# THE RELATIONSHIP BETWEEN CLINICAL TRIAL PARTICIPATION AND INHALER TECHNIQUE ERRORS IN ASTHMA AND COPD PATIENTS




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Pulmonology

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# Declaration

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# Contents

# Abstract

Background

Incorrect inhaler use is associated with poorer health outcomes, reduced quality of life, and higher healthcare utilisation in patients with asthma and COPD.

Method

We performed an observational study of pressurized metered-dose inhaler technique in patients with asthma or COPD. Patients were assessed using a six-point inhaler checklist to identify common critical inhaler technique errors. An inadequate inhaler technique was defined as the presence of one or more critical errors. A multivariate logistic regression model was used to determine the odds of an inadequate inhaler technique.

Results

During the 14-month study period, 357 patients were enrolled. At least one critical error was executed by 66.7% of participants, and 24.9% made four or more critical errors. The most common errors were: failure to exhale completely prior to pMDI activation and inhalation (49.6%), failure to perform a slow, deep inhalation following device activation (48.7%), and failure to perform a breath-hold at the end of inspiration (47.3%). The risk of a critical error was higher in COPD patients (aOR 2.25, 95%CI 1.13 – 4.47). Prior training reduced error risk specifically when trained by a doctor (aOR 0.08, 95% CI 0.1 – 0.57) or a pharmacist (aOR 0.02, 95% CI 0.01 – 0.26) compared to those with no training. Previous clinical trial participation significantly reduced error risk and rate: <3 trials (aOR 0.35, 95% CI 0.19 – 0.66) and ≥3 trials (aOR 0.17, 95% CI 0.07 – 0.42). The rate of critical errors was not significantly associated with age, sex, or prior pMDI experience.

Conclusion

This study found a high rate of critical inhaler technique errors in a mixed population of asthma and COPD patients; however, prior training and in particular, multiple previous clinical trial participation significantly reduced the risk of errors.

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# Contributions

Rubeshan Perumal conceptualised the study, designed the study, performed the data analysis, prepared the manuscript, and managed the submission process.

Richard van Zyl-Smit conceptualised the study, designed the study, and contributed to manuscript preparation.

Marcia Leite assisted with data collection, and contributed to data cleaning and preparation.

# Abbreviations

| | |
|---|---|
| aOR | Adjusted odds ratio |
| CI | Confidence interval |
| COPD | Chronic obstructive pulmonary disease |
| DPI | Dry-powder inhaler |
| HREC | Human Research Ethics Committee |
| IQR | Interquartile range |
| OR | Odds ratio |
| pMDI | Pressurised metered-dose inhaler |
| SD | Standard deviation |

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ORIGINAL RESEARCH

# The Relationship Between Clinical Trial Participation and Inhaler Technique Errors in Asthma and COPD Patients

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**Background:** Incorrect inhaler use is associated with poorer health outcomes, reduced quality of life, and higher healthcare utilisation in patients with asthma and COPD.
**Methods:** We performed an observational study of pressurized metered-dose inhaler technique in patients with asthma or COPD. Patients were assessed using a six-point inhaler checklist to identify common critical inhaler technique errors. An inadequate inhaler technique was defined as the presence of one or more critical errors. A multivariate logistic regression model was used to determine the odds of an inadequate inhaler technique.
**Results:** During the 14-month study period, 357 patients were enrolled. At least one critical error was executed by 66.7% of participants, and 24.9% made four or more critical errors. The most common errors were failure to exhale completely prior to pMDI activation and inhalation (49.6%), failure to perform a slow, deep inhalation following device activation (48.7%), and failure to perform a breath-hold at the end of inspiration (47.3%). The risk of a critical error was higher in COPD patients (aOR 2.25, 95% CI 1.13 4.47). Prior training reduced error risk specifically when trained by a doctor (aOR 0.08, 95% CI 0.1 0.57) or a pharmacist (aOR 0.02, 95% CI 0.01 0.26) compared to those with no training. Previous clinical trial participation significantly reduced error risk and rate: <3 trials (aOR 0.35, 95% CI 0.19 0.66) and ≥3 trials (aOR 0.17, 95% CI 0.07 0.42). The rate of critical errors was not significantly associated with age, sex, or prior pMDI experience.
**Conclusion:** This study found a high rate of critical inhaler technique errors in a mixed population of asthma and COPD patients; however, prior training and, in particular, multiple previous clinical trial participation significantly reduced the risk of errors.
**Keywords:** inhaler, pressurised metered-dose inhaler, clinical trials, asthma, COPD

## Introduction

Obstructive airways diseases, including asthma and chronic obstructive pulmonary disease (COPD), are common worldwide.[1] Inhaled therapies such as inhaled corticosteroids and bronchodilators are the mainstay of treatment of obstructive airways diseases and are preferential to systemic therapies.[2,3] Inhalation with subsequent airway deposition targets the site of disease, allows for reduced drug exposure, and minimises the risk of systemic side-effects.[4] Inhaled therapies in both asthma and COPD have been associated with a significant reduction in morbidity and mortality, while non-adherence to inhaler therapy is widely associated with poorer outcomes.[5–7] Adherence to inhaled therapy implies both regular as well as the correct use in accordance with the prescription, using the appropriate technique and

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dosing schedule.[4,8-11] The correct device-specific technique is required to optimise drug delivery, which requires patients to have an understanding and mastery of these variant skills.[4] An incorrect inhaler technique is associated with treatment failure, unnecessary escalation of therapy, and increased exacerbations with unplanned use of medical services and hospitalisation.[4,7,12-15]

