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REVIEW

# Choosing inhaler devices for people with asthma: Current knowledge and outstanding research needs

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**Summary**
Recommendations in asthma guidelines presuppose that practitioners have the evidence, information, knowledge, and tools to select inhaler devices appropriate for individual patients. Randomised controlled trials usually exclude patients with suboptimal inhaler technique. There is therefore little evidence on which to base inhaler selection in the real world, where patients often use their inhalers incorrectly. The lung deposition of inhaled drug varies according to inhaler device, drug particle size, inhalation technique, and pattern of inspiratory flow. Even with training, not all patients can use their inhalers correctly and maintain inhaler technique; patients may have inability to handle the inhaler, strong negative preferences, or natural breathing patterns that do not match their prescribed inhaler. Therefore, matching device to the patient may be a better course of action than increasing therapy or training and retraining a patient to use a specific inhaler device. Several research questions require answers to meet the goal of helping prescribers make a more informed choice of inhaler type. Is the level of drug deposition in the lungs a key determinant of clinical short- and long-term outcomes? What should be measured by a clinical tool designed to check inhaler technique and therefore help with device selection? If we have a tool to help in individualising inhaler choice, will we achieve better

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asthma outcomes? Do we have to refine inhaler device choice for each individual, or will we get better outcomes if we select our current best option in light of current knowledge and apply this on a population level?


**Contents**



## Introduction

Asthma guidelines recommend individualising inhaled therapy for each patient, taking into consideration patient preference, in conjunction with training and regular monitoring of inhaler technique.[1,2] These recommendations presuppose that clinicians, and other healthcare providers involved with asthma management, have the research evidence, information, knowledge, and tools to select an inhaler device appropriate for each patient. However, given the confusing array of available devices, healthcare providers may not know all the key features of inhalers and their operation, and patients often make mistakes in using their inhalers.[3]

An international panel of respiratory physicians, general practitioners, and academics with an interest in asthma and inhalation devices was convened in January 2009 by the International Primary Care Respiratory Group (IPCRG) to discuss the science of inhaler therapy as it needs to be applied in clinical practice. In particular we aimed to highlight where further evidence is needed to provide guidance on inhaler selection in community settings. This meeting built upon prior IPCRG work on practical ways to improve asthma control in clinical practice, which noted inhalation technique was a major issue in achieving asthma control (Table 1).[4,5]

Here we review the aspects of inhaler performance and use in primary care that materially affect outcomes and the available evidence that exists to guide clinical decisions in these areas. This review has enabled us to start to identify what types of further research and technological development are needed to meet the goal of helping prescribers to make more informed choices of inhaler types for their patients with asthma. Many of the issues related to inhaler

**Table 1** Reasons for poor asthma control identified at prior IPCRG international meeting.[4]

1. Wrong diagnosis or confounding illness
2. Incorrect choice of inhaler or poor technique
   - Mixed device types
   - Poor training
   - Erosion of technique
   - Unable to use the recommended inhalation method despite training
3. Unintentional or intentional nonadherence
   - Low necessity: patients' doubts regarding need for therapy
   - Persistent disease but episodic symptoms
   - Forgetfulness
   - High concerns: patients' concerns about side effects
4. Concurrent smoking
   - Relative steroid resistance
5. Comorbid rhinitis
   - Associated with worse asthma control
6. Individual variation in treatment response
7. Undertreatment

therapy are similar for asthma and chronic obstructive pulmonary disease (COPD). However, as possible differences in inhaler therapy between asthma and COPD have not been studied systematically, COPD is not discussed further here.

## Do inhaler device and the way it is used make a difference?

Reviews of randomised controlled trials comparing inhaler devices report no difference in efficacy between devices.[6–8] However, most of these trials were performed for licensing purposes and thus were designed to show noninferiority or equivalence. Of equal importance, patients enrolled in these studies received training and must have demonstrated good inhaler technique; those with improper technique were excluded. The studies, therefore, do not reflect the population of patients using inhalers.

