Comparative efficacy of LABA/LAMA combinations versus tiotropium on exercise capacity in COPD: study protocol for a randomised, four-period crossover trial

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Abstract

Introduction

Exercise intolerance in chronic obstructive pulmonary disease (COPD) is a key determinant of prognosis and healthcare burden, driven by dynamic hyperinflation. Dual bronchodilation with long-acting muscarinic antagonists (LAMA) and long-acting β_2-agonists (LABA) improves lung mechanics and exercise capacity. However, direct head-to-head comparisons among LABA/LAMA combinations are limited and regimen-specific physiological effects are not well characterised. This study will compare three LABA/LAMA combinations with tiotropium for effects on exercise endurance, inspiratory capacity (IC) and functional residual capacity (FRC).

Methods and analysis

This is a prospective, randomised, open-label, four-period crossover trial at the Medical University of Bialystok. Each of four 28-day treatment periods—umeclidinium/vilanterol, indacaterol/glycopyrronium, tiotropium/olodaterol and tiotropium—is separated by a 7-day washout. Approximately 100 patients with COPD (GOLD II–III) will complete all periods. Primary endpoints are endurance time during constant-work-rate cycle exercise (CWRCE), static and dynamic IC, and FRC by body plethysmography and cardiopulmonary exercise testing (CPET). Secondary endpoints include ventilatory efficiency, dyspnoea (Borg CR10) and health-related quality of life (St George's Respiratory Questionnaire [SGRQ], COPD Assessment Test [CAT]; functional indices Duke Activity Status Index [DASI], Veterans Specific Activity Questionnaire [VSAQ]). Primary analyses will use linear mixed-effects models with fixed effects for treatment, period and sequence and a random intercept; non-parametric paired tests (Wilcoxon, Friedman) will be performed as sensitivity analyses. We hypothesise that pooled dual bronchodilation will increase IC, reduce FRC and prolong CWRCE endurance versus tiotropium; regimen-specific differences may reflect pharmacokinetic or device factors. Exploratory pharmacoeconomic analyses will assess cost-effectiveness across physiological phenotypes.

Ethics and dissemination

Bioethics Committee of the Medical University of Bialystok (APK.002.200.300.2022). Written informed consent will be obtained from all participants. Findings will be disseminated via peer-reviewed publications and scientific conferences and may inform physiology-based COPD management.

Trial registration

ClinicalTrials.gov: submission completed; identifier pending at the time of manuscript submission. Ethics approval reference: APK.002.200.300.2022.

What is already known on this topic

- Exercise intolerance in COPD is closely linked to prognosis and healthcare use; dynamic hyperinflation is a key mechanism limiting exertion.
- Dual long-acting bronchodilation (LABA/LAMA) generally outperforms monotherapy on lung function, symptoms and rescue use, and can increase IC and prolong CWRCE.
- Direct head-to-head comparisons among different LABA/LAMA regimens are scarce, exercise-testing protocols are often non-standardised, and regimen-specific effects on dynamic hyperinflation and endurance remain uncertain.

What this study adds

- A prospective, randomised, four-period crossover comparison of three LABA/LAMA combinations versus tiotropium using a standardised CWRCE protocol (80% peak work rate, WRpeak) with assessor blinding to treatment codes.
- Physiology-centred primary outcomes (dynamic and static IC; plethysmographic FRC) measured at trough, with ventilatory efficiency and patient-reported outcomes as secondary measures.
- A pre-specified mixed-effects analysis providing within-patient estimates of regimen-specific effects, plus exploratory phenotyping (e.g. hyperinflators vs non-hyperinflators) and pharmacoeconomic evaluations.