Pressurised metered-dose inhalers (pMDIs) are the most widely prescribed inhaler devices given their relatively low cost and ability to deliver a wide variety of bronchodilators, inhaled corticosteroids and combinations thereof.[16,17] Each standardised metered-dose aerosol plume is dispensed upon depression of the canister and requires coordination of the timing of the canister depression with a slow and deep inhalation to deliver the drug to the targeted airways. In addition, a breath-hold at the end of inspiration is required to optimise deposition, mainly by enabling sedimentation. If the basic steps of the inhalation effort (too slow or too fast) or breath-holding are inadequate, airway deposition is compromised. Despite their ubiquity in asthma and COPD management, pMDI technique is inadequate in the majority of users and may remain imperfect even after expert training. In a large study of 5000 structured inhaler technique assessments in patients with moderate-to-severe asthma, 92% of patients made at least one potentially important error when using a pMDI.[6] A meta-analysis of 2634 inhaler technique assessments from 10 studies revealed that 45.6% of patients made at least one critical error when using a -pMDI.[18] The most common pMDI technique errors include failure to perform full exhalation prior to drug inhalation (48%), failure to breath-hold following drug inhalation (46%), lack of coordination between device activation and inhalation (45%), and inappropriate inhalation velocity (44%).[19] The only African study included in the aforementioned review revealed correct pMDI use in only 22.1% of asthmatic patients and found higher educational attainment and better asthma control to be associated with correct pMDI use.[20]

The evidence to support device education and inhaler technique training for improving inhaler technique is heterogeneous in terms of the nature of the required intervention, but generally supports the partial effectiveness of training interventions. A major limitation of interventions aimed at improving inhaler technique is the lack of standardised definitions for critical and non-critical errors, and lack of widely validated checklists for specific devices. In addition, the threshold for clinically significant error has not been fully elucidated. The most widely used metrics for reporting inhaler technique error are the proportion of patients with one or more critical errors and the average overall (critical or non-critical) error rate.[18] In a systematic review of 39 randomised studies of the effectiveness of educational inhaler technique interventions in asthma and COPD patients, over 90% reported a significant improvement in inhaler technique which persisted up to the median follow-up time of 5 months.[21] Factors associated with intervention success included poorer baseline inhaler technique, educational interventions in the outpatient setting, and advancing age. The provision of general disease education, number or length of intervention sessions, profession of the educator, type of intervention (live demonstration vs video demonstration vs oral presentation), and format of the education (individual vs group), had no clear impact on the effectiveness of the intervention.[21] None of the 39 studies included in the systematic review was conducted in Africa.

Inhaler technique has been shown to be better within a clinical trial irrespective of device type.[18] Potential selection bias, specific device-orientated training or the Hawthorne effect, whereby patients may modify their inhaler technique in response to their awareness of being the subject of observation, may be responsible.[6] It is less clear whether patients maintain adequate inhaler technique beyond the clinical trial as no studies, to our knowledge, have reported follow-up of inhaler technique beyond the trial period.

This study aimed to evaluate the inhaler technique of patients with asthma or COPD using at least one pMDI and to determine if previous clinical trial participation impacted on current inhaler technique.

## Methods

This was a cross-sectional study of pMDI technique in patients with asthma and COPD at a specialist respiratory service and clinical trial unit in Cape Town, South Africa. Consecutive adult patients with a physician diagnosis of asthma or COPD who were using at least one pMDI were included in the study. Patients under the age of 18 years, pregnant women, active clinical trial participants, and patients with pulmonary tuberculosis were excluded from the study. As part of the screening lung function assessment, patients were required to demonstrate their pMDI technique under direct observation. A structured six-point checklist (Figure 1) had previously been implemented to consistently evaluate the demonstrated technique and to

| Critical Step | Action |
|---|---|
| 1 | Shake the inhaler |
| 2 | Complete exhalation |
| 3 | Tight seal around the mouthpiece |
| 4 | Coordination between device activation and inhalation |
| 5 | Slow, deep inhalation |
| 6 | Breath-hold after inhalation |

**Figure 1** Checklist of critical steps in pMDI technique.

identify errors in accordance with manufacturer specifications, international guidelines and the existing literature.[13,15,16,18,19,22-29] All observations were conducted by qualified clinical technologists trained in device use. Data on age, sex, diagnosis, duration of pMDI therapy, prior MDI training, and prior clinical trial participation were captured from medical records. Prior clinical trials at this facility included the evaluation of new dry powder devices such as the Ellipta® or Breezhaler®, subcutaneous biological therapies, or novel use of an existing dry powder device such as the Turbuhaler®.

All data were analysed using SPSS software (SPSS 25.0, Armonk NY: IBM Corp). For all statistical comparisons, a 5% level of significance was used; correspondingly 95% confidence intervals were used to describe effect size. All data were assessed for normality, and non-parametric tests were used where necessary. An inadequate inhaler technique was defined as the presence of one or more critical errors. A multivariate binomial logistic regression model was used to determine the odds of an inadequate inhaler technique and included the following covariates: age, sex, diagnosis, prior clinical trial participation, duration of prior inhaler use, and prior pMDI training.

