JOURNAL OF PHARMACEUTICAL POLICY AND PRACTICE
2024, VOL. 17, NO. 1, 2415425
https://doi.org/10.1080/20523211.2024.2415425

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RESEARCH ARTICLE

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Inhaler personalisation based on peak inspiratory flow (PIF) among dry powder inhaler users: a pilot randomised control trial (RCT) in COPD

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ABSTRACT

Background: Dry powder inhalers (DPIs) are commonly used among patients with Chronic Obstructive Pulmonary Disease (COPD). These inhalers are breath-actuated, and require patients to generate sufficient peak inspiratory flow (PIF) to disaggregate the drug powder into respirable fine particles and deliver it to the lower airway tracts. Inhaler personalisation based on PIF among DPI users has not been studied in Malaysia, thus we conducted the present pilot study to determine the feasibility of conducting such research among COPD patients.

Methods: This was an open-label pilot randomised control trial, conducted from June 2021-January 2022 at the respiratory clinic of Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia. Measurement of PIF was performed with In-Check DIAL G16 among adult COPD patients treated with DPI and had suboptimal PIF. Eligible subjects were randomised using block randomisation into two groups, either the interventional group or the control group.

Results: Twenty-two COPD patients fulfilled the study criteria and were randomised to intervention (n = 11) and control (n = 11) groups. For the interventional group, there were statistically significant improvements between baseline and at 12 weeks for both FEV_1 and CAT scores. The mean (% predicted) FEV_1 were 54.6 ± 20.4% and 56.6 ± 19.8% ($p = 0.026$), pre-and post-intervention. The mean CAT score at baseline was 24.4 ± 5.8 and reduced to 19.6 ± 4.4 at 12 weeks ($p = 0.012$). For the control group, the mean (% predicted) FEV_1 at baseline was 58.0 ± 21.9% and 56.5 ± 20.7% at 12 weeks, with no statistical significance difference ($p = 0.143$). However, there was a

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statistically significant difference in CAT scores at baseline and 12 weeks, with a mean of 26.5 ± 6.1 and 23.3 ± 5.6, respectively ($p = 0.010$).
Conclusion: The findings from the present pilot RCT highlighted that inhaler personalisation based on PIF among COPD patients was feasible and practical.

ARTICLE HISTORY Received 10 August 2024; Accepted 6 October 2024

KEYWORDS Peak Inspiratory Flow (PIF); Dry powder inhaler (DPI); In-Check DIAL G16; Inhaler technique; Chronic Obstructive Pulmonary Disease (COPD)

Background

Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous lung condition characterised by chronic respiratory symptoms (dyspnea, cough, sputum production, and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction (Global Initiative for Chronic Obstructive Lung Diseases, 2024).

Pharmacological treatment delivered via inhalers is the bedrock for COPD management and dry powder inhalers (DPIs) are commonly used among these patients (Leving et al., 2021). A large real-world study that included the Asian population reported that 89% of COPD patients were prescribed DPIs (Ding et al., 2018). Dry powder inhalers are breath-actuated, which requires patients to generate sufficient peak inspiratory flow (PIF) to disaggregate the drug powder into respirable fine particles and deliver it to the lower airway tracts. The PIF is the maximal flow (typically expressed in L/minute) obtained during a forced inspiratory maneuver, either with or without resistance (Ghosh et al., 2017). The internal resistance of DPIs varies, and hence the PIF required to overcome this resistance is different from one DPI to another (Ghosh et al., 2017). A study performed among stable COPD patients in a clinic with FEV1 $\leq$ 50% predicted highlighted that 19% of the patients yielded a PIF lower than 60 L/min (suboptimal) against the resistance of a Diskus (Mahler et al., 2013). The PIFotal study, which enrolled 1434 COPD patients, found that 29% of the study's participants had suboptimal PIF with DPIs. When directed to exert their full effort, a sizable portion of individuals (16%) were successful in achieving an optimal PIF, however, they were unable to do so during a typical inhalation maneuver (W H Kocks et al., 2022).