How this study might affect research, practice or policy

- Supports a physiology-based, treatable-traits approach to COPD by linking changes in IC/FRC to exercise endurance.
- May guide regimen selection among dual bronchodilators for symptomatic GOLD II–III outpatients and inform inhaler/device choices.
- Encourages standardisation of CWRCE as a sensitive endpoint in COPD trials and provides data to inform guideline recommendations and reimbursement discussions through comparative effectiveness and cost-effectiveness analyses.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive but preventable and treatable respiratory disorder characterised by persistent airflow limitation, chronic respiratory symptoms, and systemic effects [1,2]. An estimated 391.9 million people had COPD globally in 2019 [3], and COPD is the fourth leading cause of death, responsible for about 3.5 million deaths in 2021 [4]. Patients commonly experience reduced physical activity, difficulty performing daily tasks such as walking or climbing stairs, and impaired health-related quality of life (HRQoL) [5,6].

Exercise intolerance is a key feature of COPD and is strongly associated with poor prognosis, hospitalisations, and overall healthcare burden [7]. It reflects a reduced ability to perform physical activity due to ventilatory limitation, dynamic lung hyperinflation, and gas-exchange abnormalities, representing the combined impact of pulmonary, cardiovascular, and muscular dysfunction [8,9]. Pulmonary hyperinflation is the main physiological mechanism driving this limitation. Static hyperinflation results from loss of elastic recoil and airway closure, whereas

dynamic hyperinflation develops during exertion due to incomplete lung emptying. This leads to increased end-expiratory lung volume (EELV), reduced inspiratory capacity (IC), and heightened inspiratory effort, which together cause dyspnoea and early exercise termination [8,9].

Bronchodilators are the cornerstone of COPD pharmacotherapy. According to the GOLD 2025 report, LABA and LAMA combinations are recommended as the preferred maintenance therapy for symptomatic patients with exercise limitation or inadequate control on monotherapy [10]. LAMAs reduce cholinergic bronchomotor tone, while LABAs relax airway smooth muscle. In combination, they provide additive bronchodilation, improve small-airway emptying, and reduce both static and dynamic hyperinflation [8,10–12].

Substantial clinical evidence supports the superiority of dual bronchodilation over monotherapy. Systematic reviews and randomised controlled trials consistently demonstrate greater improvements in FEV_1, dyspnoea, HRQoL (SGRQ, CAT), and reduced rescue-medication use with LABA/LAMA therapy compared with single agents [13–15]. Dual therapy also reduces hyperinflation, increases inspiratory capacity, and prolongs endurance time during CWRCE [16,17].

However, direct head-to-head comparisons between different LABA/LAMA regimens remain limited. Most existing studies compare dual bronchodilation with monotherapy or LABA/ICS combinations, often using non-standardised exercise protocols [8,9,16–18]. Network meta-analyses confirm that while all fixed-dose LABA/LAMA combinations improve lung function and symptoms, their relative effects on dynamic hyperinflation and exercise tolerance remain uncertain [19]. These gaps highlight the need for direct comparative trials using uniform physiological endpoints.

This study addresses this evidence gap by conducting a randomised, four-period crossover trial comparing three LABA/LAMA combinations with tiotropium monotherapy under standardised exercise-testing conditions.

Objective: To determine whether dual long-acting bronchodilator therapy with LABA/LAMA combinations produces greater improvements in inspiratory capacity, reduction in lung hyperinflation, and enhanced exercise endurance compared with tiotropium monotherapy. By quantifying these physiological responses under standardised testing, this study aims to identify regimen-specific benefits that may translate into improved activity tolerance and symptom control, supporting more individualised and effective COPD management.

2. Materials and Methods

2.1 Study design and setting

This is a prospective, randomised, open-label, single-centre, four-period, four-treatment crossover trial conducted at the Second Department of Lung Diseases, Lung Cancer and Internal Diseases, Medical University of Bialystok. Each treatment period lasts 28 days and is separated by a 7-day washout.

