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The effect of PIFR-based Optimized Inhalation Therapy in Patients Recovering From AECOPD: protocol of a prospective, multi-center, superiority, randomized controlled trial

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Abstract:

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is a global respiratory disease. Acute exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) is a major cause of disease progression and death, and causes huge medical expenditures. Effective inhalation therapy is important during the AE recovery period. However, the invalid inhalation using DPI due to the unrecovered inspiratory flow rate after AECOPD results in increased risk of treatment failure and early recurrence. We envisage that choosing the right inhaler based on peak inhalation flow rate (PIFR) and training inhaler techniques will contribute to reducing early relapse rates. Therefore, a prospective multicenter randomized trial is designed to verify this hypothesis.

Methods and analysis: The study is aimed at determining whether the optimized inhalation therapy based on PIFR can reduce the rate of treatment failure in patients recovering from AECOPD. In the study, 416 patients with AECOPD whose exacerbated symptoms are relieved by 5-7 days of standard therapy will be recruited and be randomized into PIFR group, which receives inhaler depending on their PIFR and is trained to use the inhaler appropriately, and control group, which receives inhaler depending on the judgment of a respiratory physician, at a 1:1 ratio. The primary outcome of the study is 30-day treatment failure rate. Other endpoints include PIFR, the error rate of inhalation device use, satisfaction with inhalation devices, 30-day mortality, 90-day mortality, symptoms and life quality of patients and COPD-related treatment costs.

Ethics and dissemination: This trial has been registered in the Ethics Committee of Zhongshan Hospital of Fudan University (B2019-142).

Trial registration: This trial has been registered in Clinical Trails (NCT04000958).

Strengths and limitations of this study:

The trial is a prospective, multi-center, single-blind, superiority, randomized study, maximizing the impact of confounders.

We will be able to verify the clinical significance of including PIFR in the discharge protocol as well as guide COPD inhaler choices and inhaler technique training through the study.

Keywords: chronic obstructive pulmonary disease, acute exacerbation of chronic obstructive pulmonary disease, peak inhalation flow rate

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a global respiratory disease that severely threatens human health. COPD has a significant socioeconomic burden, and is currently the fourth leading cause of death in the world but is projected to be the 3rd leading cause of death by 2020[1]. In China, COPD ranked among the top three leading causes of death and the direct medical cost of COPD ranged from 72 to 3,565 USD per capita per year, accounting for 33.33% to 118.09% of local average annual income[2]. The overall prevalence of spirometry-defined COPD was 8.6% among the general Chinese population aged 20 years or older[3]. Acute exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) is a major cause of disease progression and death, and causes huge medical expenditures[4].

Inhalation therapy is the core pharmaceutical therapy for COPD including inhaled corticosteroid (ICS), both short- and long-acting beta2-agonists and, more recently, muscarinic antagonists[5]. Existing common devices include pressure metered dose inhaler (pMDI), dry powder inhalers (DPIs), soft mist inhalers (SMIs), and nebulizers[6]. Common inhaler errors include insufficient inspiratory effort, no breath–hold (or holds breath for less than 3s), etc (Table 2)[7 8]. Inhaler errors are associated with poor disease outcomes (exacerbations) and greater health-economic burden[9]. MDIs require complex coordination techniques with a slow inhalation by the patient to achieve a clinically effective dose. DPIs decrease the complexity of administration, but effective medication delivery is dependent on the force of the patient's inspiratory effort to overcome internal resistance[10]. Several *in vitro* studies have demonstrated the inhalation flow rate dependency of DPI. Specifically, the results showed that both the amount of medication delivered to the patient and the effective aerodynamic particle size of the medication were adversely affected when the testing peak inhalation flow rate (PIFR) was less than 60 liters/min[11], which may result in ineffective inhalation of medications using a DPI. Several studies suggest that patients with insufficient PIFR in stable phase of COPD may have an adverse effect on prognosis using inappropriate inhaler[12 13]. Other risk factors for early AECOPD recurrence include age grades, GOLD

grades, AE frequency in the previous year, pleural effusion, use of accessory respiratory muscles, noninvasive mechanical ventilation, controlled oxygen therapy and length of hospital stay, while inhaled long-acting β-2-agonists (LABA) and inhaled corticosteroids (ICS) are protection factors[14]. An investigation suggests that one of five stable outpatients more than 60 years of age with severe COPD did not reach the recommended PIFR for DPI devices[15]. Some small sample studies has shown that a significant proportion of patients are not suitable for DPI during AECOPD because of their insufficient PIFR[13 16]. However, there is no study about the PIFR status and the impact of inhaler choices on prognosis for patients recovering from AECOPD.

Thirty-day readmission rates after hospitalization for AECOPD are approximately 15.8%-20%[17 18]. Readmissions are costly and adversely affect quality of life. But little is known about PIFRs of the patients recovering from AECOPD as well as the clinical impact of the inhaler (DPI or pMDI) selected for the patients. Generally, discharge protocols for patients recovering from COPD do not include an assessment of PIFR or patients' ability to use their inhaler device when they recuperate after discharge. Clinicians typically select the inhaler they use during the stable phase of COPD for patients who will be discharged. We hypothesize PIFR of patients recovering from AECOPD have not returned to the level at the stable phase of COPD, which may result in poor COPD management and treatment failure (including recurrence resulting in an emergency visit, admission, or need for intensified medication) for the patients due to the ineffective inhalation of medications.

The aim of this study is to determine whether the optimized inhalation therapy based PIFR can reduce the rate of treatment failure in patients recovering from AECOPD. Errors in inhaler use and quality of life are also to be evaluated.

Methods and analysis

Trial design

This is a prospective, multi-center, single-blind, superiority, randomized study of

patients hospitalized for a COPD exacerbation. This study is designed to determine whether PIFR based inhaler choice and training can reduce the rate of treatment failure in patients recovering from AECOPD. The primary study outcome is 30-day treatment failure rate. Treatment failure means AECOPD recurrence resulting in an emergency visit, admission, or need for intensified medication. Other endpoints include symptoms and life quality of patients the error rate of inhalation device use, satisfaction with inhalation devices, PIFR, 30-day mortality, 90-day mortality, and COPD-related treatment costs.

This trial has been registered in the Ethics Committee of Zhongshan Hospital of Fudan University (B2019-142) and Clinical Trails (NCT04000958).

Inclusion criteria

All patients meeting AECOPD diagnostic criteria who hospitalized for COPD related reasons will be followed. The definition of COPD follows the GOLD definition and the definition of AECOPD follows Expert Consensus on Acute Exacerbation of Chronic Obstructive Pulmonary Disease in the People's republic of China[4]. AECOPD is defined as sudden worsening of respiratory symptoms that require additional treatment (typical manifestations include dyspnea, aggravated cough, increased sputum volume, and/or sputum purulence) and is beyond normal day-to-day variations, leading to a change in medications[4 19]. The subjects will be enrolled and randomized into the study group if all of the following criteria are met: (1) 40–80 years old; (2) patients with AECOPD whose acute respiratory symptoms have been controlled and met discharge criteria after 5-7 day-standard AECOPD treatment including atomized or inhaled bronchodilator plus oral or intravenous glucocorticoid (prednisone equivalent dose 40-50mg) or Pulmicort 2mg atomization twice daily plus broad-spectrum antibiotics; (3) patients with moderate and above COPD with a recorded spirometry measured in the stable disease status, ie, post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) <70% and FEV1% predicted value <80%; (4) patients have signed an informed consent form.

Discharge criteria is as follows: (1) physician are confident that the patient can manage successfully at home; (2) long-acting bronchodilators, either beta 2-agonists and/or anticholinergics with or without inhaled corticosteroids can be used, and inhaled short-acting β2-agonist therapy is required no more frequently than every 4 hours; (3) the patient, if previously ambulatory, is able to walk across the room; (4) the patient is able to eat and sleep without frequent awakening due to dyspnea; (5) the patient has been clinically stable for 12–24 hours; (6) arterial blood gases have been stable for 12–24 hours[4].

Exclusion criteria

Exclusion criteria include:(1) patients who is already using home nebulization therapy because of the severity of the disease; (2) patients with bronchial asthma, pulmonary interstitial fibrosis, bronchiectasis, pulmonary embolism and other lung diseases; or hypertension, heart disease, chronic liver and kidney disease, diabetes, chronic gastrointestinal diseases, malignant tumors, critically ill; (3)patient's mental state cannot match the observation or suffer from cognitive impairment; (4) patient's peak inspiratory flow rates (PIFR) is less than 20L/min.

Sample size

The sample size was calculated using PASS 15.0 (Power Analysis and Sample Size Software) to ensure the study power. Several studies have found that 30-47% patients hospitalized for AECOPD had a PIFR < 60 liters/minute prior to discharge[5 10]. For the control group, 30-day treatment failure rates after hospitalization for AECOPD are approximately 20% according to the literature and our retrospective cohort study [17, 18]. For PIFR group, 30-day treatment failure rates are 10% based on our preliminary research. The participants will be divided into PIFR group and control group in a 1:1 ratio. To test the superiority hypothesis with 80% power with 2-side alpha at 0.05 level, 197 subjects will be enrolled for each group. Considering 5% dropout rate, the minimum number of the participants in the study was determined to be 208 per group.

Study outline

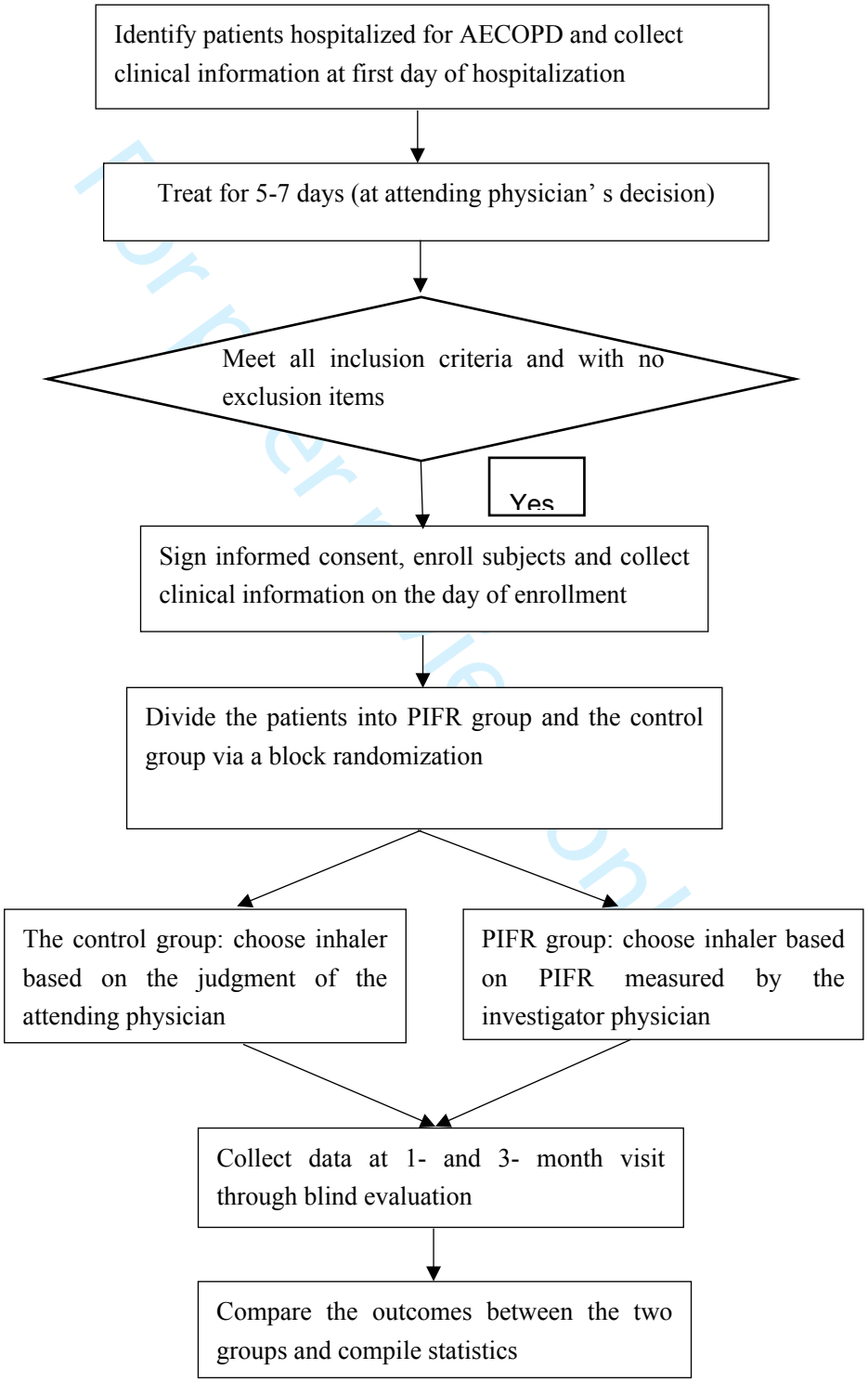
The flow chart of the study design is shown in Figure 1. The study will recruit 416 patients with AECOPD whose exacerbated symptoms are relieved by 5-7 days of standard therapy. After enrollment, the participants are divided into PIFR group and control group at a 1:1 ratio according to a random envelope method. All the patients will be given inhaled corticosteroid (ICS)/long-acting β agonist (LABA) (budesonide/ formoterol - Symbicort turbuhaler® (AstraZeneca AB) 160/4.5 μg bid or Beclometasone/ Formoterol Foster® (Chiesi Farmaceutici S.p.A.) pressure pMDI 100/6 μg 2 puff bid). For symptomatic patients before acute exacerbation, Spiriva handihaler® 18μg qd or Spiriva respimat® (Boehringer IngelheimPharma GmbH & Co.KG) 2.5μg qd will be prescribed in combination with ICS/LABA.

For PIFR group, PIFR is measured by InCheck DIAL® (Clement Clarke International Ltd, Harlow, UK and Alliance Tech Medical). The InCheck DIAL® is designed to simulate the "internal resistance" of common inhaler devices, and measure inspiratory flow. These measurements enable the healthcare professional to encourage patients to modify their inspiratory technique (by inhaling with more, or less effort), in order to achieve a flow rate consistent with clinical efficacy. The colored 'flow' icons show the clinically effective flow ranges for each different inhaler device. The InCheck DIAL® is accurate to +/− 10% or 10 L/min, whichever is greater, and is a low-range inspiratory flow meter (15 to 120 L/min) that has a selectable resistance from high to low, shown by the colored 'flow' icons calibrated to enable the measurement of airflow as if the patient was using certain different inhalers. Moreover, the InCheck DIAL® is an inhalation airflow training meter that can help educate and assess patients who use inhaler devices.