In the real world, patients often use their inhalers incorrectly (Fig. 1).[6,9–14] Efficient inhalation technique was demonstrated by only 46–59% of patients in the studies reviewed by Cochrane et al.[9] In a systematic review, the mean percentages of patients who used their inhalers without mistakes were 63% for metered dose inhalers (MDIs); 75% for breath-actuated MDIs; and 65% for dry powder inhalers (DPIs).[6] Errors are made not only in inhalation technique but also in the handling of inhaler devices, such as preparation and positioning.[10,12,13] In addition, healthcare providers may not know how to use inhalers correctly.[10,11] Importantly, poor inhalation technique can be associated with a marked (up to 50%) decrease in the amount of drug deposited in the lung. When the administered medication is a bronchodilator, the subsequent acute increase in $FEV_1$ may be lowered by one third if the device is not used properly.[15–17] Furthermore, the number of errors in inhaler use and inhalation technique has been correlated with poorer asthma control in patients using inhaled corticosteroids (ICS).[18]

Each type of inhaler requires a different inhalation technique and breathing pattern to achieve optimal delivery of drug to the lungs. To avoid confusion, it is argued that inhaler types should not be mixed for an individual patient.[19,20] Switching of ICS inhaler device without an accompanying consultation in general practice has been instituted in some countries to reduce drug costs. Such a practice may result in loss of asthma control and increased consultations (Fig. 2),[21] possibly because patients receive no training on how to use their new device.

Recent observational data suggest that, in real life, the choice of inhaler device is associated with differences in outcomes.[22–24] It is unclear whether these differences arise because some inhalers and formulations are inherently 'better' or more forgiving of poor technique or because of other patient-related factors.

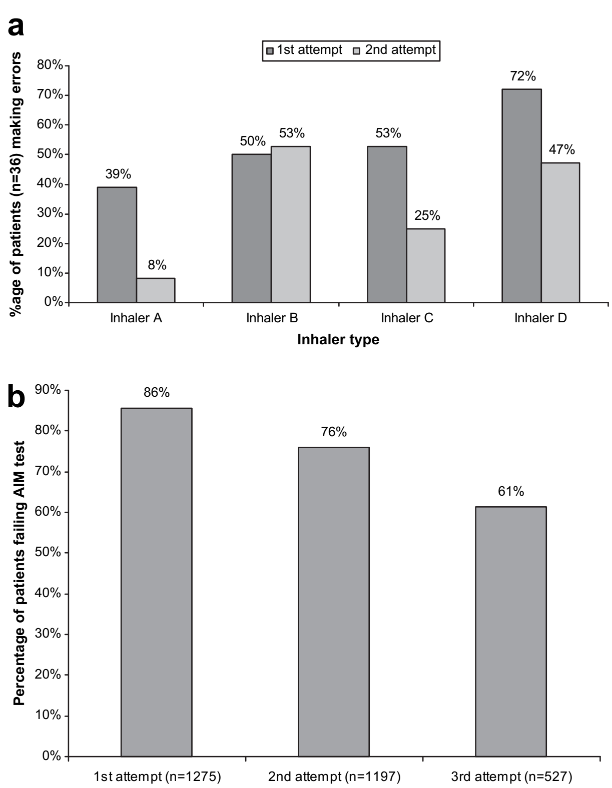


**Figure 1** (a) Frequency of critical handling errors made by patients with asthma and/or chronic obstructive pulmonary disease when using four different types of dry powder inhalers (trade names changed to types A–D). The first attempt was made after patients read the device instructions, and the second attempt was made after the investigator explained device handling. Adapted from Schulte et al.[13] (b) Percentage of patients with uncontrolled asthma who failed to use their pMDIs correctly, as tested with an Aerosol Inhalation Monitor (AIM, Vitalograph®, Vitalograph, Ltd, Buckingham, England). The second and third tests were performed after instruction on pMDI technique. Adapted from Hardwell et al.[14]

## Targets of inhaler therapy and particle size effects

The lung deposition of an inhaled drug varies according to inhaler device, features of inhalation technique, and

