

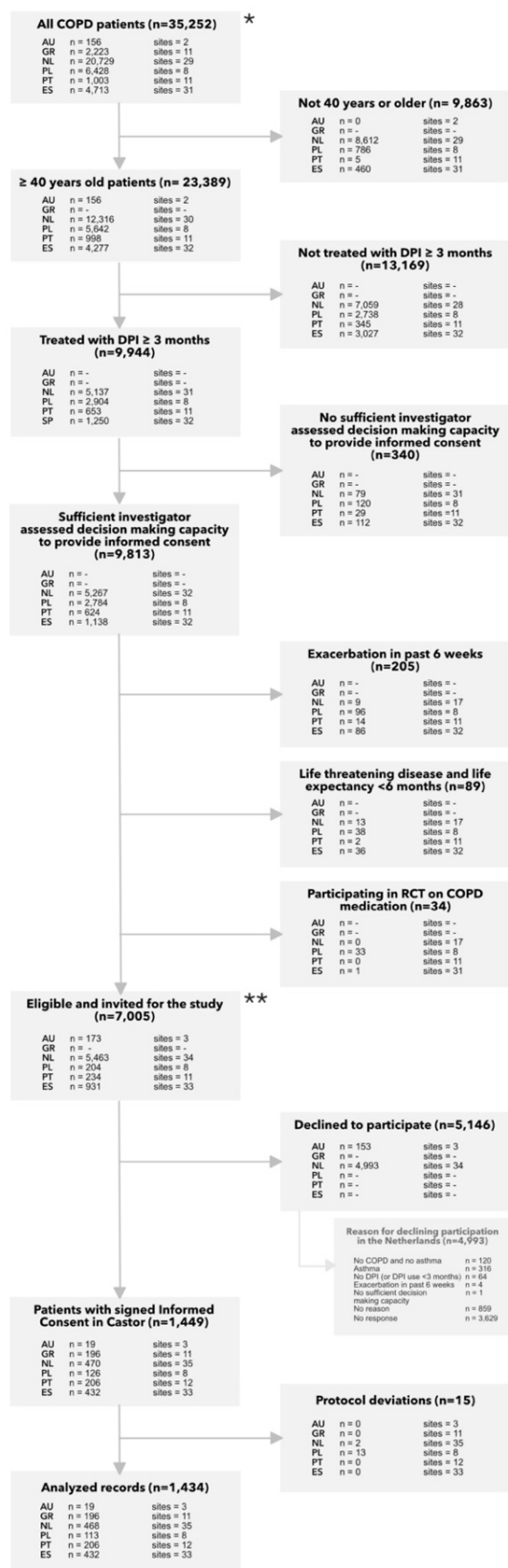
Supplementary Information

Supplementary Figure 1: Description of the study steps of the PIFotal study¹



(1) Participants were invited for clinical examination. (2) Eligibility was verified. (3) Participants provided written informed consent. (4-6) typical PIF – maximal PIF – maximal PIF at low resistance was assessed. (7) Participants filled out questionnaires to assess health status, number of exacerbations, self-reported medication adherence, medication use, and demographic and clinical covariates. (8) Participants inhaled their usual medication, which was video recorded for offline assessment by two trained researchers based on device-specific checklists. (9) Participants received tailored inhalation instructions based on the inhalation errors they made. (10) The clinical assessment was finished.

Supplementary Figure 2. Flowchart of study population selection.



* The data provided by the community pharmacies from Spain are estimations. The data from Greece are also estimations and were calculated before the COVID-19 pandemic. Three sites in Portugal reported relatively low numbers of COPD patients as the sites are specialized care units.

** Not all eligible patients in Spain, Portugal and Poland were invited to participate due to time constraints.

*** These records were archived because the measurements deviated from the study protocol.

Supplementary Table 1. Overview of Dry Powder Inhalers included in the study, the assessment priority for this study and an overview of Peak Inspiratory Flow minimal required / optimal for effective inhalation.

Inhaler type	Assessment priority	Internal device resistance	Minimal PIF required (L/min)	Optimal PIF (L/min)
Ellipta [®]	1	Medium Low	30	60 ^{19,20}
Turbuhaler [®]	2	Medium	30	60 ^{19–21}
Breezhaler [®]	3	Low	50	50 ^{19,20}
Zonda [®]	4	High	20	39*
Genuair [®]	5	Medium	40	45 ^{19,20}
Novolizer [®]	6	Medium	35	50 ^{19,20}
Spiromax [®]	7	Medium	40	40 ^{19,20}
Diskus [®]	8	Medium Low	30	60 ^{19–22}
Handihaler [®]	9	High	20	30 ^{19,20}
Nexthaler [®]	10	Medium High	35	35 ^{19,20}
Cyclohaler [®]	11	Low	40	65 ¹⁹
Easyhaler [®]	12	Medium High	30	30 ^{19,20}
Forspiro [®]	13	Medium	30	60 ^{19,20}
Elpenhaler [®]	14	Medium Low	30	60**
Clickhaler [®]	15	Medium	15	15 ²³

¹⁹Ghosh, S., Pleasants, R. A., Ohar, J. A., Donohue, J. F. & Drummond, M. B. Prevalence and factors associated with suboptimal peak inspiratory flow rates in COPD. *Int. J. COPD* 14, 585–595 (2019).