Approximately 100 patients with moderate-to-severe COPD (GOLD II–III) will complete four 28-day treatment periods—umeclidinium/vilanterol, indacaterol/glycopyrronium, tiotropium/olodaterol, and tiotropium—in randomised sequence, each separated by a 7-day washout. Primary endpoints are endurance time during CWRCE, inspiratory capacity (static and dynamic), and FRC measured by body plethysmography and CPET. Secondary outcomes include ventilatory efficiency, dyspnoea (Borg CR10), and health-related quality of life (SGRQ, CAT). Data will be analysed using linear mixed-effects models accounting for treatment, period, and sequence effects. Outcome assessors will be blinded to treatment

allocation; study medications will be coded (A–D) until database lock. The flow of participants through screening, randomisation, and completion of the four treatment periods is presented in Figure 1**.**

2.1.1 Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of this research. For the subsequent clinical trial, we plan to pilot-test participant-facing materials with a patient advisor, co-produce a plain-language summary of the results, and present the findings to local patient groups.

2.1.2 Randomisation, allocation, and blinding

Participants will be randomised 1:1:1:1 to one of four treatment sequences generated from a balanced Williams design (four treatments × four periods; balance of first-order carry-over and period effects). The computer-generated sequence will be created by an independent statistician (reproducible seed) and held off-site. Allocation concealment will be ensured with sequentially numbered, opaque, sealed envelopes prepared by personnel not involved in enrolment; envelopes will be opened only after completion of all baseline assessments. Study medications will be dispensed by an unblinded research pharmacist using identical study codes (A–D). Participants and treating clinicians will be aware of the assigned inhaler (open-label), while outcome assessors, exercise technicians, and data analysts will remain blinded to treatment codes until database lock.

2.2 Participants

Eligible participants will be adults aged ≥40 years with a diagnosis of COPD according to the GOLD 2025 criteria. Inclusion requires a post-bronchodilator FEV_1/FVC ratio <0.70 and an

FEV_1 between 35% and 70% of predicted (GOLD II–III). All participants must have a smoking history of ≥10 pack-years and be clinically stable, with no moderate or severe exacerbations within the previous six weeks. Clinical stability is defined as the absence of acute exacerbations, respiratory infections, or medication changes in the six weeks before enrolment, and no requirement for systemic corticosteroids or antibiotics. Baseline therapy and symptom control will be verified during screening to ensure stable disease before randomisation.

Participants must have symptomatic COPD (modified Medical Research Council [mMRC] ≥2 or CAT ≥10) and be able to perform reproducible pulmonary function tests and CPET in accordance with American Thoracic Society (ATS)/American College of Chest Physicians (ACCP) and European Respiratory Society (ERS) standards [20,21].

Approximately 200 patients will be screened to achieve the target of ~100 per-protocol completers, allowing for an estimated 30% screen failure, 10% run-in failure, and 10% attrition.

The inclusion and exclusion criteria are summarised in Table 1.

Inclusion Criteria	Exclusion Criteria
Age ≥40 years	Asthma, significant interstitial lung disease, or bronchiectasis
COPD diagnosed per GOLD 2025 (post-bronchodilator FEV_1/FVC <0.70)	≥2 moderate or ≥1 severe COPD exacerbation in the past 12 months

FEV_1 35–70% predicted (GOLD stage II–III)	Active malignancy or unstable cardiovascular disease (e.g. recent myocardial infarction <6 months, uncontrolled arrhythmia, critical aortic stenosis)
Smoking history ≥10 pack-years	Use of inhaled corticosteroids (ICS), theophylline, roflumilast, long-term oxygen therapy (LTOT), or pulmonary rehabilitation within the past 3 months
Clinically stable (no exacerbation within 6 weeks before enrolment)	Contraindications to CPET (per ATS/ERS guidelines)
Symptomatic (mMRC ≥2 or CAT ≥10)	
Able to perform reproducible lung function and CPET	

Table 1. Inclusion and exclusion criteria.

2.3 Interventions and comparator

Participants will receive, once daily and in a randomised sequence, four 28-day treatment periods, each separated by a 7-day washout to prevent pharmacological carry-over:

- umeclidinium/vilanterol (Anoro Ellipta®),
- indacaterol/glycopyrronium (Ultibro Breezhaler®),
- tiotropium/olodaterol (Spiolto Respimat®),
- comparator: tiotropium (Spiriva Respimat®).

