6.27 (1.25) *and* 'All steps correct': group 42/68; individual 33/68; control 12/68	Numbers all correct and scores estimated from a graph Assumed equal completion in all groups (86% overall)
Windsor *et al.*, 1990[309] Evaluation of the efficacy and cost-effectiveness of health education methods to increase medication adherence among adults with asthma	*Design*: randomised, parallel trial *Interventions*: 30 minutes one-to-one teaching, 60 small group session and 2 telephone calls *Control*: undefined *Device*: pMDI *Duration*: assessed at 12 months	*Participants*: 167 clinic asthmatics (125 completed) *Scoring system*: 10-point scale; nature of scale and method of assessment unclear *Study quality*: Cochrane B	*Significant differences in*: Inhaler 'all correct' at 1 year: taught 63/124; control 10/101	

TABLE 26 *Included 'before and after' studies*

Study	Methodology	Details	Results (SD)	Comments
Appel, 1982[310]	61 consecutive patients attending for pulmonary function tests; 56 completed and analysed	Inhaler technique correct if bronchodilator response, or, if no response, the technique appeared adequate to an observer; those who were inadequate were taught and assessed weekly twice more	13/56 correct at baseline 47/56 correct at final assessment	Unusual definition of correct technique
Chmelik & Doughty, 1994[311]	20 patients with asthma Part of an education programme, video, one-to-one and written teaching	6-point scale	All correct: baseline 6/20; 5 weeks 19/20 Mean score: baseline 5.0 (0.86); 5 weeks 5.9 (0.45)	
Choy *et al.*, 1999[312]	230 asthma clinic patients: 192 completed Groups of 10 for 2-h asthma session with nurse, video in clinic and consultation reinforcement	Inhaler technique rated (1) poor, (2) adequate or (3) good, and used as a continuous variable	Baseline score: 2.33 (0.56) 1 year score: 2.50 (0.6) $p < 0.01$ from original paper	Unclear if the technique data were analysed as a parametric or non-parametric variable
Christiansen *et al.*, 1997[313]	18 control asthmatics; 32 treatment asthmatics (fourth-grade) Not randomised, school-based asthma education programme, 5 x 20-minute sessions	pMDI assessed using a 7-point scale	Baseline score: control 2.5 (1.6); education 2.3 (1.47) Post intervention: control 2.2 (1.32); education 4.3 (1.47)	Non-randomised, alternate school year-groups specified as control or teaching
Cocqui & Zuriek, 1997[314]	2467 patients with 'poor inhaler technique' starting on an Autohaler	Assessed on a specific 6-point scale relating to the package insert instructions	856/2467 all correct after reading package instructions only 1858/2467 all correct after package insert and personal instruction	
De Blaquiere *et al.*, 1989[315]	101 asthma and COPD patients; any 'inadequate' technique patients had personal teaching (randomised to 2 different forms)	pMDI assessed using a 3-point scale	38/100 all correct at baseline At 6–10 weeks after teaching 69/94 were correct	
De Oliveira *et al.*, 1997[316]	40 asthmatics enrolled into a 6-month education programme: 31 assessed	Correct pMDI used as the outcome but not specified how measured	All correct: before 19/31; after 27/31	
Ivanovich *et al.*, 1996[317]	12 asthmatics; assessed before and after teaching with an auditory inspiratory aid	pMDI assessed using a 3-point scale	All correct: 0/12 baseline; 12/12 after teaching Mean score: 0.83 (0.58) before; 3.0 (0.0) after	Assessment was immediately after teaching
King *et al.*, 1991[318]	57 inpatients with asthma or COPD	4-point pMDI scale	All correct: baseline 18/57; after 2nd teaching 47/57	

continued

TABLE 26 contd *Included 'before and after' studies*

Study	Methodology	Details	Results (SD)	Comments
Lee, 1983[319]	42 children with asthma aged 7–15 years and using a pMDI > 6 months	Technique described as correct or incorrect based on observation and recording via an airflow monitor attached to the pMDI	Correct at baseline: 24/42 Correct 2 weeks after teaching: 15/18	In those 18 patients 'incorrect', PEFR increased from 207 to 213 after using their pMDI. After teaching, the PEFR increased 210 to 261 with pMDI use. No errors or significance value given
O'Bey *et al.*, 1982[320]	19 clinic asthma and COPD patients; assessed and taught on 3 occasions	Scored on a 10-point pMDI scale (converted to a % in the study)	Before/after teaching at: visit 1, 55.5/89%, *n* = 19 visit 2, 76/91%, *n* = 9 visit 3, 79/92%, *n* = 5	Large dropout rate
Oliver & Rees, 1997[321]	20 COPD patients were taught 7 devices and assessed at 1 h	Inhaler-specific scoring system, each with 12-points. Number of 'lethal' faults was the outcome measure but these were not defined	Median scores for the devices were 9.0 (Diskhaler) to 11.13 (Accuhaler) with pMDI at 10.88	No data useable within the meta-analysis
Reesor-Nimmo *et al.*, 1993[322]	30 inpatients with asthma or COPD previously using a pMDI were taught to use a Diskhaler or Turbuhaler	Baseline pMDI assessed on 11-point scale; Diskhaler on 8-point scale; Turbuhaler on 9-point scale (all converted to %)	pMDI at baseline: 7/20 all correct; mean score 9.1 DPI 3 days after teaching: 16/30 all correct; mean score 91%	
Van der Palen *et al.*, 1999[323]	166 asthmatics before and after a self-management programme	pMDI, Diskhaler, Turbuhaler score on 8-point scale; Rotahaler scored on 10-point scale (all converted to %)	Baseline score: pMDI 85.25%; DPI 86.15% After programme: pMDI 91.69%; DPI 91.83%	Estimated SD of 40 used for all

TABLE 27 *Included 'baseline' or cross-sectional studies*

Study	Patients	Details	Results	Comments
Baciewicz & Kyllonen, 1989[324]	25 children aged 7.5–18 years, mean 12.5 years	Excluded if use a spacer or had formal instruction within 6 months 12-step scoring pMDI alone	No children with all steps correct Mean score: 6.92	
Beerendonk *et al.*, 1998[325]	316 patients with COPD or asthma; 23 who had received previous instruction were excluded	56 using pMDI alone, 257 using DPI 8-point score for each	Mean scores: pMDI 6.05; DPI 5.46	Estimated SD used (3) for each
Campos *et al.*, 1998[326]	150 randomly selected outpatients	50 each for pMDI, pMDI + spacer and Turbuhaler Used 7, 6, 5 steps respectively	All correct: pMDI 25, pMDI + spacer 28, Turbuhaler 29 Mean scores: pMDI 68.6%, pMDI + spacer 50%, DPI 60%	Estimated SD used (30) for each

continued

TABLE 27 contd *Included 'baseline' or cross-sectional studies*

Study	Patients	Details	Results	Comments
Chapman & Brubaker, 1993[327]	80 patients aged 63–85 years who were referred for pulmonary function testing	Taught pMDI and BA-pMDI technique and assessed afterwards Scoring criteria unclear	All steps correct: pMDI 48/80; BA-pMDI 63/80	Used only for the 'optimal inhaler' analysis
Connolly, 1995[328]	40 inhaler-naive patients with COPD, aged 70–92 years	All patients taught pMDI alone and pMDI + spacer technique and immediately assessed Scored as 'perfect', 'minor errors' or 'inadequate'	Numbers with 'perfect': pMDI alone 16/40; pMDI + spacer 27/40	Used only for the 'optimal inhaler' analysis
De Boeck *et al.*, 1999[329]	161 consecutive children requiring an inhaler, aged 5–17 years, mean 9.8 years	All taught and immediately assessed Scoring on 3 steps: device upright, proper preparation of dose, inspiration > 40 litres/minutes	All steps correct: 131/161	Used only for the 'optimal inhaler' analysis Scoring system less steps than most and does not consider, for example, inspiratory volumes and breath-holding
Dompeling *et al.*, 1992[330]	41 patients with asthma or bronchitis, part of a 2-year efficacy study	All patients observed and taught inhaler technique at several points during the study protocol 'Good' technique based on 4 critical steps; score based on 7 steps	Good technique in 2/41 patients Mean score: 4.34	
Epstein *et al.*, 1979[331]	130 patients with COPD or asthma attending for pulmonary function testing, aged 18–83 years, mean 53.9 years	Scored on 11-point scale	All steps correct: 14/130 Mean score: 7.3 (3.67)	
Hilton, 1990[332]	422 asthmatics (mixed adults and children) recruited from 34 GPs	Score based on 4 points applicable to all inhaler device types: preparation, inspiration/head position, inspiratory technique, holding breath	All steps correct: pMDI 118/262; pMDI + spacer 21/36; DPI 63/111 Mean scores: pMDI 2.85 (1.28); pMDI + spacer 3.14 (1.22); DPI 3.22 (1.0)	
Kamps *et al.*, 2000[333]	66 children newly referred to an asthma clinic and 29 patients previously within a clinical trial were assessed	Score based on the standardised checklist from the Netherlands' Asthma Foundation 8 points for DPI, 7 points for pMDI + spacer	Five essential steps all correct, new and study patients: pMDI + spacer 33/49 and 11/13 DPI 5/17 and 13/13 Mean scores, new and study patients: pMDI + spacer 4.53 (0.82) and 4.77 (0.6) DPI 4.0 (0.79) and 5.0 (0.0)	
Kumana *et al.*, 1993[334]	74 patients from an asthma clinic	Score based on 11 points	Mean score: 7.4	

continued

TABLE 27 contd *Included 'baseline' or cross-sectional studies*

Study	Patients	Details	Results	Comments
Larsen *et al.*, 1994[335]	501 patients 12 years or older (16–85 years, mean 43.3 years) recruited from 51 physicians	pMDI scored on 9 points	Mean score: 7.29 All steps correct: 113/507 (using either of the 2 observers registering a correct step)	
Lindgren *et al.*, 1987[336]	23 asthma clinic patients, aged 20–71 years, mean 55 years	pMDI scored on 4 points	All correct: 10/23 Mean score: 3.35	Technique assessed with changes in FEV_1
Manzella *et al.*, 1989[337]	238 clinic patients (part of a larger study of an asthma education programme)	34% of patients were using a spacer (no separate analysis given) Scored on 10-point scale	All correct: 31/238 Mean score: 6.89 (2.28)	
Pedersen *et al.*, 1986[338]	256 clinic patients on regular inhaled medication, aged 4–16 years, mean 9.7 years	pMDI, pMDI + spacer and Rotahaler assessed All scored on a 9-point scale	All correct: pMDI 61/132; pMDI + spacer 50/85; Rotahaler 18/39 Mean scores: pMDI 5.7; pMDI + spacer 6.4; Rotahaler 5.7	Technique assessed with changes in FEV_1: if FEV_1 increased > 15% the mean score was 7.1; if FEV_1 increased < 15% the mean score was 3.4 Estimated SD 3.0 used
Plaza & Sanchis, 1998[339]	746 patients from 12 centres using pMDI (also assessed 466 nurses and 428 physicians); mean age 36 years	pMDI scored on a 9-point scale	All correct: 67/746 Mean score: 5.24	All correct: physicians 28%; nurses 15%; patients 9%
Rivera *et al.*, 1996[340]	296 patients from an allergy outpatient clinic and primary practice	pMDI and pMDI + spacer on a 5-point scale; DPI on a 3-point scale	All correct: pMDI 47/117; pMDI + spacer 33/83; DPI 75/96 (statistically significantly)	Large difference in number of steps used. DPI users tended to be younger (22 years vs 32 years)
Shrestha *et al.*, 1996[341]	125 asthmatics presenting to an emergency room in the USA	7-point pMDI scale	All correct: 26/125 Mean score: 4.8 (1.7)	All instructed for mean 8.3 minutes. All ended with an ideal inhaler technique at immediate assessment
Thompson *et al.*, 1994[342]	Chart review of hospitalised patients to identify pMDI users 127 patients; mean age 60 years	8-point scale for pMDI; 7-point scale for pMDI + spacer Limited separate analysis	All correct: 27/127 Mean scores: pMDI alone 5.26; pMDI + spacer 5.1	
GP, general practitioner				

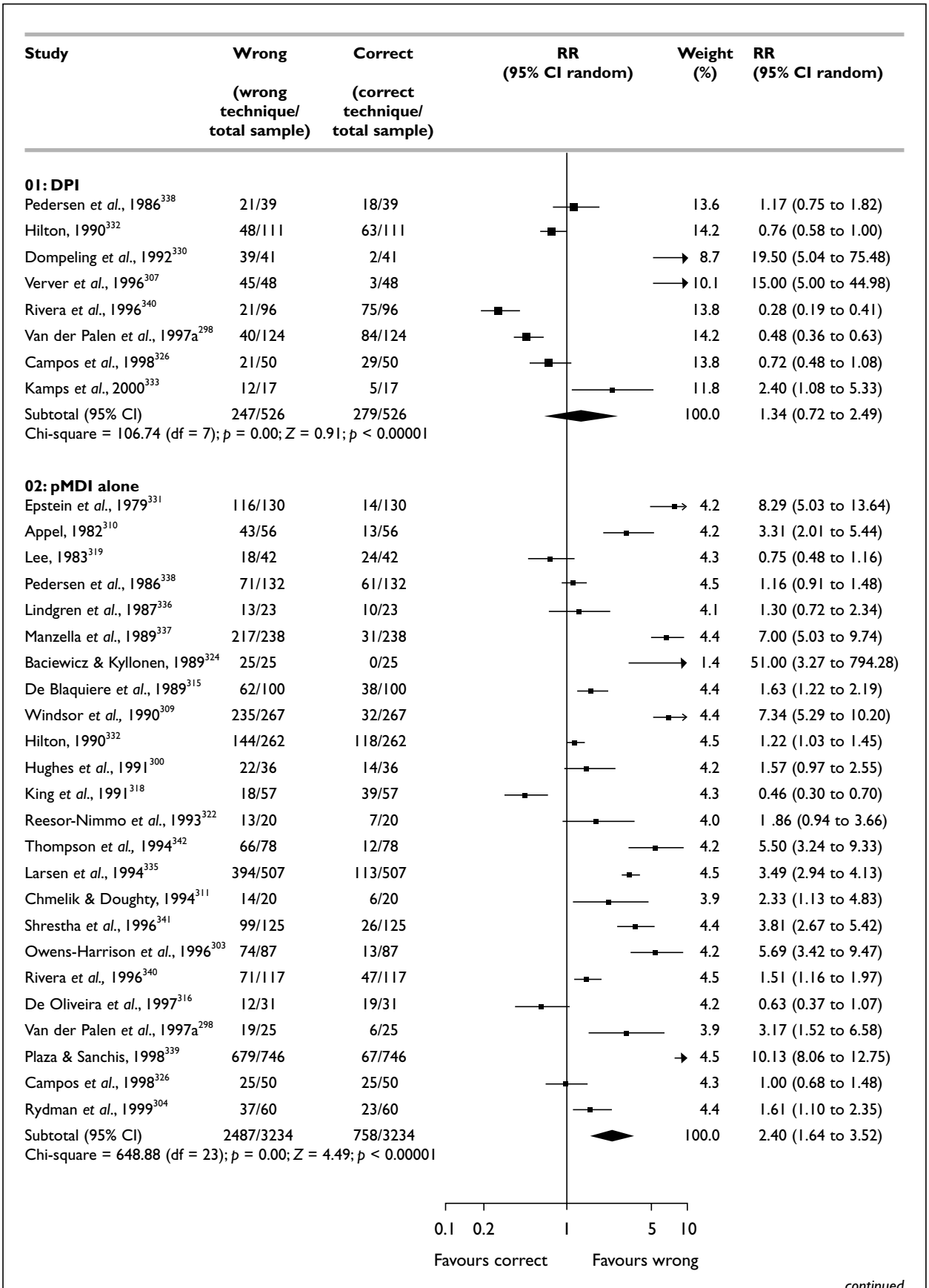


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FIGURE 12 *Baseline technique data by device*