The study was approved and conducted under the oversight of the University of Cape Town Faculty of Health Sciences Human Ethics Research Committee (HREC 430/2017), and in accordance with the Declaration of Helsinki. All patients provided written informed consent.

## Results

During the study period, 357 consecutive asthma or COPD patients using a pressurized metered-dose inhaler were enrolled over a 14-month period. The baseline characteristics of the study participants are presented in Table 1. The mean age of participants was 52.5 years (SD 15.6 years), and 56.7% were female. A diagnosis of asthma was present is 57.4% of participants and of COPD in 42.6%. Participants had a median of 10 years (IQR 5–20) prior experience using a pMDI. The majority (79.2%) reported receiving prior training on pMDI inhaler technique by their physician, 9% by a nurse, and 2.8% by a pharmacist. While the majority (77.3%) of participants had never participated in a clinical trial, 14.3% had participated in fewer than 3 trials and 8.4% had participated in three or more trials. Participants with asthma were younger, more likely to be female, and had longer prior experience on a pMDI than patients with COPD (Table 1). There was no significant difference in prior pMDI training exposure and previous clinical trial participation between participants with asthma and COPD.

**Table 1** Baseline Characteristics of Study Participants Stratified by Diagnosis

| Characteristics | Asthma (N=205) | COPD (N=152) | Total (N=357) | *p*-value |
|---|---|---|---|---|
| Age, mean(SD) | 45.2(15.8) | 62.4(8.0) | 52.5(15.6) | <0.001* |
| Sex | | | | |
| Male, n(%) | 58(28.3) | 96(63.2) | 154(43.1) | <0.001€ |
| Prior pMDI experience (years), median (IQR) | 15(6–26) | 6(3–11) | 10(5–20) | <0.001¥ |
| Prior pMDI training | | | | |
| None, n(%) | 13(6.3) | 19(12.5) | 32(9.0) | |
| Doctor, n(%) | 165(80.5) | 118 (77.6) | 283(79.2) | 0.20€ |
| Nurse, n(%) | 21(10.2) | 11(7.2) | 32(9.0) | |
| Pharmacist, n(%) | 6(2.9) | 4(2.6) | 10(2.8) | |
| Prior clinical trial participation | | | | |
| None, n(%) | 150(73.2) | 126 (82.9) | 276(77.3) | 0.09€ |
| <3 trials, n(%) | 34(16.6) | 17(11.2) | 51(14.3) | |
| ≥3 trials, n(%) | 21(10.2) | 9(5.9) | 30(8.4) | |

**Notes:** *Independent samples *t*-test, €Pearson chi-square, ¥Mann–Whitney *U*-test.
**Abbreviations:** SD, standard deviation; IQR, interquartile range; pMDI, pressurised metered-dose inhaler.

At least one critical error was executed by 66.7% of participants, and 24.9% made four or more critical errors (Table 2). The most common errors were: failure to exhale completely prior to pMDI activation and inhalation (49.6%), failure to perform a slow, deep inhalation following device activation (48.7%), and failure to perform a breath-hold at the end of inspiration (47.3%).

**Table 2** Frequency of Critical Errors in All Participants

| Step | Error Frequency (N=357) |
|---|---|
| Shake the inhaler | 15.1% |
| Complete exhalation | 49.6% |
| Tight seal around the mouthpiece | 12% |
| Coordination between device activation and inhalation | 25.2% |
| Slow, deep inhalation | 48.7% |
| Breath-hold after inhalation | 47.3% |
| Cumulative errors | |
| One or more error(s) | 66.7% |
| Four or more errors | 24.9% |

**Table 3** Multivariate Binomial Logistic Regression Analysis to Evaluate the Determinants of Inadequate Inhaler Technique

| Characteristics | Adjusted OR | 95% CI | p-value |
|---|---|---|---|
| Age | 1.0 | 0.98–1.01 | 0.61 |
| Sex | | | |
| Female | Reference | | |
| Male | 0.72 | 0.42–1.2 | 0.21 |
| Diagnosis | | | |
| Asthma | Reference | | |
| COPD | 2.25 | 1.13–4.47 | 0.02 |
| Prior pMDI experience | 1.01 | 0.98–1.03 | 0.66 |
| Prior pMDI training | | | |
| None | Reference | | |
| Nurse | 0.26 | 0.03–2.55 | 0.25 |
| Doctor | 0.08 | 0.01–0.57 | 0.01 |
| Pharmacist | 0.02 | 0.01–0.26 | 0.002 |
| Prior clinical trial participation | | | |
| None | Reference | | |
| <3 trials | 0.35 | 0.19–0.66 | 0.001 |
| ≥3 trials | 0.17 | 0.07–0.42 | <0.001 |

**Abbreviations:** OR, odds ratio; CI, confidence interval; pMDI, pressurised metered-dose inhaler.

The multivariate logistic regression model (Table 3) revealed that the risk of a critical error was significantly increased in participants with COPD (aOR 2.25, 95% CI 1.13–4.47), and significantly decreased in participants who were previously trained by a doctor (aOR 0.08, 95% CI 0.1–0.57) or a pharmacist (aOR 0.02, 95% CI 0.01–0.26) compared to no previous training, and in participants with prior clinical trial exposure [<3 trials (aOR 0.35, 95% CI 0.19–0.66) and ≥3 trials (aOR 0.17, 95% CI 0.07–0.42). The rate of critical errors was not significantly associated with age, sex, or prior pMDI experience.