If PIFR is less than 60L/min , the patient will be given pMDI with spacer. If PIFR value is over 60 L/min, the patient will be given dry powder inhaler (DPI). Furthermore, InCheck DIAL® will be used for an inhalation device training. The control group will be given DPI or pMDI with spacer according to the judgment of a respiratory physician.

Both groups will be taught to use the device after the prescription, and then be reminded to use medication via a WeChat public account.

Figure 1. The flow chart of the study



Study step

The participants will be followed up for 3 months and 3 visits will be performed at baseline(symptoms of AECOPD are relieved by 5-7 days of standard therapy), 1 and 3 months after enrollment.

Demographics, clinical characteristics, evaluation of respiratory symptoms and quality of life in the stable phase, PIFR, routine laboratory tests for AE patients(e.g. blood routine, C-reactive protein, liver and kidney function, blood electrolytes, B-type natriuretic peptide, D-dimer), chest X-ray or CT and echocardiography or electrocardiogram in the stable phase will be collected at baseline. Demographics includes age, gender, age, height, weight, ethnicity, occupation(number of years of work), marital status, location, etc. Clinical characteristics includes past disease history, history of drug sensitivity, history of vaccination, family disease history, current medical history, comorbidities, medications, etc. Respiratory symptoms will be assessed with the modified Medical Research Council (mMRC) dyspnea scale and the COPD Assessment Test (CAT) score for the patients. Quality of life will be assessed with St.George's Respiratory Questionnaire(SGRQ) scale. All baseline data will be collected by attending physician on the day of enrollment.

CAT score, mMRC score, SGRQ score, PIFR, spirometry, the error rate of inhalation device use, satisfaction with inhalation devices, condition of AE and COPD medicine treatment will be collected at both 1- and 3-month visit. The data to be collected for each visit is shown in Table 1.

Table 1. Data collected at each visit

	V0	V1	V2	V3
	Hospitalization±1 day	At the time of discharge (meet discharge standards)	1 month after discharge	3 month after discharge
Basic Information	√			

Information of COPD at stable phase	√			
Blood routine	√	√		
Liver and kidney function	√	√		
Electrolyte	√	√		
C-reactive protein	√	√		
procalcitonin	√	√		
brain natriuretic peptide	√	√		
D-dimer 、 Fibrinogen	√	√		
cardiac troponin T	√	√		
CAT score	√	√	√	√
mMRC	√	√	√	√
SGRQ		√	√	√
Drug for COPD	Stable phase	AE phase	Stable phase	Stable phase
PIFR		PIFR√	PIFR√	PIFR√
Prognosis			√	√
Pulmonary function		√	√	√
Echocardiography at stable phase				
CT at stable phase				
CT at AE phase				
Error of inhaler use			√	√
Satisfaction with the inhaler			√	√
Daily cost of COPD related treatment			√	√

Endpoints

The primary endpoint is 30-day treatment failure rate of AECOPD. Treatment failure means AECOPD recurrence resulting in an emergency visit, admission, or need for intensified medication.

Secondary endpoints include PIFR, the error rate of inhalation device use, satisfaction with inhalation devices, 30-day mortality, 90-day mortality, symptoms and

life quality of patients and COPD-related treatment costs.

Patients' satisfaction with inhalation devices will be assessed by the following items. If the patient meets any of the following, the result will be unsatisfactory: (1)the patient has forgotten to use the inhaler; (2)the patient has forgotten to use the inhaler in the last two weeks; (3)the patient has reduced the frequency of using inhaler without medical advice; (4)the patient has forgotten to bring an inhaler when traveling or leaving home; (5)the patient has quitted the inhaler without medical advice when feeling his condition improved; (6)he patient has felt it difficult to comply with the COPD treatment plan; (7)the patient has felt it difficult to use the inhaler.

The symptoms of patients are evaluated by the COPD assessment test (CAT) and the modified Medical Research Council (mMRC) dyspnea scale. The patients' quality of life are evaluated by St.George's Respiratory Questionnaire(SGRQ).

PIFR is measured by InCheck DIAL® (Clement Clarke International Ltd, Harlow, UK and Alliance Tech Medical).

The error rate of inhalation device use is described in Table 2[7 8].

Table 2. The error rate of inhalation device use

Turbuhaler (7 critical errors)	**Diskus/Accuhaler (3 critical errors)**	**pMDI (7 critical errors)**
Cover is not removed/ Cover is not covered properly.	-	Cover is not removed/ Cover is not covered properly.
Patient reduces dose due to shaking or tilting during preparation.	-	NA
Patient forces insufficiently when inhaling.	Patient forces insufficiently when inhaling.	-
Patient does not tilt head to make the chin slightly upturned.	-	Patient does not tilt head to make the chin slightly upturned.
Patient does not exhale to empty the lung before inhaling.	Patient does not exhale to empty the lung before inhaling.	Patient does not exhale to empty the lung before inhaling.
-	-	Patient exhales into the

		device before inhaling.
Patient does not seal the mouthpiece with the lips.	-	Patient does not seal the mouthpiece with the lips.
NA	NA	Releasing drug is out of sync with inhaling.
Patient does not hold breath(or hold breath less than 3s).	Patient does not hold breath(or hold breath less than 3s).	Patient does not hold breath(or hold breath less than 3s).

Randomization

Enrollment and randomization are performed at Zhongshan Hospital of Fudan University. After enrollment, patients will be assigned into two groups via a random envelope method in a 1:1 ratio to the PIFR group and control group by random number table method generated by SPSS.

Blinding

The study adopts blind evaluation. The investigator will enroll participants and assign them into two groups. All data at baseline, 1- and 3-month visit will be collected by attending physician, who will not be informed of which group the patient has been assigned. In addition, patients will not know the group they belong to. Blind evaluation maximizes the objectivity and reliability of the study.

Statistical analysis

1. Statistical analysis datasets

- Modified intent-to-treat set (MITTS)

Subjects that have undergone randomization and interventions, and carry out primary endpoints evaluation.

- Safety set (SS)

Subjects that are randomized, undergo the intervention, and with safety evaluation

data.

2. Statistical analysis methods

Statistical analyses were performed using SPSS 22.0. Continuous variables are described as mean (SD) or median (p25,p75) and count variables are described as frequency and percentage. All tests were both sided and statistical analysis, 0.05 was set as the P value for significance. For discrete variables including 30-day treatment failure rate, the error rate of inhalation device use, satisfaction with inhalation devices, 30-day mortality and 90-day mortality, a chi-squared ($\chi 2$) test, Fisher's exact test or CMH $\chi 2$ test will be used. For continuous variable including PIFR, CAT score, mMRC score, SGRQ score and COPD-related treatment costs, Student's t-tests or Mann-Whitney test will be used.

Patient and public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination of our research. The results will be available to the public if necessary.

Discussion

Drug delivery by DPI depends on the inbuilt resistance of the inhaler and the PIFR generated by the patient. PIFR generally depends on an individual's effort as well as the respiratory muscle force, which may be decreased in patients with COPD due to airway stenosis, lung hyperinflation, hypoxemia, and muscle wasting. DPI are breath-actuated that require the individual to create turbulent forces to disaggregate the powder into respirable particles which can reach the lower respiratory tract. Patients with a sufficient PIFR (PIFR > 60 L/min) are able to release the powder and deaggregate the drug resulting in lung deposition.

Sharma and colleagues have found that 31.7% of patients at discharge following hospitalization for an exacerbation of COPD had PIFR less than 60 L/min[3]. Patients with a PIFR less than 60 L/min have been considered not be able to inhale medications

using a DPI effectively into the lower respiratory tract according to the literature, while a PIFR less than 30 liters/minute is insufficient[20 21]. However, most clinicians in china prescribe DPI to the patients recovering from AECOPD routinely due to the lack of the availability of long-acting bronchodilators with pMDI without measuring their PIFR. Inappropriate inhaler selection may result in treatment failure of AECOPD. Before our study, it remains unclear whether treatment failure rate is related to PIFR-based inhaler description. A suitable inspiratory flow rate helps to improve the treatment efficacy. In addition to inhaler selection, PIFR group also receive inhaler training to help patients master the correct inhalation method.

Our research has proposed to measure PIFR of patients recovering from AECOPD by InCheck DIAL® and guide COPD inhaler choices and inhaler technique training. The aim of this study is to determine whether the optimized inhalation therapy based on PIFR measured against the simulated resistance can reduce the rate of treatment failure in patients recovering from AECOPD. Therefore, we plan to verify the clinical significance of including PIFR in the discharge protocol through comparing the difference in 30-day treatment failure rates and other endpoints between PIFR group and the control group.

Conclusion

The study investigates the effect of optimized inhalation therapy based on PIFR measured against the simulated resistance in patients recovering from AECOPD on reducing 30-day treatment failure rates. Other outcomes including symptoms and life quality of patients, the error rate of inhalation device use, satisfaction with inhalation devices, 30-day mortality, 90-day mortality, PIFR and COPD-related treatment costs will also be evaluated. We expect to reduce treatment failure rate of AECOPD and promote COPD management through guiding COPD treatment choices based on PIFR.

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Contributors: JLH and JZ designed the protocol, drafted and critically revised the manuscript. WZ planned the Statistical analysis methods. All authors revised and approved the manuscript.

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Figure 1. The flow chart of the study

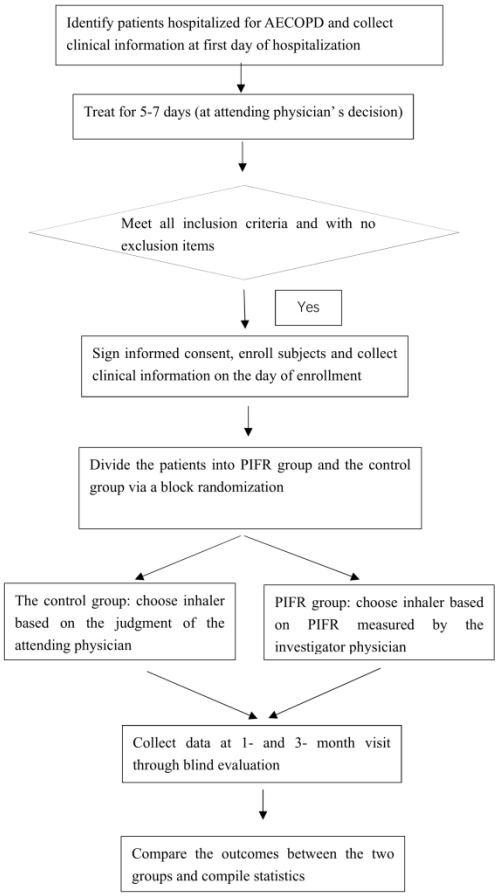

Figure 1

209x297mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The effect of PIFR-based Optimized Inhalation Therapy in Patients Recovering From Acute exacerbation of Chronic Obstructive Pulmonary Disease: protocol of a prospective, multi-center, superiority, randomized controlled trial

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The effect of PIFR-based Optimized Inhalation Therapy in Patients Recovering From Acute exacerbation of Chronic Obstructive Pulmonary Disease: protocol of a prospective, multi-center, superiority, randomized controlled trial

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Abstract:

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is a global respiratory disease. Acute exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) is a major cause of disease progression and death, and causes huge medical expenditures. Effective inhalation therapy is important during the AE recovery period. However, the invalid inhalation using DPI due to the unrecovered inspiratory flow rate after AECOPD results in increased risk of treatment failure and early recurrence. We envisage that choosing the right inhaler based on peak inhalation flow rate (PIFR) and training inhaler techniques will contribute to reducing early relapse rates. Therefore, a prospective multicenter randomized trial is designed to verify this hypothesis.

Methods and analysis: The study is aimed at determining whether the optimized inhalation therapy based on PIFR can reduce the rate of treatment failure in patients recovering from AECOPD. In the study, 416 patients with AECOPD whose exacerbated symptoms are relieved by 5-7 days of standard therapy will be recruited and be randomized into PIFR group, which receives inhaler depending on their PIFR and is trained to use the inhaler appropriately, and control group, which receives inhaler depending on the judgment of a respiratory physician, at a 1:1 ratio. The primary outcome of the study is 30-day treatment failure rate. Other endpoints include PIFR, the error rate of inhalation device use, satisfaction with inhalation devices, 30-day mortality, 90-day mortality, symptoms and life quality of patients and COPD-related treatment costs.

Ethics and dissemination: This trial has been registered in the Ethics Committee of Zhongshan Hospital of Fudan University (B2019-142). Participants will be screened and recruited from hospitalized patients by physicians. No public recruitment documents will be used for participants enrollment.

Trial registration: This trial has been registered in Clinical Trials (NCT04000958).

Strengths and limitations of this study:

1. To our knowledge, this is the first multicenter, randomized trial designed to study the efficacy of PIFR-based inhaler prescription in preventing short-term re-execration in patients recovering from severe acute exacerbation of COPD.

2. InCheck DIAL® is used to measure PIFR and objectively evaluate the capacity of using dry powder inhalers.

3. The inhaler technique will be trained as well to achieve optimal inhalation therapy.

4. Inhalers studied in this trial include turbuhaler, handihaler, respimat and pMDI.

5.The limitation of the study is the single-blind study design, which would yield bias, although blind evaluation is adopted to minimize the bias.

Keywords: chronic obstructive pulmonary disease, acute exacerbation of chronic obstructive pulmonary disease, peak inhalation flow rate

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a global respiratory disease that severely threatens human health. COPD has a significant socioeconomic burden, and is currently the fourth leading cause of death in the world but is projected to be the 3rd leading cause of death by 2020[1]. In China, COPD ranked among the top three leading causes of death and the direct medical cost of COPD ranged from 72 to 3,565 USD per capita per year, accounting for 33.33% to 118.09% of local average annual income[2]. The overall prevalence of spirometry-defined COPD was 8.6% among the general Chinese population aged 20 years or older[3]. Acute exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) is a major cause of disease progression and death, and causes huge medical expenditures[4].