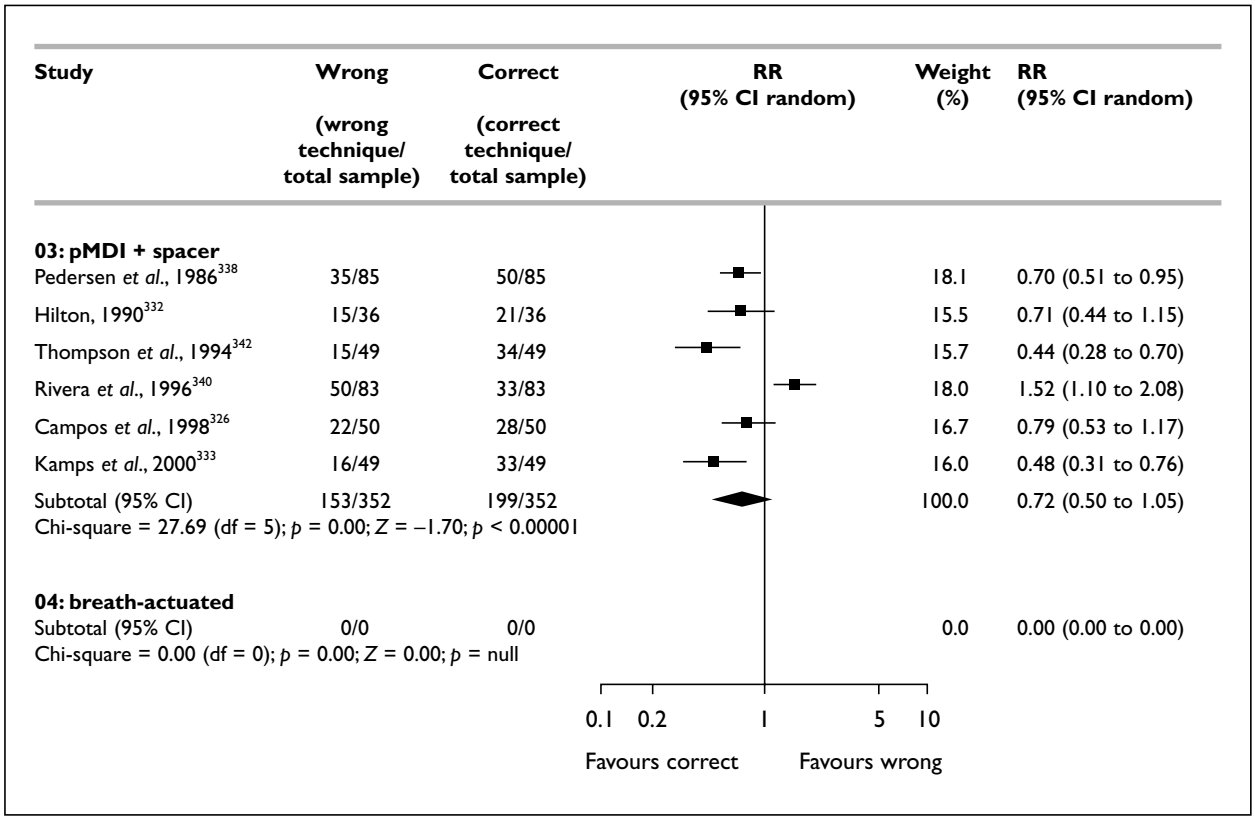

FIGURE 12 contd *Baseline technique data by device*

In all, 24 studies considered the pMDI and eight considered the DPI, so that the majority of studies assess pMDI technique in isolation (see 'Discussion', page 99). A more meaningful comparison is one where studies are only included that score more than one type of inhaler device. When this is done the same scores are, for DPI: 59% (95% CI, 51% to 67%); for pMDI alone: 43% (95% CI, 36% to 50%); and for pMDI + spacer: 55% (95% CI, 49% to 61%).

The alternative method of assigning inhaler technique is to score on the number of steps performed correctly out of the total number of possible steps. Seven studies, comparing the DPI to the pMDI with or without spacer, are available that present scores in this manner. Combining using SMD gives the result 0.04 (95% CI, –0.18 to 0.27) in favour of the pMDI. This result is in units of a 'standard deviation' and can be applied to other actual or representative data to convert to clinically meaningful figures. Using typical study data of a 60% correct technique score with a SD of 30, the inhaler technique score is 1.4% higher (absolute) for the pMDI than the DPI (95% CI, –5.4% to 8.4%).

'Post-intervention' technique data

A total of 20 studies were available with data. This data is from the combination of post-intervention/ teaching of inhaler technique in trials from the included before and after studies and RCTs.

Using the outcome of 'ideal' inhaler technique, 65% (95% CI, 59% to 71%) of patients using a DPI made no mistakes compared with 63% (95% CI, 60% to 67%) using a pMDI alone and 75% (95% CI, 74% to 76%) using a BA-pMDI. The latter has a much narrower 95% CI. This is due to the result being almost entirely down to one study of 2467 patients. This was a multicentre open assessment of patients' abilities to use a new device.

The preferred analysis of considering studies comparing more than one device as above is not possible: only one study[298] presented such results. This showed a non-significant difference in the direction of the pMDI (18 of 20 patients correct) versus the DPI (77 of 95 patients correct).

Effect of teaching

The effect of educational interventions on inhaler technique is investigated in two ways. The first method is by consideration of the included RCTs. In these, patients have been randomised to either teaching or to some form of control ('usual care' or passive intervention, e.g. information leaflet). Secondly, in the included before and after studies,

the same patients' inhaler techniques are scored before and after a process of teaching, at various time points.

- ***RCT data***
  Using 'ideal' technique as the outcome, the RR of all steps correct in the intervention group compared to the control group is 2.27 (95% CI, 1.76 to 2.95). This is illustrated in *Figure 13*, which also shows the before and after data.

In terms of the 'number needed to treat' or, in this instance, the number needed to teach, the result is 2.6 patients (95% CI, 2.2 to 3.3). This number is for 'teaching' of the whole population. In practice, assessment would identify those patients with adequate technique and teaching would only be directed at those with inadequate technique. Therefore, the number needed to treat to achieve one 'ideal' would be less.

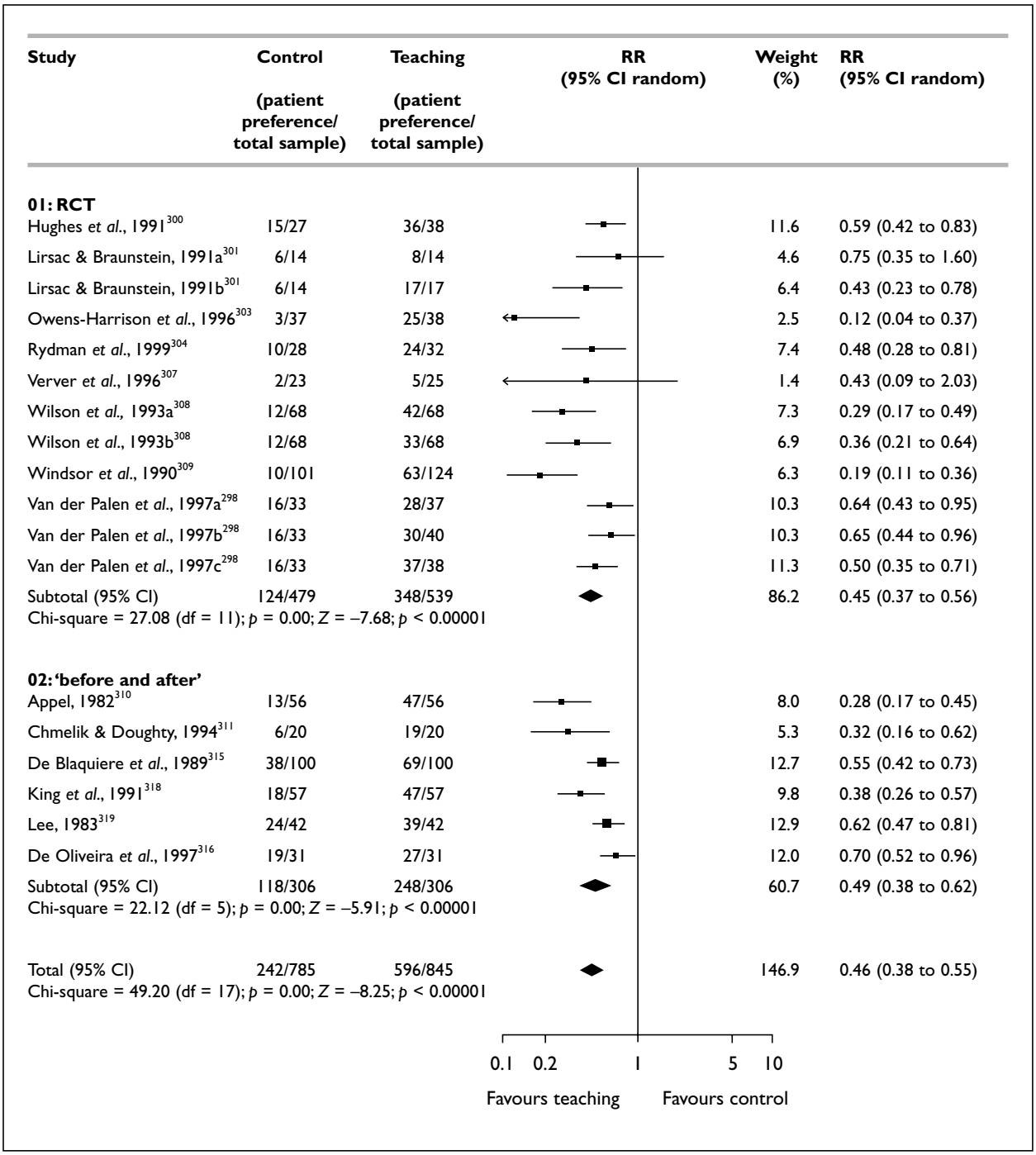

FIGURE 13 *Effect of teaching (before and after/RCT subgroups) by all steps correct/ideal technique*

The result of scoring from the number of steps performed correctly out of the total number of possible steps and combining the data using the SMD is 0.95 SD units (95% CI, 0.74 to 1.17) in favour of teaching intervention over control. In terms of example data of a mean technique score of 60% correct with a SD of 20, teaching would improve the score to 79% (95% CI, 74.8% to 83.4%).

- ***Before and after data***
  This is in effect paired data but in the current analysis is combined and treated as unpaired data due to the limitations of the original studies (usually presenting group data only rather than the error for individual patient change). Using 'ideal' technique as the outcome, the RR of all steps correct in the teaching intervention group compared to the control group is 2.08 (95% CI, 1.59 to 2.78).

  The result of scoring from the number of steps performed correctly out of the total number of possible steps and combining the data using the SMD is 0.68 SD units (95% CI, 0.27 to 1.09) in favour of teaching intervention over control. Whilst more prone to bias than RCT data and losing some of the statistical precision by not analysing as paired data, these are in close agreement with the RCT data and do provide complementary support.

It was not possible to analyse by different inhaler types because studies comparing more than one device were in the minority, and none of these analysed the effect of teaching separated by device type.

Discussion

Whilst the difference appears striking in the worst case scenario for the pMDI alone (all studies considered at 'baseline'), there may be factors that can at least partly account for this. There is a significant amount of heterogeneity within the scores for all types of inhaler device as might be expected from the different scoring systems and devices used and the characteristics of the patients being tested. In all, 24 studies were in the pMDI alone group and eight considered the DPI. The reasons are discussed individually below.

This data has weaknesses by its nature of collection, sampling and scoring systems used amongst others. Data on baseline or cross-sectional inhaler technique may come from a number of sources (audit data, marketing surveys, aspects of other types of trial comparing inhaler devices), some of which may be poorly covered by the usual method of electronic searching of medical databases. However, the primary objective is to obtain comparative data between the different inhaler devices and as such all have been subject to the same systematic review of the evidence.

Publication bias

This is likely to work in the direction of favouring devices other than the pMDI. Studies only considering the pMDI are significant only in illustrating the clinical point that the pMDI technique is poor. In studies comparing the pMDI against another device type, then the 'positive' finding is to show that another device has some superiority.

Heterogeneity

Significant heterogeneity of the data, at baseline, after teaching and the effect of teaching, is present for nearly all outcomes considered. As a result, a random effects model was used throughout. All outcomes will be heavily dependent on the background characteristics of the sample population. These are diverse, from those presenting with asthma exacerbation to an inner-city hospital to those recruited from within an established asthma clinic with an existing teaching programme. For absolute measures (as in cross-sectional data), better population technique will be reflected in better scores. The converse is true for relative measures (as in the effect of teaching), where a worse population technique at baseline allows more scope for improvement after intervention. This is addressed in two ways. By the systematic nature of the review, any selection bias in the inclusion of studies is lessened. Secondly, most of the interventional studies will contribute data to the cross-sectional baseline and the 'optimal' analysis. The bias would tend to work in different directions in each case.

Validity of scoring systems

The included studies, in contrast with most clinical studies, have essentially defined their own outcome measure. Also, if two or more devices are considered within one study, then the defined measure may be different for each of the devices. This may introduce bias. The more steps that are included for a device, the more potential mistakes are available to be made and possibly a lower score may result. Alternatively, if extra steps are introduced that are unduly easy and are performed correctly by most patients, then the score may be raised (at least relatively). Scoring systems are non-standard and there is no defined standard.

Some studies cite references and form a consensus of the 'necessary' steps needed for good inhaler technique. Others do not define the steps that have been used.

Also, the outcome of 'all steps correct' or 'ideal' inhaler technique may have been used for convenience. In practice, less than all steps correct may still give full or adequate clinical response. In scoring the number of steps correct, not all steps are of equal weight with respect to clinical response; for example, failing to remove the lid of a device leading to a complete failure, but failing to shake a pMDI before inhalation being only a partial failure.

Prior teaching experience

The available inhaler devices and clinical practice have been a developing area over the timescale of the studies in the review with the introduction of large volume spacer devices, DPIs and breath-actuated inhalers. For patients assessed using devices other than a pMDI alone, it is likely that generally the patients will have been using the device for a shorter period of time and teaching of inhaler technique is more likely to have occurred more recently. Similarly, patients established for a long period on a pMDI may be assumed to know how to use their inhaler, and checking and teaching of inhaler technique is less likely to occur. Conversely, it could be argued that patients on an alternative to a pMDI may have had it specifically prescribed due to a previous 'treatment failure' with a pMDI. The extent of such reasons for prescribing practice would depend upon local practice.

Summary

The data does support the view stated in many reviews and study introductions that pMDI devices are largely poorly used and an uncritical view of the DPI data would suggest that these are better used (on all steps correct, MDI alone was 23%, DPI was 53%, and pMDI + spacer 57%). However, these figures are a 'worst case scenario' for the pMDI alone. Alternative analyses do support either a much closer agreement between devices or in some cases equivalence.