**Table 4** Frequency of Critical Errors Stratified by Prior Clinical Trial Participation

| Step | None | <3 Trials | ≥3 Trials | Total (N=357) | p-value |
|---|---|---|---|---|---|
| Shake the inhaler | 17% | 11.8% | 3.3% | 15.1% | 0.10* |
| Complete exhalation | 54.3% | 37.3% | 26.7% | 49.6% | 0.003 |
| Tight seal around mouthpiece | 15.2% | 0% | 3.3% | 12% | 0.001* |
| Coordination between device activation and inhalation | 28.6% | 19.6% | 3.3% | 25.2% | 0.006 |
| Slow, deep inhalation | 57.2% | 27.5% | 6.7% | 48.7% | <0.001 |
| Breath-hold after inhalation | 54.3% | 31.4% | 10% | 47.3% | <0.001 |
| Cumulative errors | | | | | |
| One or more error(s) | 74.6% | 47.1% | 26.7% | 66.7% | <0.001 |
| Four or more errors | 29% | 15.7% | 3.3% | 24.9% | 0.002 |

**Notes:** *Fisher's exact test. Pearson chi-square for all other comparisons.

The rate of critical errors showed a graded reduction with increased prior clinical trial participation for all critical errors (Table 4). Overall, 74% of participants with 3 or more clinical trials experience had a perfect inhaler technique compared to 52.9% of those with less than 3 trials experience and only 24.4% of those who had never participated in a clinical trial. Only 3.3% of the most trial-experienced participants had a grossly inadequate technique (4 or more errors) compared to 29% of trial-naïve participants. The magnitude of reduction in the error rate of each step, in participants with no clinical trial experience versus those with participation in three or more clinical trials, ranged from 50.8% to 88.5%, with a statistically significant reduction in five out of six critical error steps (Table 4).

## Discussion

Incorrect inhaler use is associated with poorer health outcomes, reduced quality of life, and higher healthcare utilisation in patients with asthma and COPD.[4,7,13,15] Identifying and characterizing incorrect inhaler use is a crucial first step toward designing context-specific interventions for improving inhaler technique. This study of inhaler technique in a mixed population of asthma and COPD patients at a specialist respiratory service in sub-Saharan Africa found, not unexpectedly, a high rate of critical errors in pMDI use, with over two-thirds (66.7%) of participants making at least one critical error. Similarly, a quarter of participants made errors in more than half (≥4/

6) of the critical steps. A novel finding in this study is that previous participation in a clinical trial was associated with a 65% (aOR 0.35, 95% CI 0.19–0.66) reduction in the risk of making an error in one or more of the six steps. Participation in three or more previous clinical trials reduced the risk of errors by 83% (aOR 0.17, 95% CI 0.07–0.42).

These findings are alarming for a country with one of the highest asthma mortality rates and the highest incidence of COPD in the world.[1,30,31] Identifying inhaler misuse and improving inhaler technique is a low-cost scalable intervention to improve asthma and COPD care in this resource-limited setting. The failure of a longer duration of pMDI use to translate into improved inhaler technique may reflect the fact that most errors are repetitive and persist over time, and that patients may be susceptible to overconfidence in device use which may further perpetuate inhaler misuse.[23,32] Moreover, the gains in experience in inhaler practice over time may be offset by advancing age, the onset of comorbidities, and disease progression which may all negatively affect inhaler technique.[17,33,34]

Similar to studies in other settings, the most commonly performed errors were failure of complete exhalation prior to inhaler use, failure to perform a slow deep inhalation following device activation, and failure to maintain a breath-hold after complete inspiration.[17,22,32,35,36] Errors in exhalation and in breath-holding have been shown to significantly reduce drug deposition and may be linked to uncontrolled asthma.[22,37] Although not as frequent, errors in coordinating device activation with breathing were made in over a quarter of the participants (25.2%), and confirms this widely-held disadvantage of pMDIs which has negative consequences for treatment outcomes.[22] These breathing errors were more common than device handling errors which are more commonly seen with DPIs.[22] The use of a spacer device may simplify inhaler use by obviating the need for coordinating device activation and the correct rate and depth of inhalation.[38] Moreover, spacer devices may enhance drug deposition in the lung by reducing drug particle velocity due to air resistance and reducing delivered particle size by evaporation.[38] However, spacer devices are relatively large, cumbersome, and infrequently carried with patients, which may limit their use in practice.[29] Concerningly, spacer device use has recently been associated with poorer inhaler technique and lower effective dosing owing to increased task complexity.[29,33]

The risk of making one or more critical errors was increased in COPD (aOR 2.25, 95% CI 1.13–4.47) compared with asthma and persisted in the model when adjusted for age, prior inhaler experience, and previous inhaler training. This finding has been variably reported in studies comparing inhaler technique in patients with asthma and COPD.[14,17] While a study by Melanie et al found a higher risk of inhaler technique errors in patients with COPD, the association diminished after adjusting for age and prior inhaler training.[14] Similarly, no significant difference in the rate of errors was reported by other studies comparing inhaler technique in patients with asthma or COPD.[14,17,23,29,32,34,39]