Only short-acting β_2-agonist (SABA) rescue medication is permitted, following predefined withholding rules. Inhaler technique is demonstrated and verified at the start of each period using a standardised checklist.

The 7-day interval ensures pharmacological clearance consistent with effective/terminal half-lives and prior crossover bronchodilator studies: tiotropium (receptor-level ≈35 h; terminal 5–6 days), indacaterol (40–56 h), glycopyrronium (33–53 h), and umeclidinium/vilanterol (19–21 h) [22–25].

2.4 Outcomes

The study evaluates primary, secondary, and exploratory outcomes reflecting physiological, functional, and patient-reported responses.

Primary outcomes

1. Endurance time during CWRCE (from onset of loaded pedalling to task failure);
2. Dynamic IC during CPET at rest, isotime, and end-exercise;
3. Static IC by whole-body plethysmography;
4. FRC by plethysmography.

Secondary outcomes

- Exercise physiology: VO_2peak, VCO_2, respiratory exchange ratio (RER), and ventilatory equivalents (VE/VO_2, VE/VCO_2), including nadir VE/VCO_2.
- Lung volumes and diffusion: TLC, RV, DLCO.
- Symptoms and patient-reported outcomes: Borg CR10 (dyspnoea, leg effort), SGRQ, CAT, functional capacity (DASI, VSAQ).

Exploratory outcomes

- Physiological phenotyping (e.g. hyperinflators vs non-hyperinflators; ventilatory inefficiency patterns).
- Post hoc pharmacoeconomic analysis: total treatment cost (PLN), incremental cost-effectiveness ratio (ICER), threshold net price per regimen, stratified by physiological phenotype.

A detailed summary of all outcomes, measurement methods, and units is provided in Table 2.

Category	Endpoint	Measurement Method / Tool	Unit / Assessment
Primary	Endurance time	Constant-work-rate cycle exercise (CWRCE)	Seconds (s)
	Dynamic inspiratory capacity (IC)	Cardiopulmonary exercise test (CPET) – rest, isotime, end-exercise	Litres (L)
	Static inspiratory capacity (IC)	Whole-body plethysmography	Litres (L)
	Functional residual capacity (FRC)	Whole-body plethysmography	Litres (L)
Secondary	VO_2peak, VCO_2, RER	CPET with metabolic cart	$mL \cdot kg^{-1} \cdot min^{-1}$; ratio
	Ventilatory equivalents (VE/VO_2, VE/VCO_2), nadir VE/VCO_2	CPET analysis software	Unitless ratios

	Total lung capacity (TLC), residual volume (RV), diffusing capacity (DLCO)	Plethysmography, single-breath DLCO	Litres; mL/min/mmHg
	Dyspnoea and leg effort	Borg CR10 scale	0–10 score
	Health-related quality of life	SGRQ, CAT questionnaires	Composite score
	Functional capacity	DASI, VSAQ questionnaires	Score
Exploratory	Physiological phenotypes (hyperinflators vs non-hyperinflators)	Derived from IC and FRC responses during CPET and plethysmography	Classification
	Pharmacoeconomic outcomes (cost, ICER, threshold net price)	Health-economic analysis (post-hoc)	PLN; ratio

Table 2. Summary of study endpoints and corresponding measurement methods.

2.5 Study procedures and assessments

Screening and baseline

Eligibility, consent, demographics; blood pressure and anthropometrics (height, weight, BMI); SGRQ, CAT, mMRC, BODE index (body mass index, airflow obstruction, dyspnoea, and exercise capacity). Lung function: spirometry with bronchodilator reversibility, body plethysmography, single-breath diffusing capacity for carbon monoxide (DLCO), and multiple-breath washout (MBW) with lung clearance index (LCI). Exercise capacity: incremental CPET to determine WRpeak and six minute walk test (6MWT). Imaging: chest

radiograph CXR and transthoracic echocardiography. Laboratory tests: CBC with differential, hsCRP, troponin, NT-proBNP, arterial blood gases, electrolytes, creatinine, and thyroid function (TSH, fT3, fT4).