By considering only studies that compared more than one inhaler device and therefore avoiding some of the biasing effects, this shows a much closer agreement in inhaler technique. The percentage of patients with all steps correct is 43% for pMDI alone, 55% for pMDI + spacer and 59% for DPI. There is statistical difference between pMDI alone and DPI or pMDI + spacer, but whether this is clinically significantly different is more difficult to judge, particularly if cost-efficacy is considered. The evidence of 'post-intervention' inhaler technique, that is what can be achieved again, shows close agreement; all steps correct is then 63% using a pMDI alone compared with 65% of patients using a DPI. The effect of teaching is shown to have a large positive effect upon inhaler technique. This is despite the fact that in most trials patients remained on their previous inhalers, which had been prescribed, used and trained on for some time.

The evidence as it exists after teaching (i.e. 'best case scenario' or in effect good clinical practice) shows that there is no difference between the pMDI and DPI (63% and 65% all steps correct, respectively).

Thus, any initial difference between the pMDI and DPI appears to be related partly to selection bias (as evidenced by the difference in cross-sectional results between 'all trials' and trials only comparing more than one inhaler) and partly to the fact that teaching of the appropriate inhaler technique has been lacking (as evidenced by the significant improvements achieved after a period of teaching and the equivalent results between the pMDI and DPI post-intervention) rather than to inherent differences in the devices themselves.

Differences between studies and heterogeneity of the results make it difficult to draw conclusions about inhaler technique differences between device types. The review of technique after teaching the correct technique suggests that there is no difference in patients' abilities to use DPIs or pMDIs.

Chapter 7

Economic impact of alternative inhaler devices

Introduction

Asthma is a major, common, chronic disorder, which affects both children and adults. The severity of the disease ranges from intermittent, mild symptoms such as coughs and wheezing, to severe, life-threatening attacks, which require immediate hospital treatment. *Table 28* gives the proportion of people with doctor-diagnosed asthma by age and sex in 1995. This indicates that the proportion of people with asthma diagnosed by a doctor is highest in children and young people up to the age of 16 (19–22%) than in those over 16 years old (8–17%).

TABLE 28 *Prevalence of asthma*

Age (years)	Rate per 100 population	
	Males	Females
People with doctor-diagnosed asthma[347]		
2–6	25	19
7–10	22	14
11–15	22	19
16–24	17	17
25–34	12	13
35–44	10	11
45–54	7	12
55–64	9	11
65–74	8	11
75+	8	8
People with treated asthma*		
0–4	9	6
5–15	12	10
16–24	7	8
25–34	5	6
35–44	4	5
45–54	4	6
55–64	5	7
65–74	7	7
75–84	7	7
85+	5	4

* *Estimated from European Community Respiratory Health Survey (1996)*[348]

Table 28 also gives the prevalence of treated asthma. Again, this indicates that the condition particularly affects children and young people under the age of 16 years old. However, the prevalence of treated asthma is lower than the number of people with a diagnosis of the condition. This may be due to a number of factors, including a proportion of people with mild disease who do not require formal healthcare services to manage the condition.

The management of asthma includes both primary care services, such as GP and practice nurse visits, hospital inpatient and outpatient care for diagnosis, routine follow up, patient education and advice, emergency visits and prescribed drugs. The range of services used, combined with the intensity of use and the prevalence of the disease means that the costs of healthcare for people with asthma are high. In 1992/93, the disease accounted for 0.52% of hospital inpatient and outpatient expenditure, 1.42% of primary care expenditure and significant pharmaceutical expenditure. Asthma and COPD accounted for 11% of the total drug spend.[343]

There are indications that the number of people who seek treatment for asthma is increasing. This may be partly due to increased awareness and diagnosis of the disease, the availability of pharmaceutical therapies to prevent and control acute attacks, and educational or behavioural strategies to minimise factors that may precipitate acute attacks. These factors have led to increases in the use of primary health services for care and treatment. In 1981/82, the number of people consulting their GP at least once during the year was 200 per 10,000 person years at risk for males and 159 per 10,000 person years at risk for females. These rates had risen to 429 (males) and 422 (females) per 10,000 person years at risk in 1991/92.[344] New GP episodes for asthma have also increased. In 1988/89, there were 1774 new GP episodes per 10,000 population, which rose to 2624 in 1993/94.[344] However, the rate of hospital admissions fell over this period from 223 per 10,000 population in 1988/89

TABLE 29 *Prescription and cost data for inhaler therapy, 1998*

Drug name		Prescriptions (Pxs)	Net ingredient cost (NIC)	NIC/Pxs
		000s	£000s	£
Salbutamol	DPI	1,375	15,249	11
	pMDI	12,806	46,997	4
	Nebuliser	726	14,856	20
Terbutaline	DPI	1,062	11,153	11
	pMDI	477	3,520	7
	Nebuliser	1,539	14,673	10
Ipratropium	DPI	13	209	16
	pMDI	1,192	8,006	7
	Nebuliser	421	14,078	33
Budesonide	DPI	1,226	31,527	26
	pMDI	520	10,997	21
	Nebuliser	136	17,919	131
Fluticasone	DPI	613	20,983	34
	pMDI	931	41,224	44
Beclometasone	DPI	871	21,926	25
	pMDI	7,336	119,256	16
All	DPI	5,160	101,047	20
	pMDI	23,262	229,999	10
	Nebuliser	2,822	61,525	22
	Total	**31,244**	**392,572**	**13**

Refers to prescriptions dispensed in the community; this excludes hospital prescriptions dispensed in pharmacies

All inhaler therapies recorded as prescribed under chapter 3 of the British National Formulary,[32] *'Respiratory system'*

Excludes combined or compound inhaler therapies, which are not recommended

Source: extracted from Department of Health, Prescription cost analysis: England, *1998,*[349] *http://www.doh.gov.uk/stats/pca98.htm*

to 202 per 10,000 population in 1993/94.[344] The number of prescriptions for asthma also increased from 15 million in 1980 to 29 million in 1990.[344]

Inhaled therapy is a key component of the management of and care of people with both acute and non-acute asthma. *Table 29* summarises community-dispensed prescribing and cost data for inhaled therapies used for all respiratory conditions. The therapies shown are those typically used for the management of asthma. However, the data also include prescriptions for people treated for other respiratory conditions, so only give an indication of the upper limit of the costs of community-dispensed inhaled therapy for asthma. The total number of prescriptions for inhaler therapy in 1998 was over 31 million, with a net ingredient cost in excess of £392 million. The net ingredient cost per prescription ranged from £4 to £131, depending on the combination of drug and device category and dose.

Three broad categories of device are available for inhaled therapy – pMDIs, DPIs and nebulisers – with bronchodilators and steroids for symptom relief and control of inflammatory activity, and beta-agonists for acute exacerbations. *Table 29* indicates that the average net ingredient cost of these was £10 per prescription for pMDI inhaler therapy, £20 for DPI inhaler therapy and £22 for nebuliser inhaler therapy. Within these categories there are several alternative device and drug combinations. *Table 30* lists the drug and device combinations from which prescribers can choose. As the table indicates, there are wide variations in the retail price of the combinations. For example, the price for beclometasone ranges from £4 to £40, depending on device, dose u nits and the number of doses per pack.

In clinical practice, the fundamental principle of prescribing is the use of the most clinical and cost-effective drug. This needs to take into account the ability of the patient to use the device effectively

TABLE 30 *Types of inhaler device and cost, by drug*

Drug	Device type		Name	Number of doses	Dose	Drug cost (£)	Device cost (£)	Refill (if device separate) (£)	CFC-free?
Beclometasone dipropionate	DPI		Asmabec Clickhaler	200	50 µg	7.18	–	–	No
Beclometasone dipropionate	DPI		Asmabec Clickhaler	200	100 µg	10.55	–	–	No
Beclometasone dipropionate	DPI		Becodisks	112	100 µg	10.99	–	10.42	–
Beclometasone dipropionate	DPI		Becodisks	112	200 µg	20.9	–	20.33	–
Beclometasone dipropionate	DPI		Becotide Rotacaps	112	100 µg	8.47	–	–	–
Beclometasone dipropionate	DPI		Becotide Rotacaps	112	200 µg	16.07	–	–	–
Beclometasone dipropionate	DPI		Becotide Rotacaps	112	400 µg	30.54	–	–	–
Beclometasone dipropionate	DPI		Asmabec Clickhaler	100	250 µg	13.24	–	–	–
Beclometasone dipropionate	DPI		Becloforte Diskhaler	112	400 µg	39.7	–	39.13	–
Beclometasone dipropionate	pMDI	BA	Aerobec 50 Autohaler	200	50 µg	11	–	–	No
Beclometasone dipropionate	pMDI	BA	Aerobec 100 Autohaler	200	100 µg	13.5	–	–	No
Beclometasone dipropionate	pMDI	BA	Becotide Easi-Breathe	200	50 µg	4.34	–	–	No
Beclometasone dipropionate	pMDI	BA	Becotide Easi-Breathe	200	100 µg	8.24	–	–	No
Beclometasone dipropionate	pMDI	BA	Qvar® 50 Autohaler	200	50 µg	8.24	–	–	Yes
Beclometasone dipropionate	pMDI	BA	Qvar® 100 Autohaler	200	100 µg	18.02	–	–	Yes
Beclometasone dipropionate	pMDI	BA	AeroBec Forte	200	250 µg	25.2	–	–	No
Beclometasone dipropionate	pMDI	BA	Becloforte Easi-Breathe	200	250 µg	18.02	–	–	No
Beclometasone dipropionate	pMDI	with Becloforte Integra® spacer	Becloforte	200	250 µg	23.1	–	18.02	No
Beclometasone dipropionate	pMDI		Various	200	50 µg	4.34	–	–	No
Beclometasone dipropionate	pMDI		Various	200	100 µg	8.24	–	–	No
Beclometasone dipropionate	pMDI		Various	200	200 µg	15.68	–	–	No
Beclometasone dipropionate	pMDI		Becotide	200	50 µg	5.43	–	–	No
Beclometasone dipropionate	pMDI		Becotide	200	100 µg	10.32	–	–	No

continued

TABLE 30 contd *Types of inhaler device and cost, by drug*

Drug	Device type		Name	Number of doses	Dose	Drug cost (£)	Device cost (£)	Refill (if device separate) (£)	CFC-free?
Beclometasone dipropionate	pMDI		Becotide	200	200 µg	19.61	–	–	No
Beclometasone dipropionate	pMDI		Qvar 50	200	50 µg	8.24	–	–	Yes
Beclometasone dipropionate	pMDI		Qvar 100	200	100 µg	18.02	–	–	Yes
Beclometasone dipropionate	pMDI		Various	200	250 µg	18.02	–	–	No
Budesonide	DPI		Pulmicort Turbohaler	200	100 µg	18.5	–	–	–
Budesonide	DPI		Pulmicort Turbohaler	100	200 µg	18.5	–	–	–
Budesonide	DPI		Pulmicort Turbohaler	50	400 µg	18.5	–	–	–
Budesonide	Nebuliser		Respules	20	500 µg	32	–	–	–
Budesonide	Nebuliser		Respules	20	1000 µg	44.64	–	–	–
Budesonide	pMDI	with spacer or standard inhaler	Pulmicort	200	200 µg	19	–	–	No
Budesonide	pMDI		Pulmicort LS	200	50 µg	6.66	–	–	No
Fluticasone	DPI		Flixotide Accuhaler	60	50 µg	8.23	–	–	–
Fluticasone	DPI		Flixotide Accuhaler	60	100 µg	12.8	–	–	–
Fluticasone	DPI		Flixotide Accuhaler	60	250 µg	24.23	–	–	–
Fluticasone	DPI		Flixotide Accuhaler	60	500 µg	40.23	–	–	–
Fluticasone	DPI		Flixotide Diskhaler	56	50 µg	8.23	–	7.66	–
Fluticasone	DPI		Flixotide Diskhaler	56	100 µg	12.8	–	12.23	–
Fluticasone	DPI		Flixotide Diskhaler	56	250 µg	24.23	–	23.66	–
Fluticasone	DPI		Flixotide Diskhaler	56	500 µg	40.23	–	39.66	–
Fluticasone	pMDI		Flixotide	120	25 µg	6.86	–	–	No
Fluticasone	pMDI		Flixotide	120	50 µg	11.43	–	–	No
Ipratropium bromide	DPI		Atrovent Aerohaler (Aerocaps)	100	40 µg	14.35	–	10.53	–
Ipratropium bromide	Nebuliser		Various	60	250 µg	20.25	3.8	–	–

continued

TABLE 30 contd *Types of inhaler device and cost, by drug*

Drug	Device type		Name	Number of doses	Dose	Drug cost (£)	Device cost (£)	Refill (if device separate) (£)	CFC-free?
Ipratropium bromide	Nebuliser		Atrovent nebuliser solution	20	500 µg	8	3.8	–	–
Ipratropium bromide	Nebuliser		Ipratropium Steri-Neb	20	500 µg	7.2	3.8	–	–
Ipratropium bromide	Nebuliser		Respontin	20	500 µg	6.4	3.8	–	–
Ipratropium bromide	pMDI	BA	Atrovent Autohaler	200	20 µg	10.43	–	–	No
Ipratropium bromide	pMDI		Atrovent (aerosol inhalation)	200	20 µg	4.21	–	–	No
Ipratropium bromide	pMDI		Atrovent Forte	200	20 µg	6.22	–	–	No
Salbutamol	DPI		Asmasal Clickhaler	200	95 µg	6.32	–	–	–
Salbutamol	DPI		Ventodisks	112	200 µg	12.02	–	11.45	–
Salbutamol	DPI		Ventolin Accuhaler	60	200 µg	5	–	–	–
Salbutamol	DPI		Ventolin Rotocaps	112	200 µg	5.92	0.78	–	–
Salbutamol	DPI		Ventolin Rotocaps	112	400 µg	10.01	0.78	–	–
Salbutamol	Nebuliser		Salamol Steri-Neb	50	2.5 mg	3.2	3.8	–	–
Salbutamol	Nebuliser		Ventolin Nebules	20	5 mg	7.67	3.8	–	–
Salbutamol	pMDI	BA	Aerolin Autohaler	200	100 µg	10.51	–	–	No
Salbutamol	pMDI	BA	Ventolin Easi-Breathe	200	100 µg	6.3	–	–	No
Salbutamol	pMDI		Various	200	100 µg	1.78	–	–	No
Salbutamol	pMDI		Airomir	200	100 µg	2.06	–	–	Yes
Salbutamol	pMDI		Ventolin (aerosol inhalation)	200	100 µg	2.3	–	–	No
Salbutamol	pMDI		Ventolin Evohaler	200	100 µg	2.3	–	–	Yes
Terbutaline	DPI		Bricanyl Turbohaler	100	500 µg	7.96	–	–	–
Terbutaline	Nebuliser		Bricanyl Respules	20	5 mg	2.64	3.8	–	–
Terbutaline	Nebuliser		Bricanyl Respirator solution	20	10 mg	2.64	3.8	–	–
Terbutaline	pMDI		Bricanyl	400	250 µg	5.31	–	–	No
Terbutaline	pMDI		Bricanyl with spacer	400	250 µg	7.21	–	–	No

and patient preferences, which will affect adherence with therapy. Both of these factors will affect the activity of the inhaled therapy to prevent and/or relieve acute exacerbations.