In our comparison of errors made in individual steps, participants with COPD made significantly more breathing errors (failure of complete exhalation, and failure to take a slow, deep inhalation). It is plausible that these limitations are related to the physiological and mechanical features of COPD, including more severe limitations to airflow, and a higher functional residual capacity. Furthermore, it has been shown that inhaler errors are associated with peak flow rate, and patients with COPD have been shown to have significantly lower peak inspiratory and expiratory flow rates than patients with asthma.[39] In addition, patients with COPD are more likely to have co-morbidities such as heart failure, cognitive impairment, and weak grip strength, which have been associated with poorer inhaler technique.[5,33,34,40] Age, sex and duration of prior pMDI experience did not significantly predict the risk of inhaler technique error and is consistent with published studies and systematic reviews.[15,17,34]

Prior inhaler technique trainer was associated with a variable reduction in risk of errors dependent on the profession of the trainer, the best appearing to be a pharmacist (aOR 0.02, 95% CI 0.01–0.26) followed by a doctor (aOR 0.08, 95% CI 0.01–0.57). This is consistent with previous studies demonstrating the effectiveness of training interventions for sustained improvement in inhaler use.[21,41] Inhaler training conducted by doctors was associated with a reduced risk of inhaler errors and has been demonstrated to be a significant predictor of flawless inhaler technique.[23,29] Sadly, the majority of doctors do not check inhaler technique when inhaler therapy is prescribed, believing instead that this important intervention will be performed elsewhere within the healthcare system.[42,43] In this study, training by a pharmacist was associated with the greatest reduction in the risk for inhaler errors and is consistent with studies demonstrating high levels of effectiveness in pharmacist-driven inhaler training interventions.[44–46] The most appropriate and effective person to provide inhaler technique training is challenging to

designate in low-resource settings where the ratio of patients to doctors or pharmacists are very high. Worryingly, prior inhaler training by a nurse did not reduce the risk of inhaler errors in this study (aOR 0.26, 95% CI 0.03–2.55). This has major implications for nurse-driven primary healthcare services, such as in low and middle-income countries, where the majority of patients access care from a nurse practitioner and require referral onward to a doctor only in highly selected cases. This finding likely reflects a lack of training and opportunity for nurses to learn about inhaler technique, as the success of the nurse-driven antiretroviral therapy programme in South Africa, the largest in the world, is a reassuring example that task-shifting and upskilling of primary care nurses is possible.[47] Significant training of the nursing fraternity will be required for a widespread inhaler technique intervention in a nurse-driven primary care setting.

The major novel finding of this study was that prior participation in clinical trials significantly reduced the risk of inhaler errors. Increasing clinical trial participation incrementally reduced the risk of errors. A perfect inhaler technique was observed in 25.4% of participants with no clinical trial experience and in 73.3% of participants enrolled previously in more than three clinical trials. It is explicable that participants who have previously participated in clinical trials have better inhaler technique, as clinical trials often include frequent standardised high-quality device education and training. While it is possible that the lower rate and risk of inhaler errors in participants with clinical trial experience reflects the selection bias of clinical trials, the clear graded response of the risk reduction in error rate with increasing clinical trial participation ($0, \leq 3, > 3$) is highly suggestive of a true intervention-like effect. It has also, to the best of our knowledge, never been shown that inhaler technique adequacy during clinical trial participation persists beyond the actual clinical trial period. This finding highlights a potentially unintended but advantageous result of asthma and COPD clinical trial participation. Encouraging patients to participate in clinical trials should always be considered in the interest of promoting science and access to new interventions, provided the patient is willing, but this study suggests that clinical trials may have unintended but beneficial long-term post-trial consequences. The graded association also suggests that directed interventions for inhaler technique training will likely have to be repetitive, intensive, and prolonged over the course of the patient's inhaler use, and that many of the failed inhaler intervention studies may have just been too short and not intensive enough.[48–52]

This study is one of only a few observational studies of inhaler technique in Africa[20,53] but has some limitations. Although moderately sized, and conducted in a prospective observational manner, evaluation of inhaler technique is subject to inter- and intra-rater variability. This was minimised by using a few select and highly trained lung function technologists. The association between previous clinical trial experience and inhaler adequacy may be confounded by the differential inclusion of participants with adequate technique into clinical trials. However, the majority of the trials conducted at this site did not require perfect pMDI technique as a study entry requirement as they were evaluating new dry powder devices such as the Ellipta® or Breezhaler®, subcutaneous biological therapies, or novel use of an existing dry powder device such as the Turbuhaler®. The association may, therefore, be better explained by pMDI inhaler technique being evaluated and reinforced routinely during the trial. The limited access to clinical trial participation in rural areas may limit the generalisability of our findings with regards to trial participation as a potential intervention, but the implication remains that long-term intensive patient training is required to impact on inhaler technique. A major limitation of inhaler technique studies is the lack of consensus on a definition of inadequate inhaler technique, and so-called critical and non-critical errors. We used a common six-point checklist including known critical errors demonstrated to reduce the effective dosing and impact on treatment outcome. Nonetheless, there remains a desperate need for further validation of a standardised tool to advance this field of study.

Poor inhaler technique is common and is relatively resistant to improvement as demonstrated by many failed short-term interventions to improve technique. This study found a high rate of critical inhaler technique errors in a mixed population of asthma and COPD patients; however, previous clinical trial participation significantly reduced the risk of errors. The graded reduction in the likelihood of errors, as well as error rate, with increasing trial participation, suggests that long-term intensive inhaler training and review may be required to impact on inhaler error rates. Who is best suited to deliver this training, how often, and for how long, remain unanswered questions in this field.