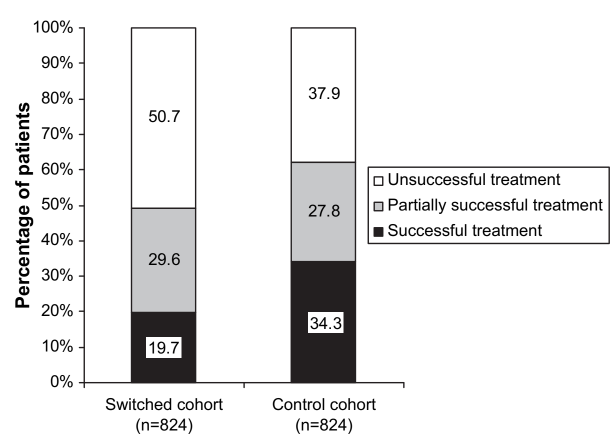


**Figure 2** Outcome of asthma treatment during study year 2 for patients whose inhaled corticosteroid device was switched without an accompanying consultation (switched cohort) and matched controls: percentages of patients experiencing successful asthma treatment, partially successful treatment, and unsuccessful treatment. Reprinted from Thomas et al.[21]

particle size. Reported lung deposition for different inhaler devices varies greatly from 4% for beclometasone delivered by chlorofluorocarbon (CFC)-propellant MDIs to 53% for extra-fine beclometasone delivered by CFC-free hydroflouroalkane (HFA)-propellant MDIs.[25] However, variation in study methods and differences in how the deposition fraction is expressed (eg, nominal dose vs. emitted dose vs. fine particle dose) make direct comparisons between devices difficult.[6] Moreover, inhaler device technique can substantially affect the amount of drug delivered to the lung.[9] Other factors that could influence the level and extent of deposition include pharyngeal and lower airway anatomy, severity of obstruction, homogeneity of ventilation, and hygroscopic properties of the aerosol.

For inhaled asthma therapy to achieve optimal effects, delivery of drug to the appropriate regions of the lung should be maximised and deposition of drug in the oropharynx minimised. Deposition in the large and conducting airways (down to branch 16 of the bronchial tree) may be preferred for bronchodilators. These agents, most commonly β2 agonists, will have an effect if deposited in these airways because there are β2 receptors present in conjunction with smooth muscle (Fig. 3).[26–28] Instead, a more uniform lung distribution may be preferred for ICS to also reach the smaller peripheral airways, important sites of airway inflammation in asthma.[29,30]

Particles will deposit in different regions of the lungs depending on their size and the speed of the patient's inhalation.[31] Overall, smaller inhaled particle sizes are better able to be distributed throughout the lungs and reach the distal airways.[32] In theory, particles $<1$ μm can reach the peripheral airways, where they will have some local clinical effect. Given the heterogeneous ventilation of the lungs of people with asthma, and the differing particle sizes of different therapies (ICS and $\beta_2$ agonists), differential deposition of these drugs might result. The clinical consequences of such a non-homogenous distribution are unclear and need further investigation.

Results of recent studies suggest that delivering ICS with smaller particle formulations is associated with better outcomes.[33,34] However, it is difficult to dissociate dose and deposition, and further studies are needed.[35] These formulations provide better lung deposition with possibly improved efficacy and greater systemic delivery because of

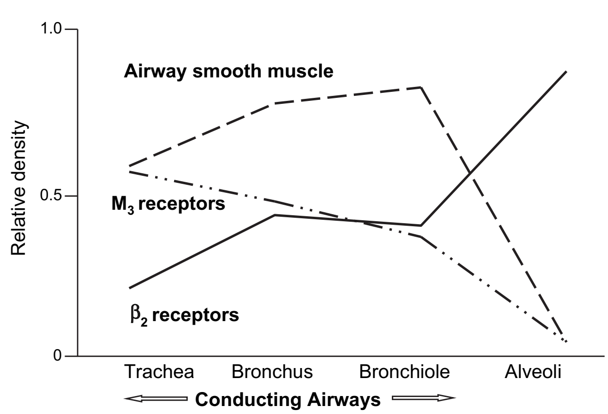


**Figure 3** Location of targets for bronchodilators. Adapted from Carstairs et al.,[26] Mak and Barnes,[27] and Jeffery.[28]