Methods

Aims and objectives

The overall aims of the economic analysis were (1) to synthesise data on effectiveness with cost information, to identify the relative cost-effectiveness of the alternative devices and (2) to assess the budgetary impact on the NHS of changing prescribing patterns based on the cost-effectiveness of the alternative devices. Specific objectives were:

- to determine the relative cost-effectiveness of currently available hand-held inhaler devices for delivery of corticosteroids (beclometasone, budesonide and fluticasone) for the treatment of stable asthma
- to determine the relative cost-effectiveness of currently available hand-held inhaler devices for delivery of bronchodilators (beta-agonists) for the treatment of stable asthma
- to determine the relative cost-effectiveness of nebulisers for the delivery of short-acting bronchodilators compared with any hand-held inhaler device.

Comparators for analysis

The hand-held inhaler devices were classified as (1) a standard pMDI inhaler with or without a spacer device, (2) a DPI, and (3) nebulisers.

Patient population

The patient population for the economic analysis were the same as for the clinical reviews.

Perspective

The perspective of the analysis was limited to the costs to the NHS in England, which is the primary source of healthcare for the patient population considered, and to health outcomes for patients. The impact of the choice of devices on other sections of society is assumed to be limited. In this case the perspective used approximates to a societal one.

Time frame of analysis

Two time frames of analysis were used: 28 days and 1 year. The 28-day period was chosen to provide a standardised cost between the different number of doses and drug per dose delivered by the alternative devices. The 1-year period allows the description of the longer-term cost and outcome implications of the choice of inhaler device.

Analytic framework and measures

An economic model was developed to assess the relative expected costs and effectiveness of the inhaler devices to address the research questions above.

The primary outcome measure and framework of analysis for the economic evaluation was defined for two scenarios. First, if there were differences in clinical effectiveness between the inhaler devices, cost-effectiveness analysis would be used. The preferred primary outcome measure would be health-related quality of life. If the available data were sufficiently robust this would be used to estimate expected costs per quality-adjusted life-year. If the available data were uncertain (due to poor quality of study design, measurement methods used or limited data) the primary outcome measure was number of symptom-free days.

Secondly, if there were no differences in clinical effectiveness between the devices then cost minimisation analysis would be used. Any differences in total cost per person treated would then be due to differences in the standardised cost per 28 days of the device used. Some patients may prefer the more expensive types of inhaler device because of differences in non-health-related aspects of inhaled therapy delivery (such as ease of use, compactness, perception of effectiveness). The cost difference would give an estimate of the minimum value (or willingness-to-pay) patients would need to place on those preferences for the higher cost devices to be worthwhile.

The costs included in the analysis were the standardised costs of the device, and the costs of primary and secondary healthcare to manage acute exacerbations and changes in maintenance inhaled therapy. The costs were estimated as resource use multiplied by the costs of those resources.

The standardised costs of the inhaler devices were calculated for each combination of drug and device currently available. These were then averaged to estimate a mean cost for each class of device. The standardised cost for each drug and device combination was estimated as the retail price divided by the number of doses available in the package. This was then multiplied by the number of doses needed to deliver a standard daily dose. High and low standard daily doses were defined, giving high and low estimates of the standardised cost per day. These were multiplied up to give a cost per 28-day period.

Economic model

The evaluation of the economic costs and consequences used a decision analysis model and computer-based simulation to derive point estimates and evaluate the range of uncertainty around these estimates. Decision analytic techniques were used to systematically and explicitly structure complex decisions, to determine the optimal or efficient course of action amongst competing healthcare choices. In particular, decision analysis provides a method for combining data from a number of sources, to predict the expected economic costs and consequences of alternative choices, given the uncertainty surrounding the data available, multiple objectives and decision criteria.[345,346]

The decision tree is shown in *Figure 14*. The model starts with the decision to prescribe a specific drug for inhaled therapy. A choice needs to be made between the inhaler devices available. A flow of events follows from initiation of the inhaled therapy. The sequence and type of events is assumed to be dependent on the drug prescribed, and so is the same for each device. However, if there are differences in clinical efficacy, safety and acceptability between the devices, the probability of these events will differ by device used.

Following initiation of the inhaled therapy with a specific device, there is a probability that it is acceptable to the patient in terms of perceived ability to use the device appropriately and preferences for non-clinical attributes. If the device is not acceptable, there will be a change in therapy.

If the device is acceptable, there may be differences in the patient's actual ability to use the device appropriately and/or adherence with therapy. These will affect the overall amount of drug delivered and effectiveness of the drug to prevent acute exacerbations. There is then a probability of acute exacerbations due to inadequate inhaler therapy. The acute exacerbation may be controlled adequately by the patient, necessitate a primary care visit or attendance at an emergency department. However the acute exacerbation is treated, there is a probability that the inhaler therapy will be changed or continued.

Data

The model combined three distinct categories of data.

- First, evidence on the intermediate outcomes of patients associated with the alternative inhaler devices, in terms of lung function, number and severity of acute exacerbations, and location of acute treatment (e.g. home, primary care, hospital emergency department). The model used the estimates of outcome derived from the systematic review of the clinical literature.
- Secondly, evidence on the global asthma severity and health-related quality of life of patients of each of the options. The model used data derived from the systematic review of clinical literature. Where necessary this was supplemented by data from published and unpublished literature of non-trial evaluations.
- Thirdly, data on the resources used to provide management and care for acute and non-acute management, within the primary care and hospital setting, and use of other formal and informal health and social care services. This was derived from the systematic review of clinical literature and databases, supplemented where necessary by expert opinion and imputed values.

Analysis of data

The principal analysis of data was of the 28-day and 1-year expected costs and outcomes associated with each of the defined classes of inhaler device. Separate analyses were conducted for each of the economic objectives to correspond with the relevant clinical systematic reviews.

It was recognised that the quality and reliability of the data may be highly uncertain. Measures of variance were also calculated, based on the use of Monte Carlo simulation techniques. The number of simulations required to obtain convergence was determined by the use of a computer software package (Palisade Decision Tools Suite®).

One-way sensitivity analysis of the impact of the values for each variable on the results was also conducted for each simulation. This used the extreme minimum and maximum values for each variable. The sensitivity analysis provides information about the relative robustness of the results and identifies those variables that are likely to have a major impact. The model was defined as sensitive to the value of a variable if the sensitivity analysis indicated that the results switched from net expected saving to net expected cost (or vice versa) in response to changes in the value of that variable.

For those variables to which the model was sensitive, threshold analyses were conducted to determine the value of the variable at which the net costs or net outcomes were zero.

Results

Costs

The standardised 28-day costs of the devices by classification and drug are given in *Table 31*. *Tables 32–34* present the resource use, average unit costs and cost of each class of drug, and the costs of events included in the model. Overall, the standardised 28-day cost of pMDIs was lower than DPIs. Both pMDIs and DPIs had lower standardised 28-day costs than nebulisers.

Outcomes

The systematic review of the clinical literature found no evidence to support differences in the ability to use the pMDI or DPI inhaler devices. In addition, there was no evidence to support differences in clinical efficacy between any inhaler device. There was some evidence that there may be differences in patient preferences and side-effects between DPIs and pMDIs. These favoured pMDIs. These results would suggest that there is no reason to suppose differences in the rate of acute exacerbation due to the inhaler device used, but there may be some differences in the overall quality of life and symptom-free days due to patient preferences and side-effects.

There was some evidence that HFA-pMDIs may be associated with lower use of oral steroid treatment and treatment failures or dropouts, which may lead to a difference in acute exacerbations and overall quality of life or symptom-free days.

Analytic framework

The systematic review of the clinical literature found no evidence of quality of life or symptom-free days that could be used in the economic analysis. The overall conclusions of the reviews were that there was no evidence to support clinically important differences between inhaler devices. In addition, the evidence was in many cases uncertain due to problems with the design and quality of the clinical trials for review. Where there were differences, these were judged to be in favour of the lower cost pMDIs.

For these reasons it was decided that the primary economic analysis would be a comparison of costs only. Threshold analyses would be used to explore the minimum differences required in acute exacerbation rates and values for patient preferences. This also meant that additional data collection to supplement the clinical information reported and available national data statistics on resource costs were not required.

Expected costs

Table 35 presents the probability values used for the model to estimate the expected costs for each of the comparisons made. *Table 36* presents the expected costs. These were derived from the mean costs of device/drug combinations, and so represent the expected costs for a class of device rather than individual devices. *Figures 15–17* present the probability curves for each class of device. For the decision to prescribe inhaled therapy within a class of device, these curves show the probability of the 28-day cost. The costs of both the DPI and nebulisers are substantially higher than pMDI devices for all classes of drug. These results of the simulations indicated that the costs were sensitive to the costs of the device and to the rate of acute exacerbation. The rank correlation coefficients were greater than 0.9 for the cost of the device and greater than 0.2 for the rate of acute exacerbations.

Threshold analyses

Figures 18–20 present the results of the threshold analyses for differences in acute exacerbation rates that would be required for the more expensive drugs to be cost-effective. Only the comparison for corticosteroids showed a threshold value for acute exacerbations for pMDIs (*Figure 18*). This indicated that if the rate of acute exacerbations was set at 1.0 for pMDIs and 0.3 for DPIs, then the expected costs would be equivalent. This would also be true if the rate of acute exacerbations was reduced to 0.6 for pMDIs and 0.0 for DPIs.

Figures 21–23 present the results of the threshold analyses for the probability that the device is acceptable to patients. Even if the pMDI was not acceptable to patients, and all patients had to change device, the expected costs of pMDIs would still be lower than those of DPIs and nebulisers.

Budgetary impact

Figures 24–26 give the results of the analysis of budgetary impact. This uses a prevalence population of 3.3 million people with asthma, and shows the overall expected costs of inhaler therapy for different percentages of the population who use DPIs or nebulisers compared to pMDIs. For all analyses, the higher the rate of pMDI use, the lower the expected cost. Threshold analyses indicated that, as above, there were no threshold values for acute exacerbation or patient acceptability rates.

Summary

Overall, there were no differences in patient outcomes between the devices. On the assumption

that the devices were clinically equivalent, pMDIs were the most cost-effective.

DPIs were only equivalent in overall cost if it was assumed that the rate of acute exacerbation was 0.3 with the DPI and 1.0 with the pMDI, for corticosteroid drugs. There were no situations where the devices could be equivalent in cost for any of the other drug classes.

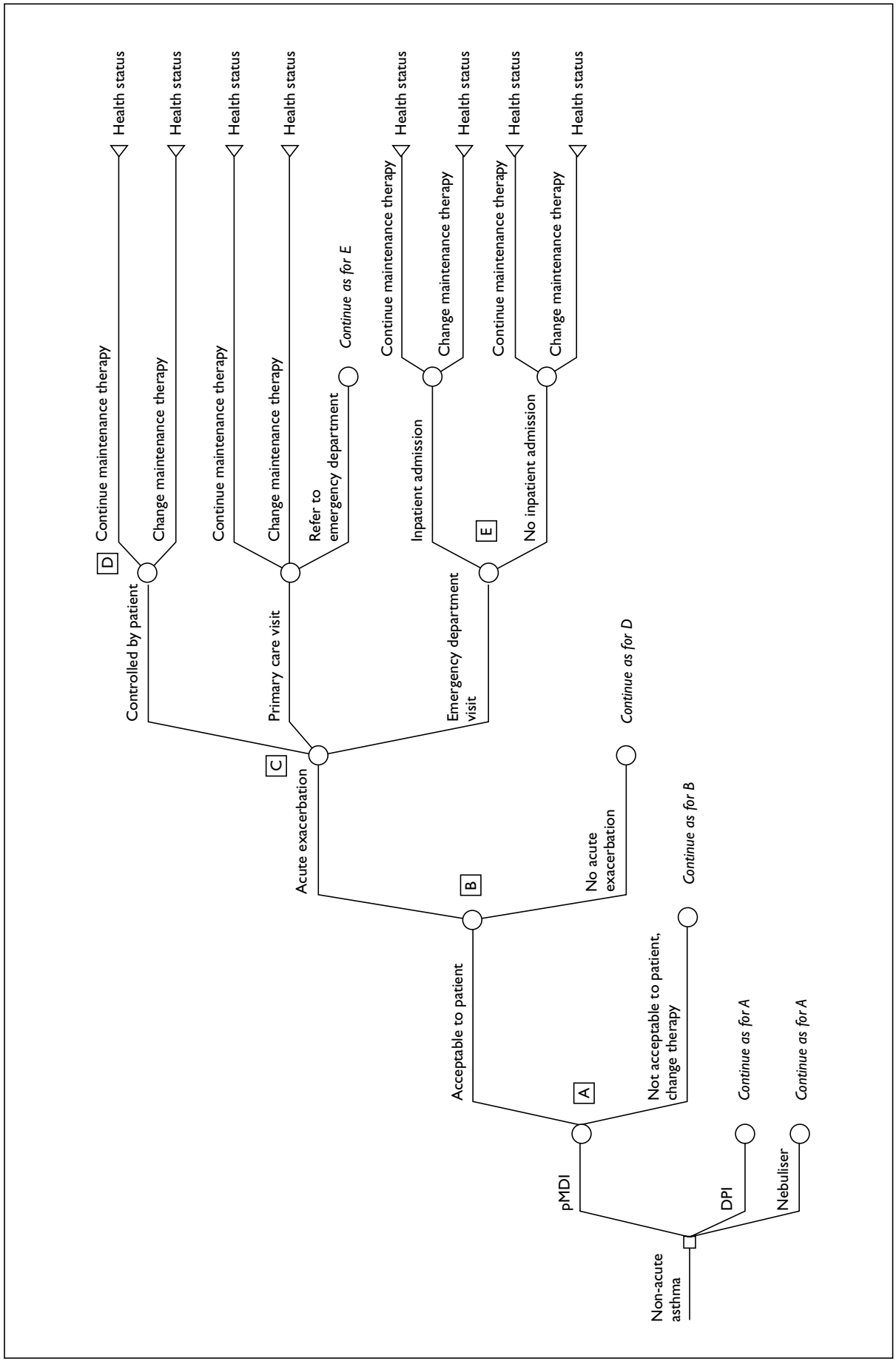

FIGURE 14 *Decision tree for an inhaler device in chronic stable asthma*

TABLE 31 *Standardised 28-day cost of devices and drug*

(A)

Drug	Device class	Standardised 28-day cost £, mean (SD)	
		Low dose	High dose
Beclometasone dipropionate	Standard pMDI	6.06 (2.15)	24.25 (8.61)
	BA-pMDI	7.06 (2.90)	28.24 (11.60)
	DPI	8.38 (1.82)	33.50 (7.26)
Budesonide	Standard pMDI	6.39 (1.51)	25.56 (6.05)
	DPI	10.36 (0.00)	10.36 (0.00)
	Nebuliser	30.42 (7.67)	121.68 (30.66)
Fluticasone	Standard pMDI	11.74 (1.51)	46.95 (6.05)
	DPI	11.36 (3.35)	45.43 (13.39)
Ipratropium bromide	Standard pMDI	3.89 (1.78)	1.95 (0.89)
	DPI	16.07 (0.00)	16.07 (0.00)
	Nebuliser	43.49 (3.87)	16.09 (4.50)
Salbutamol	Standard pMDI	2.36 (1.97)	2.36 (1.97)
	BA-pMDI	2.36 (1.97)	2.36 (1.97)
	DPI	8.16 (3.39)	3.97 (1.40)
	Nebuliser	28.86 (10.96)	10.96 (5.06)
Terbutaline	Standard pMDI	1.75 (0.38)	0.88 (0.19)
	DPI	8.92 (0.00)	2.23 (0.00)
	Nebuliser	1.75 (0.38)	9.34 (2.61)