²⁰van der Palen, J. Peak inspiratory flow through Diskus and Turbuhaler, measured by means of a peak inspiratory flow meter (In-Check DIAL[®]). *Respir. Med.* (2003) doi:10.1053/rmed.2003.1289.

²¹Clark, A. R., Weers, J. G. & Dhand, R. The Confusing World of Dry Powder Inhalers: It Is All About Inspiratory Pressures, Not Inspiratory Flow Rates. *J. Aerosol Med. Pulm. Drug Deliv.* 33, 1–11 (2020).

²²Virchow, J. C., Weuthen, T., Harmer, Q. J. & Jones, S. Identifying the features of an easy-to-use and intuitive dry powder inhaler for asthma and chronic obstructive pulmonary disease therapy: Results from a 28-day device handling study, and an airflow resistance study. *Expert Opin. Drug Deliv.* (2014) doi:10.1517/17425247.2014.949236.

²³Newhouse MT, Nantel NP, Chambers CB, Pratt B, Parry-Billings M. Clickhaler (a novel dry powder inhaler) provides similar bronchodilation to pressurized metered-dose inhaler, even at low flow rates. *Chest.* 115(4), 952–6 (1999).

*Correspondence with manufacturer TEVA, Nov 18 2020.

**Correspondence with Paul Hagedoorn, Head of Inhalation Research Laboratory, RUG.

Supplementary Table 2. Inhalation technique errors

Inhalation step category*	Error designation
Preparation of the device incorrect	Preparation
No removal of the protective cap	Remove protective cap
Patient did not sit up/stand straight, or head was not tilted such that chin was slightly upwards	Sit up/stand straight & tilt head
Patient did not hold the inhaler in the correct position during preparation	Hold inhaler in correct position during preparation
Patient did not hold inhaler in the correct position during the inhalation	Hold inhaler in correct position during inhalation
Patient did not breathe out to empty lungs before inhalation	Breathe out completely before inhalation
Patient did not seal teeth and lips around the mouthpiece	Teeth and lips sealed around mouthpiece
Patient's mouth is not empty.	Empty mouth before inhalation
Patient did not inhale either strong and deep, or calm and deep (device-specific)	Breathe in
No breath-hold following the inhalation manoeuvre (or holds breath <6 seconds)	Hold breath
Patient did not breathe out calmly after inhalation	Breathe out calmly after inhalation
Patient did not rinse mouth briefly with water.	Rinse mouth

*Adjusted from LAN. Netherlands Lung Alliance (www.inhalatorgebruik.nl)

Supplementary Table 3. Overview of confounder candidates for the different associations

All models:

Variable		Total (N=1434)
Country of residence	Australia, n (%)	19 (1.3)
	Spain, n (%)	432 (30.1)
	Greece, n (%)	196 (13.7)
	The Netherlands, n (%)	468 (32.6)
	Poland, n (%)	113 (7.9)
	Portugal, n (%)	206 (14.4)
Age	Mean (SD)	69.2 (9.3)
Sex	Female, n (%)	718 (50.1)
	Male, n (%)	716 (49.9)
Body Mass Index	Mean (SD)	27.8 (5.3)
Smoking status	Current, n (%)	436 (30.4)
	Former, n (%)	824 (57.5)
	Never, n (%)	174 (12.1)
Educational level	Primary, n (%)	436 (30.4)
	Secondary, n (%)	301 (21.0)
	Post-secondary vocational, n (%)	368 (25.7)
	University, n (%)	327 (22.8)
Medication class in device	LABA, n (%)	112 (7.8)
	LAMA, n (%)	385 (26.8)
	LABA/LAMA, n (%)	357 (24.9)
	LABA/LAMA/ICS, n (%)	63 (4.4)
	ICS, n (%)	9 (0.6)
	ICS/LABA, n (%)	506 (35.3)

	Short-acting, n (%)	2 (0.1)
Overall COPD regimen	Triple Therapy, n (%)	331 (23.1)
	ICS + (LAMA or LABA), n (%)	419 (29.2)
	LAMA+LABA, n (%)	359 (25.0)
	LAMA or LABA or ICS mono, n (%)	325 (22.7)
SARS-COV-2 history	Negative, n (%)	1353 (95.1)
	Positive - Managed at home, n (%)	56 (3.9)
	Positive - Managed at hospital, n (%)	13 (0.9)
Lung comorbidity	n (%)	122 (8.5)
Cardiovascular comorbidity	n (%)	642 (45.0)
Depression	n (%)	288 (20.2)
Anxiety	n (%)	344 (24.1)
Diabetes mellitus	n (%)	295 (20.7)

Specific for predictor *Inhalation Quality (combination of PIF and error 'Breathe in'* (RQ2):

- Non-adherence
- All inhalation errors (except error 'Breathe in')

Specific for predictor *Deliberate non-adherence* (RQ 3):

- All inhalation errors (except error related to PIF: 'Breathe in' incorrect)

Supplementary Table 4. Inhalation effort with and without exacerbation correction on Peak Inspiratory

Flow

	After exacerbation reduction of 20% of PIFs			
Normal classification	Can and will do	Can, but will not do	Cannot do	Total
Can and will do	651 (66.0)	184 (18.6)	152 (15.4)	987 (71.1)
Can, but will not do		84 (38.5)	134 (61.5)	218 (15.7)
Cannot do			184 (100.0)	184 (13.2)
Total	651 (46.9)	268 (19.3)	470 (33.8)	1,389