Suboptimal PIF with DPIs has been associated with poorer clinical outcomes among COPD patients (Mahler et al., 2014). Kocks et al. conducted a large multi-country (Greece, the Netherlands, Poland, Portugal, Spain, and Australia) cross-sectional observational study among COPD patients in primary care settings. The study reported associations between suboptimal PIF and poor outcomes among the COPD population such as impaired health status and increased risk of severe exacerbations (Kocks et al., 2023). In another study,

Loh et al. enrolled 123 COPD patients and reported that 52% of the subjects had suboptimal PIF on the day of discharge. When compared with the optimal PIF group, the suboptimal group had fewer days of all-cause readmission (65.5 vs. 101 days, $p = 0.009$) and rates of 90-day COPD readmissions (28.1 vs. 13.6%; $p = 0.048$). In the multivariate analysis, PIF was the only significant variable associated with readmission (Loh et al., 2017).

The measurement of PIF is not commonly practiced among health care professionals neither during hospital admissions for exacerbation nor outpatient visits. One of the tools recommended to measure PIF among COPD patients is the In-Check DIAL G16 (Figure 1), a multi-patient device with an adjustable dial that can be set to resemble the resistance of the inhalers (Sanders, 2017). This is important as some patients may not be able to generate adequate flow due to several factors commonly seen in COPD patients, such as hyperinflation of the lungs, poor muscle strength, and exacerbations; hence DPIs may not be suitable for them (Leving et al., 2022; Usmani, 2019). The GOLD report recommends healthcare professionals assess inspiratory flow among DPI users to ensure optimal use (Global Initiative for Chronic Obstructive Lung Diseases, 2024). Chen et al. conducted a study on PIF-guided inhalation therapy among COPD patients at the National Taiwan University Hospital. The PIF-guided inhalation therapy was based on a predefined algorithm and In-Check DIAL G16 was used to assess the inspiratory flow. Among 383 COPD patients, there was a significant reduction in the incidence of severe acute exacerbation in the PIF-guided inhalation therapy (PIF group) than conventional inhaler education (control group) (11.9 vs. 21.1%, $p = 0.019$) (Chen et al., 2021). Healthcare professionals have

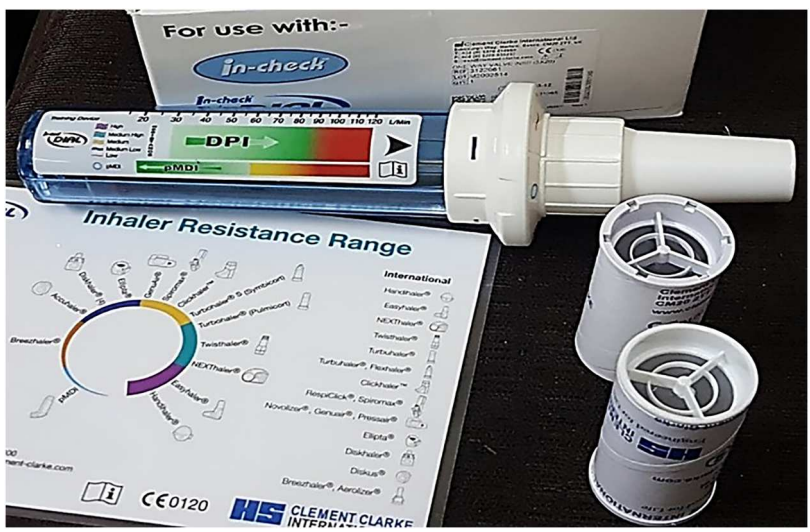

Figure 1. The In-Check DIAL G16.

to personalise the selection of inhaler devices by matching the unique features of the inhaler delivery system to individual patient factors (Global Initiative for Chronic Obstructive Lung Diseases, 2024; Mahler & Halpin, 2023). The PIF along with patients' cognitive function and manual function/dexterity are crucial factors in selecting the right inhaler device for the right patient (Mahler & Halpin, 2023; Usmani, 2019). Patients with suboptimal PIF with DPIs may benefit from switching to pressurised metered dose inhalers (pMDIs) or soft mist inhalers (SMIs), that do not require significant inspiratory effort (Chen et al., 2021; Usmani, 2019). To the best of our knowledge inhaler selection or personalisation based on PIF among DPI users has not been studied in Malaysia, thus large-scale research could be designed to evaluate the approach. We conducted the present pilot study to determine the feasibility of conducting such research among COPD patients.

Methods

Study design

This was an open-label pilot randomised control trial (RCT) that was approved by the Research Ethics Committee with reference number FF-2020-363. The outcome assessors were not blinded in the study.