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Correction: Reference 53. Vanderwagen J, Smith C. Inhaler technique in patients attending an urban pulmonology practice. African Journal of Thoracic and Critical Care Medicine. 2017;23(1):5-7.

# Appendix A – HREC Approval



FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

## FHS016: Annual Progress Report / Renewal

| HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below. | | | |
|---|---|---|---|
| ☑ Approved | Annual progress report | Approved until/next renewal date | 30.09.2020 |
| ☐ Not approved | See attached comments | | |
| Signature Chairperson of the HREC | Signature Removed | Date Signed | 15/11/2019 |

| Comments to PI from the HREC |
|---|
| Please watch expiry date; Thank you |

**Principal Investigator to complete the following:**

**1. Protocol information**

| | | | |
|---|---|---|---|
| Date (when submitting this form) | 12 November 2019 | | |
| HREC REF Number | 430/2017 | Current Ethics Approval was granted until | 30 Sep 2019 |
| Protocol title | Evaluation of Inhaler Technique and Impact of Clinical Trial Participation | | |
| Protocol number (if applicable) | NA | | |
| Are there any sub-studies linked to this study? | ✓ Yes ☐ No | | |
| If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study | 468/2018 | | |
| Principal Investigator | Associate Professor Richard van Zyl-Smit | | |
| Department / Office Internal Mail Address | Lung Clinical Research Unit, UCT Lung Institute, George Street, Mowbray | | |

| | | |
|---|---|---|
| 1.1 Does this protocol receive US Federal funding? | ☐ Yes | ✓ No |



(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

| | | |
|---|---|---|
| 1.2 If the study receives US Federal Funding, does the annual report require full committee approval?<br><br>Note: Any annual approvals for **Full Committee** review MUST be submitted on the monthly HREC submission dates<br><br>(Please send electronic copy for full committee review to hrec enquiries@uct.ac.za) | ☐ Yes | ☐ No |
| **If yes in 1.2 please complete section 1.3 below for invoicing purposes** | | |
| 1.3 Annual Approval for **full committee** review | R 3450 (inclusive of vat) | |
| For invoicing purposes, please provide: | | |
| Sponsor's name | NA | |
| Contact person | | |
| Address | | |
| Telephone number | | |
| Email Address | | |

## 2. List of documentation for approval

| |
|---|
| NA |

## 3. Protocol status (tick ✓)

| | |
|---|---|
| ☐ | Open to enrolment |
| ☐ | Closed to enrolment (tick ✓) |
| ☐ | Research-related activities are ongoing |
| ☐ | Research-related activities are complete, long-term follow-up only |
| ✓ | Research-related activities are complete, data analysis only |
| ☐ | Main study is complete but sub-study research-related activities are ongoing |
| ☐ | Study is closed → Please submit a Study Closure Form (FHS010) |

## 4. Enrolment

| | |
|---|---|
| Number of participants enrolled to date | 339 |
| Number of participants enrolled, since last HREC Progress report (continuing review) | 139 |
| Additional number of participants still required | 0 |

## 5. Refusals

| | |
|---|---|
| Total number of refusals (participants invited to join the study, but refused to take part) | 0 |

## 6. Cumulative summary of participants

| | |
|---|---|
| Total number of participants who provided consent | 0 |



(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

| | |
|---|---|
| Number of participants determined to be ineligible (i.e. after screening) | 0 |
| Number of participants currently active on the study | 0 |
| Number of participants completed study (without events leading to withdrawal) | 0 |
| Number of participants withdrawn at participants' request (i.e. changed their mind) | 0 |
| Number of participants withdrawn by PI due to toxicity or adverse events | 0 |
| Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance) | 0 |
| Number of participants lost to follow-up.<br>Please comment below on reasons for loss of follow-up. | 0 |
| | |
| Number of participants no longer taking part for reasons not listed above.<br>Please provide reasons below: | 0 |
| | |

## 7. Progress of study

| Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC: |
|---|
| The data collection reviewing all inhaler technique sheets has completed, and we had presented data at the ATS congress this year. We are now in the process of writing up the manuscript – and it will be used for an MPhil project. |

## 8. Protocol violations and exceptions (tick ✓ all that apply)

| | |
|---|---|
| ✓ | No prior violations or exceptions have occurred since the original approval |
| ☐ | Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved |
| ☐ | Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review |

## 9. Amendments (tick ✓ all that apply)

| | |
|---|---|
| ✓ | No prior amendments have been made since the original approval |
| ☐ | Prior amendments have been reported since the last review and have already been approved |
| ☐ | New protocol changes/ amendments are requested as part of this continuing review (See note below) |

**Note:** If new protocol changes are being requested in this review, please complete an amendment form (FHS006).
Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.