Inhalation therapy is the core pharmaceutical therapy for COPD including inhaled corticosteroid (ICS), both short- and long-acting beta2-agonists and, more recently, muscarinic antagonists[5]. Existing common devices include pressure metered dose inhaler (pMDI), dry powder inhalers (DPIs), soft mist inhalers (SMIs), and nebulizers[6]. Common inhaler errors include insufficient inspiratory effort, no breath–hold (or holds breath for less than 3s), etc[7 8]. Inhaler errors are associated with poor disease outcomes (exacerbations) and greater health-economic burden[9]. MDIs require complex coordination techniques with a slow inhalation by the patient to achieve a clinically effective dose. DPIs decrease the complexity of administration, but effective medication delivery is dependent on the force of the patient's inspiratory effort to

overcome internal resistance[10]. Several *in vitro* studies have demonstrated the inhalation flow rate dependency of DPI. Specifically, the results showed that both the amount of medication delivered to the patient and the effective aerodynamic particle size of the medication were adversely affected when the testing peak inhalation flow rate (PIFR) was less than 60 liters/min (measured at no resistance)[11], which may result in ineffective inhalation of medications using a DPI. Several studies suggest that patients with insufficient PIFR in stable phase of COPD may have an adverse effect on prognosis using inappropriate inhaler[12 13]. Moreover, it should be noted that expiratory flow rate (such as FEV_1) is not correlated linearly with inspiratory flow parameters, and it do not predict PIFR. Other risk factors for early AECOPD recurrence include age grades, GOLD grades, AE frequency in the previous year, pleural effusion, use of accessory respiratory muscles, noninvasive mechanical ventilation, controlled oxygen therapy and length of hospital stay, while inhaled long-acting β-2-agonists (LABA) and inhaled corticosteroids (ICS) are protection factors[14]. An investigation suggests that one of five stable outpatients more than 60 years of age with severe COPD did not reach the recommended PIFR for DPI devices[15]. Some small sample studies has shown that a significant proportion of patients are not suitable for DPI during AECOPD because of their insufficient PIFR[13 16]. However, there is no study about the PIFR status and the impact of inhaler choices on prognosis for patients recovering from AECOPD.

Thirty-day readmission rates after hospitalization for AECOPD are approximately 15.8%-20%[17 18]. Readmissions are costly and adversely affect quality of life. But little is known about PIFRs of the patients recovering from AECOPD as well as the clinical impact of the inhaler (DPI or pMDI) selected for the patients. Generally, discharge protocols for patients recovering from AECOPD do not include an assessment of PIFR or patients' ability to use their inhaler device when they recuperate after discharge. Clinicians typically select the inhaler they use during the stable phase of COPD for patients who will be discharged. Furthermore, although some evidence has suggested that incorrect use of inhalers is associated with poor prognosis, studies on the effect of training patients on the use of inhalers to reduce relapses are still scarce. We hypothesize PIFR of patients recovering from AECOPD have not returned to the level

at the stable phase of COPD as well as untrained patients have higher rate of inhaler errors. It may result in suboptimal COPD management and treatment failure (including recurrence resulting in an emergency visit, admission, or need for intensified medication) for the patients due to the ineffective inhalation of medications.

The aim of this study is to determine whether the optimized inhalation therapy based PIFR can reduce the rate of treatment failure in patients recovering from AECOPD. Errors in inhaler use and quality of life are also to be evaluated.

Methods and analysis

Trial design

This is a prospective, multi-center, single-blind, superiority, randomized study of patients hospitalized for a COPD exacerbation. This study is designed to determine whether PIFR based inhaler choice and training can reduce the rate of treatment failure in patients recovering from AECOPD. The primary study outcome is 30-day treatment failure rate. Treatment failure means AECOPD recurrence resulting in an emergency visit, admission, or need for intensified medication. Other endpoints include symptoms and life quality of patients the error rate of inhalation device use, satisfaction with inhalation devices, PIFR, 30-day mortality, 90-day mortality, and COPD-related treatment costs. The enrollment, conduct and data analysis of the trail are performed at Zhongshan Hospital of Fudan University, Shanghai Jing 'an District Central Hospital, Shanghai Qingpu District Central Hospital and North Branch of Shanghai Ninth People's Hospital in China. The study is expected to last for 2 years. Recruitment of participants has started since November 2019.

This trial has been registered in the Ethics Committee of Zhongshan Hospital of Fudan University (B2019-142) and Clinical Trails (NCT04000958).

Inclusion criteria

All patients meeting AECOPD diagnostic criteria who hospitalized for COPD related

reasons will be followed. The definition of COPD follows the GOLD definition and the definition of AECOPD follows Expert Consensus on Acute Exacerbation of Chronic Obstructive Pulmonary Disease in the People's republic of China[4]. AECOPD is defined as sudden worsening of respiratory symptoms that require additional treatment (typical manifestations include dyspnea, aggravated cough, increased sputum volume, and/or sputum purulence) and is beyond normal day-to-day variations, leading to a change in medications[4 19]. The subjects will be enrolled and randomized into the study group if all of the following criteria are met: (1) 40–80 years old; (2) patients with AECOPD whose acute respiratory symptoms have been controlled and met discharge criteria after 5-7 day-standard AECOPD treatment including atomized or inhaled bronchodilator plus oral or intravenous glucocorticoid (prednisone equivalent dose 40-50mg) or Pulmicort 2mg atomization twice daily plus broad-spectrum antibiotics; (3) patients with moderate and above COPD with a recorded spirometry measured in the stable disease status, ie, post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) <70% and FEV1% predicted value <80%; (4) patients have signed an informed consent form.

Discharge criteria is as follows: (1) physician are confident that the patient can manage successfully at home; (2) long-acting bronchodilators, either beta 2-agonists and/or anticholinergics with or without inhaled corticosteroids can be used, and inhaled short-acting β2-agonist therapy is required no more frequently than every 4 hours; (3) the patient, if previously ambulatory, is able to walk across the room; (4) the patient is able to eat and sleep without frequent awakening due to dyspnea; (5) the patient has been clinically stable for 12–24 hours; (6) arterial blood gases have been stable for 12–24 hours[4].

Exclusion criteria

Exclusion criteria include:(1) patients who is already using home nebulization therapy because of the severity of the disease; (2) patients with bronchial asthma, pulmonary interstitial fibrosis, bronchiectasis, pulmonary embolism and other lung

diseases; or hypertension, heart disease, chronic liver and kidney disease, diabetes, chronic gastrointestinal diseases, malignant tumors, critically ill; (3)patient's mental state cannot match the observation or suffer from cognitive impairment; (4) patient's peak inspiratory flow rates (PIFR) is less than 20L/min.

Sample size

The sample size was calculated using PASS 15.0 (Power Analysis and Sample Size Software) to ensure the study power. Several studies have found that 30-47% patients hospitalized for AECOPD had a PIFR < 60 liters/minute prior to discharge[5 10]. For the control group, 30-day treatment failure rates after hospitalization for AECOPD are approximately 20% according to the literature and our retrospective cohort study [17, 18]. For PIFR group, 30-day treatment failure rates are 10% based on our preliminary research. The participants will be divided into PIFR group and control group in a 1:1 ratio. To test the superiority hypothesis with 80% power with 2-side alpha at 0.05 level, 197 subjects will be enrolled for each group. Considering 5% dropout rate, the minimum number of the participants in the study was determined to be 208 per group.

Study outline

The flow chart of the study design is shown in Figure 1. The study will recruit 416 patients with AECOPD whose exacerbated symptoms are relieved by 5-7 days of standard therapy. After enrollment, the participants are divided into PIFR group and control group at a 1:1 ratio according to a random envelope method. All the patients will be given inhaled corticosteroid (ICS)/long-acting β agonist (LABA) (budesonide/ formoterol - Symbicort turbuhaler® (AstraZeneca AB) 160/4.5 μg bid or Beclometasone/ Formoterol Foster® (Chiesi Farmaceutici S.p.A.) pressure pMDI 100/6 μg 2 puff bid). For symptomatic patients (mMRC ≥ 2, CAT ≥ 10) before acute exacerbation, Spiriva handihaler® 18μg qd or Spiriva respimat® (Boehringer IngelheimPharma GmbH & Co.KG) 2.5μg qd will be prescribed in combination with

ICS/LABA.

For PIFR group, PIFR is measured by InCheck DIAL® (Clement Clarke International Ltd, Harlow, UK and Alliance Tech Medical). The InCheck DIAL® is designed to simulate the "internal resistance" of common inhaler devices, and measure inspiratory flow. These measurements enable the healthcare professional to encourage patients to modify their inspiratory technique (by inhaling with more, or less effort), in order to achieve a flow rate consistent with clinical efficacy. The colored 'flow' icons show the clinically effective flow ranges for each different inhaler device. The InCheck DIAL® is accurate to +/− 10% or 10 L/min, whichever is greater, and is a low-range inspiratory flow meter (15 to 120 L/min) that has a selectable resistance from high to low, shown by the colored 'flow' icons calibrated to enable the measurement of airflow as if the patient was using certain different inhalers. In this study, we set the resistance of the InCheck DIAL® to zero when measuring PIFR. Before measuring. We will first train patients to use the InCheck DIAL® correctly. After patients are able to reach their maximum value of PIFR steadily, we will measure the PIFR 3 times and take the average as a result.

Moreover, the InCheck DIAL® is an inhalation airflow training meter that can help educate and assess patients who use inhaler devices. When training the patient, we will set the corresponding resistance for the InCheck DIAL® according to the inhaler that the patient is prescribed. We will also explain to the patient the proper operation of the inhaler and demonstrate some common mistakes.

If PIFR is less than 60L/min (measured without a resistance), the patient will be given pMDI with spacer. If PIFR value is over 60 L/min (measured without a resistance), the patient will be given dry powder inhaler (DPI). Furthermore, InCheck DIAL® will be used for an inhalation device training. The control group will be given DPI or pMDI with spacer according to the judgment of a respiratory physician.

Both groups will be taught to use the device after the prescription, and then be reminded to use medication via a WeChat public account.

Study step

The participants will be followed up for 3 months and 3 visits will be performed at baseline(symptoms of AECOPD are relieved by 5-7 days of standard therapy), 1 and 3 months after enrollment.

Demographics, clinical characteristics, evaluation of respiratory symptoms and quality of life in the stable phase, PIFR, routine laboratory tests for AE patients(e.g. blood routine, C-reactive protein, liver and kidney function, blood electrolytes, B-type natriuretic peptide, D-dimer), chest X-ray or CT and echocardiography or electrocardiogram in the stable phase will be collected at baseline. Demographics includes age, gender, age, height, weight, ethnicity, occupation(number of years of work), marital status, location, etc. Clinical characteristics includes past disease history, history of drug sensitivity, history of vaccination, family disease history, current medical history, comorbidities, medications, etc. Respiratory symptoms will be assessed with the modified Medical Research Council (mMRC) dyspnea scale and the COPD Assessment Test (CAT) score for the patients. Quality of life will be assessed with St.George's Respiratory Questionnaire(SGRQ) scale. All baseline data will be collected by attending physician on the day of enrollment.

CAT score, mMRC score, SGRQ score, PIFR, spirometry, the error rate of inhalation device use, satisfaction with inhalation devices, condition of AE and COPD medicine treatment will be collected at both 1- and 3-month visit. The data to be collected for each visit is shown in Table 1.

Table 1. Data collected at each visit

	V0	V1	V2	V3
	Hospitalization±1 day	At the time of discharge (meet discharge standards)	1 month after discharge	3 month after discharge
Basic Information	√			

Information of COPD at stable phase	√			
Blood routine	√	√		
Liver and kidney function	√	√		
Electrolyte	√	√		
C-reactive protein	√	√		
procalcitonin	√	√		
brain natriuretic peptide	√	√		
D-dimer 、 Fibrinogen	√	√		
cardiac troponin T	√	√		
CAT score	√	√	√	√
mMRC	√	√	√	√
SGRQ		√	√	√
Drug for COPD	Stable phase	AE phase	Stable phase	Stable phase
PIFR		PIFR√	PIFR√	PIFR√
Prognosis			√	√
Pulmonary function		√	√	√
Echocardiography at stable phase				
CT at stable phase				
CT at AE phase				
Error of inhaler use			√	√
Satisfaction with the inhaler			√	√
Daily cost of COPD related treatment			√	√

Endpoints

The primary endpoint is 30-day treatment failure rate of AECOPD. Treatment failure means AECOPD recurrence resulting in an emergency visit, admission, or need for intensified medication.

Secondary endpoints include PIFR, the error rate of inhalation device use, satisfaction with inhalation devices, 30-day mortality, 90-day mortality, symptoms and

life quality of patients and COPD-related treatment costs.

Patient's satisfaction with inhalation devices will be assessed by FSI-10 questionnaire. The FSI-10 questionnaire is completed by patients themselves, which has been widely applied to assess patients' opinions about ease of use, portability, and usability of inhalers[20].The symptoms of patients are evaluated by the COPD assessment test (CAT) and the modified Medical Research Council (mMRC) dyspnea scale. The patients' quality of life are evaluated by St.George's Respiratory Questionnaire(SGRQ).

PIFR is measured by InCheck DIAL® (Clement Clarke International Ltd, Harlow, UK and Alliance Tech Medical).

The error rate of inhalation device use is described in Table 2[7 8].

Table 2. The error rate of inhalation device use

Turbuhaler	**Handihaler/Accuhaler**	**pMDI**	**Respimat**
Cover is not removed/ Cover is not covered properly.	Cover is not removed/ Cover is not covered properly.	Cover is not removed/ Cover is not covered properly.	Cover is not removed/ Cover is not covered properly.
Patient reduces dose due to shaking or tilting during preparation.	-	Patient dose not shake device before inhaling	The device is not installed correctly before use.
Device is not held upright.	-	Device is not held upright.	-
Patient does not twist grip at the base or twist around and then back until click is heard.	-	-	Patient dose not turn the device toward the arrow in the label until it clicks.
Patient forces insufficiently when inhaling.	Patient forces insufficiently when inhaling.	Patient dose not inhale deeply and slowly.	Patient dose not inhale deeply and slowly.
Patient does not tilt head to make the chin slightly upturned.	Patient does not hold the head in a vertical position.	Patient does not tilt head to make the chin slightly upturned.	Patient dose not point the inhaler toward the back of throat.

Patient does not exhale to empty the lung before inhaling.	Patient does not exhale to empty the lung before inhaling.	Patient does not exhale to empty the lung before inhaling.	Patient does not exhale to empty the lung before inhaling.
-	Patient does not turn the head away from device and exhale.	Patient exhales into the device before inhaling.	Patient covers the air entries while inhaling.
Patient does not seal the mouthpiece with the lips.	Patient does not put the mouthpiece in mouth, and close the lips.	Patient does not seal the mouthpiece with the lips.	Patient does not seal the mouthpiece with the lips.
NA	NA	Releasing drug is out of sync with inhaling.	Releasing drug is out of sync with inhaling.
Patient does not hold breath(or hold breath less than 3s).	Patient does not hold breath(or hold breath less than 3s).	Patient does not hold breath(or hold breath less than 3s).	Patient does not hold breath(or hold breath less than 10s).
Patient does not put the cover back and wait for 30-60 seconds for the second dose.	Patient dose not dispose of the capsule and put the cover back on the device.	Patient does not exhale and wait for 30-60 seconds before the second puff.	Patient dose not inhales twice to complete the total daily dosage.