The inclusion criteria were: adult patients with a confirmed diagnosis of COPD according to the GOLD; received treatment with either long-acting muscarinic antagonist (LAMA), long-acting beta-agonist (LABA), inhaled corticosteroids (ICS) or any of the combination delivered via a DPI and had suboptimal PIF; adherent to their inhalers (prescription refill records were used to measure medication adherence); and patients could perform spirometry. Patients were excluded if they had a diagnosis of chronic lung diseases like asthma, asthma-COPD overlap, interstitial lung disease or lung cancer; unstable cardiovascular diseases; and patients with underlying neuromuscular disorders. All advanced COPD patients on long-term oxygen therapy (LTOT) were also excluded.

Procedure

Measurement of PIF was performed with In-Check DIAL G16 (Figure 1) and disposable single-patient mouthpieces. The In-Check DIAL G16 has been used widely in previous studies to measure PIFR in COPD patients (Janssens et al., 2008; Jarvis et al., 2007; Mahler et al., 2013; van der Palen, 2003). The tool has an accuracy of +/− 10% or 10 L/min, whichever is greater, and it can measure flow rate in the range of 15 to 120 L/min (Alliance Tech Medical I., n.d.). Subjects made 3 attempts of PIF after being instructed by the investigator to inhale as forcefully and deeply as possible after a complete exhalation. As per the recommendation from the previous studies, the

highest PIF value was recorded and used for analysis (Janssens et al., 2008; Jarvis et al., 2007; Mahler et al., 2013; van der Palen, 2003). For the present study, we measured the PIF at different levels of resistance: low (R1), medium-low (R2), medium (R3), medium-high (R4) and high (R5). The resistance levels were set based on patients' current inhalers. The cut-off values for suboptimal PIF were based on the publication by Ghosh and colleagues (Ghosh et al., 2017).

The COPD Assessment Tool (CAT) was used to measure the patient's health status. It is a single-dimensional questionnaire and is available in multi-language versions depending on the subject's preferences. An exacerbation is defined as an acute worsening of respiratory symptoms that results in additional therapy (Global Initiative for Chronic Obstructive Lung Disease, 2024). It is categorised into two types: moderate (treated with short-acting bronchodilators plus systemic steroids and/or antibiotics) and severe (hospitalised or emergency department visit).

Spirometry was performed by a trained technician using SpiroUSB (CareFusion). According to the American Thoracic Society (ATS) criteria, patients were asked to blow for a minimum duration of 6 s. Subjects have to blow at least 3 times, which can be done up to a maximum of 8 tests depending on the quality of the test. The spirometry results were acceptable if the difference between the two best readings was less than 5% and 150mls. To engage with the COVID-19 pandemic, a negative COVID Rapid Test Kit-Antigen (RTK-Ag) / Reverse Transcriptase Polymerase Chain Reaction (RT–PCR) swab test 48 hours before spirometry was required as a pre-requisite. Other measures to minimise COVID-19 transmission throughout the procedure are by applying level 3 Personal Protective Equipment (PPE) by the technician and the usage of a disposable, single-patient mouthpiece.

The pharmacy department provided a list of patients who were on COPD inhalers, and the patients were screened from that list. Subsequently, the medical records office was consulted for their records. Following the screening, baseline PIF was measured for all subjects, and eligible subjects were then randomised using block randomisation into 2 groups, either the interventional group or the control group. Opaque-sealed envelopes were used for allocation concealment. The subject's current DPI was changed to an appropriate inhaler (either pMDIs or SMI) in the interventional group according to their measured PIF. The subjects received inhaler education with a focus on the new inhaler technique and inhalational maneuvers. For the control group, subjects were asked to continue using the same DPIs after receiving inhaler education, that emphasised the correct inhaler use and inhalation flow. Other factors such as patients' cognitive function and manual function/ dexterity are optimised in both interventional and control groups. The pharmacological categories in both study groups were not alerted.

At week 4 and week 8, all subjects in both groups were followed up via phone calls, and assessed on their health status (CAT score) and exacerbation. At week 12, in addition to the CAT score and exacerbation assessment, spirometry was repeated.