(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

## 10. Adverse events

| 10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established. |
|---|
| NA |

| 10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)? | | |
|---|---|---|
| ☐ Yes | ☐ No | ✓ Not applicable |
| If yes, please describe: | | |
| | | |

## 11. Summary of Monitoring and Audit Activities (tick ✓)

| 11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)? | | |
|---|---|---|
| ☐ Yes | ☐ No | ✓ Not applicable |

| 11.2 Did a Data and Safety Monitoring Board publish a report? | | |
|---|---|---|
| ☐ Yes | ☐ No | ✓ Not applicable |

| 11.3 If yes, please identify the agency and attach a summary of the findings. | | | | | |
|---|---|---|---|---|---|
| Agency Name | | Report attached | ☐ Yes | ☐ No | ☐ Not applicable |
| | | DSMB report attached | ☐ Yes | ☐ No | ☐ Not applicable |

| 11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team? | |
|---|---|
| ☐ Yes | ✓ No |
| If yes, please explain: | |
| | |

## 12. Level of risk (tick ✓)

| 12.1 In light of your experience of this research, please indicate whether the level of risk to participants has: | |
|---|---|
| ☐ | Increased |
| ☐ | Decreased |
| ✓ | Shown no change |
| If there has been a change, please explain: | |



(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

| |
|---|
| |

| 12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk. |
|---|
| NA |

## 13. Statement of conflict of interest

| Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓) | |
|---|---|
| ☐ Yes | ✓ No |
| If yes, please explain and if necessary, attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013): | |
| | |

## 14. Signature

| My signature certifies that the above is complete and correct. | | | |
|---|---|---|---|
| Signature of PI | Signature Removed | Date | 13/11/19 |



(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

# Appendix B – Questionnaire and Checklist

| | |
|---|---|
| Patient Initials | PID |
| Age | __ __ years |
| Sex | □ Female<br>□ Male |
| Previous diagnosis | □ COPD<br>□ Asthma<br>□ Other: _____ |
| Did you participate in clinical trials before? | □ No<br>□ Yes<br>No. of trials _____ |
| How long have you been using pumps/inhalers? | _____ years |
| Did someone explain or demonstrate how to use the pump/inhaler? | □ No<br>□ Yes<br>If yes, who? _____ |

| **Step** | **Performed correctly?**<br>**Yes or No**<br>**If no, describe the error** |
|---|---|
| 1. Shake well | |
| 2. Exhale completely | |
| 3. Tight seal around the mouthpiece | |
| 4. Coordination between device activation and inhalation | |
| 5. Slow AND deep inhalation | *('Yes' if both components are performed correctly)* |
| 6. Breath-hold after inhalation | |

# Appendix C – Reviewer comments

Manuscript ID number:
249620

Title of paper:
The impact of clinical trial participation on inhaler technique errors in asthma and COPD patients

## Reviewer 1

### Evaluations (peer review comments for the author)

1. In general, how do you rate the degree to which the paper is easy to follow and its logical flow?
Good

2. Do the title and abstract cover the main aspects of the work?
Yes. The title could be improved. Only an association can be demonstrated, not a causal relationship
Suggestion:
The relationship between clinical trial participation and inhaler technique errors in asthma and COPD patients. An observational study.

3. If relevant are the results novel? Does the study provide an advance in the field?
No. A novel finding in this study is that previous participation in a clinical trial was associated with a reduction in the risk of making an error.
Other findings are similar to other studies.

4. Did the study gain ethical approval appropriate to the country in which the research was performed if human or animal subjects, human cell lines or human tissues were involved and is it stated in the manuscript?
Yes

Does the paper raise any ethical concerns?
No. The study was approved and conducted under the oversight of the University of Cape Town Faculty of Health Sciences Human Ethics Research Committee

5. If relevant, are the methods clear and replicable?
Yes. It would be advisable to explain in the methods why were the selected patients prescribed pMDI? It is not clear if these patients had any specific characteristics for being prescribed pMDI's instead of DPI's.

When the authors refer to patients previously included in clinical trials, it is not clear what kind of trials this is. Are the authors referring to clinical trials about inhaler use? This needs to be clarified in the Methods section. It is explained later in the discussion, but not in this section

6. If relevant, do all the results presented match the methods described?
Yes

7. If relevant, is the statistical analysis appropriate to the research question and study design?
Yes

8. If relevant, is the selection of the controls appropriate for the study design. Have attempts been made to address potential bias through analytic methods, eg., sensitivity analysis
NA

9. How do you rate how clearly and appropriately the data are presented
Good

10. If relevant, did the authors, make the underlying data available to the readers?
Yes

11. Do the conclusions correlate to the results found?

Yes

12. Are the figures and tables clear and legible?
Yes

Are images clear and free from unnecessary modification?
Yes

13. I have serious concerns about the validity of this manuscript
No

14. Does the paper use appropriate references in the correct style to promote understanding of the content?
Yes

15. Do you think that the manuscript requires its English grammar, punctuation or spelling to be corrected?
No

Evaluation
The title could be improved. Only an association can be demonstrated, not a causal relationship. Suggestion: The relationship between clinical trial participation and inhaler technique errors in asthma and COPD patients. An observational study.
Introduction
Good points: the authors state that a major limitation of interventions aimed at improving the inhaler technique is the lack of standardised definitions for critical and non-critical errors and lack of widely validated checklists for specific devices and that the threshold for clinically significant error has not been fully elucidated.
Another good point is that none of the 39 studies included in the systematic review was conducted in Africa.
Methods section
It would be advisable to explain why were the selected patients prescribed pMDI? It is not clear if these patients had any specific characteristics for being prescribed pMDI's instead of DPI's.
When the authors refer to patients previously included in clinical trials, it is not clear what kind of trials this is. Are the authors referring to clinical trials about inhaler use? This needs to be clarified in the Methods section. It is explained later in the discussion, but not in this section
Discussion:
The authors state that "The use of a spacer device may simplify inhaler use by obviating the need for coordinating device activation and the correct rate and depth of inhalation. Nevertheless, the assessment of the inhaler technique was done only in patients using pMDI's without a spacer. There is no information about the percentage of patients prescribed with a spacer in the total population of pMDI's users in the studied population.
The authors state that spacer devices are relatively large, cumbersome, and infrequently carried with patients, thereby limiting their use in practice. Nevertheless, the majority of patients with asthma or COPD would use their inhalers once or twice daily, at home. Most of them wouldn't need to carry the spacer with them, so this statement seems inconsistent.
There is a fairly good discussion of the study limitations.