Randomization

Enrollment and randomization are performed at Zhongshan Hospital of Fudan University. After enrollment, patients will be assigned into two groups via a random envelope method in a 1:1 ratio to the PIFR group and control group by random number table method generated by SPSS.

Blinding

The study adopts blind evaluation. The investigator will enroll participants and assign them into two groups. All data at baseline, 1- and 3-month visit will be collected by attending physician, who will not be informed of which group the patient has been assigned. In addition, patients will not know the group they belong to. Blind evaluation

maximizes the objectivity and reliability of the study.

Statistical analysis

1. Statistical analysis datasets

- Modified intent-to-treat set (MITTS)

Subjects that have undergone randomization and interventions, and carry out primary endpoints evaluation.

- Safety set (SS)

Subjects that are randomized, undergo the intervention, and with safety evaluation data.

2. Statistical analysis methods

Statistical analyses were performed using SPSS 22.0. Continuous variables are described as mean (SD) or median (p25,p75) and count variables are described as frequency and percentage. All tests were both sided and statistical analysis, 0.05 was set as the P value for significance. For discrete variables including 30-day treatment failure rate, the error rate of inhalation device use, satisfaction with inhalation devices, 30-day mortality and 90-day mortality, a chi-squared ($\chi 2$) test, Fisher's exact test or CMH $\chi 2$ test will be used. For continuous variable including PIFR, CAT score, mMRC score, SGRQ score and COPD-related treatment costs, Student's t-tests or Mann-Whitney test will be used. Subgroup analysis by exacerbation history and GOLD grades will be performed to rule out the influence of confounding factors to the certain extent.

Patient and public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination of our research. The results will be available to the public if necessary.

Ethics and dissemination

This trial has been registered in the Ethics Committee of Zhongshan Hospital of Fudan University (B2019-142). In this study, diagnosis and treatment were performed in accordance with the routine management of COPD. Neither Additional drug intervention nor invasive examination and charges are needed. Therefore, the study is relatively safe with minimal additional risks. Participants will be screened and recruited from hospitalized patients by physicians. No additional public recruitment documents will be used for participants enrollment. All participants will sign informed consent. All information of participants will be kept private and will not be provided to any company or institution.

Discussion

Drug delivery by DPI depends on the inbuilt resistance of the inhaler and the PIFR generated by the patient. PIFR generally depends on an individual's effort as well as the respiratory muscle force, which may be decreased in patients with COPD due to airway stenosis, lung hyperinflation, hypoxemia, and muscle wasting. DPI are breath-actuated that require the individual to create turbulent forces to disaggregate the powder into respirable particles which can reach the lower respiratory tract. Patients with a sufficient PIFR (PIFR > 60 L/min) are able to release the powder and deaggregate the drug resulting in lung deposition.

Sharma and colleagues have found that 31.7% of patients at discharge following hospitalization for an exacerbation of COPD had PIFR less than 60 L/min[3]. Patients with a PIFR less than 60 L/min have been considered not be able to inhale medications using a DPI effectively into the lower respiratory tract according to the literature, while a PIFR less than 30 liters/minute is insufficient[21 22]. However, most clinicians in china prescribe DPI to the patients recovering from AECOPD routinely due to the lack of the availability of long-acting bronchodilators with pMDI without measuring their PIFR. Inappropriate inhaler selection may result in treatment failure of AECOPD. Before our

study, it remains unclear whether treatment failure rate is related to PIFR-based inhaler description. A suitable inspiratory flow rate helps to improve the treatment efficacy. In addition to inhaler selection, PIFR group also receive inhaler training to help patients master the correct inhalation method.

Our research has proposed to measure PIFR of patients recovering from AECOPD by InCheck DIAL® and guide COPD inhaler choices and inhaler technique training. The aim of this study is to determine whether the optimized inhalation therapy based on PIFR measured against the simulated resistance can reduce the rate of treatment failure in patients recovering from AECOPD. Therefore, we plan to verify the clinical significance of including PIFR in the discharge protocol through comparing the difference in 30-day treatment failure rates and other endpoints between PIFR group and the control group.

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2019/07/20]

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Figure legends : Figure 1. The flowchart shows the process of patient's admission, recruitment, intervention and visits. V0, V1, V2, and V3 are all time points to collect data.

Contributors: JLH and JZ planned the study. WZ planned the Statistical analysis methods. All authors contributed to design and development of the trail (JLH, JZ, WZ, HFC, CLD, JYM and YHZ). JLH drafted the manuscript. JZ , HFC, CLD, JYM and YHZ contributed to revised the manuscript. All authors read and approved the final manuscript.

Ethics and dissemination: This trial has been registered in the Ethics Committee of Zhongshan Hospital of Fudan University (B2019-142) and Clinical Trails (NCT04000958).

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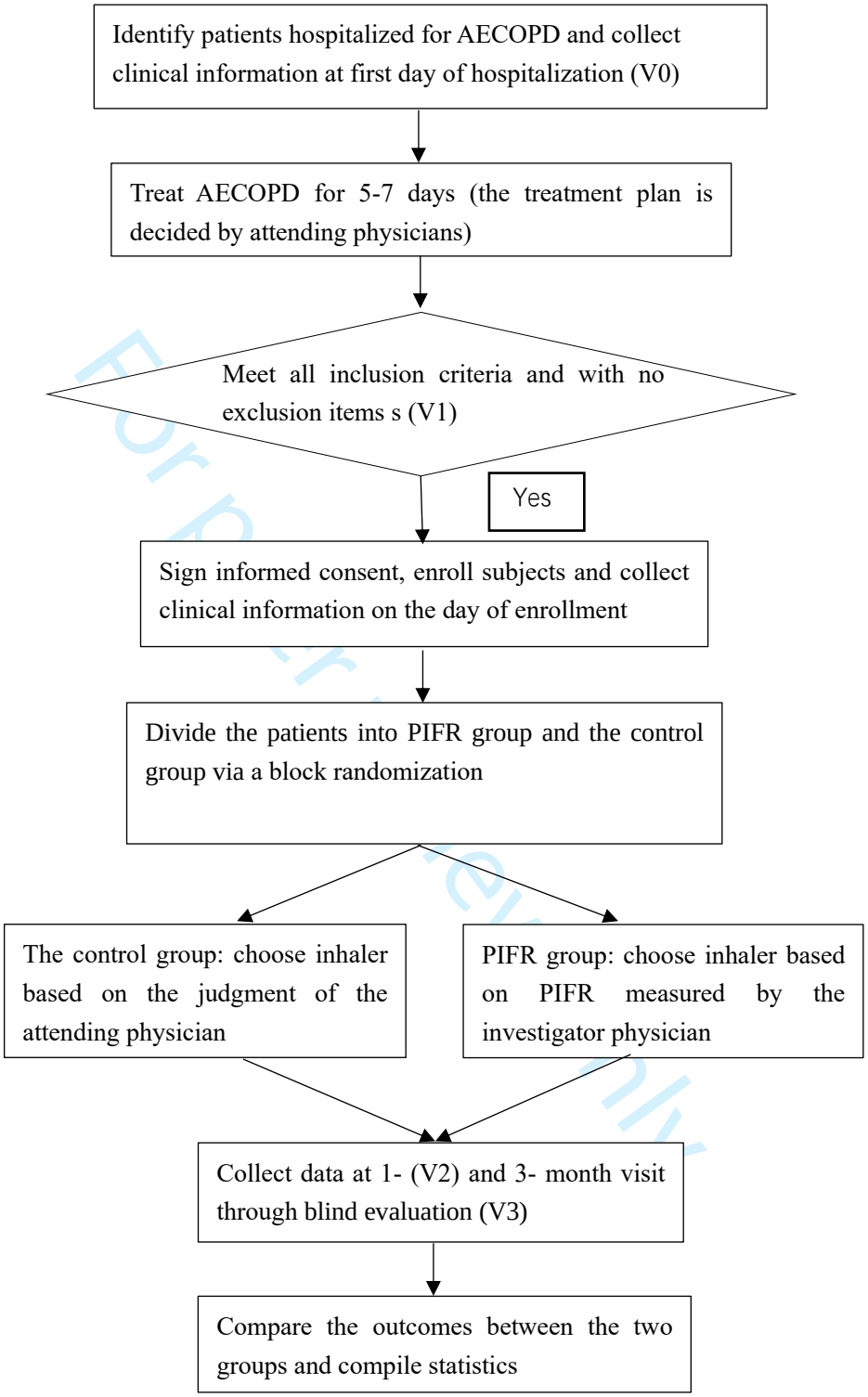
Word Count: 5024

Figure 1. The flow chart of the study



SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	N/A
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
	6b	Explanation for choice of comparators	3-5

Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7-8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-10
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	14
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9-10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	N/A
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	N/A

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The effect of PIFR-based Optimized Inhalation Therapy in Patients Recovering From Acute exacerbation of Chronic Obstructive Pulmonary Disease: protocol of a prospective, multi-center, superiority, randomized controlled trial

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Keywords:	RESPIRATORY MEDICINE (see Thoracic Medicine), Chronic airways disease < THORACIC MEDICINE, MEDICAL EDUCATION & TRAINING

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The effect of PIFR-based Optimized Inhalation Therapy in Patients Recovering From Acute exacerbation of Chronic Obstructive Pulmonary Disease: protocol of a prospective, multi-center, superiority, randomized controlled trial

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Abstract:

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is a global respiratory disease. Acute exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) is a major cause of disease progression and death, and causes huge medical expenditures. Effective inhalation therapy is important during the AE recovery period. However, the invalid inhalation using DPI due to the unrecovered inspiratory flow rate after AECOPD results in increased risk of treatment failure and early recurrence. We envisage that choosing the right inhaler based on peak inhalation flow rate (PIFR) and training inhaler techniques will contribute to reducing early relapse rates. Therefore, a prospective multicenter randomized trial is designed to verify this hypothesis.

Methods and analysis: The study is aimed at determining whether the optimized inhalation therapy based on PIFR can reduce the rate of treatment failure in patients recovering from AECOPD. In the study, 416 patients with AECOPD whose exacerbated symptoms are relieved by 5-7 days of standard therapy will be recruited and be randomized into PIFR group, which receives inhaler depending on their PIFR and is trained to use the inhaler appropriately, and control group, which receives inhaler depending on the judgment of a respiratory physician, at a 1:1 ratio. The primary outcome of the study is 30-day treatment failure rate. Other endpoints include PIFR, the error rate of inhalation device use, satisfaction with inhalation devices, 30-day mortality, 90-day mortality, symptoms and life quality of patients and COPD-related treatment costs.

Ethics and dissemination: This trial has been registered in the Ethics Committee of Zhongshan Hospital of Fudan University (B2019-142). Participants will be screened and recruited from hospitalized patients by physicians. No public recruitment documents will be used for participants enrollment. The results will be disseminated through peer-reviewed journals and conference presentations, and proliferation activities will include diverse social non-academic groups and patients.

Trial registration: This trial has been registered in Clinical Trials (NCT04000958).

Strengths and limitations of this study:

1. To our knowledge, this is the first multicenter, randomized trial designed to study the efficacy of PIFR-based inhaler prescription in preventing short-term re-execration in patients recovering from severe acute exacerbation of COPD.

2. InCheck DIAL® is used to measure PIFR and objectively evaluate the capacity of using dry powder inhalers.

3. The inhaler technique will be trained as well to achieve optimal inhalation therapy.

4. Inhalers studied in this trial include turbuhaler, handihaler, respimat and pMDI.

5.The limitation of the study is the single-blind study design, which would yield bias, although blind evaluation is adopted to minimize the bias.

Keywords: chronic obstructive pulmonary disease, acute exacerbation of chronic obstructive pulmonary disease, peak inhalation flow rate

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a global respiratory disease that severely threatens human health. COPD has a significant socioeconomic burden, and is currently the fourth leading cause of death in the world but is projected to be the 3rd leading cause of death by 2020[1]. In China, COPD ranked among the top three leading causes of death and the direct medical cost of COPD ranged from 72 to 3,565 USD per capita per year, accounting for 33.33% to 118.09% of local average annual income[2]. The overall prevalence of spirometry-defined COPD was 8.6% among the general Chinese population aged 20 years or older[3]. Acute exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) is a major cause of disease progression and death, and causes huge medical expenditures[4].

Inhalation therapy is the core pharmaceutical therapy for COPD including inhaled corticosteroid (ICS), both short- and long-acting beta2-agonists and, more recently, muscarinic antagonists[5]. Existing common devices include pressure metered dose inhaler (pMDI), dry powder inhalers (DPIs), soft mist inhalers (SMIs), and nebulizers[6]. Common inhaler errors include insufficient inspiratory effort, no breath–hold (or holds breath for less than 3s), etc[7 8]. Inhaler errors are associated with poor disease outcomes (exacerbations) and greater health-economic burden[9]. MDIs require complex coordination techniques with a slow inhalation by the patient to achieve a clinically

effective dose. DPIs decrease the complexity of administration, but effective medication delivery is dependent on the force of the patient's inspiratory effort to overcome internal resistance[10]. Several *in vitro* studies have demonstrated the inhalation flow rate dependency of DPI. Specifically, the results showed that using a DPI both the amount of medication delivered to the patient and the effective aerodynamic particle size of the medication were adversely affected when the testing peak inhalation flow rate (PIFR) was less than a certain threshold (60 liters/min measured at no resistance) [11], which may result in ineffective inhalation of medications using a DPI. Several studies suggest that patients with insufficient PIFR in stable phase of COPD may have an adverse effect on prognosis using inappropriate inhaler[12 13]. Moreover, it should be noted that expiratory flow rate (such as FEV_1) is not correlated linearly with inspiratory flow parameters, and it do not predict PIFR. Other risk factors for early AECOPD recurrence include age grades, GOLD grades, AE frequency in the previous year, pleural effusion, use of accessory respiratory muscles, noninvasive mechanical ventilation, controlled oxygen therapy and length of hospital stay, while inhaled long-acting β-2-agonists (LABA) and inhaled corticosteroids (ICS) are protection factors[14]. An investigation suggests that one of five stable outpatients more than 60 years of age with severe COPD did not reach the recommended PIFR for DPI devices[15]. Some small sample studies has shown that a significant proportion of patients are not suitable for DPI during AECOPD because of their insufficient PIFR[13 16]. However, there is no study about the PIFR status and the impact of inhaler choices on prognosis for patients recovering from AECOPD.