Statistical analysis

All statistical analyses were performed using Statistical Package for Social Sciences version 27.0 (SPSS Inc, Chicago, IL, USA). Frequency distribution histogram plots were used to verify the normality of continuous data. Inferential analysis was conducted through independent t-test (between-group) and paired t-test (within group); meanwhile, for categorical data, chi-square or Fisher's exact test was used. The significance level was set at 5%. Since the present study was a pilot RCT, the sample size was not calculated; however, the literature suggests a minimum of 10 subjects per arm should be used (Cocks & Torgerson, 2013).

Results

A total of 89 COPD patients were screened between June 2021 and January 2022. Twenty-two COPD patients fulfilled the study criteria and were randomised. The mean age was 67.4 ± 9.1 years and 69.7 ± 9.3 years in the interventional and control groups respectively. The study design and CONSORT flow diagram as shown in Figure 2. The demographic and baseline characteristics are listed in Table 1.

The mean percentage FEV1 at baseline in the interventional group was 1.43 ± 0.63 L (54.6 ± 20.4% predicted) and 1.58 ± 0.71 L (58.0 ± 21.9% predicted) for the control group. For the interventional group, there were statistically significant improvements between baseline and at 12 weeks of follow-up for both FEV1 and CAT scores. The mean (% predicted) FEV1 were 54.6 ± 20.4% and 56.6 ± 19.8% ($p = 0.026$), pre-and post-intervention. The mean CAT score at baseline was 24.4 ± 5.8 and reduced to 19.6 ± 4.4 at 12 weeks ($p = 0.012$), as listed in Table 2. For the control group, the mean (% predicted) FEV1 at baseline was 58.0 ± 21.9% and 56.5 ± 20.7% at 12 weeks, with no statistical significance difference ($p = 0.143$). However, there was a statistically significant difference in CAT scores at baseline and 12 weeks, with a mean of 26.5 ± 6.1 and 23.3 ± 5.6, respectively ($p = 0.010$), as reported in Table 2.

The mean percentage change of FEV1 was 1.91 after 12 weeks of follow-up in the interventional group and −1.82 in the control group. There was a statistically significant difference in the mean percentage change FEV1 between both groups (Table 3). On the other hand, there was no statistically significant difference between the interventional (−4.73) and control (−3.18) groups concerning the mean difference in CAT score at week 12 (Table 3).