The 28-day costs were calculated as follows:
Cost 1 – bronchodilators, 2 relieves twice daily; costicosteroids, low dose twice daily (see part B)
Cost 2 – bronchodilators, 28-day cost standard dose; costicosteroids, high dose twice daily (see part B)

(B)

	Daily dose	Daily low dose	Daily high dose
Salbutamol pMDI	400		
Salbutamol DPI	400		
Salbutamol nebuliser	5		
Terbutaline pMDI	500		
Terbutaline DPI	500		
Terbutaline nebuliser	10		
Ipratropium pMDI	40		
Ipratropium DPI	40		
Ipratropium nebuliser	500		
Beclometasone pMDI		400	1600
Beclometasone DPI		400	1600
Beclometasone nebuliser		400	1600
Budesonide pMDI		400	1600
Budesonide DPI		400	1600
Budesonide nebuliser		400	1600
Fluticasone pMDI		200	800
Fluticasone DPI		200	800
Fluticasone nebuliser		200	800
Nebuliser daily cost	3.8		

TABLE 32 *Resource use of events*

Event	Resource use
Therapy not acceptable	
GP visit	1.00
Acute exacerbation	
Primary care only	
GP visit	1.00
Primary care A & E referral, no inpatient admission*	
GP visit	1.00
A & E visit	1.00
Primary care A & E referral, inpatient admission	
GP visit	1.00
A & E visit	1.00
Length of stay (days)	3.60
Patient A & E referral, no inpatient admission	
A & E visit	1.00
Patient A & E referral, inpatient admission	
A & E visit	1.00
Length of stay (days)	3.60

* *The length of inpatient stay was estimated as the weighted average of inpatient stay for asthma*[350]

A & E, accident and emergency

TABLE 33 *Unit costs of resources*

Resource	Unit cost (£)
GP visit	15.50
A & E visit	37.00
Inpatient stay	
A & E	359.00
Other	222.00
Therapy/28 days [mean (SD)]	
All drugs	
DPI cost 1	9.75 (3.06)
DPI cost 2	26.75 (19.02)
nebuliser cost 1	32.97 (13.53)
nebuliser cost 2	34.83 (47.10)
pMDI cost 1	5.57 (3.23)
pMDI cost 2	19.37 (15.43)
Corticosteroids	
DPI cost 1	9.87 (2.75)
DPI cost 2	34.80 (15.20)
nebuliser cost 1	NA
nebuliser cost 2	NA
pMDI cost 1	7.02 (2.78)
pMDI cost 2	28.06 (11.13)
Beta-agonists	
DPI cost 1	8.29 (3.05)
DPI cost 2	3.68 (1.44)
nebuliser cost 1	23.72 (13.29)
nebuliser cost 2	10.15 (2.88)
pMDI cost 1	2.21 (1.69)
pMDI cost 2	1.99 (1.80)
All bronchodilators	
DPI cost 1	9.40 (4.05)
DPI cost 2	3.73 (1.32)
nebuliser cost 1	33.61 (12.20)
nebuliser cost 2	13.12 (4.42)
pMDI cost 1	2.67 (1.81)
pMDI cost 2	1.98 (1.56)
Additional therapy	9.35–15.39

The costs of hospital and primary care were taken from estimated cost data for the UK, reported in the 'Unit costs of health and social care'[351]

The costs of devices and drugs were estimated from the British National Formulary[32]

The cost of additional therapy was calculated as 50% of the average cost of all low-dose therapies

TABLE 34 *Costs of events*

Event	Cost per service (£)	Total cost (£)
Therapy not acceptable		
GP visit	15.50	–
Additional therapy	9.35–15.35	24.85–30.89
Acute exacerbation		
Primary care only		
GP visit	15.50	15.50
Primary care A & E referral, no inpatient admission		
GP visit	15.50	–
A & E visit	37.00	52.50
Primary care A & E referral, inpatient admission		
GP visit	15.50	–
A & E visit	37.00	–
Length of stay	1292.40	1344.90
Patient A & E referral, no inpatient admission		
A & E visit	37.00	37.00
Patient A & E referral, inpatient admission		
A & E visit	37.00	–
Length of stay	1292.40	1329.40

TABLE 35 *Probability of events*

Event	DPI	Nebuliser	pMDI
Therapy acceptable	1.000	1.000	1.000
Acute exacerbation	0.000	0.000	0.000
Acute exacerbation controlled by patient	0.263	0.263	0.263
Acute exacerbation primary care	0.494	0.494	0.494
Acute exacerbation A & E visit	0.243	0.243	0.243
Controlled by patient, continue maintenance therapy	0.810	0.810	0.810
Controlled by patient, change maintenance therapy	0.190	0.190	0.190
Inpatient admission	0.024	0.024	0.024

The probability of a patient attending primary care or A & E departments was the average from the trials included in a Cochrane Collaboration systematic review of educational interventions for people with asthma[352]

The probability that a patient would seek a change in therapy following an acute exacerbation which they had controlled themselves was estimated from survey data[353]

The annual probability of an inpatient admission was estimated from the annual number of inpatient admissions for asthma[350] *divided by the number of people with asthma in England (Government Statistical Service, 1999)*

TABLE 36 *Expected costs of devices*

(A) Corticosteroids

Outcome	Expected cost (£)	
	DPI	**pMDI**
Therapy acceptable, 28 days		
No acute exacerbation, continue maintenance therapy	10.75	7.96
No acute exacerbation, change maintenance therapy	0.000	0.000
Acute exacerbation, controlled by patient, continue maintenance therapy	0.000	0.000
Acute exacerbation, controlled by patient, change maintenance therapy	0.000	0.000
Acute exacerbation, primary care, continue maintenance therapy	0.000	0.000
Acute exacerbation, primary care, change maintenance therapy	0.000	0.000
Acute exacerbation, primary care, inpatient admission, continue maintenance therapy	0.000	0.000
Acute exacerbation, primary care, inpatient admission, change maintenance therapy	0.000	0.000
Acute exacerbation, A & E visit, inpatient admission, continue maintenance therapy	0.000	0.000
Acute exacerbation, A & E visit, inpatient admission, change maintenance therapy	0.000	0.000
Acute exacerbation, A & E visit, no inpatient admission, continue maintenance therapy	0.000	0.000
Acute exacerbation, A & E visit, inpatient admission, no change maintenance therapy	0.000	0.000
Total therapy acceptable [mean (SD)]	10.69 (2.14)	8.04 (1.83)
Therapy not acceptable, change therapy	0.000	0.000
Total cost, 28 days	10.69 (2.14)	8.04 (1.83)
Net difference vs pMDI, 28 days	2.65 (2.90)	
Total cost, 12 months	139.38 (27.92)	104.85 (23.90)
Net difference vs pMDI, 12 months	34.52 (37.76)	

(B) Beta-agonists

Outcome	Expected cost (£)		
	DPI	**Nebuliser**	**pMDI**
Therapy acceptable			
No acute exacerbation, continue maintenance therapy	7.95	22.50	3.19
No acute exacerbation, change maintenance therapy	0.000	0.000	0.000
Acute exacerbation, controlled by patient, continue maintenance therapy	0.000	0.000	0.000
Acute exacerbation, controlled by patient, change maintenance therapy	0.000	0.000	0.000
Acute exacerbation, primary care, continue maintenance therapy	0.000	0.000	0.000
Acute exacerbation, primary care, change maintenance therapy	0.000	0.000	0.000
Acute exacerbation, primary care, inpatient admission, continue maintenance therapy	0.000	0.000	0.000
Acute exacerbation, primary care, inpatient admission, change maintenance therapy	0.000	0.000	0.000
Acute exacerbation, A & E visit, inpatient admission, continue maintenance therapy	0.000	0.000	0.000
Acute exacerbation, A & E visit, inpatient admission, change maintenance therapy	0.000	0.000	0.000
Acute exacerbation, A & E visit, no inpatient admission, continue maintenance therapy	0.000	0.000	0.000
Acute exacerbation, A & E visit, inpatient admission, no change maintenance therapy	0.000	0.000	0.000
Total therapy acceptable [mean (SD)]	7.96 (1.74)	22.53 (1.42)	3.19 (1.02)
Therapy not acceptable, change therapy	0.000	0.000	0.000
Total cost, 28 days	7.96 (1.74)	22.53 (1.42)	3.19 (1.02)
Net difference vs pMDI, 28 days	4.77 (2.01)	19.34 (1.74)	
Total cost, 12 months	103.75 (22.65)	293.74 (18.53)	41.59 (13.26)
Net difference vs pMDI, 12 months	62.16 (26.25)	252.15 (22.74)	

continued

TABLE 36 contd *Expected costs of devices*

(C) All bronchodilators			
Outcome	**Expected cost (£)**		
	DPI	**Nebuliser**	**pMDI**
Therapy acceptable			
No acute exacerbation, continue maintenance therapy	9.67	33.60	2.90
No acute exacerbation, change maintenance therapy	0.000	0.000	0.000
Acute exacerbation, controlled by patient, continue maintenance therapy	0.000	0.000	0.000
Acute exacerbation, controlled by patient, change maintenance therapy	0.000	0.000	0.000
Acute exacerbation, primary care, continue maintenance therapy	0.000	0.000	0.000
Acute exacerbation, primary care, change maintenance therapy	0.000	0.000	0.000
Acute exacerbation, primary care, inpatient admission, continue maintenance therapy	0.000	0.000	0.000
Acute exacerbation, primary care, inpatient admission, change maintenance therapy	0.000	0.000	0.000
Acute exacerbation, A & E visit, inpatient admission, continue maintenance therapy	0.000	0.000	0.000
Acute exacerbation, A & E visit, inpatient admission, change maintenance therapy	0.000	0.000	0.000
Acute exacerbation, A & E visit, no inpatient admission, continue maintenance therapy	0.000	0.000	0.000
Acute exacerbation, A & E visit, inpatient admission, no change maintenance therapy	0.000	0.000	0.000
Total cost therapy acceptable [mean (SD)]	9.67 (2.57)	33.64 (6.12)	2.89 (1.07)
Therapy not acceptable, change therapy	0.000	0.000	0.000
Total cost, 28 days	9.67 (2.57)	33.64 (6.12)	2.89 (1.07)
Net difference vs pMDI, 28 days	6.79 (2.78)	30.75 (6.23)	
Total cost, 12 months	126.16 (33.48)	438.52 (79.83)	37.66 (13.98)
Net difference vs pMDI, 12 months	88.50 (36.21)	40.86 (81.18)	

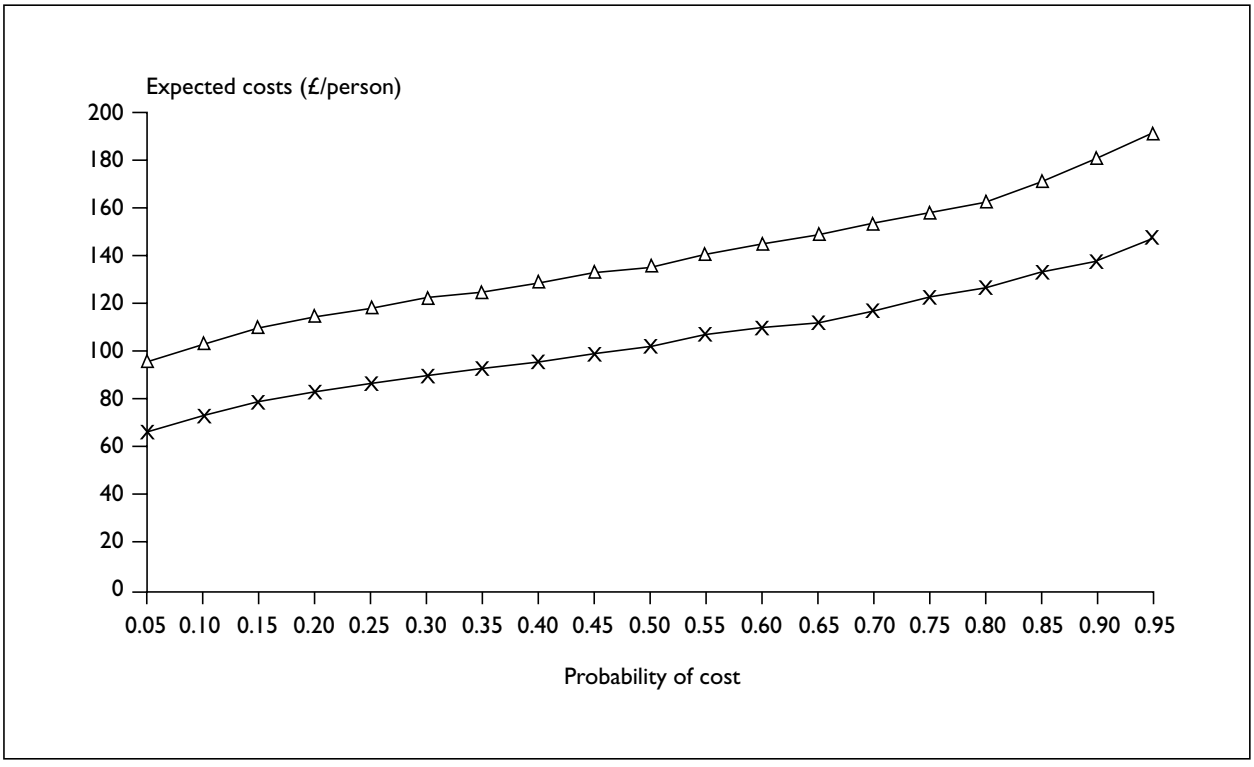

FIGURE 15 *Probability of expected costs of inhaler devices (corticosteroids) (–△–, DPI; –X–, pMDI)*

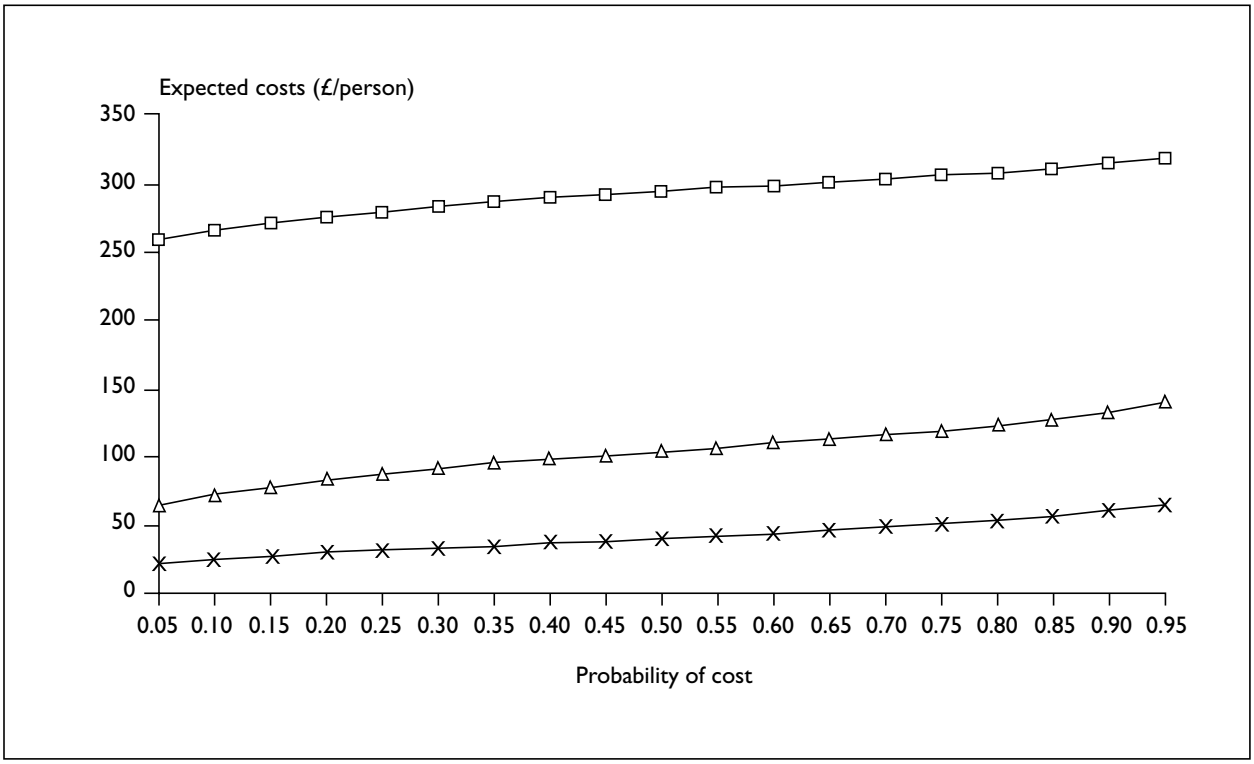

FIGURE 16 *Probability of expected costs of inhaler devices (beta-agonists) (–△–, DPI; –□–, Nebuliser; –✕–, pMDI)*