End-of-period assessments

Blood pressure, anthropometrics; SGRQ, CAT, mMRC, DASI, VSAQ, BODE; spirometry; plethysmography (TLC, RV, FRC, IC); DLCO; MBW/LCI; CWRCE with Borg scoring; laboratory tests as at baseline. CXR if clinically indicated. Adverse events and SABA use are recorded throughout.

Testing conditions and withholding.

Inter-period washout 7 days (no LABA/LAMA, ICS, theophylline, roflumilast, or LTOT; SABA allowed). Before each test: withhold SABA ≥8 h, LABA 24 h, LAMA 48 h; avoid caffeine and nicotine for 12 h; alcohol and strenuous exercise for 24 h; large meals within 3 h before CPET. Assessments occur at similar times of day; study medication is administered after testing (trough measurements).

Exercise testing methodology

Incremental CPET on an electronically braked ergometer (COSMED Quark) with an individualised ramp protocol targeting 8–12 min to symptom-limited peak; cadence 60 rpm; continuous 12-lead ECG and SpO_2 monitoring; daily two-point gas/flow calibration, per ATS/ACCP and ERS guidance [20,21]. For CWRCE, work rate is 80% WRpeak; cadence 60 rpm; endurance time from onset of loaded pedalling to task failure. IC is measured at rest, isotime, and end-exercise. Termination criteria follow ATS/ERS safety standards. All lung-function and CPET assessments will be performed by respiratory physiologists/technicians trained to ATS/ERS standards under consultant supervision. Equipment calibration,

verification, and quality-control procedures follow ATS/ACCP (2003) and ERS (2007/2019) guidance, with daily two-point gas and flow checks recorded in logs.

The schedule of study visits, procedures, and assessments for each 28-day period is summarised in Table 3.

Study Day	Procedures	Assessments
Day –7 → 0	Screening / baseline	Eligibility, consent, demographics, full lung function (spirometry, plethysmography, DLCO), CPET, CXR, ECG, laboratory tests
Day 1	Period start	Randomised treatment (A–D), inhaler training, baseline symptom questionnaires (CAT, SGRQ, mMRC)
Days 2–27	Treatment phase	Daily study drug; adverse event monitoring; rescue SABA log
Day 28	End-of-period visit	Spirometry, plethysmography (TLC, RV, FRC, IC), CPET/CWRCE, Borg scale, blood gases, laboratory tests
Days 29–35	Washout	No long-acting bronchodilators; SABA rescue allowed; monitor for stability
Repeat × 4 periods		Each participant completes all regimens in crossover sequence

Table 3. Study schedule and procedures per 28-day treatment period.

2.6 Sample size and statistical analysis

Sample size. Based on the primary endpoint (CWRCE endurance), assuming MCID 60–90 s and within-subject SD 180–200 s from prior studies, ~56 completers provide 90% power (two-sided $\alpha=0.05$) in a four-period crossover to detect a clinically relevant difference. Allowing ~20% attrition across periods, the target is ~100 randomised participants to ensure ≥56 evaluable completers [26–29].

Analysis populations. Modified intention-to-treat (mITT): all randomised participants with ≥1 post-baseline efficacy assessment. Per-protocol (PP): participants completing all four periods without major deviations. Primary analyses will use mITT; PP will be sensitivity.

Primary analysis. The main contrast is the pooled mean effect of the three LABA/LAMA regimens versus tiotropium. A linear mixed-effects model will include fixed effects for treatment, period, and sequence, and a random intercept for subject. Pairwise treatment contrasts will be explored with Holm adjustment. Results will be presented as estimated mean differences with 95% CIs.