Thirty-day readmission rates after hospitalization for AECOPD are approximately 15.8%-20%[17 18]. Readmissions are costly and adversely affect quality of life. But little is known about PIFRs of the patients recovering from AECOPD as well as the clinical impact of the inhaler (DPI or pMDI) selected for the patients. Generally, discharge protocols for patients recovering from AECOPD do not include an assessment of PIFR or patients' ability to use their inhaler device when they recuperate after discharge. Clinicians typically select the inhaler they use during the stable phase of COPD for patients who will be discharged. Furthermore, although some evidence has suggested

that incorrect use of inhalers is associated with poor prognosis, studies on the effect of training patients on the use of inhalers to reduce relapses are still scarce. We hypothesize PIFR of patients recovering from AECOPD have not returned to the level at the stable phase of COPD as well as untrained patients have higher rate of inhaler errors. It may result in suboptimal COPD management and treatment failure (including recurrence resulting in an emergency visit, admission, or need for intensified medication) for the patients due to the ineffective inhalation of medications.

The aim of this study is to determine whether the optimized inhalation therapy based PIFR can reduce the rate of treatment failure in patients recovering from AECOPD. Errors in inhaler use and quality of life are also to be evaluated.

Methods and analysis

Trial design

This is a prospective, multi-center, single-blind, superiority, randomized study of patients hospitalized for a COPD exacerbation. This study is designed to determine whether PIFR based inhaler choice and training can reduce the rate of treatment failure in patients recovering from AECOPD. The primary study outcome is 30-day treatment failure rate. Treatment failure means AECOPD recurrence resulting in an emergency visit, admission, or need for intensified medication. Other endpoints include symptoms and life quality of patients the error rate of inhalation device use, satisfaction with inhalation devices, PIFR, 30-day mortality, 90-day mortality, and COPD-related treatment costs. The enrollment, conduct and data analysis of the trail are performed at Zhongshan Hospital of Fudan University, Shanghai Jing 'an District Central Hospital, Shanghai Qingpu District Central Hospital and North Branch of Shanghai Ninth People's Hospital in China. The study is expected to last for 2 years. Recruitment of participants has started since November 2019.

This trial has been registered in the Ethics Committee of Zhongshan Hospital of Fudan University (B2019-142) and Clinical Trails (NCT04000958).

Inclusion criteria

All patients meeting AECOPD diagnostic criteria who hospitalized for COPD related reasons will be followed. The definition of COPD follows the GOLD definition and the definition of AECOPD follows Expert Consensus on Acute Exacerbation of Chronic Obstructive Pulmonary Disease in the People's republic of China[4]. AECOPD is defined as sudden worsening of respiratory symptoms that require additional treatment (typical manifestations include dyspnea, aggravated cough, increased sputum volume, and/or sputum purulence) and is beyond normal day-to-day variations, leading to a change in medications[4 19]. The subjects will be enrolled and randomized into the study group if all of the following criteria are met: (1) 40–80 years old; (2) patients with AECOPD whose acute respiratory symptoms have been controlled and met discharge criteria after 5-7 day-standard AECOPD treatment including atomized or inhaled bronchodilator plus oral or intravenous glucocorticoid (prednisone equivalent dose 40-50mg) or Pulmicort 2mg atomization twice daily plus broad-spectrum antibiotics; (3) patients with moderate and above COPD with a recorded spirometry measured in the stable disease status, ie, post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) <70% and FEV1% predicted value <80%; (4) patients have signed an informed consent form.

Discharge criteria is as follows: (1) physician are confident that the patient can manage successfully at home; (2) long-acting bronchodilators, either beta 2-agonists and/or anticholinergics with or without inhaled corticosteroids can be used, and inhaled short-acting β2-agonist therapy is required no more frequently than every 4 hours; (3) the patient, if previously ambulatory, is able to walk across the room; (4) the patient is able to eat and sleep without frequent awakening due to dyspnea; (5) the patient has been clinically stable for 12–24 hours; (6) arterial blood gases have been stable for 12–24 hours[4].

Exclusion criteria

Exclusion criteria include:(1) patients who is already using home nebulization therapy because of the severity of the disease; (2) patients with bronchial asthma, pulmonary interstitial fibrosis, bronchiectasis, pulmonary embolism and other lung diseases; or hypertension, heart disease, chronic liver and kidney disease, diabetes, chronic gastrointestinal diseases, malignant tumors, critically ill; (3)patient's mental state cannot match the observation or suffer from cognitive impairment; (4) patient's peak inspiratory flow rates (PIFR) is less than 20L/min.

Sample size

The sample size was calculated using PASS 15.0 (Power Analysis and Sample Size Software) to ensure the study power. Several studies have found that 30-47% patients hospitalized for AECOPD had a PIFR < 60 liters/minute prior to discharge[5 10]. For the control group, 30-day treatment failure rates after hospitalization for AECOPD are approximately 20% according to the literature and our retrospective cohort study [17, 18]. For PIFR group, 30-day treatment failure rates are 10% based on our preliminary research. The participants will be divided into PIFR group and control group in a 1:1 ratio. To test the superiority hypothesis with 80% power with 2-side alpha at 0.05 level, 197 subjects will be enrolled for each group. Considering 5% dropout rate, the minimum number of the participants in the study was determined to be 208 per group.

Study outline

The flow chart of the study design is shown in Figure 1. The study will recruit 416 patients with AECOPD whose exacerbated symptoms are relieved by 5-7 days of standard therapy. After enrollment, the participants are divided into PIFR group and control group at a 1:1 ratio according to a random envelope method. All the patients will be given inhaled corticosteroid (ICS)/long-acting β agonist (LABA) (budesonide/ formoterol - Symbicort turbuhaler® (AstraZeneca AB) 160/4.5 μg bid or Beclometasone/ Formoterol Foster® (Chiesi Farmaceutici S.p.A.) pressure pMDI 100/6

μg 2 puff bid). For symptomatic patients (mMRC ≥ 2, CAT ≥ 10) before acute exacerbation, Spiriva handihaler® 18μg qd or Spiriva respimat® (Boehringer IngelheimPharma GmbH & Co.KG) 2.5μg qd will be prescribed in combination with ICS/LABA.

For PIFR group, PIFR is measured by InCheck DIAL® (Clement Clarke International Ltd, Harlow, UK and Alliance Tech Medical). The InCheck DIAL® is designed to simulate the "internal resistance" of common inhaler devices, and measure inspiratory flow. These measurements enable the healthcare professional to encourage patients to modify their inspiratory technique (by inhaling with more, or less effort), in order to achieve a flow rate consistent with clinical efficacy. The colored 'flow' icons show the clinically effective flow ranges for each different inhaler device. The InCheck DIAL® is accurate to +/− 10% or 10 L/min, whichever is greater, and is a low-range inspiratory flow meter (15 to 120 L/min) that has a selectable resistance from high to low, shown by the colored 'flow' icons calibrated to enable the measurement of airflow as if the patient was using certain different inhalers. In this study, we set the resistance of the InCheck DIAL® both to zero (correspond to pMDI) and Med High resistance level of InCheck DIAL® (correspond to turbuhaler®) when measuring PIFR. Before measuring , we will first train patients to use the InCheck DIAL® correctly. After patients are able to reach their maximum value of PIFR steadily, we will measure the PIFR 3 times and take the average as a result.

Moreover, the InCheck DIAL® is an inhalation airflow training meter that can help educate and assess patients who use inhaler devices. When training the patient, we will set the corresponding resistance for the InCheck DIAL® according to the inhaler that the patient is prescribed. We will also explain to the patient the proper operation of the inhaler and demonstrate some common mistakes.

If PIFR is less than 60L/min (measured without a resistance), the patient will be given pMDI with spacer. If PIFR value is over 60 L/min (measured without a resistance), the patient will be given dry powder inhaler (DPI). Furthermore, InCheck DIAL® will be used for an inhalation device training.

The control group will be given DPI or pMDI with spacer according to the judgment of a respiratory physician.

Both groups will be taught to use the device after the prescription, and then be reminded to use medication via a WeChat public account.

Study step

The participants will be followed up for 3 months and 3 visits will be performed at baseline(symptoms of AECOPD are relieved by 5-7 days of standard therapy), 1 and 3 months after enrollment.

Demographics, clinical characteristics, evaluation of respiratory symptoms and quality of life in the stable phase, PIFR, routine laboratory tests for AE patients(e.g. blood routine, C-reactive protein, liver and kidney function, blood electrolytes, B-type natriuretic peptide, D-dimer), chest X-ray or CT and echocardiography or electrocardiogram in the stable phase will be collected at baseline. Demographics includes age, gender, age, height, weight, ethnicity, occupation(number of years of work), marital status, location, etc. Clinical characteristics includes past disease history, history of drug sensitivity, history of vaccination, family disease history, current medical history, comorbidities, medications, etc. Respiratory symptoms will be assessed with the modified Medical Research Council (mMRC) dyspnea scale and the COPD Assessment Test (CAT) score for the patients. Quality of life will be assessed with St.George's Respiratory Questionnaire(SGRQ) scale. All baseline data will be collected by attending physician on the day of enrollment.

CAT score, mMRC score, SGRQ score, PIFR, spirometry, the error rate of inhalation device use, satisfaction with inhalation devices, condition of AE and COPD medicine treatment will be collected at both 1- and 3-month visit. The data to be collected for each visit is shown in Table 1.

Table 1. Data collected at each visit

	V0	V1	V2	V3
	Hospitalization±1 day	At the time of discharge (meet discharge standards)	1 month after discharge	3 month after discharge
Basic Information	√			
Information of COPD at stable phase	√			
Blood routine	√	√		
Liver and kidney function	√	√		
Electrolyte	√	√		
C-reactive protein	√	√		
procalcitonin	√	√		
brain natriuretic peptide	√	√		
D-dimer 、 Fibrinogen	√	√		
cardiac troponin T	√	√		
CAT score	√	√	√	√
mMRC	√	√	√	√
SGRQ		√	√	√
Drug for COPD	Stable phase	AE phase	Stable phase	Stable phase
PIFR		PIFR√	PIFR√	PIFR√
Prognosis			√	√
Pulmonary function		√	√	√
Echocardiography at stable phase				
CT at stable phase				
CT at AE phase				
Error of inhaler use			√	√
Satisfaction with the inhaler			√	√
Daily cost of COPD related treatment			√	√

Endpoints

The primary endpoint is 30-day treatment failure rate of AECOPD. Treatment failure means AECOPD recurrence resulting in an emergency visit, admission, or need for intensified medication.

Secondary endpoints include PIFR, the error rate of inhalation device use, satisfaction with inhalation devices, 30-day mortality, 90-day mortality, symptoms and life quality of patients and COPD-related treatment costs.

Patient's satisfaction with inhalation devices will be assessed by FSI-10 questionnaire. The FSI-10 questionnaire is completed by patients themselves, which has been widely applied to assess patients' opinions about ease of use, portability, and usability of inhalers[20].The symptoms of patients are evaluated by the COPD assessment test (CAT) and the modified Medical Research Council (mMRC) dyspnea scale. The patients' quality of life are evaluated by St.George's Respiratory Questionnaire(SGRQ).

PIFR is measured by InCheck DIAL® (Clement Clarke International Ltd, Harlow, UK and Alliance Tech Medical).

The error rate of inhalation device use is described in Table 2[7 8].

Table 2. The error rate of inhalation device use

Turbuhaler	**Handihaler/Accuhaler**	**pMDI**	**Respimat**
Cover is not removed/ Cover is not covered properly.	Cover is not removed/ Cover is not covered properly.	Cover is not removed/ Cover is not covered properly.	Cover is not removed/ Cover is not covered properly.
Patient reduces dose due to shaking or tilting during preparation.	-		The device is not installed correctly before use.
Device is not held upright.	-	Device is not held upright.	-
Patient does not twist grip at the base or twist around and then back until click is	-	-	Patient dose not turn the device toward the arrow in the label until it clicks.

heard.			
Patient forces insufficiently when inhaling.	Patient forces insufficiently when inhaling.	Patient dose not inhale deeply and slowly.	Patient dose not inhale deeply and slowly.
Patient does not tilt head to make the chin slightly upturned.	Patient does not hold the head in a vertical position.	Patient does not tilt head to make the chin slightly upturned.	Patient dose not point the inhaler toward the back of throat.
Patient does not exhale to empty the lung before inhaling.	Patient does not exhale to empty the lung before inhaling.	Patient does not exhale to empty the lung before inhaling.	Patient does not exhale to empty the lung before inhaling.
-	Patient does not turn the head away from device and exhale.	Patient exhales into the device before inhaling.	Patient covers the air entries while inhaling.
Patient does not seal the mouthpiece with the lips.	Patient does not put the mouthpiece in mouth, and close the lips.	Patient does not seal the mouthpiece with the lips.	Patient does not seal the mouthpiece with the lips.
NA	NA	Releasing drug is out of sync with inhaling.	Releasing drug is out of sync with inhaling.
Patient does not hold breath(or hold breath less than 3s).	Patient does not hold breath(or hold breath less than 3s).	Patient does not hold breath(or hold breath less than 3s).	Patient does not hold breath(or hold breath less than 10s).
Patient does not put the cover back and wait for 30-60 seconds for the second dose.	Patient dose not dispose of the capsule and put the cover back on the device.	Patient does not exhale and wait for 30-60 seconds before the second puff.	Patient dose not inhales twice to complete the total daily dosage.

Randomization

Enrollment and randomization are performed at Zhongshan Hospital of Fudan University. After enrollment, patients will be assigned into two groups via a random envelope method in a 1:1 ratio to the PIFR group and control group by random number table method generated by SPSS.

Blinding

The study adopts blind evaluation. The investigator will enroll participants and assign them into two groups. All data at baseline, 1- and 3-month visit will be collected by attending physician, who will not be informed of which group the patient has been assigned. In addition, patients will not know the group they belong to. Blind evaluation maximizes the objectivity and reliability of the study.

Statistical analysis

1. Statistical analysis datasets

- Modified intent-to-treat set (MITTS)

Subjects that have undergone randomization and interventions, and carry out primary endpoints evaluation.

- Safety set (SS)

Subjects that are randomized, undergo the intervention, and with safety evaluation data.

2. Statistical analysis methods

Statistical analyses were performed using SPSS 22.0. Continuous variables are described as mean (SD) or median (p25,p75) and count variables are described as frequency and percentage. All tests were both sided and statistical analysis, 0.05 was set as the P value for significance. For discrete variables including 30-day treatment failure rate, the error rate of inhalation device use, satisfaction with inhalation devices, 30-day mortality and 90-day mortality, a chi-squared ($\chi 2$) test, Fisher's exact test or CMH $\chi 2$ test will be used. For continuous variable including PIFR, CAT score, mMRC score, SGRQ score and COPD-related treatment costs, Student's t-tests or Mann-Whitney test will be used. Subgroup analysis by exacerbation history and GOLD grades will be performed to rule out the influence of confounding factors to the certain extent.

Patient and public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination of our research. The results will be available to the public if necessary.