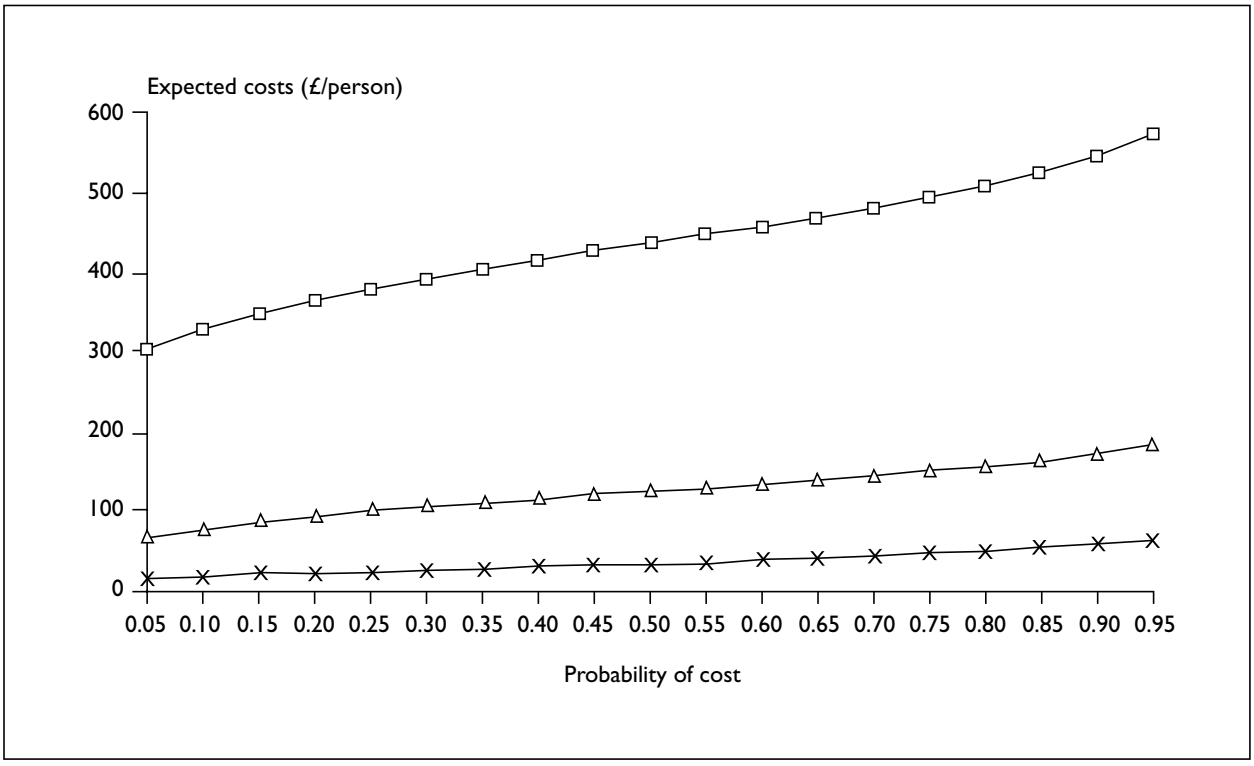

FIGURE 17 *Probability of expected costs of all bronchodilators (–△–, DPI; –□–, Nebuliser; –✕–, pMDI)*

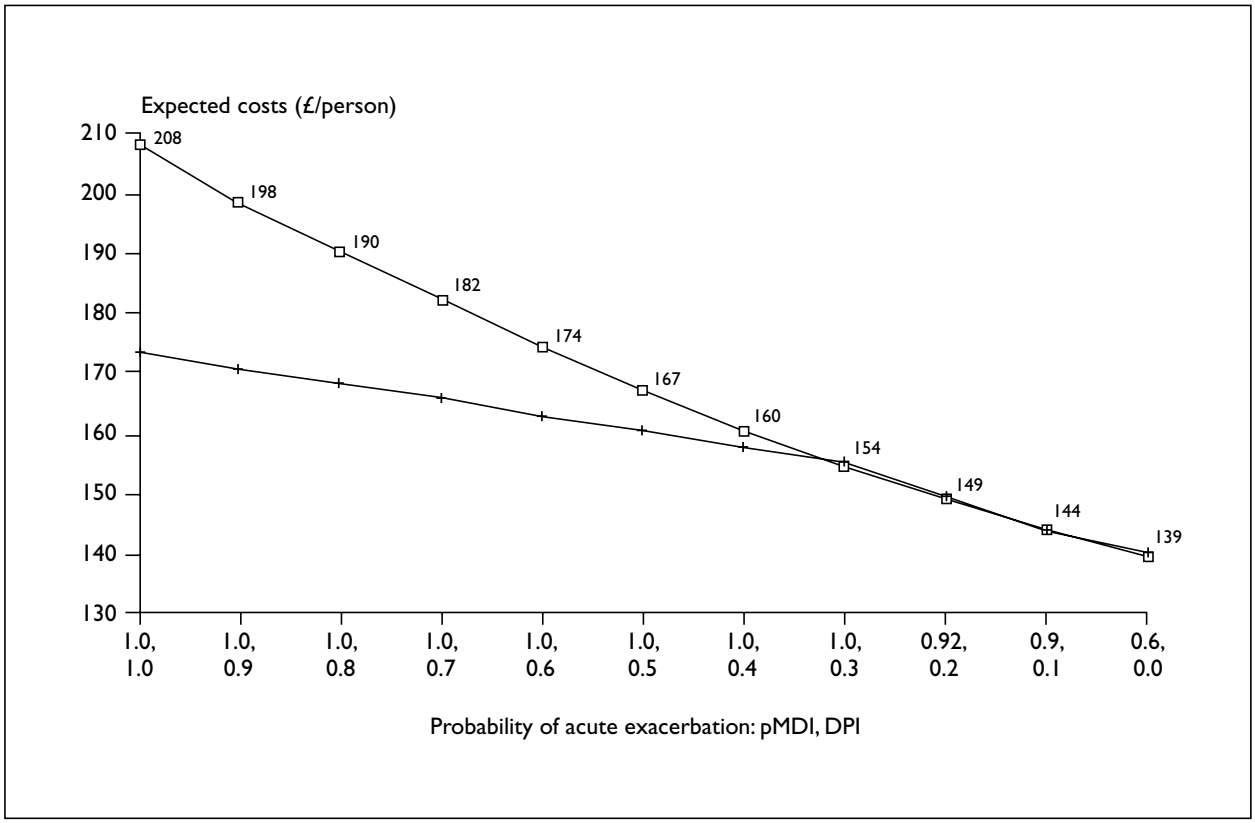

FIGURE 18 *Expected costs of corticosteroids by rate of acute exacerbation (–□–, DPI; –+–, pMDI)*

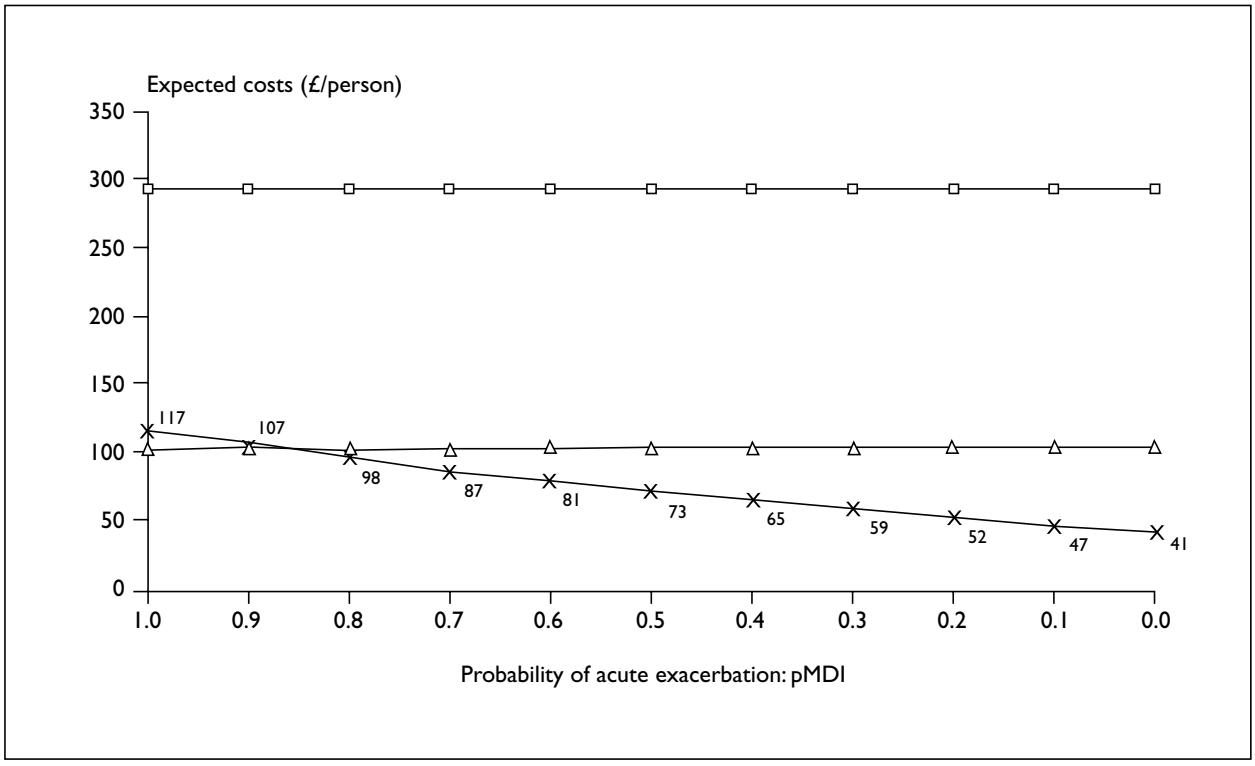

FIGURE 19 *Expected costs of beta-agonists by rate of acute exacerbation (–△–, DPI; –□–, Nebuliser; –X–, pMDI)*

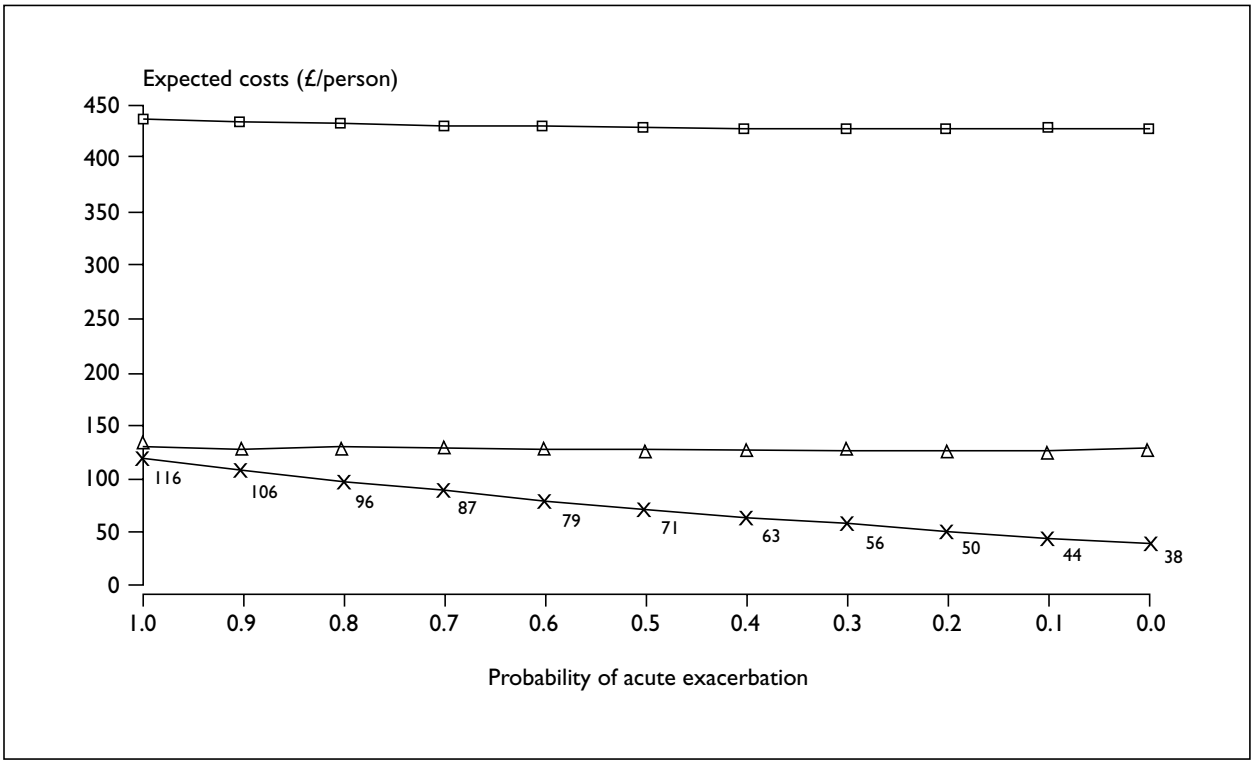

FIGURE 20 *Expected costs of all bronchodilators by rate of acute exacerbation (–△–, DPI; –□–, Nebuliser; –✕–, pMDI)*