Secondary/exploratory analyses. Continuous outcomes will be analysed with analogous mixed-effects models. Where assumptions are questionable, non-parametric paired methods (e.g. Wilcoxon signed-rank; Friedman for omnibus across four treatments) will be used as sensitivity analyses, with Hodges–Lehmann estimates and 95% CIs. Pre-specified subgroups: GOLD stage (II vs III), smoking status, baseline dyspnoea (mMRC 2 vs ≥3).

Missing data and multiplicity. Mixed models assume missing-at-random; multiple-imputation sensitivity will be performed if needed. No multiplicity adjustment for the single primary comparison; secondary/exploratory tests will control family-wise error using Holm’s procedure.

Period/sequence/carry-over. Descriptive summaries by period and sequence will be presented. Potential carry-over will be explored (including an explicit term and early-period-only sensitivity), acknowledging the 7-day washout and drug pharmacology.

Software. Analyses will be conducted in R and Python with reproducible code and independent statistical review prior to database lock. No interim analyses, formal stopping rules, or early efficacy/futility boundaries are planned for this single-centre crossover study.

2.7 Safety considerations

All adverse events (AEs), serious AEs, COPD exacerbations, and exercise-related incidents will be prospectively recorded and classified according to ICH-GCP and ATS/ACCP (2003) and ERS (2007) CPET guidance [20,21,30]. Emergency equipment and appropriately trained medical personnel will be available during all testing. Predefined CPET termination criteria and stopping rules will be strictly applied.

2.8 Ethics and dissemination

The study protocol was approved by the Bioethics Committee of the Medical University of Bialystok (APK.002.200.300.2022). All participants will provide written informed consent. The trial will be conducted in accordance with the Declaration of Helsinki [31], ICH-GCP, and relevant national regulations. Results will be disseminated via peer-reviewed open-access publications and scientific meetings; plain-language summaries will be offered to participants on request. Confidentiality and data protection will be maintained throughout.

3. Discussion

Exercise intolerance is tightly linked to prognosis, hospitalisations, and healthcare costs in COPD [5,6,32]. Endurance time (ET) during constant-load exercise directly reflects the integrated physiological response to bronchodilation and represents the most sensitive and reproducible indicator of improved exercise tolerance in COPD clinical trials [26–29]. CWRCE is validated and sensitive for detecting pharmacological effects on submaximal exercise performance [26–29].

Dual bronchodilation reduces static and dynamic hyperinflation, lowers operational lung volumes, and increases inspiratory capacity (IC) [7,16,17]. Mechanistic studies have demonstrated improvements in small-airway function and reductions in air trapping under load, translating into enhanced ventilatory efficiency and exercise endurance [33–35]. While dual therapy generally outperforms monotherapy, regimen-specific differences in pharmacokinetics, receptor kinetics, particle deposition, and inhaler performance may influence the magnitude of clinical benefit [35,36]. Physiological and comparative data also reveal variability in the effects on dynamic hyperinflation and ventilatory responses during exercise among different treatments [19,37]. Therefore, direct head-to-head comparisons using standardised protocols with washout periods are necessary.

If our hypotheses are confirmed, the findings will support a more comprehensive, physiology-based approach to managing COPD that incorporates exercise and lung volume assessments in addition to spirometry. The crossover study design strengthens causal inference by reducing between-subject variability and enabling direct within-patient comparisons of treatment effects.

Improvements in inspiratory capacity and reductions in functional residual capacity are not only physiological markers but also correlate with important clinical outcomes [7,8,29,32,34]. These improvements lead to real-world benefits such as reduced exertional dyspnoea, improved ventilatory efficiency, and the ability to sustain daily physical activities, including walking or climbing stairs. Enhanced lung emptying decreases the work of breathing, contributing to better exercise tolerance and overall quality of life [7,8,34,38]. Clinically, recognising treatable traits like marked hyperinflation reversibility enables tailored therapy; such COPD phenotyping can direct dual bronchodilation toward phenotypes with the highest probability of response.