## Reviewer 2

### Evaluations (peer review comments for the author)

1. In general, how do you rate the degree to which the paper is easy to follow and its logical flow?
Good

2. Do the title and abstract cover the main aspects of the work?
Yes. While the title and abstract cover the main aspects of the manuscript, I worry about the applicability of the findings to a clinical population (rather than a clinical trials population) of COPD and asthma patients. Because of tight and multiple exclusion criteria, < 10% of real world patients will qualify for a clinical drug trial (Herland K, et al. Respir Med 2005; 99: 11–19).

3. If relevant are the results novel? Does the study provide an advance in the field?
Yes. See above. Much is written about inhaler technique. These authors had the opportunity to investigate several other potentially interesting questions:
1) did duration of time since teaching affect errors
2) what constitutes a critical error and why
3) how did error rate for pMDI compare with DPI or other devices such as soft mist or nebulizers?
4) who were these "trained technologists" and how effective were they ar inhaler teaching c/w doctors, pharmacists and nurses?

4. Did the study gain ethical approval appropriate to the country in which the research was performed if human or animal subjects, human cell lines or human tissues were involved and is it stated in the manuscript?
Yes

Does the paper raise any ethical concerns?
No

5. If relevant, are the methods clear and replicable?
No. See above. Never defined "critical error"

6. If relevant, do all the results presented match the methods described?
Yes

7. If relevant, is the statistical analysis appropriate to the research question and study design?
Yes

8. If relevant, is the selection of the controls appropriate for the study design. Have attempts been made to address potential bias through analytic methods, eg., sensitivity analysis
No. Findings were not age adjusted as in comparable studies

9. How do you rate how clearly and appropriately the data are presented
Good

10. If relevant, did the authors, make the underlying data available to the readers?
NA

11. Do the conclusions correlate to the results found?
Yes

12. Are the figures and tables clear and legible?
Yes

Are images clear and free from unnecessary modification?
Yes

13. I have serious concerns about the validity of this manuscript
No

14. Does the paper use appropriate references in the correct style to promote understanding of the content?
Yes

15. Do you think that the manuscript requires its English grammar, punctuation or spelling to be corrected?
No

Evaluation
While this is well written and clear, there are several issues that quell my enthusiasm for publication:
These include:
1) this info not only is not new, nor does it expand on the published literature. These authors had ample opportunity to use their data base to provide new insights on patients' difficulties with inhaler use. As noted above, several other potentially interesting questions could be investigated:
a) did duration of time since teaching or number of times trained affect error rate
b) how did error rate for pMDI compare with DPI or other devices such as soft mist or nebulizers?
c) who were these "trained technologists" and how effective were they at inhaler teaching c/w doctors, pharmacists and nurses?
d) did errors in inhaler use affect healthcare utilization, symptoms scores (CAT, SGRQ or mMRC) or exacerbation rate in this population
2) The introduction and discussion are much too long and repetitive
3) The term "critical error" was never defined nor explained why these errors were "critical"

Minor issues:
1) line 134-135 in the intro is mentioned twice
2) line 159 in the methods section; what is a qualified clinical technologist?
3) lines 260-263 in the discussion are repetitive of previous statements
4) line 337 in the discussion "not unsurprising" is a double negative and confusing

## Reviewer 3

### Evaluations (peer review comments for the author)

1. In general, how do you rate the degree to which the paper is easy to follow and its logical flow?
Fair

2. Do the title and abstract cover the main aspects of the work?
Yes

3. If relevant are the results novel? Does the study provide an advance in the field?
No. It is very common study. It does not provide an advance in the area.

4. Did the study gain ethical approval appropriate to the country in which the research was performed if human or animal subjects, human cell lines or human tissues were involved and is it stated in the manuscript?
Yes

Does the paper raise any ethical concerns?
No

5. If relevant, are the methods clear and replicable?
Yes

6. If relevant, do all the results presented match the methods described?
Yes

7. If relevant, is the statistical analysis appropriate to the research question and study design?
Yes

8. If relevant, is the selection of the controls appropriate for the study design. Have attempts been made to address potential bias through analytic methods, eg., sensitivity analysis
Yes

9. How do you rate how clearly and appropriately the data are presented
Fair

10. If relevant, did the authors, make the underlying data available to the readers?
Yes

11. Do the conclusions correlate to the results found?
Yes

12. Are the figures and tables clear and legible?
No. The tables are difficult to follow.

Are images clear and free from unnecessary modification?
No

13. I have serious concerns about the validity of this manuscript
Yes. It is not a new finding.

14. Does the paper use appropriate references in the correct style to promote understanding of the content?
Yes

15. Do you think that the manuscript requires its English grammar, punctuation or spelling to be corrected?
No

Evaluation

This paper is a very common study. It is not novel and contributes new knowledge in the area.
The volunteers of clinical study should have better knowledge than the naive volunteers.It is generally reported for a long time that the inhaler technique will affect the drug administartion. Therefore the teaching orientation is necessary for patients who are likely to use inhaler device.

# Appendix D – Instructions to authors

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