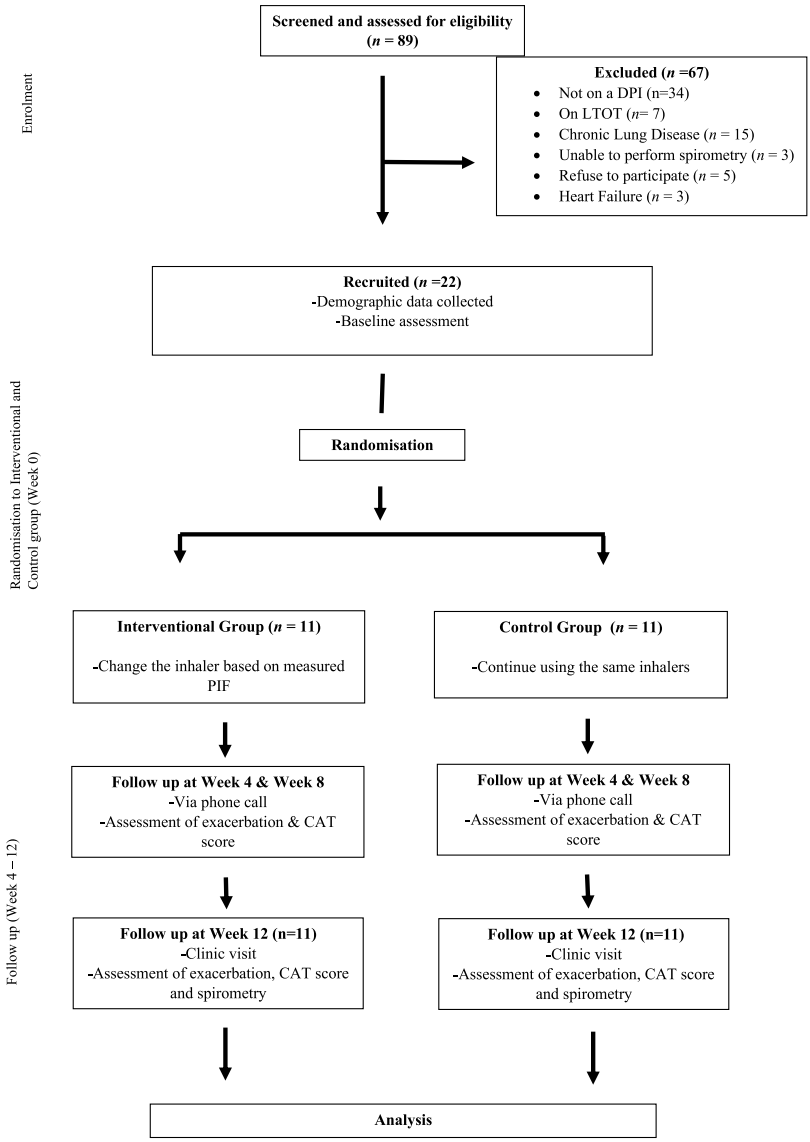

Figure 2. Study design and flow diagram.

Only 2 subjects (18.2%) experienced exacerbations in each interventional and control group throughout the study period (Table 4).

Discussion

This pilot RCT is the first in Malaysia to assess inhaler personalisation strategy among COPD patients with DPIs. The patients with suboptimal PIF in the

Table 1. Demographic and baseline characteristics between interventional and control groups ($n = 22$).

		Interventional Group $n = 11$	Control group $n = 11$
Age (mean ± SD), years		67.4 ± 9.1	69.7 ± 9.3
Body mass index (mean ± SD), kg/m^2		26.6 ± 4.8	24.6 ± 5.3
Gender	Male	11 (100)	11 (100)
Ethnicity	Malay	8 (72.7)	6 (54.5)
	Chinese	3 (27.3)	5 (45.5)
Smoking status	Active smoker	5 (45.5)	4 (36.4)
	Ex-smoker	6 (54.5)	7 (63.6)
FEV_1 percentage (in %) (mean ± SD)		54.6 ± 20.4	58.0 ± 21.9
FEV_1 in Litres (mean ± SD)		1.43 ± 0.63	1.58 ± 0.71
GOLD Stages	I	1 (9.1)	1 (9.1)
	II	5 (45.5)	7 (63.6)
	III	4 (36.3)	1 (9.1)
	IV	1 (9.1)	2 (18.2)
Cat Score at baseline, (Mean ± SD)		24.36 ± 5.8	26.5 ± 6.1
Impact level of CAT Score, (At baseline)	Medium (11–20)	2 (18.2)	1 (9.1)
	High (21–30)	8 (72.7)	7 (63.6)
	Very high (>30)	1 (9.1)	3 (27.3)
mMRC** Grading	2	7 (63.6)	6 (54.5)
	3	4 (36.4)	5 (45.5)
Number of exacerbations in the past year	0	2 (18.2)	1 (9.1)
	1	0 (0)	6 (54.5)
	2	5 (45.5)	4 (36.4)
	≥3	4 (36.3)	0 (0)
DPIs	Turbuhaler	1 (9.1)	0 (0)
	Accuhaler	5 (45.4)	6 (54.5)
	Breezhaler	4 (36.4)	5 (45.5)
	Ellipta	1 (9.1)	0 (0)

Data presented as frequency (%) unless stated otherwise. **mMRC: Modified Medical Research Council

Table 2. Comparison of FEV_1 and CAT scores within interventional and control group.

Variables	Interventional Group ($n = 11$)			Control Group ($n = 11$)		
	Before mean (SD)	After mean (SD)	*p*-value	Before mean (SD)	After mean (SD)	*p*-value
FEV_1 (%) predicted	54.6 ± 20.4	56.6 ± 19.8	0.026	58.0 ± 21.9	56.5 ± 20.7	0.143
CAT Score	24.4 ± 5.8	19.6 ± 4.4	0.012	26.5 ± 6.1	23.3 ± 5.6	0.010

FEV_1: Forced expiratory volume in 1s, CAT: COPD Assessment Test

Table 3. Association of the mean difference (baseline and at week 12) of FEV_1 and CAT score between the two groups.

Variables	Interventional Group mean difference (SD)	Control Group mean difference (SD)	*p*-value
Δ mean FEV_1 (%) predicted	1.91 (2.43)	−1.82 (3.79)	0.012
Δ mean CAT Score	−4.73 (5.16)	−3.18 (3.34)	0.414

FEV_1: Forced expiratory volume in 1s, CAT: COPD Assessment Test

Table 4. Exacerbations during the study period.