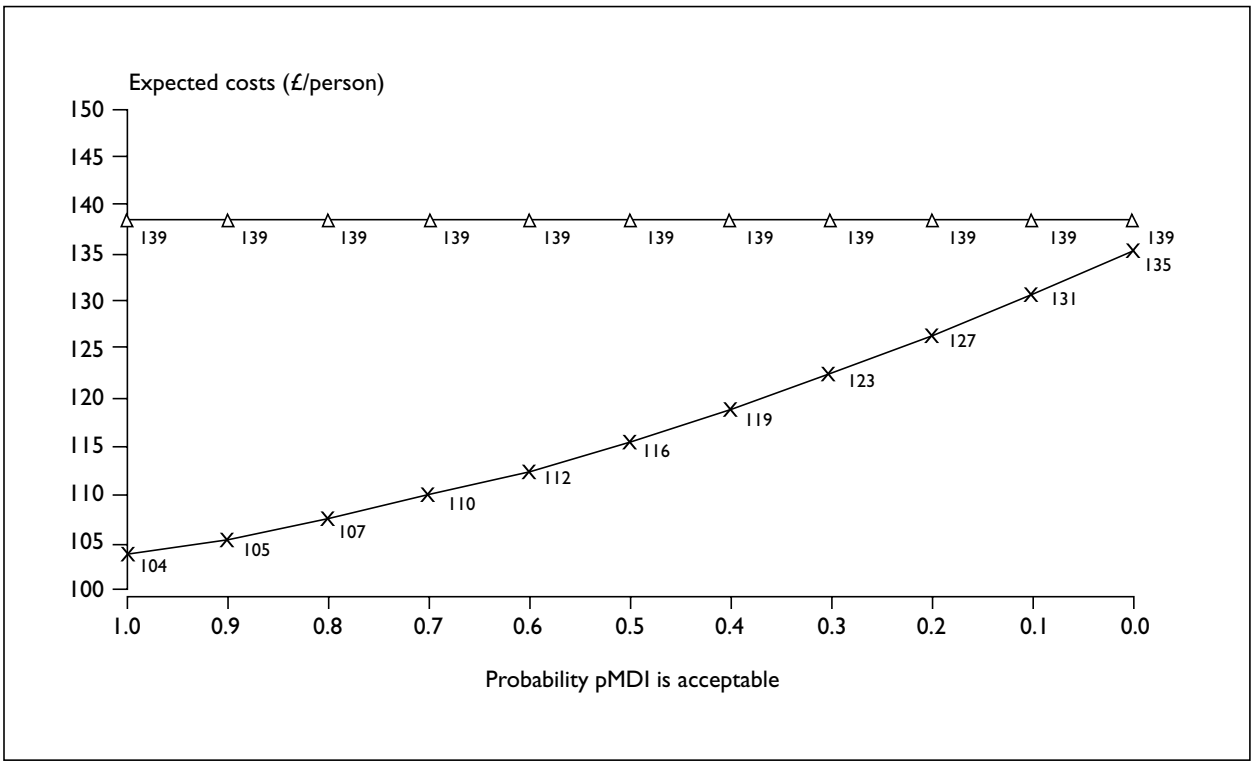

FIGURE 21 *Expected costs of corticosteroids by rate of acceptability to patient (–△–, DPI; –✕–, pMDI)*

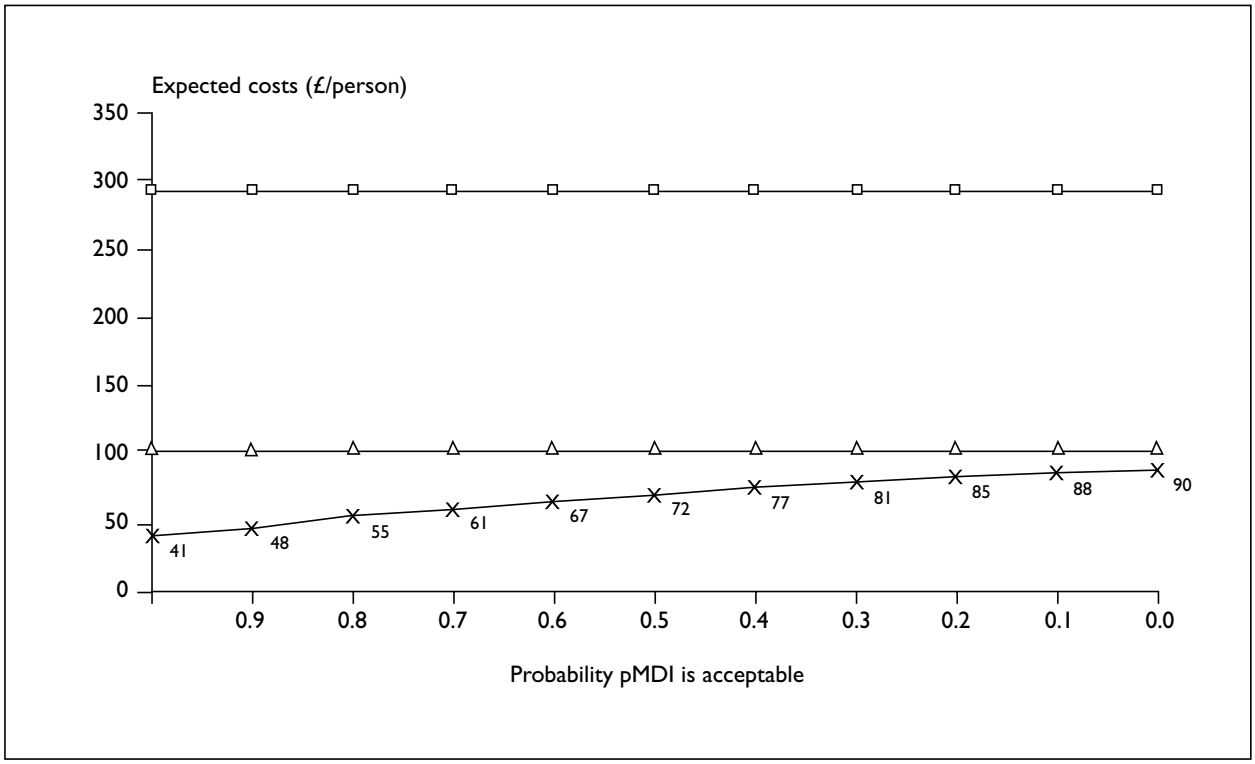

FIGURE 22 *Expected costs of beta-agonists by rate of acceptability to patient (–△–, DPI; –□–, Nebuliser; –X–, pMDI)*

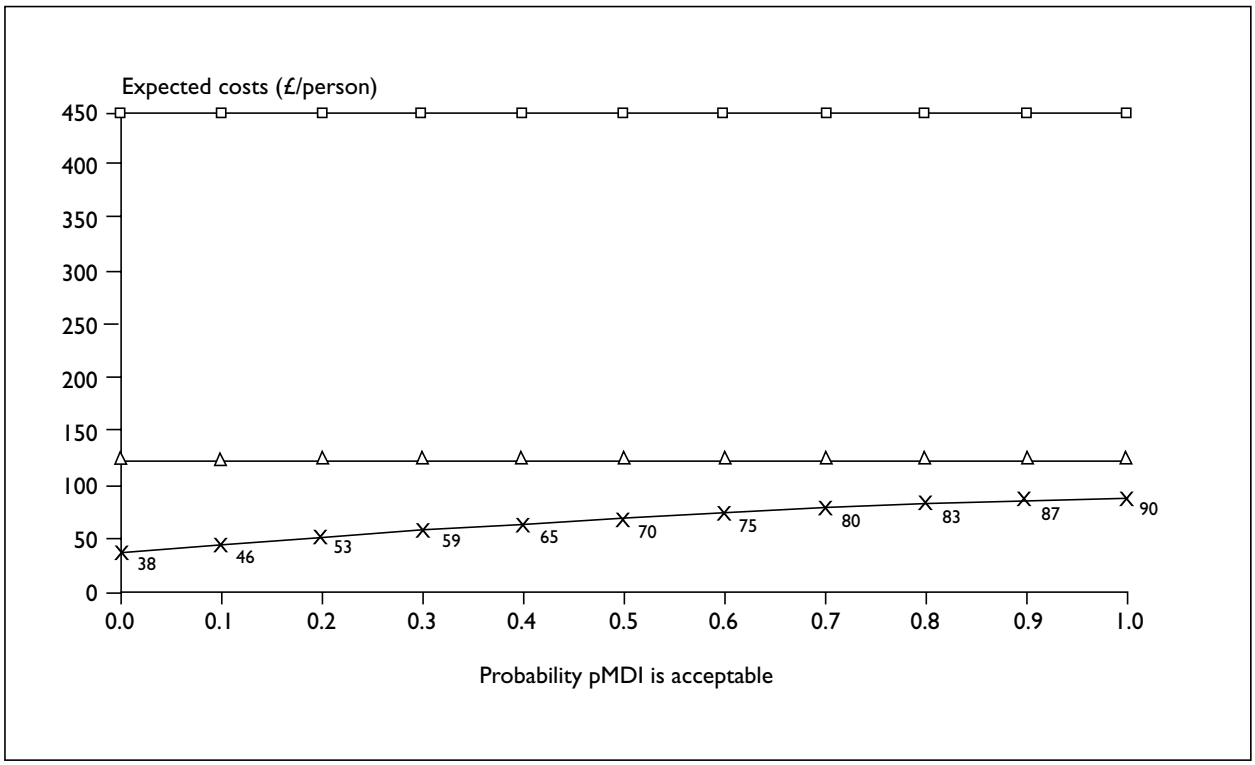

FIGURE 23 *Expected costs of all bronchodilators by rate of acceptability to patient (–△–, DPI; –□–, Nebuliser; –X–, pMDI)*

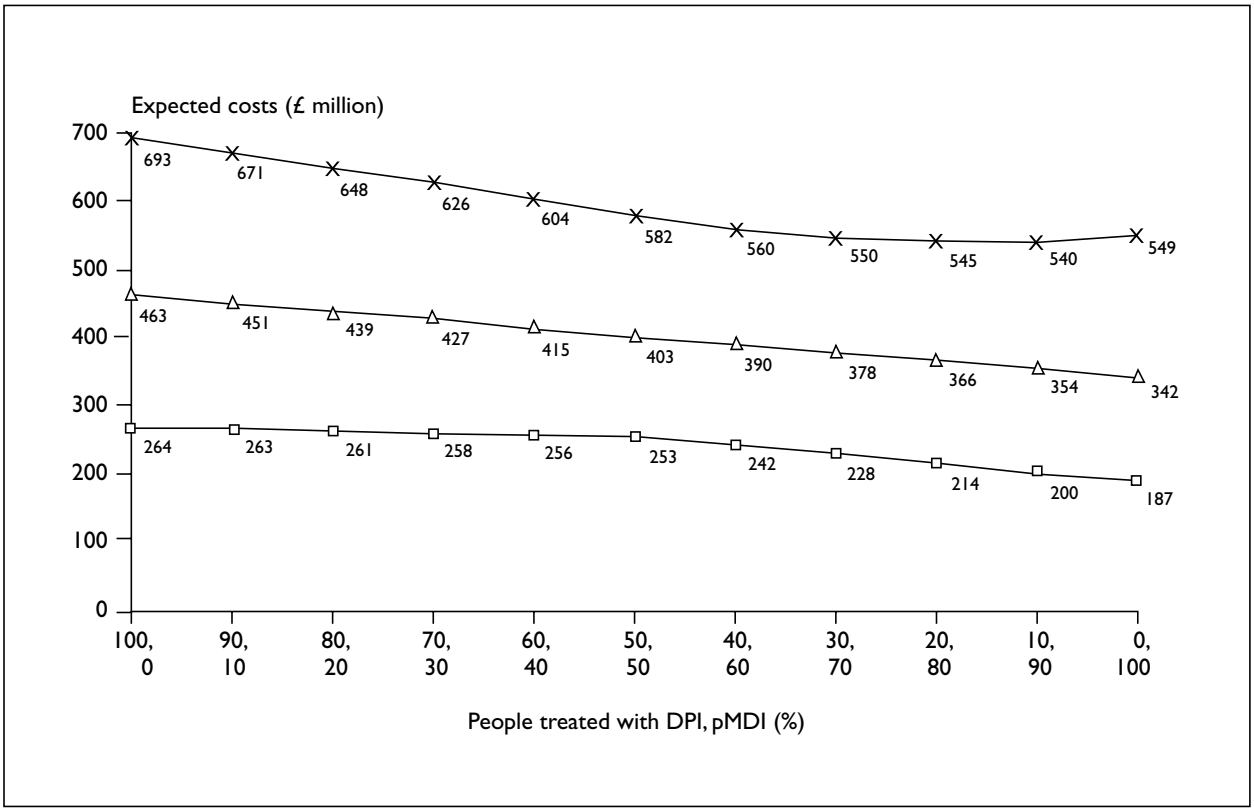

FIGURE 24 *Expected budgetary impact of devices for corticosteroids by percentage of people treated with device: DPI, pMDI (–□–, minimum; –△–, mean; –✕–, maximum)*

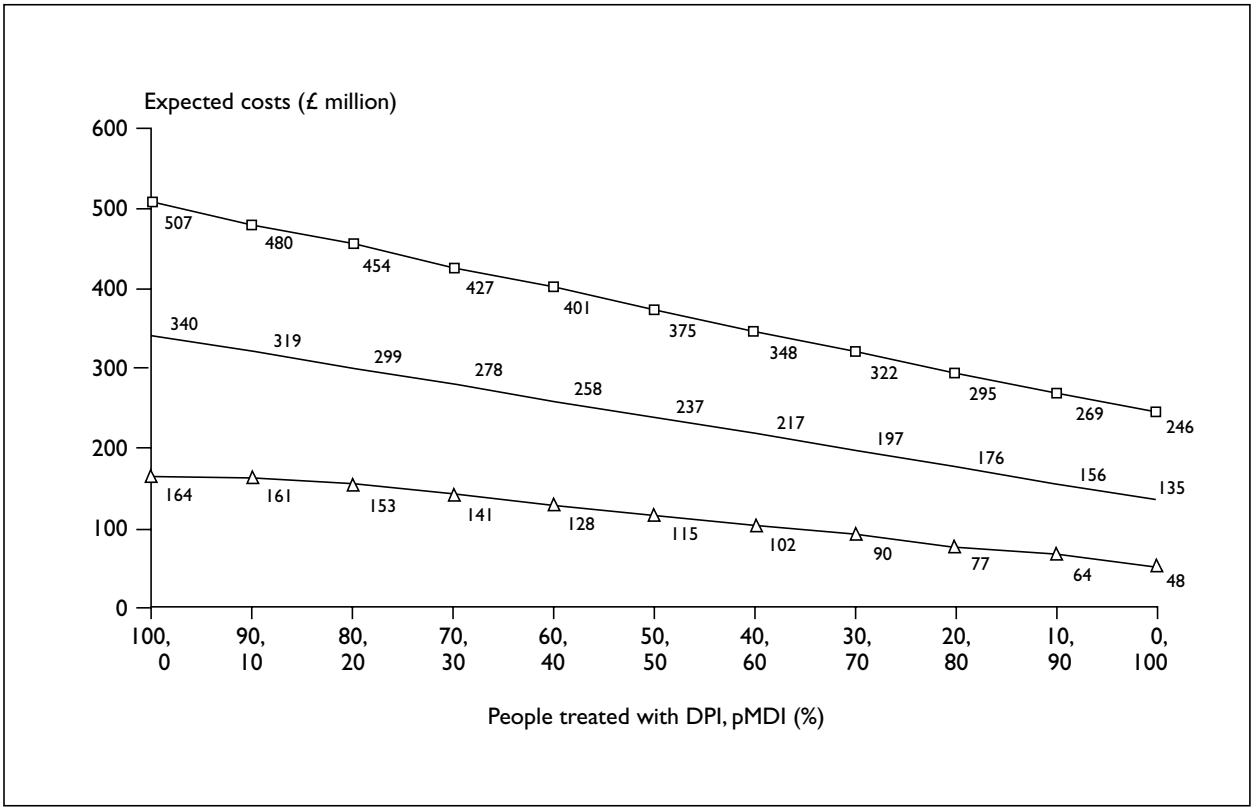

FIGURE 25a *Expected budgetary impact of devices for beta-agonists by percentage of people treated with device: DPI, pMDI (–△–, minimum; ——, mean; –□–, maximum)*