improved pulmonary delivery as well as reduced impaction in the oropharynx. Although small particles (~1 μm) have a greater potential to be exhaled (approximately 10% of the dose), this is counterbalanced by high pulmonary deposition (60%), and the net effect is that oropharyngeal deposition is reduced (30%).[36] To maintain similar efficacy and safety it is, therefore, recommended that the dose of these products is halved.[36,37] Particles 1–5 μm will reach the large and conducting airways where they will exert their clinical effect and be subsequently absorbed from the lungs. Particles $>5$ μm tend to settle into the mouth and oesophageal region, where they produce no clinical effect but can potentially produce both local side effects and systemic side effects after gastrointestinal absorption.

## Key factors affecting delivery of drug to the lungs

### Metered dose inhalers require slow and deep inhalation as well as co-ordination

Exhalation to functional residual capacity or residual volume should precede the inhalation.[38] This translates to a full inspiratory vital capacity, which is required for all MDIs and DPIs. For MDIs, although good coordination is required and can be a problem for some patients, the most important aspect of inhalation technique is a slow ($<60$ L/min) and deep inhalation.[39–41] In practice this translates to a full inhalation that lasts for 2 s (small child) to 5 s (adult). Failure to use a slow and deep inhalation is the most common mistake made by patients using an MDI and is more common than failure of coordination.[33,42,43] Ideally, the actuator should be pressed at the start of the inhalation; however, we now know that the split-second coordination of actuation and inhalation is less critical if the inhalation is slow[39] and especially if actuation occurs after the start of inhalation.[41] Moreover, breath holding to facilitate sedimentation at the end of the inhalation is less critical if the inhalation is slow.[39]

A faster inhalation rate increases the likelihood of oropharyngeal deposition with an MDI.[32] Larger particles tend to settle in the oropharyngeal region with fast inhalations, whereas smaller particles (1.5 μm) show little difference in lung and oropharyngeal deposition whether the inhalation is fast or slow.[32]

### Dry powder inhalers require a rapid and forcible inhalation

Before inhalation, the formulation of all DPIs has no potential for lung deposition. It is the patient's inhalation that transforms the powder in a DPI into an emitted dose of particles with the appropriate characteristics for deposition in the lungs. When a patient inhales through a DPI, turbulent energy inside the device is created by the pressure drop ($\Delta P$) that results from the interaction between the patient's inhalation flow *(Q)* and the internal design of the DPI, which translates into a resistance to airflow ($R$). Since the turbulent energy is represented by the relationship $\sqrt{\Delta P} = Q \times R$,[44] inhalation flow should not be viewed in isolation when comparing DPIs. It is, however, correct to refer to inhalation flow with regard to one type of DPI because the resistance will not change.

For each inhaler there is a minimum energy, hence inhalation flow, required to provide efficient disaggregation of the formulation. The minimum inhalation flow, while not clearly defined for each device, is important because there is the potential for a patient to receive no dose. In general, very young and elderly patients and those experiencing a severe exacerbation may not be able to generate inhalation flow sufficient to create turbulent energy that produces a dose reaching the lungs from some devices. However, it should be stressed that there are some stable patients of any age and severity of obstruction who may not be capable of generating sufficient energy inside their DPI, and so this needs to be checked routinely for all patients.[44]

When a patient inhales through a DPI containing doses stored inside the device (either in a reservoir or as single-dose blisters), disaggregation of the powder occurs almost immediately as the dose leaves the device. Fig. 4 depicts two possible inhalation profiles generated through the same device by a patient, an ideal profile and a more usual profile.[45] Superimposed onto these profiles is when the dose would leave a reservoir or blister DPI and a capsule DPI. It is evident that the rate of increase in flow (and hence turbulent energy) will be greater, and the disaggregation of the powder inside the DPI more efficient, for the patient who generates the ideal inhalation profile. Failure to use a fast inhalation from the start through a DPI results in the emission of particles that are too big to be deposited in the lungs and so the dose is deposited in the oropharynx and subsequently swallowed.[46] If the inhalation is too fast, which is possible for a DPI with a low resistance, the powder may not disaggregate before it leaves the inhaler. This, as well as the particle's momentum in a fast moving airstream, will lead to greater deposition in the oropharynx.