Moderate/severe exacerbations	Interventional Group *n* (%)	Control Group *n* (%)	*p*-value
No	9 (81.8)	9 (81.8)	1.000
Yes	2 (18.2)	2 (18.2)	

interventional group underwent device switching while the control group patients received inhaler education only (standard care). The pilot study demonstrated that it was feasible to conduct PIF-based personalisation of inhaler devices among COPD patients in local settings. The In-Check DIAL G16 was a practical tool to measure PIF among DPI users and the strategy can be expanded to larger studies or in clinical practice. Our pilot RCT also highlighted that it was viable to measure the required parameters such as lung function, exacerbations, CAT score, and others.

The interventional group documented a significant increase in FEV1 compared with the control group (had suboptimal PIF with DPIs). Patients with suboptimal PIF may not optimally inhale the medication out of the DPIs, thereby leading to reduced delivery of the fine-particle dose to the lower airways, unfavourably affecting clinical outcomes (Mahler & Halpin, 2023). Mahler and colleagues investigated COPD patients treated with a beta-agonist inhaled via nebulisation compared with DPI with suboptimal PIF. The study delineated that volume responses were greater with bronchodilators delivered via nebuliser compared with DPIs in patients with COPD who had suboptimal PIF (Mahler et al., 2014). Another randomised, double-blind, Phase 3b study compared bronchodilation effects with the long-acting muscarinic antagonist delivered via nebulisation versus the DPI in patients with COPD. The investigators reported smaller changes in trough FEV1 among patients with FEV1 < 50% predicted and suboptimal PIF among DPI users (Mahler et al., 2019). The present study documented similar findings. Leving et al. highlighted that 13% (n = 138) of COPD patients had suboptimal PIF with DPIs even after inhaler training. These patients were not able to generate sufficient inspiratory effort for the DPIs and alternative devices such as pMDI and SMI were recommended in this group of patients (Lee et al., 2016). The dose and fine particle emission from pMDI and SMI are not dependent on PIF (Usmani, 2019). These principles were the basis of our study, indeed, a Taiwanese study that utilised the same concept, had published its findings recently (Chen et al., 2021). The authors reported improvements in clinical outcomes with PIF-guided inhalation therapy in COPD patients (Chen et al., 2021).

The symptom improvements measured with the CAT score were not significantly different between the interventional and control groups. Both groups had improvements in the CAT score from the baseline, suggesting that the provided inhaler education had some benefits in the suboptimal PIF group. According to a Korean study, there was an improvement in CAT

scores among COPD patients who received a structured education intervention (Lee et al., 2016). However it is important to note that Sharma et al. did not find any statistically significant difference in CAT scores between the suboptimal and optimal PIF cohorts (Sharma et al., 2017)**;** in contrast, the PIFotal study demonstrated a significant association with poorer CAT scores among COPD patients who made errors in DPI inspiratory flows (Kocks et al., 2023). The findings on the CAT score should be investigated further in a larger adequately powered RCT. Suboptimal PIF also has been associated with an increased risk of COPD exacerbations (Loh et al., 2017), however, in our study, the number of events was too low to make any clinically relevant interpretations.

Our study has several limitations. The study was not blinded as it was cumbersome to do so. As a pilot RCT, the study was not powered to analyse the differences in clinical outcomes and effect sizes; hence these findings should be interpreted with caution. Much larger numbers of patients with appropriate sample size calculations would be required to establish whether this approach would be worthwhile routinely in the clinical setting for patients with COPD. In addition, we only measured PIF in the present study, other important parameters such as acceleration, time to PIF, inhalation volume, and inhalation time were not assessed. Another limitation of this study was the mouthpiece dimension of the In-Check DIAL G16 was not an accurate representation of the patient's actual DPI. The study also recruited male patients only and this could potentially be another limitation as the literature suggests that the PIF is influenced by gender.

Conclusion

The findings from the present pilot RCT highlighted that inhaler personalisation based on PIF among COPD patients was feasible and practical. It is vital to conduct an adequately powered study to establish more vigorous evidence regarding clinical outcomes.

Disclosure statement

Rabia Hussain serves as Section Editor and Jaya Muneswarao as Associate Editor for the *Journal of Pharmaceutical Policy & Practice*. Neither was involved in handling this manuscript, including the editorial review, peer review, and decision-making processes. The authors declare no other competing interests.

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