Ethics and dissemination

This trial has been registered in the Ethics Committee of Zhongshan Hospital of Fudan University (B2019-142). In this study, diagnosis and treatment were performed in accordance with the routine management of COPD. Neither Additional drug intervention nor invasive examination and charges are needed. Therefore, the study is relatively safe with minimal additional risks. Participants will be screened and recruited from hospitalized patients by physicians. No additional public recruitment documents will be used for participants enrollment. All participants will sign informed consent. All information of participants will be kept private and will not be provided to any company or institution. The results will be disseminated through peer-reviewed journals and conference presentations, and proliferation activities will include diverse social non-academic groups and patients.

Discussion

Drug delivery by DPI depends on the inbuilt resistance of the inhaler and the PIFR generated by the patient. PIFR generally depends on an individual's effort as well as the respiratory muscle force, which may be decreased in patients with COPD due to airway stenosis, lung hyperinflation, hypoxemia, and muscle wasting. DPI are breath-actuated that require the individual to create turbulent forces to disaggregate the powder into respirable particles which can reach the lower respiratory tract. Patients with a sufficient PIFR (PIFR > 60 L/min) are able to release the powder and deaggregate the drug resulting in lung deposition.

Sharma and colleagues have found that 31.7% of patients at discharge following

hospitalization for an exacerbation of COPD had PIFR less than 60 L/min[3]. Patients with a PIFR less than 60 L/min have been considered not be able to inhale medications using a DPI effectively into the lower respiratory tract according to the literature, while a PIFR less than 30 liters/minute is insufficient[21 22]. However, most clinicians in china prescribe DPI to the patients recovering from AECOPD routinely due to the lack of the availability of long-acting bronchodilators with pMDI without measuring their PIFR. Inappropriate inhaler selection may result in treatment failure of AECOPD. Before our study, it remains unclear whether treatment failure rate is related to PIFR-based inhaler description. A suitable inspiratory flow rate helps to improve the treatment efficacy. In addition to inhaler selection, PIFR group also receive inhaler training to help patients master the correct inhalation method.

Our research has proposed to measure PIFR of patients recovering from AECOPD by InCheck DIAL® and guide COPD inhaler choices and inhaler technique training. The aim of this study is to determine whether the optimized inhalation therapy based on PIFR measured against the simulated resistance can reduce the rate of treatment failure in patients recovering from AECOPD. Therefore, we plan to verify the clinical significance of including PIFR in the discharge protocol through comparing the difference in 30-day treatment failure rates and other endpoints between PIFR group and the control group.

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Figure legends : Figure 1. The flowchart shows the process of patient's admission, recruitment, intervention and visits. V0, V1, V2, and V3 are all time points to collect data.

Contributors: JLH and JZ planned the study. WZ planned the Statistical analysis methods. All authors contributed to design and development of the trail (JLH, JZ, WZ, HFC, CLD, JYM and YHZ). JLH drafted the manuscript. JZ , HFC, CLD, JYM and YHZ contributed to revised the manuscript. All authors read and approved the final manuscript.

Ethics and dissemination: This trial has been registered in the Ethics Committee of Zhongshan Hospital of Fudan University (B2019-142) and Clinical Trails (NCT04000958).

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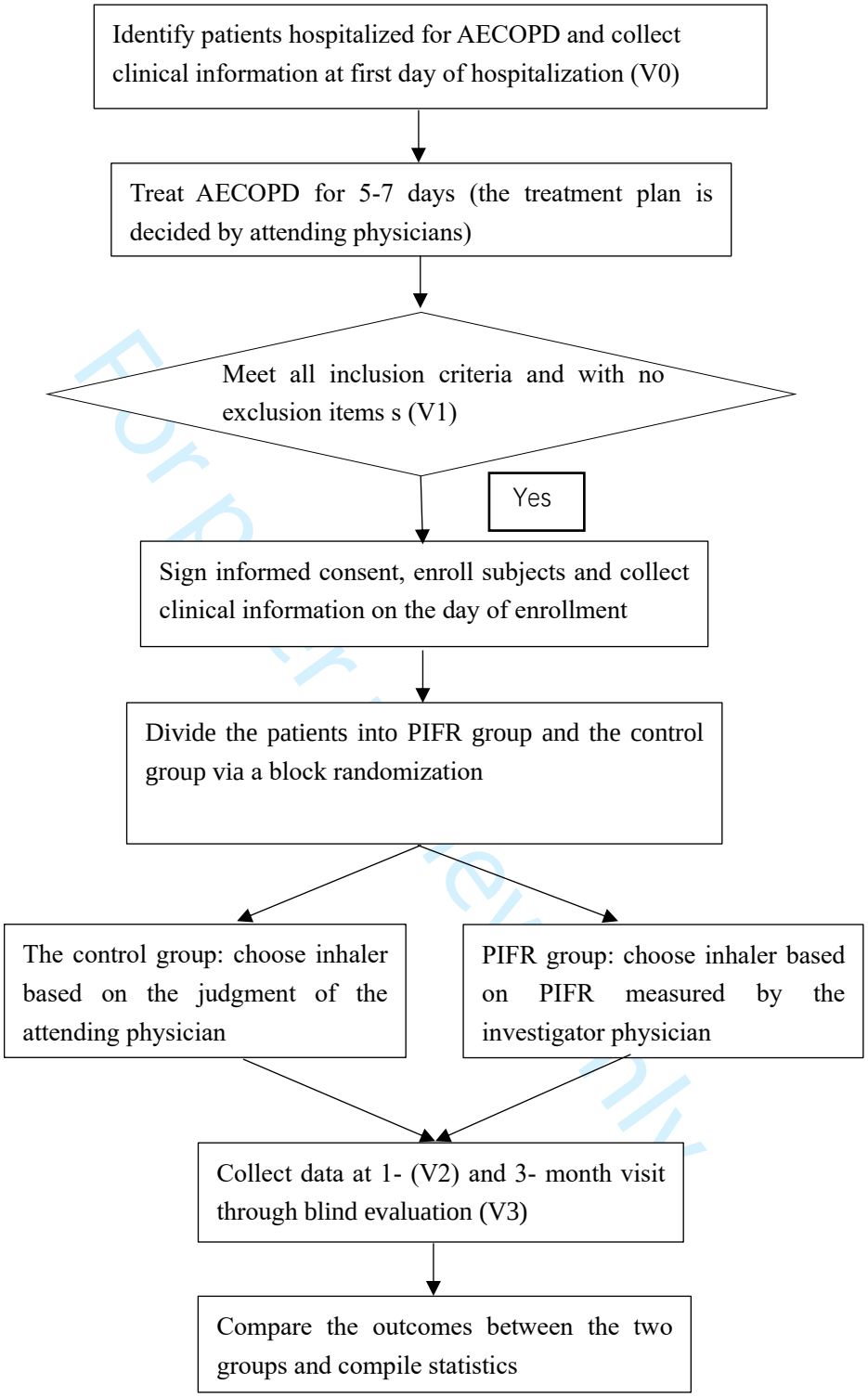
Competing interests statement: None declared.

Word Count: 5085

Figure 1. The flow chart of the study



SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	N/A
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
	6b	Explanation for choice of comparators	3-5

Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7-8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-10
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	14
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9-10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	N/A
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	N/A

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The effect of PIFR-based Optimized Inhalation Therapy in Patients Recovering From Acute exacerbation of Chronic Obstructive Pulmonary Disease: protocol of a prospective, multi-center, superiority, randomized controlled trial

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The effect of PIFR-based Optimized Inhalation Therapy in Patients Recovering From Acute exacerbation of Chronic Obstructive Pulmonary Disease: protocol of a prospective, multi-center, superiority, randomized controlled trial

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Abstract:

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is a global respiratory disease. Acute exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) is a major cause of disease progression and death, and causes huge medical expenditures. Effective inhalation therapy is important during the AE recovery period. However, the invalid inhalation using DPI due to the unrecovered inspiratory flow rate after AECOPD results in increased risk of treatment failure and early recurrence. We envisage that choosing the right inhaler based on peak inhalation flow rate (PIFR) and training inhaler techniques will contribute to reducing early relapse rates. Therefore, a prospective multicenter randomized trial is designed to verify this hypothesis.

Methods and analysis: The study is aimed at determining whether the optimized inhalation therapy based on PIFR can reduce the rate of treatment failure in patients recovering from AECOPD. In the study, 416 patients with AECOPD whose exacerbated symptoms are relieved by 5-7 days of standard therapy will be recruited and be randomized into PIFR group, which receives inhaler depending on their PIFR and is trained to use the inhaler appropriately, and control group, which receives inhaler depending on the judgment of a respiratory physician, at a 1:1 ratio. The primary outcome of the study is 30-day treatment failure rate. Other endpoints include PIFR, the error rate of inhalation device use, satisfaction with inhalation devices, 30-day mortality, 90-day mortality, symptoms and life quality of patients and COPD-related treatment costs.

Ethics and dissemination: This trial has been registered in the Ethics Committee of Zhongshan Hospital of Fudan University (B2019-142). Participants will be screened and recruited from hospitalized patients by physicians. No public recruitment documents will be used for participants enrollment. The results will be disseminated through peer-reviewed journals and conference presentations, and proliferation activities will include diverse social non-academic groups and patients.

Trial registration: This trial has been registered in ClinicalTrials.gov (NCT04000958).

Strengths and limitations of this study:

1. To our knowledge, this is the first multicenter, randomized trial designed to study the efficacy of PIFR-based inhaler prescription in preventing short-term re-execration in patients recovering from severe acute exacerbation of COPD.

2. InCheck DIAL® is used to measure PIFR and objectively evaluate the capacity of using dry powder inhalers.

3. The inhaler technique will be trained as well to achieve optimal inhalation therapy.

4. Inhalers studied in this trial include turbuhaler, handihaler, respimat and pMDI.

5.The limitation of the study is the single-blind study design, which would yield bias, although blind evaluation is adopted to minimize the bias.

Keywords: chronic obstructive pulmonary disease, acute exacerbation of chronic obstructive pulmonary disease, peak inhalation flow rate

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a global respiratory disease that severely threatens human health. COPD has resulted in a significant socioeconomic burden, and is currently the fourth leading cause of death in the world. Moreover, it is projected to be the 3rd leading cause of death by 2020[1]. In China, COPD ranked among the top three leading causes of death and the direct medical cost of COPD ranged from 72 to 3,565 USD per capita per year, accounting for 33.33% to 118.09% of local average annual income[2]. The overall prevalence of spirometry-defined COPD was 8.6% among the general Chinese population aged 20 years or older[3]. Acute exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) is a major cause of disease progression and death, and causes huge medical expenditures[4].

Inhalation therapy is the core pharmaceutical therapy for COPD including inhaled corticosteroid (ICS), both short-acting and long-acting beta2-agonists and, more recently, muscarinic antagonists[5]. Existing common inhalers include pressure metered dose inhaler (pMDI), dry powder inhalers (DPIs), soft mist inhalers (SMIs), and nebulizers[6]. Common inhaler errors include insufficient inspiratory effort, no breath–hold (or holds breath for less than 3s) [7 8]. Inhaler errors are associated with poor disease outcomes (exacerbations) and greater health-economic burden[9]. MDIs require complex coordination techniques with a slow inhalation by the patient to achieve a clinically

effective dose. DPIs decrease the complexity of administration, but effective medication delivery is dependent on the force of the patient's inspiratory effort to overcome internal resistance[10]. Several *in vitro* studies have demonstrated the inhalation flow rate dependency of DPI. Specifically, the results showed that using a DPI both the amount of medication delivered to the patient and the effective aerodynamic particle size of the medication were adversely affected when the testing peak inhalation flow rate (PIFR) was less than a certain threshold (60 liters/min measured at no resistance) [11], which may result in ineffective inhalation of medications using a DPI. Several studies suggested that patients with insufficient PIFR in stable phase of COPD may have an adverse effect on prognosis using inappropriate inhaler[12] [13]. Moreover, it should be noted that expiratory flow rate (such as FEV_1) is not correlated linearly with inspiratory flow parameters, and it cannot predict PIFR. Other risk factors for early AECOPD recurrence include age grades, GOLD grades, AE frequency in the previous year, pleural effusion, use of accessory respiratory muscles, noninvasive mechanical ventilation, controlled oxygen therapy and length of hospital stay, while inhaled long-acting β-2-agonists (LABA) and inhaled corticosteroids (ICS) are protection factors[14]. An investigation suggested that one of five stable outpatients more than 60 years of age with severe COPD did not reach the recommended PIFR for DPI devices[15]. Some small sample studies have shown that a significant proportion of patients are not suitable for DPI during AECOPD because of their insufficient PIFR[13] [16]. However, there is no study about the PIFR status and the impact of inhaler choices on prognosis for patients recovering from AECOPD.

Thirty-day readmission rates after hospitalization for AECOPD are approximately 15.8%-20%[17] [18]. Readmissions are costly and adversely affect quality of life. But little is known about PIFRs of the patients recovering from AECOPD as well as the clinical impact of the inhaler (DPI or pMDI) selected for the patients. Generally, discharge protocols for patients recovering from AECOPD do not include an assessment of PIFR or patients' ability to use their inhaler device when they recuperate after discharge. Clinicians typically select the inhaler which they use during the stable phase of COPD for patients about to be discharged. Furthermore, although some evidence has suggested

that incorrect use of inhalers is associated with poor prognosis, studies on the effect of training patients on the use of inhalers to reduce relapses are still scarce. We hypothesize that PIFR of patient recovering from AECOPD has not returned to the level at the stable phase of COPD as well as untrained patients have higher rate of inhaler errors. It may result in suboptimal COPD management and treatment failure (including recurrence resulting in an emergency visit, admission, or need for intensified medication) for the patients due to the ineffective inhalation of medications.

The aim of this study is to determine whether the optimized inhalation therapy based PIFR can reduce the rate of treatment failure in patients recovering from AECOPD. Errors in inhaler use and quality of life are also to be evaluated.

Methods and analysis

Trial design

This is a prospective, multi-center, single-blind, superiority, randomized study of patients hospitalized for a COPD exacerbation. This study is designed to determine whether PIFR based inhaler choice and training can reduce the rate of treatment failure in patients recovering from AECOPD. The primary study outcome is 30-day treatment failure rate. Treatment failure means AECOPD recurrence resulting in an emergency visit, admission, or need for intensified medication. Other endpoints include symptoms and life quality of patients the error rate of inhalation device use, satisfaction with inhalation devices, PIFR, 30-day mortality, 90-day mortality, and COPD-related treatment costs. The enrollment, conduct and data analysis of the trail are performed at Zhongshan Hospital of Fudan University, Shanghai Jing 'an District Central Hospital, Shanghai Qingpu District Central Hospital and North Branch of Shanghai Ninth People's Hospital in China. The study is expected to last for 2 years. Recruitment of participants has started since November 2019. A blank copy of the original consent form is provided and shown as a supplementary document.