4. Limitations

First, the 28-day intervention periods capture short-term pharmacodynamic responses rather than long-term physiological adaptations, such as changes in activity behaviour, peripheral conditioning, or adherence variability.

Second, the open-label design may bias subjective outcomes; this is mitigated through assessor blinding, standardised procedural scripts, and prioritisation of objective physiological endpoints [39].

Third, crossover trials carry inherent risks of period, sequence, and carry-over effects if washout or pre-test withholding is incomplete; to address this, a 7-day washout, rigorous withholding protocols, prespecified analytical tests, and sensitivity analyses are implemented [41,42].

Fourth, measurement variability and learning effects may confound endurance-time outcomes. To control for this, pedal cadence is fixed at 60 rpm, isotime analyses are used, and all equipment is calibrated in line with ATS/ACCP and ERS CPET standards. Inspiratory-

capacity manoeuvres are coached and aligned to rest, isotime, and end-exercise phases [20,40].

Fifth, inhaler technique and medication adherence materially influence effectiveness; critical device-use errors remain common despite structured education and repeated checks [43].

Sixth, acute confounders—including short-acting β_2-agonists (SABA), caffeine, nicotine, and strenuous physical activity—may modify responses despite pre-test withholding and rescheduling.

Seventh, external validity is limited by the single-centre setting and the inclusion of GOLD II–III outpatients without long-term oxygen therapy (LTOT) or inhaled corticosteroids (ICS); extrapolation to very severe or frequently exacerbating phenotypes is uncertain [10].

Finally, missing data and early withdrawal may introduce bias if data are not missing at random; mixed-effects modelling with multiple-imputation sensitivity analyses will be applied [41,42].

5. Conclusions

This randomised, four-period crossover trial will directly compare three LABA/LAMA regimens with tiotropium, using robust physiological endpoints including dynamic and static inspiratory capacity (IC), functional residual capacity (FRC), and a standardised CWRCE protocol. The findings are expected to clarify regimen-specific differences, inform clinical guideline development and support more individualised, physiology-based therapy for COPD.

6. AI-assisted writing and data analysis tools

In accordance with COPE guidance on the responsible use of generative artificial intelligence, several AI-based tools were used solely for technical assistance (language improvement, paraphrasing, preliminary data handling and bibliographic organisation). All scientific content, interpretation and conclusions were developed, reviewed and approved by the authors. No AI system was used to generate original scientific ideas, to formulate hypotheses or to perform autonomous statistical inference. All authors confirm that the final text, data interpretation and statistical analyses were human-verified and scientifically accountable, in line with the COPE position statement: “AI tools may assist in manuscript preparation but cannot be listed as authors or assume responsibility for the content.”

Authors’ contributions

Study concept and protocol plan were developed by ŁM and RMM. All authors contributed to drafting and revising the main body of the manuscript and approved the final version. Supervision of the work was provided by RMM, AH and ŁM.

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Role of the funding source and disclaimer

The Medical University of Białystok (grant no. 2023/24/25) had no role in the study design; in data collection, management, analysis, or interpretation; in writing the manuscript; or in the decision to submit for publication. The funder will not have access to interim data and will

not influence reporting. The views expressed are those of the authors and not necessarily those of the Medical University of Białystok. An application has also been submitted to the Polish Medical Research Agency; no funding from this agency had been received at the time of submission.

Competing interests statement

The authors declare no competing interests.

Data availability statement

No data are available for this protocol article. Upon trial completion and publication of the primary results, de-identified individual participant data, the SAP, and analysis code (R/Python) will be made available on reasonable request to the corresponding author and via the institutional repository, subject to a data-sharing agreement and ethics approval. The full protocol and the prespecified Statistical Analysis Plan (SAP) will be deposited on the trial registry

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Figure legends:

Figure 1 – Participant flow through screening, randomisation, treatment periods, and study completion.