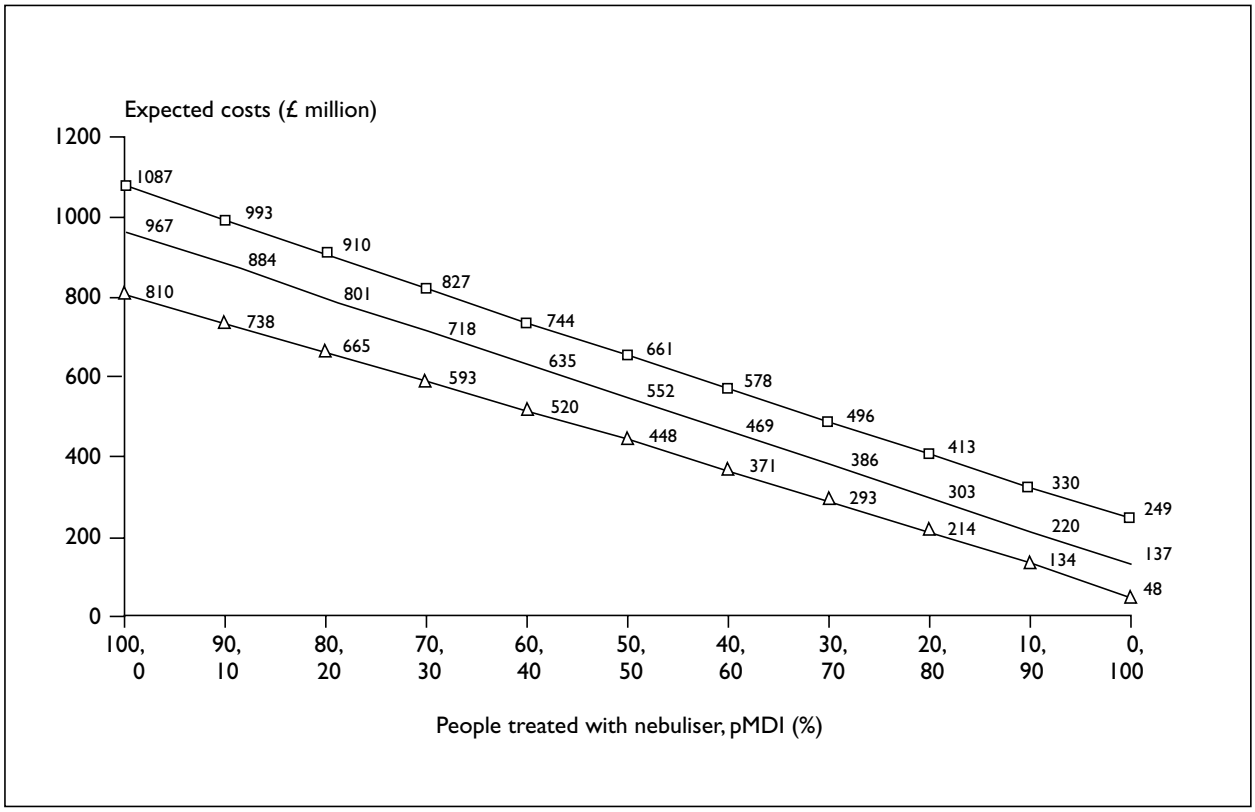

FIGURE 25b *Expected budgetary impact of devices for beta-agonists by percentage of people treated with device: nebuliser, pMDI (-△-, minimum; ——, mean; -□-, maximum)*

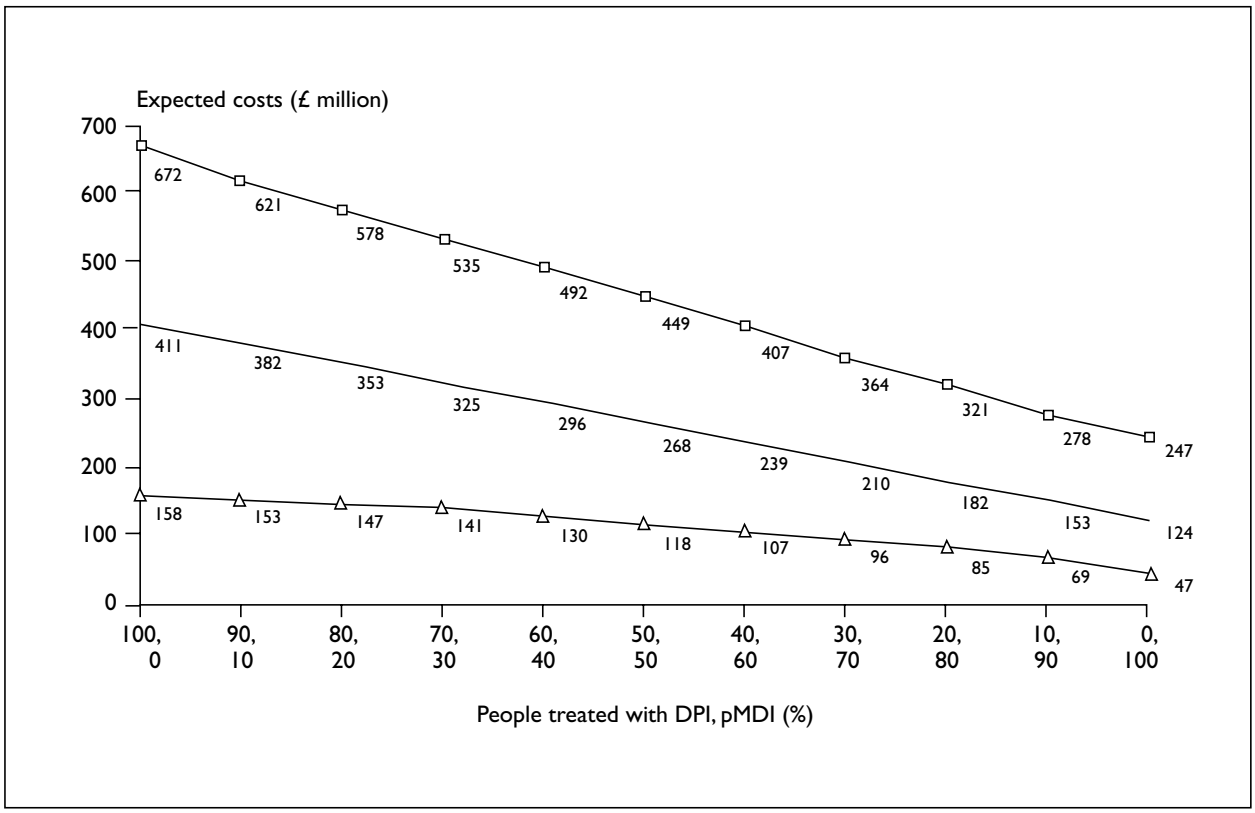

FIGURE 26a *Expected budgetary impact of devices for all bronchodilators by percentage of people treated with device: DPI, pMDI (-△-, minimum; ——, mean; -□-, maximum)*

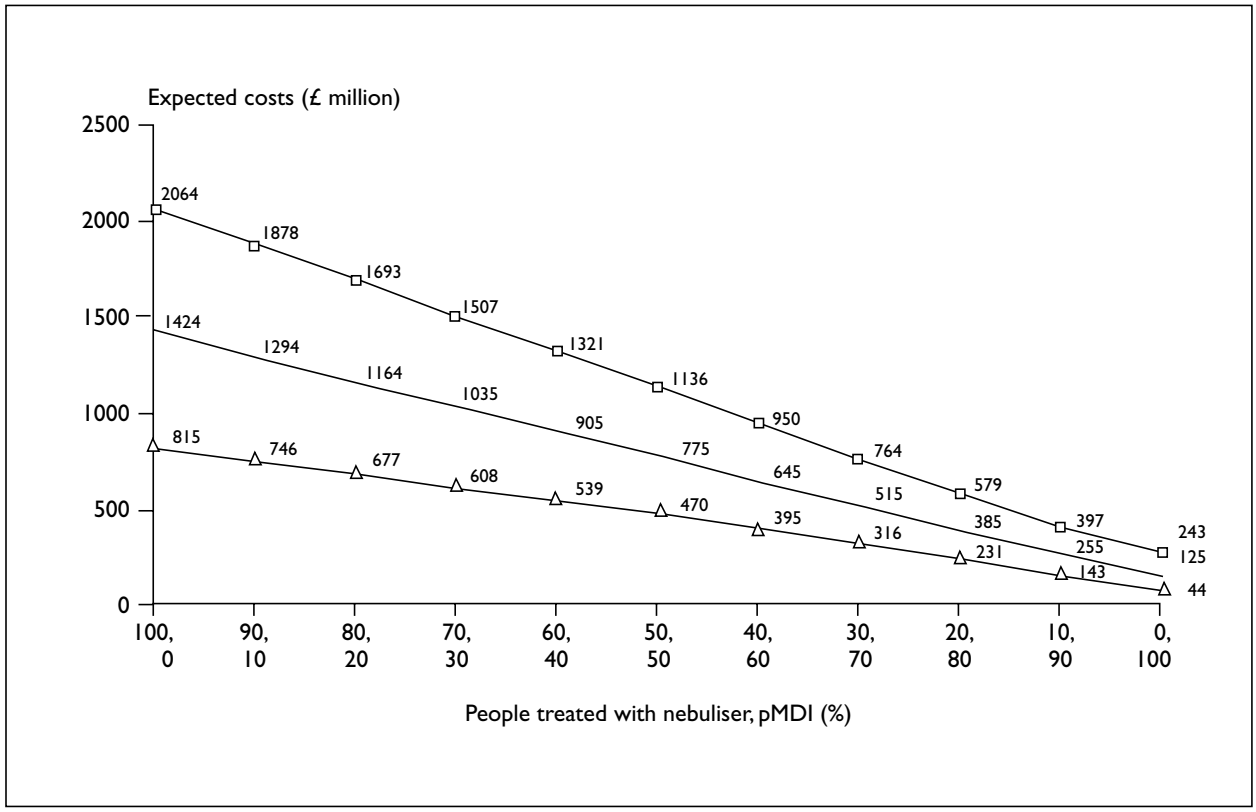

FIGURE 26b *Expected budgetary impact of devices for all bronchodilators by percentage of people treated with device: nebuliser, pMDI (–△–, minimum; ——, mean; –□–, maximum)*

Chapter 8

Summary and conclusions

Overall, there is no evidence from the published clinical literature that there is any difference in clinical efficacy among alternative inhaler devices compared with a standard pMDI with or without spacer device for the delivery of inhaled corticosteroids. Notably there is no evidence for a difference in systemic effects (hoarse voice, oral thrush or serum cortisol levels) among the different inhaler devices.

The evidence from the published clinical literature suggests no difference in clinical efficacy among alternative inhaler devices compared with a standard pMDI with or without spacer device for the delivery of short-acting β_2-bronchodilators in stable asthma. There is a statistically significant difference in pulse rate but this is of uncertain clinical significance. There is a statistically significant difference in treatment failure rate and in the requirement for oral steroids in patients treated with HFA inhalers, and this requires further confirmatory research.

There is no evidence from the published clinical literature to suggest that there is any statistically significant difference in treatment effect of a nebuliser over a standard pMDI + spacer or a DPI. For measures of pulmonary function (FEV_1 and PEFR) the evidence suggests clinical equivalence. For other outcome measures there is no statistically significant difference in treatment effect but clinical equivalence cannot be assumed due to the low precision around the point estimate of treatment effect.

Inhaler technique

The evidence from published studies cannot address an individual patient's ability with any particular inhaler device. In addition, differences between studies and heterogeneity of the results make it difficult to draw conclusions about inhaler technique differences between device types. The review of technique after teaching the correct technique suggests that there is no difference in patients' abilities to use DPIs or pMDIs. Adequate patient education as part of good clinical practice is important.

Economic analysis

The total number of NHS prescriptions for inhaler therapy for asthma in 1998 was over 31 million, with a net ingredient cost in excess of £392 million. Economic analysis demonstrated that, overall, there were no differences in patient outcomes among the devices. On the assumption that the devices were clinically equivalent, pMDIs were the most cost-effective devices for asthma treatment.

Weaknesses in published trials

Common weaknesses in the published trial evidence include the lack of patient-centred outcomes. The outcomes that were used may not have been sensitive enough to detect differences in devices where they existed. In addition, the timescales used to measure outcomes may have been too short, for example in trials of inhaled steroids. Finally, there were few community-based trials that would provide more generalisable evidence for routine clinical practice.

Conclusions

This systematic review reports the average clinical effects from the average trial results across drugs, doses and devices. It may well be that individual patients require devices tailored to their individual needs, just as their dose is. However, on the basis of the published evidence, there is no evidence to suggest that on grounds of relative clinical efficacy there is any reason to use one inhaler device type over another. The cost-effectiveness evidence therefore favours pMDIs (or the cheapest inhaler device) as first-line treatment in all patients with stable asthma unless other specific reasons are identified.

Recommendations for research

At present, the introduction of a new device for the delivery of inhaled drugs needs far less rigorous testing than does a new drug delivered by an old device. The licensing requirement is to demonstrate equivalence to an existing device.

Equivalence is not the same as failing to detect a difference, and the design and powering of trials is specific and not without controversy. It may be that stricter controls are needed before approval. Many of the weaknesses identified in the study designs will contribute towards lack of treatment effect being shown and the danger of showing a type II error.

If differences in treatment effect are to be demonstrated, then the trial design should be double-blinded. If studies are of crossover design, then there should be an adequate washout period. Duration should be in excess of 4 weeks in the case of corticosteroids. The participants need to be in a phase of their disease when treatment may make a difference (newly diagnosed or greater severity) and the doses chosen should be clinically appropriate, that is not too high and therefore at the upper end of the dose–response curve.

Data should be more fully reported. In absolute terms both at baseline and at study completion, and report percentage and absolute differences from baseline for all outcomes measured in the study – not only significant differences. There is a need for journal editors (and it is also the duty of all authors) to fully and explicitly report all results, methodology and details from studies so that trials can be duplicated in the exact manner in which they were conducted without readers having to infer what was probably done. Poor reporting of study data restricts not only duplication of studies but also makes the task of conducting a systematic review (meta-analysis) difficult. It is hoped that all authors publishing studies are aware of the CONSORT statement.[354]

Given the chronic nature of asthma and its significant effects on morbidity, outcome measures should include validated measures of symptoms and quality of life. Also, adverse effects and systemic effects need to be reported more completely. If clinical effect is equivalent among devices, then secondary factors such as adverse effects become much more significant.

Further RCTs are required in order to be able to make valid recommendations on the use of the various inhaler devices available for the treatment of asthma. This is of particular importance due to the phasing out of CFC propellants in pMDIs.

The teaching of inhaler technique is another important area for future research. Studies should explore the effectiveness and frequency of patient education and consider interventions to improve it. Additionally, studies of teaching of inhaler technique should measure health-related outcomes because the relationship between inhaler technique and clinical outcome has not been established in such trials.

Acknowledgements

This review was commissioned by the NHS R&D Health Technology Assessment Programme, project number 97/23/02.

The Group are indebted to Mrs Margaret Haigh for her excellent administrative and secretarial support. We would also like to thank the staff at the Cochrane Airways Review Group for their superb efforts in identifying trials and obtaining papers.

We are very grateful to the referees for their constructive and valuable reviews and comments.

The reviews expressed in this report are those of the authors, who are also responsible for any errors.

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We look forward to hearing from you.

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ISSN 1366-5278