This trial has been registered in the Ethics Committee of Zhongshan Hospital of

Fudan University (B2019-142) and ClinicalTrials.gov (NCT04000958).

Inclusion criteria

All patients meeting AECOPD diagnostic criteria who hospitalized for COPD related reasons will be followed. The definition of COPD follows the GOLD definition and the definition of AECOPD follows Expert Consensus on Acute Exacerbation of Chronic Obstructive Pulmonary Disease in the People's republic of China[4]. AECOPD is defined as sudden worsening of respiratory symptoms that require additional treatment (typical manifestations include dyspnea, aggravated cough, increased sputum volume, and/or sputum purulence) and is beyond normal day-to-day variations, leading to a change in medications[4 19]. The subjects will be enrolled and randomized into the study group if all of the following criteria are met: (1) 40–80 years old; (2) patients with AECOPD whose acute respiratory symptoms have been controlled and met discharge criteria after 5-7 day-standard AECOPD treatment including atomized or inhaled bronchodilator plus oral or intravenous glucocorticoid (prednisone equivalent dose 40-50mg) or Pulmicort 2mg atomization twice daily plus broad-spectrum antibiotics; (3) patients with moderate and above COPD with a recorded spirometry measured in the stable disease status, ie, post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) <70% and FEV1% predicted value <80%; (4) patients have signed an informed consent form.

Discharge criteria are as follows: (1) physician are confident that the patient can manage successfully at home; (2) long-acting bronchodilators, either beta 2-agonists and/or anticholinergics with or without inhaled corticosteroids can be used, and inhaled short-acting β2-agonist therapy is required no more frequently than every 4 hours; (3) the patient, if previously ambulatory, is able to walk across the room; (4) the patient is able to eat and sleep without frequent awakening due to dyspnea; (5) the patient has been clinically stable for 12–24 hours; (6) arterial blood gases have been stable for 12–24 hours[4].

Exclusion criteria

Exclusion criteria include:(1) patients who are already using home nebulization therapy because of the severity of the disease; (2) patients with bronchial asthma, pulmonary interstitial fibrosis, bronchiectasis, pulmonary embolism and other lung diseases; or hypertension, heart disease, chronic liver and kidney disease, diabetes, chronic gastrointestinal diseases, malignant tumors, critically ill; (3)patient's mental state cannot match the observation or they suffer from cognitive impairment; (4) patient's peak inspiratory flow rates (PIFR) is less than 20L/min.

Sample size

The sample size was calculated using PASS 15.0 (Power Analysis and Sample Size Software) to ensure the study power. Several studies have found that 30-47% patients hospitalized for AECOPD had a PIFR < 60 liters/minute prior to discharge[5 10]. For the control group, 30-day treatment failure rates after hospitalization for AECOPD are approximately 20% according to the literature and our retrospective cohort study [17, 18]. For PIFR group, 30-day treatment failure rates are 10% based on our preliminary research. The participants will be divided into PIFR group and control group in a 1:1 ratio. To test the superiority hypothesis with 80% power with 2-side alpha at 0.05 level, 197 subjects will be enrolled for each group. Considering 5% dropout rate, the minimum number of the participants in the study has been determined to be 208 per group.

Study outline

The flow chart of the study design is shown in Figure 1. The study will recruit 416 patients with AECOPD whose exacerbated symptoms are relieved by 5-7 days of standard therapy. After enrollment, the participants are divided into PIFR group and control group at a 1:1 ratio according to a random envelope method. All the patients will be given inhaled corticosteroid (ICS)/long-acting β agonist (LABA) (budesonide/

formoterol - Symbicort turbuhaler® (AstraZeneca AB) 160/4.5 μg bid or Beclometasone/ Formoterol Foster® (Chiesi Farmaceutici S.p.A.) pressure pMDI 100/6 μg 2 puff bid). For symptomatic patients (mMRC ≥ 2, CAT ≥ 10) before acute exacerbation, Spiriva handihaler® 18μg qd or Spiriva respimat® (Boehringer IngelheimPharma GmbH & Co.KG) 2.5μg qd will be prescribed in combination with ICS/LABA.

For PIFR group, PIFR is measured by InCheck DIAL® (Clement Clarke International Ltd, Harlow, UK and Alliance Tech Medical). The InCheck DIAL® is designed to simulate the "internal resistance" of common inhaler devices, and measure inspiratory flow. These measurements enable the healthcare professional to encourage patients to modify their inspiratory technique (by inhaling with more, or less effort), in order to achieve a flow rate consistent with clinical efficacy. The colored 'flow' icons show the clinically effective flow ranges for each different inhaler device. The InCheck DIAL® is accurate to +/− 10% or 10 L/min, whichever is greater, and is a low-range inspiratory flow meter (15 to 120 L/min) that has a selectable resistance from high to low, shown by the colored 'flow' icons calibrated to enable the measurement of airflow as if the patient was using certain different inhalers. In this study, we will set the resistance of the InCheck DIAL® both to zero (correspond to pMDI) and Med High resistance level of InCheck DIAL® (correspond to turbuhaler®) when measuring PIFR. Before measuring , we will first train patients to use the InCheck DIAL® correctly. After patients are able to reach their maximum value of PIFR steadily, we will measure the PIFR 3 times then take the average as a result.

Moreover, the InCheck DIAL® is an inhalation airflow training meter contributing to assess and improve patients' ability to use inhalers. When training the patient, we will set the corresponding resistance for the InCheck DIAL® according to the inhaler that the patient is prescribed. We will also explain to the patient the proper operation of the inhaler and demonstrate some common mistakes.

If PIFR is less than 60L/min (measured without a resistance), the patient will be given pMDI with spacer. If PIFR value is over 60 L/min (measured without a resistance), the

patient will be given dry powder inhaler (DPI). Furthermore, InCheck DIAL® will be used for an inhalation device training.

The control group will be given DPI or pMDI with spacer according to the judgment of a respiratory physician.

Both groups will be taught to use the device after the prescription, and then be reminded to use medication via a WeChat public account.

Study step

The participants will be followed up for 3 months. 3 visits will be performed at baseline(symptoms of AECOPD are relieved by 5-7 days of standard therapy), 1 and 3 months after enrollment.

Demographics, clinical characteristics, evaluation of respiratory symptoms and quality of life in the stable phase, PIFR, routine laboratory tests for AE patients(e.g. blood routine, C-reactive protein, liver and kidney function, blood electrolytes, B-type natriuretic peptide, D-dimer), chest X-ray or CT and echocardiography or electrocardiogram in the stable phase will be collected at baseline. Demographics includes age, gender, age, height, weight, ethnicity, occupation(number of years of work), marital status, location, etc. Clinical characteristics includes past disease history, history of drug sensitivity, history of vaccination, family disease history, current medical history, comorbidities, medications, etc. Respiratory symptoms will be assessed with the modified Medical Research Council (mMRC) dyspnea scale and the COPD Assessment Test (CAT) score for the patients. Quality of life will be assessed with St.George's Respiratory Questionnaire(SGRQ) scale. All baseline data will be collected by attending physician on the day of enrollment.

CAT score, mMRC score, SGRQ score, PIFR, spirometry, the error rate of inhalation device use, satisfaction with inhalation devices, condition of AE and COPD medicine treatment will be collected at both 1-month and 3-month visit. The data to be collected for each visit is shown in Table 1.

Table 1. Data collected at each visit

	V0	V1	V2	V3
	Hospitalization±1 day	At the time of discharge (meet discharge standards)	1 month after discharge	3 month after discharge
Basic Information	√			
Information of COPD at stable phase	√			
Blood routine	√	√		
Liver and kidney function	√	√		
Electrolyte	√	√		
C-reactive protein	√	√		
procalcitonin	√	√		
brain natriuretic peptide	√	√		
D-dimer 、 Fibrinogen	√	√		
cardiac troponin T	√	√		
CAT score	√	√	√	√
mMRC	√	√	√	√
SGRQ		√	√	√
Drug for COPD	Stable phase	AE phase	Stable phase	Stable phase
PIFR		PIFR√	PIFR√	PIFR√
Prognosis			√	√
Pulmonary function		√	√	√
Echocardiography at stable phase				
CT at stable phase				
CT at AE phase				
Error of inhaler use			√	√
Satisfaction with the inhaler			√	√
Daily cost of COPD related treatment			√	√

Endpoints

The primary endpoint is 30-day treatment failure rate of AECOPD. Treatment failure means AECOPD recurrence resulting in an emergency visit, admission, or need for intensified medication.

Secondary endpoints include PIFR, the error rate of inhalation device use, satisfaction with inhalation devices, 30-day mortality, 90-day mortality, symptoms and life quality of patients and COPD-related treatment costs.

Patient's satisfaction with inhalation devices will be assessed by FSI-10 questionnaire. The FSI-10 questionnaire is supposed to be completed by patients themselves, which has been widely applied to assess patients' opinions about ease of use, portability, and usability of inhalers[20].The symptoms of patients are evaluated by the COPD assessment test (CAT) and the modified Medical Research Council (mMRC) dyspnea scale. The patients' quality of life are evaluated by St.George's Respiratory Questionnaire(SGRQ).

PIFR is measured by InCheck DIAL® (Clement Clarke International Ltd, Harlow, UK and Alliance Tech Medical).

The error rate of inhalation device use is described in Table 2[7 8].

Table 2. The error rate of inhalation device use

Turbuhaler	**Handihaler/Accuhaler**	**pMDI**	**Respimat**
Cover is not removed/ Cover is not covered properly.	Cover is not removed/ Cover is not covered properly.	Cover is not removed/ Cover is not covered properly.	Cover is not removed/ Cover is not covered properly.
Patient reduces dose due to shaking or tilting during preparation.	-		The device is not installed correctly before use.
Device is not held upright.	-	Device is not held upright.	-

Patient does not twist grip at the base or twist around and then back until click is heard.	-	-	Patient dose not turn the device toward the arrow in the label until it clicks.
Patient forces insufficiently when inhaling.	Patient forces insufficiently when inhaling.	Patient dose not inhale deeply and slowly.	Patient dose not inhale deeply and slowly.
Patient does not tilt head to make the chin slightly upturned.	Patient does not hold the head in a vertical position.	Patient does not tilt head to make the chin slightly upturned.	Patient dose not point the inhaler toward the back of throat.
Patient does not exhale to empty the lung before inhaling.	Patient does not exhale to empty the lung before inhaling.	Patient does not exhale to empty the lung before inhaling.	Patient does not exhale to empty the lung before inhaling.
-	Patient does not turn the head away from device and exhale.	Patient exhales into the device before inhaling.	Patient covers the air entries while inhaling.
Patient does not seal the mouthpiece with the lips.	Patient does not put the mouthpiece in mouth, and close the lips.	Patient does not seal the mouthpiece with the lips.	Patient does not seal the mouthpiece with the lips.
NA	NA	Releasing drug is out of sync with inhaling.	Releasing drug is out of sync with inhaling.
Patient does not hold breath(or hold breath less than 3s).	Patient does not hold breath(or hold breath less than 3s).	Patient does not hold breath(or hold breath less than 3s).	Patient does not hold breath(or hold breath less than 10s).
Patient does not put the cover back and wait for 30-60 seconds for the second dose.	Patient dose not dispose of the capsule and put the cover back on the device.	Patient does not exhale and wait for 30-60 seconds before the second puff.	Patient dose not inhales twice to complete the total daily dosage.

Randomization

Enrollment and randomization are performed at Zhongshan Hospital of Fudan

University. After enrollment, patients will be assigned into two groups in a 1:1 ratio to the PIFR group and control group by random number table method generated by SPSS 22.0.

Blinding

The study adopts blind evaluation. The investigator will enroll participants and assign them into two groups. All data at baseline, 1-month and 3-month visit will be collected by attending physician, who will not be informed of which group the patient has been assigned. In addition, patients will not know the group they belong to. Blind evaluation maximizes the objectivity and reliability of the study.

Statistical analysis

1. Statistical analysis datasets

- Modified intent-to-treat set (MITTS)

Subjects that have undergone randomization and interventions, and carry out primary endpoint evaluation.

- Safety set (SS)

Subjects that are randomized, undergo the intervention, and with safety evaluation data.

2. Statistical analysis methods

Statistical analyses will be performed using SPSS 22.0. Continuous variables are described as mean (SD) or median (p25,p75) and count variables are described as frequency and percentage. All tests were both sided and statistical analysis, 0.05 was set as the P value for significance. For discrete variables including 30-day treatment failure rate, the error rate of inhalation device use, satisfaction with inhalation devices, 30-day mortality and 90-day mortality, a chi-squared ($\chi 2$) test, Fisher's exact test or CMH $\chi 2$ test will be used. For continuous variables including PIFR, CAT score, mMRC score, SGRQ score and COPD-related treatment costs, Student's t-tests or Mann-Whitney test will be used. Subgroup analysis by exacerbation history and GOLD grades

will be performed to rule out the influence of confounding factors to the certain extent.

Patient and public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination of our research. The results will be available to the public if necessary.

Ethics and dissemination

This trial has been registered in the Ethics Committee of Zhongshan Hospital of Fudan University (B2019-142). In this study, diagnosis and treatment will be performed in accordance with the routine management of COPD. Neither Additional drug intervention nor invasive examination and charges will be needed. Therefore, the study is relatively safe with minimal additional risks. Participants will be screened and recruited from hospitalized patients by physicians. No additional public recruitment documents will be used for participants enrollment. All participants will be supposed to sign an informed consent. All information of participants will be kept private and will not be provided to any company or institution. The results will be disseminated through peer-reviewed journals and conference presentations, and proliferation activities will include diverse social non-academic groups and patients.

Discussion

Drug delivery by DPI depends on the inbuilt resistance of the inhaler and the PIFR generated by the patient. PIFR generally depends on an individual's effort as well as the respiratory muscle force, which may be decreased in patients with COPD due to airway stenosis, lung hyperinflation, hypoxemia, and muscle wasting. DPIs are breath-actuated that require the individuals to create turbulent forces to disaggregate the powder into respirable particles which can reach the lower respiratory tract. Patients

with a sufficient PIFR (PIFR > 60 L/min) are able to release the powder and disaggregate the drug resulting in lung deposition.

