Online Supplement

Prospective Randomized Study on Switching Triple Inhaler Therapy in COPD from Multiple Inhaler Devices to a Single Inhaler Device in a Chinese Population

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Supplementary table 1 Critical errors of the inhalers

Device	Critical error
Dry powder inhaler	
Turbuhaler	1. Did not correctly open the device
	2. Did not prime with device upright
	1. Did not seal lips around mouthpiece during inhalation
	2. Did not inhale deeply or forcefully
Breezhaler	1. Did not correctly open the device
	2. Did not place capsule in the chamber
	3. Did not close the mouthpiece
	4. Did not press button to pierce the capsule
	1. Did not seal lips around mouthpiece during inhalation
	2. Did not inhale deeply or forcefully
	3. Did not remove capsule and check for any residual powder
Ellipta	1. Did not open the device correctly
	1. Did not seal lips around mouthpiece during inhalation
	2. Did not inhale deeply or forcefully
Acuhaler	1. Did not correctly open the device
	2. Did not pull the lever fully back
	1. Did not seal lips around mouthpiece during inhalation
	2. Did not inhale deeply or forcefully
Genuair	1. Did not correctly open the device
	2. Did not hold the inhaler horizontally (with the green button facing

	upwards) for priming
	1. Did not seal lips around mouthpiece during inhalation
	2. Did not inhale deeply or forcefully
Soft mist device/Respimat	1. Did not twist the base one half-turn
	2. Did not correctly open the device
	1. Did not seal lips around mouthpiece during inhalation
	2. Did not synchronize actuation and inhalation
	3. Did not inhale deeply or forcefully
Metered dose inhaler	1. Did not correctly open the device
	2. Did not shake the inhaler well (For suspension formulations)
	3. Did not keep inhaler upright
	1. Did not seal lips around mouthpiece during inhalation
	2. Did not synchronize actuation and inhalation
	3. Did not inhale slowly and deeply

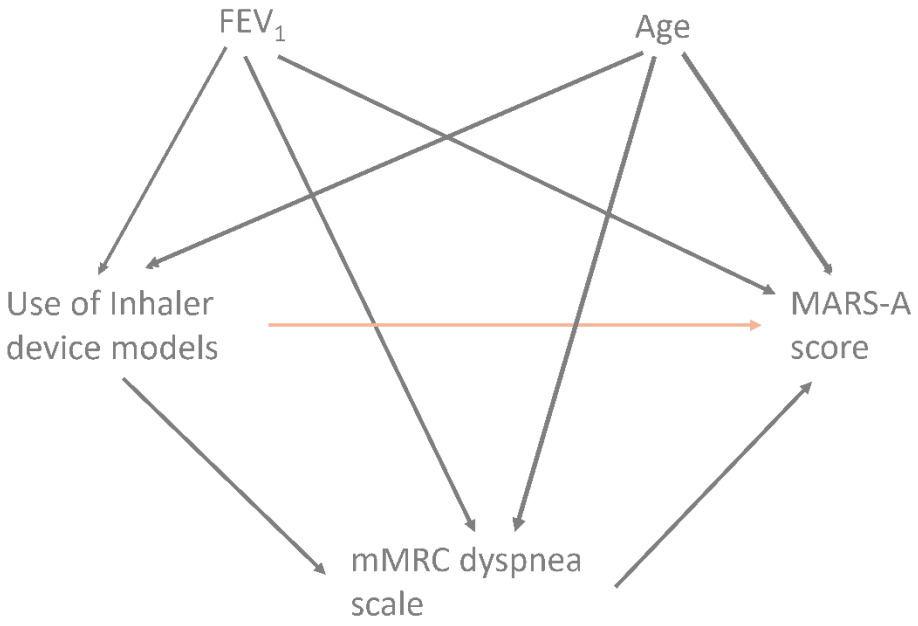
Adopted and modified from Jang, J.G., et al. Comparative study of inhaler device handling technique and risk factors for critical inhaler errors in Korean COPD patients. *Int J Chron Obstruct Pulmon Dis*. 2021; 16:1051-1059.

Supplementary table 2 Analysis results based on the hypothetical directed acyclic graph

	Odds ratio	95% CI, p-value
Average Indirect Effect	0.988	0.923 - 1.020, p= 0.462
Total Effect	0.702	0.557 - 0.878, p = 0.004
Average Direct Effect	0.711	0.564 - 0.896, p = 0.006

CI = Confidence interval

Supplementary Figure 1 Directed acyclic graph to illustrate potential confounders to be adjusted for despite randomization



Appendix 1 – Sample size calculation

Sample size can be determined by the effect size of relative hypotheses such as patient satisfaction and error rate. On the other hand, van der Palen et al. (1) considered open-label, cross-over design for comparing Ellipta® and a combination of multiple devices for Patients with COPD. van der Palen et al.(2) compared Ellipta® with other devices by interviewing both COPD and asthma patients about their error rate and other attributes of the inhaler and their preference for the Ellipta® relative to their currently-prescribed inhalers, while Svedsater et al. (3) focused in the qualitative assessment of inhalers.

The sample size can be calculated based on the results about error rate of patients from (2) for Ellipta against other devices. In particular, (1) shows that the proportions of Patients with COPD who made any error are about 20% and 50% for using Ellipta® and other device after reading the patient information leaflet respectively. The Fisher's Exact test can be used to compare the proportion in the two treatment groups (4). Assuming balanced design, the required sample size is given by 28 for each group to achieve the descried statistical power at least 80% under 95% significance level.

For other key responses, such as symptom control, the effective sizes of related statistical hypothesis would be smaller and hence lead to a larger required sample size. Moreover, some key responses, such as satisfaction and compliance in patients, would only be in ordinal scale and subject to the questionnaire design. From (3), about 75% of Patients with COPD would prefer Ellipta®. Using the approximated sample size of Wilcoxon signed-rank test (28), we have the required sample size is given by

$$n \approx \frac{(1.645 + \ 0.841)^2}{3\left(\frac{3}{4} - \frac{1}{2}\right)^2} \approx 33$$

Nevertheless, other non-parametric methods, such as Wilcoxon rank sum test, would be implemented in this study, which typically require a larger sample size. Overall, we suggest a sample size of 35 in each group for potential remedy such as randomization test and dropout.

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