For some DPIs, a powder-containing capsule is loaded into the device by the patient, and the dose has to be emptied from the DPI by the inhalation manoeuvre. Inhalation volume is, therefore, another important consideration for capsule DPIs, as pictured in Fig. 4. It is for this reason that the patient information leaflet for these DPIs directs patients to use two inhalation manoeuvres per dose.

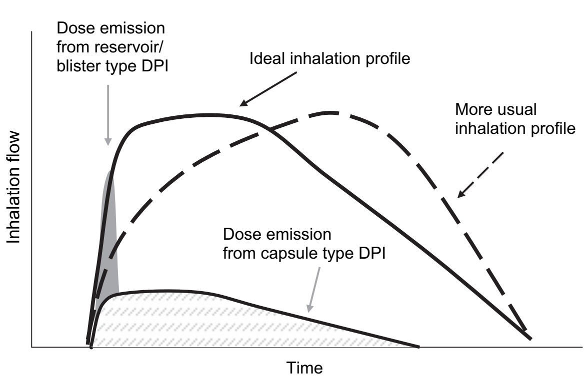


**Figure 4** Schematic depicting the relationship between particle emission rate from a dry powder inhaler (DPI; capsule & reservoir/blister type) and patient inhalation profiles that are usual vs. ideal for DPI dose emission. Actual shape will vary with device used. Adapted with permission from Chrystyn and Price.[45]

Optimal dose emission from a DPI, therefore, depends on the combination of inhalation volume, inhalation flow, acceleration rate, and the inhaler. The acceleration of the inhalation flow (at the start of inhalation), whilst the most important factor, correlates to peak inhalation flow when the inhalation starts with a fast acceleration.[46] In vitro, the fine particle dose is increased at higher flow rates.[47,48] As a corollary, total lung deposition in vivo is greater with faster inhalation rates, although the fast inhalation required by DPIs results in substantial oropharyngeal deposition even at higher rates.[49,50] Combining all the information in Fig. 4 highlights that the generic instruction to a patient using a DPI should be to "inhale as deep and hard as possible, from the start of the inhalation and for as long as you can."

The combined effect of different flows, acceleration rates, and inhalation volumes need to be studied in 'real life' situations. Some limited studies have been reported using the electronic lung.[51–53] However, the electronic lung involves the use of a holding chamber, and patients in these studies were highly trained to use each DPI and excluded if they could not use the DPIs after training. There is therefore a need for ex vivo methods to research dose emission from real life inhalation profiles. This should include different strengths and formulations in the same inhaler device, because the effect of any changes to these factors is not known.

## Optimising inhaler therapy

Table 2 summarises the key points regarding the inhalation manoeuvre required when using MDIs and DPIs. Before performing each inhalation manoeuvre, patients should be instructed to adhere to the manufacturer's instruction on the preparation of the dose. Failure to perform this correctly could result in no dose being received irrespective of the inhalation manoeuvre. Confirming proper inhaler technique is an essential step in optimising drug delivery to the lungs. Verbal training in proper inhaler technique, both as a sole measure and coupled with individualised instruction in self-management of asthma, improves outcomes for patients with asthma, in part because of improved compliance.[54–56] Moreover, regular assessment and reinforcement are needed to maintain handling and inhalation technique.[10]

For patients who cannot coordinate actuation and inhalation with an MDI, switching to a breath-actuated MDI may be a solution.[15] However, choice of pharmacologic therapy may be limited and the unaccustomed delivery may cause (a temporary) cough. The use of a spacer reduces oropharyngeal deposition and can as much as double lung deposition[57] by overcoming actuation/coordination difficulties but is the option least preferred by patients.[12] On a practical note, both small and large spacers reduce oropharyngeal deposition.[58]

For DPIs, a prolonged fast inhalation from the start is important. This can be checked visually and in part with the use of an In-Check Dial (Clement Clark International, Harlow, Essex, UK), to ensure that the patient can generate a minimum effective flow, which at present is universally accepted as 30 L/min. This meter is limited in that firstly,

**Table 2** Summary of the optimal inhalation manoeuvre and key points regarding metered dose inhalers and dry powder inhalers.

| Metered dose inhalers (MDIs) | Dry powder inhalers (DPIs) |
|---|---|
| Inhalation technique:<br>1. exhale gently as fully as possible,<br>2. begin to inhale and<br>3. actuate the dose,<br>4. continue with slow (<60 L/min) and deep inhalation over 2 s (child) to 4–5 s (adult),<br>5. hold breath for 10 s, or as long as possible.<br>• Ideal co-ordination calls for dose release (actuation) at start of inhalation.<br>• Good co-ordination is less critical if the inhalation is slow, but the dose has to be released after the start of the inhalation.<br>• Too fast an inhalation increases the likelihood of oropharyngeal deposition.<br>• Patients with poor coordination of actuation and inhalation can be switched to a breath-actuated MDI.<br>• MDIs can be used with spacers, large or small, although spacers score low in patient preference. | Inhalation technique:<br>1. exhale gently as fully as possible,<br>2. inhale sharply: as fast and as deeply as possible,<br>3. hold breath for 10 s, or as long as possible.<br>• DPIs are breath-actuated and require adequate acceleration on inhalation: the patient must inhale deeply and forcibly *at the start of the inhalation*.<br>• If the patient does not inhale fast enough or long enough:<br>○ Not all the dose is emitted;<br>○ Particles generated are too big to enter the lungs, resulting in increased oropharyngeal deposition.<br>• If the dose is supplied in a capsule then two inhalations are required to empty the dose.<br>• DPIs should not be prescribed to patients with insufficient inspiratory effort, including children <5 years old and the elderly.<br>• DPIs are sensitive to moisture: must store in a dry place and avoid exhaling through the inhaler. |

testing is not available for all DPIs, and secondly, it will not give an indication of the acceleration rate. If the patient's natural inhalation is too fast through a particular DPI, then switching them to a DPI with a higher resistance will reduce the speed of their inhalation. This should improve drug distribution in the lungs and limit oropharyngeal impaction.

## Individualising inhaler device choice

A choice of possible inhaler devices is defined first by choice of drug, device availability, and any relevant reimbursement restrictions. Consideration of patient age or ability to use the inhaler may help further refine the list as, for example, children <5 years old and some elderly patients should not be prescribed DPIs because they cannot generate sufficient inspiratory flow. At this point, the prescriber may still be left with several choices of inhaler devices. How best to proceed?

One review of inhaler technique after training concluded that there is no difference in the ability of patients to use DPIs or MDIs.[6] However, even with training, not all patients can use their inhalers correctly; this is true for both MDIs and DPIs.[12,59] In practice there are indications that patient preferences for devices vary and, furthermore, that preference is linked to ability to perform good inhaler technique, and ultimately this may influence compliance.[12,13] Most patients inhale too fast with an MDI,[42,43] and many inhale too slowly with a DPI.[60]

These findings suggest that not all patients can master the proper technique for each type of inhaler and, in addition, that patients may have natural inspiration patterns that do not match their prescribed inhaler. Therefore, rather than training and retraining a patient to use a specific inhaler device, a better course of action could be to match a device to the patient. In other words, instead of insisting that patients use a particular device, we should try to match device with their behaviour. Following this logic, the ideal patient to use an MDI is a patient who tends to use slow deep inhalations, whereas the ideal patient to use a DPI is one who can easily perform a rapid, deep, and prolonged inspiration.

We need a clinical tool to characterise a patient's inhalation pattern, check inhaler technique, and enable a match with an inhaler device; this tool should be inexpensive and easy to use.

Furthermore, we need more complete information on inhaler device types. For each MDI, information should include the maximum rate and minimum length of inhalation to achieve good lung deposition. For DPIs, research is required to define the minimum inhalation flow for each type of device and the effect of the initial acceleration of the inhalation flow. This is important because there is the potential for patients to receive no dose into their lungs if they do not inhale fast enough through a DPI. This information could then be matched with information generated by the clinical tool to individualise inhaler choice.

Finally, it would be useful to better standardize the way devices and drug-device combinations are studied and the way study results are reported to health authorities and physicians. This would facilitate the understanding of technical and delivery/deposition characteristics, optimal inhalation technique, ease of use, and patient preference.

## Conclusions

Inhaler technique is an important factor in achieving adequate asthma control; increasing or adding treatment is not a substitute for adequate inhaler technique.

Key questions requiring further research are the following:

1. To what extent is the level of lung deposition a key determinant of clinical short- and long-term outcomes?

Do different drugs require different levels of deposition?
2. Do devices that are easier to use produce better outcomes in well-conducted studies?
3. What should be measured by a clinical tool designed to check breathing pattern and/or inhaler technique?
4. If we have such tools to check breathing pattern, check inhaler handling technique, and help in individualising inhaler choice, will their use in influencing inhaler device choice provide better maintenance of good inhaler technique and better asthma outcomes? Do we have to refine inhaler device choice for each individual?
5. Or, alternatively, will we get better outcomes if we systematically select the device that we believe represents the best or the least bad option in light of current knowledge and apply this on a population level?

## Conflict of interest

J.H. has received fees for consultancy, travel and subsistence, or honoraria for presentations from AstraZeneca, GlaxoSmithKline, Merck, Sharp & Dohme, Mundipharma, Novartis, Nycomed, and Teva.

D.P. has consultant arrangements with Aerocrine, Boehringer Ingelheim, Dey Pharmaceuticals, GlaxoSmithKline, Merck, Sharpe and Dohme, Novartis, Schering-Plough, and Teva. He or his team have received grants and research support for research in respiratory disease from the following organisations: UK National Health Service, Aerocrine, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck, Sharpe and Dohme, Novartis, Pfizer, Schering Plough, and Teva. He has spoken for: Boehringer Ingelheim, GlaxoSmithKline, Merck, Sharpe and Dohme, Pfizer, and Teva.

N.C.B. has no shares. He has received honoraria for lectures or consultancy from GSK, AZ, BI, Novartis, Chiesi, Teva, SkyePharma, and Mundipharma. He has received research grants from GSK, AZ, Novartis, BI, and Chiesi.

J.C.V. has received honoraria for presentations from Asche-Chiesi, AstraZeneca, Avontec, Bayer, Bencard, Bionorica, Boehringer-Ingelheim, Essex/Schering-Plough, GSK, Janssen-Cilag, Leti, MEDA, Merck, MSD, Munidpharma, Novartis, Nycomed/Altana, Pfizer, Revotar, Sandoz-Hexal, Stallergens, TEVA, UCB/Schwarz-Pharma, and Zydus/Cadila; and consultancy fees from Asche-Chiesi, Avontec, Boehringer-Ingelheim, Essex/Schering-Plough, GSK, Janssen-Cilag, MSD, Mundipharma, Novartis, Revotar, Sandoz-Hexal, UCB/Schwarz-Pharma, as well as research funding from GSK and MSD.

N.R. has no shares in any pharmaceutical companies. He has received fees for consultancy and honoraria for presentations from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Novartis, Nycomed, and Pfizer.

H.C. has no shares in any pharmaceutical companies. He has received sponsorship to carry out studies, together with some consultant agreements and honoraria for presentations, from several pharmaceutical companies that market inhaled products. These include AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Innovata Biomed, Meda, Napp Pharmaceuticals, Omron, Teva, Trinity Chiesi, Truddell, and UCB. Research sponsorship has also been received from grant awarding bodies (EPSRC and MRC).

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