Sharma and colleagues have found that 31.7% of patients at discharge following hospitalization for an exacerbation of COPD had PIFR less than 60 L/min[3]. Patients with a PIFR less than 60 L/min have been considered not be able to inhale medications using a DPI effectively into the lower respiratory tract according to the literature, while a PIFR less than 30 liters/minute is insufficient[21 22]. However, most clinicians in china prescribe DPI to the patients recovering from AECOPD routinely due to the lack of the availability of long-acting bronchodilators with pMDI without measuring their PIFR. Inappropriate inhaler selection may result in treatment failure of AECOPD. Before our study, it remains unclear whether treatment failure rate is related to PIFR-based inhaler description. A suitable inspiratory flow rate helps to improve the treatment efficacy. In addition to inhaler selection, PIFR group also receive inhaler training to help patients master the correct inhalation method.

Our research has proposed to measure PIFR of patients recovering from AECOPD by InCheck DIAL® and guide COPD inhaler choices and inhaler technique training. The aim of this study is to determine whether the optimized inhalation therapy based on PIFR measured against the simulated resistance can reduce the rate of treatment failure in patients recovering from AECOPD. Therefore, we are planning to verify the clinical significance of including PIFR in the discharge protocol through comparing the difference in 30-day treatment failure rates and other endpoints between PIFR group and the control group.

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Figure legends : Figure 1. The flowchart shows the process of patient's admission, recruitment, intervention and visits. V0, V1, V2, and V3 are all time points to collect data.

Contributors: JLH and JZ planned the study. WZ planned the Statistical analysis methods. All authors contributed to design and development of the trail (JLH, JZ, WZ, HFC, CLD, JYM and YHZ). JLH drafted the manuscript. JZ , HFC, CLD, JYM and YHZ contributed to revised the manuscript. All authors read and approved the final manuscript.

Ethics and dissemination: This trial has been registered in the Ethics Committee of Zhongshan Hospital of Fudan University (B2019-142) and Clinical Trails (NCT04000958).

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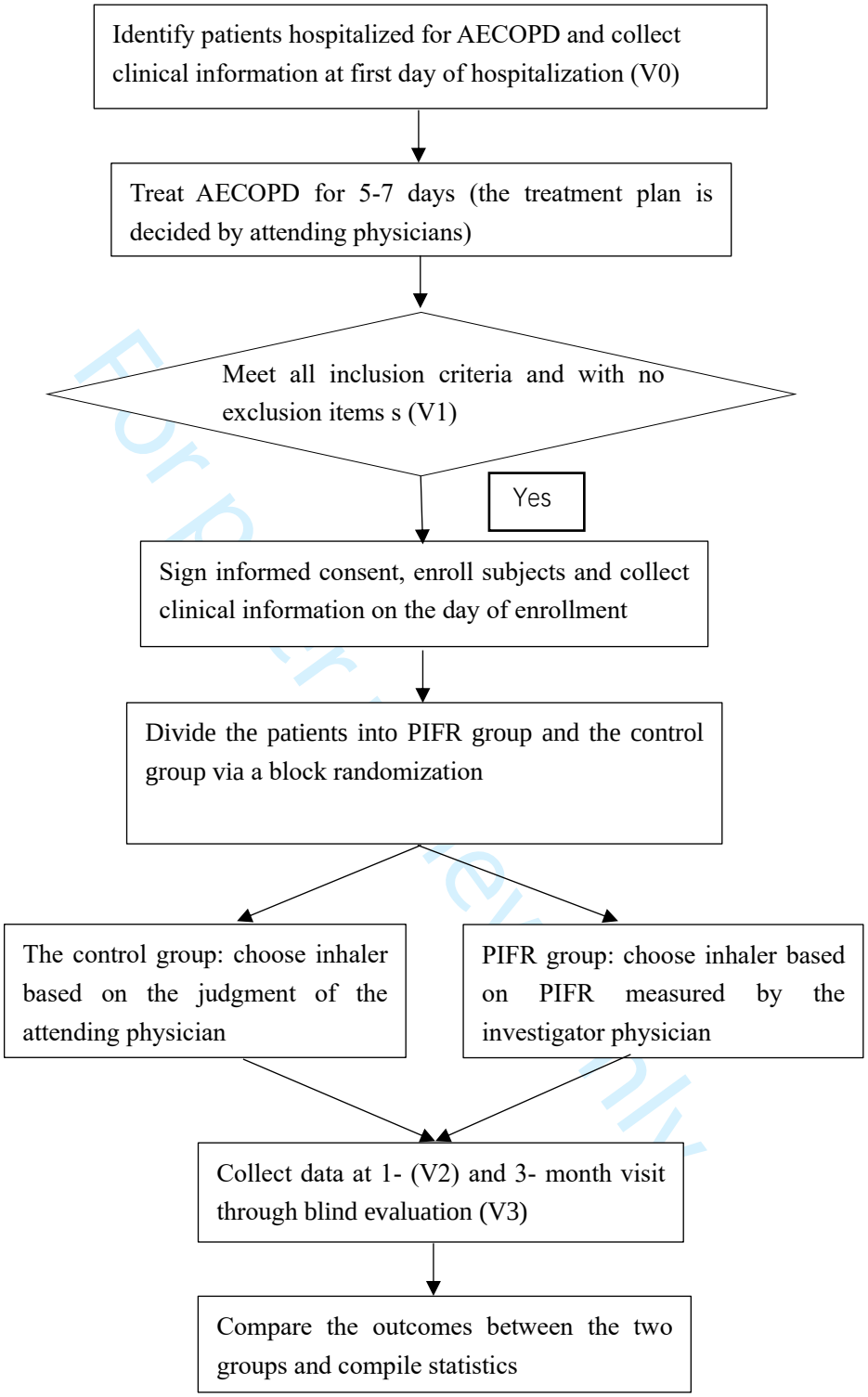
Competing interests statement: None declared.

Word Count: 5111

Figure 1. The flow chart of the study



Informed consent

Participant Information Page

Project Title: Optimized Inhalation Therapy Based on Peak Inspiratory Flow Rates Measured Against the Simulated Resistance in Patients Recovering From Acute Exacerbation of Chronic Obstructive Pulmonary Disease: a Randomized Trial

Principal investigator: Jing Zhang

Sponsor: Zhongshan Hospital, Fudan University

Dear participant:

You are invited to participate in a clinical study of Optimized Inhalation Therapy Based on Peak Inspiratory Flow Rates Measured Against the Simulated Resistance in Patients Recovering From Acute Exacerbation of Chronic Obstructive Pulmonary Disease, supported by Zhongshan Hospital, Fudan University. Please read this informed consent carefully and make a careful decision on whether to participate in this study. Participation in this research is entirely your autonomous choice. As a subject, you need to give your written consent before joining the clinical study. When your research doctor or researcher discusses your informed consent with you, you can ask him / her to explain to you what you don't understand. We encourage you to discuss this thoroughly with your family and friends before making a decision to participate in this research. You have the right to refuse to participate in the study and to withdraw from the study at any time without penalty and without losing your rights. If you are participating in another study, please inform your research doctor or researcher. The background, purpose, research process and other important information of this research are as follows:

1. Background

Chronic obstructive pulmonary disease (COPD) is a common, multiple, highly disabling and highly lethal respiratory disease. Epidemiological surveys in different

periods in China have suggested that COPD has caused a heavy burden of disease. The prevalence of people over 40 years of age is as high as 8.2-13.7%, and it is on the rise. The number of disabled and deadly people caused by COPD exceeds 5 million and 1.28 million each year respectively. Expenditure for patients with advanced COPD accounts for 40% of household income. Therefore, the prevention and treatment of COPD is an important part of Chinese current health undertakings.

Inhalation therapy directly affects the lungs, which has the advantages of rapid onset, excellent curative effect, and good safety. It has an irreplaceable clinical status and is the first-line basic treatment method for COPD. There are three main types of inhalation devices: aerosols, dry powder inhalers (DPI) and miniature nebulizers. Aerosols are divided into pressure metered dose inhaler (pMDI), pMDI and spacers, new pMDI, soft mist inhaler (SMI) and so on. Different inhalation devices have different requirements on the hand and mouth coordination and inhalation ability of patients, and their use methods also have their own characteristics. Research results at home and abroad show that some patients with severe COPD are unable to effectively inhale DPI due to suboptimal lung function. In addition, 28% -68% of patients are unable to benefit from prescription drugs due to improper use of inhalers. Quite a few patients have poor adherence to inhalation therapy, and they have stopped their medication or used irregularly when their symptoms have improved slightly. Therefore, the key to improving the standardization and efficacy of inhalation therapy is: (1) how to choose the most suitable inhaler for patients; (2) how to improve the patients' capacity to use inhalers; (3) how to improve patients' compliance.

In response to these problems, we have designed an optimized inhalation treatment plan, which mainly includes 3 innovative measures and process improvements: (1) selecting the most suitable inhalers for patients based on peak inspiratory flow rates (PIFR), (2) the prescription was made after training and evaluation of the inhalation device, (3) The WeChat public account will regularly push the inhaler using videos and remind patients to take medication regularly to improve the accuracy and standardization of patients' medication.

2. Study purpose

The aim of this study is to determine whether the optimized inhalation therapy based PIFR can reduce the rate of treatment failure in patients recovering from AECOPD and improve patients' prognosis. Errors in inhaler use and quality of life are also to be evaluated.

3. Study outline

(1) How many patients will participate in this study?

This study is a multi-center and approximately 250 people will participate in the study at our hospital.

(2) Study steps

If you agree to participate in this study, please sign this informed consent form. Before you are enrolled in the study, the doctor will ask, record your medical history, and collect information about your previous relevant examinations. We hope that you can truthfully and fully report your medical history and condition to your doctor in order to accurately evaluate your condition and determine whether you are suitable to participate in this study.

After determining that you will participate in this study, the doctor will assign you into the control or optimized group using a random envelope method. The control group will be treated and followed up according to the prescription drugs and devices of Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2019 Report. The optimized group will be given the appropriate inhaler based on their PIFR, and will be evaluated and trained their ability to use the inhalers before prescription. After the prescription, the WeChat public account will also be used to remind the medication regularly and provide patient education.

You will be needed to complete a total of 3 visits, including 2 on-site visits (i.e. baseline visits and 1-month visit), and 1 telephone visits (3-month visit).

The baseline visit was completed on the day of enrollment, including: (1) Basic information: ① Demographic data, including age, gender, age, height, weight, ethnicity,

occupation (years of work), marital status, region, etc. ②General clinical data, including past disease history, drug susceptibility history, vaccination history, family history, current disease history, comorbidities and medication. (2) Evaluation of respiratory symptoms and quality of life: ① the COPD Assessment Test (CAT) Scale, the modified Medical Research Council (mMRC) dyspnea scale; ② St.George's Respiratory Questionnaire(SGRQ) scale. (3) 6-minute walking distance; (4) Survey of satisfaction with inhalers; (5) Measurement of pulmonary ventilation function; (6) Types and dosages of COPD-related drugs.

1-month on-site visit includes: (1) Evaluation of respiratory symptoms and quality of life: ① the COPD Assessment Test (CAT) Scale, the modified Medical Research Council (mMRC) dyspnea scale; ② St.George's Respiratory Questionnaire(SGRQ) scale. (2) Survey of satisfaction with inhalation devices; (3) the error rates of inhaler use; (4) Measurement of pulmonary ventilation function; (5) Acute exacerbation conditions of patients; (6) Types and dosages of COPD-related drugs.

3-month telephone visit includes: (1) Evaluation of respiratory symptoms: the COPD Assessment Test (CAT) Scale the modified Medical Research Council (mMRC) dyspnea scale; (2)the error rates of inhaler use; (3) Acute exacerbation conditions of patients; (4) Types and dosages of COPD-related drugs.

The inspections required during the visit are all based on the clinical needs of regular diagnosis and treatment. There is no need to take additional specimens, which will not increase your burden and risk outside of routine medical treatment.

(3) How long will this study last?

It took 3 months from enrollment to the end of observation. You can opt out of the study at any time without losing any benefits you would have received. However, if you decide to withdraw from the study during the study, we encourage you to discuss it with your doctor first. If you have a serious adverse event, or if your research doctor feels that continuing to participate in the study is not in your best interest, he / she will decide to withdraw you from the study. The sponsor or regulator may also terminate the study during the study period. Your withdrawal will not affect your normal medical treatment and rights.

If you withdraw from the study for any reason, you may be asked about your participation condition in the study. If your doctor thinks it is necessary, you may also be asked to perform laboratory tests and physical examinations.

(4) Information and biological specimens collected during study

This study will collect your basic clinical information, relevant questionnaire information, and information about your condition changes. No extra invasive biological specimen collection will be performed.

The clinical information and samples will be coded by subject numbers and stored in the Department of Respiratory Medicine, Zhongshan Hospital, Fudan University. They will be destroyed after the publish of study and data analysis.

4.Risks and benefits

(1) What are the risks of participating in this study?

The risks that you may take from participating in this study are as follows. You can discuss these risks with your research doctor if you prefer.

During the study, you may have some, all, or none of these adverse events (adverse medical events after the patient or clinical trial subject receives a test product such as a drug / medical device), risks, discomfort, inconvenience, such as:

① There is no additional operation and medication, which will not affect the normal diagnosis and treatment, and will not increase the medical risks other than the normal diagnosis and treatment.

② Participation in this research may involve risks in information security. We will do our best to protect your information from leakage. Some of the questions we ask you in this study may make you feel uncomfortable. You can refuse to answer such questions, and you can rest at any time during the study process. You can also withdraw from the study at any time during the study.

If you experience any discomfort or a new change in your condition or any unexpected condition during the study, whether or not it is related to the study, you should promptly notify your doctor, who will make a judgment and give appropriate

medical treatment.

During the study, you need to be followed up to the hospital on time and do some examinations. It will take some of your time and may cause some trouble or inconvenience.

(2) What are the benefits of participating in the study?

Immediate Benefit: If you agree to participate in this study, you will receive follow-up and free medical counseling for your disease during the study.

Potential benefits: This study may contribute to the improvement of the treatment methods of COPD, and your contribution to the medical cause is very meaningful. We hope that the information you get from this study will benefit you or another patient same as your condition in the future.

5. Alternative treatment options

No alternative treatment options.

6. Use of study results and confidentiality of personal information

All your information during the study is strictly confidential. Only relevant personnel can view your medical records so that they can check the accuracy of the information collected and ensure that the study proceeds normally. Any electronically transmitted information will be renamed to ensure the confidentiality of the information. Information on all computers will be protected with a password. Results of the study may be reported at medical conferences and published in scientific journals. However, no personally identifiable information will be used.

With your and other subjects' understanding and assistance, the results of the research through this project may be published in medical journals, but we will keep your research records confidential as required by law. The personal information of the study subjects will be kept strictly confidential, and your personal information will not be disclosed unless required by relevant laws. When necessary, government administrations, hospital ethics committees, and other relevant researchers can review your data as required.

7. Study costs and related compensation

(1) Drugs / devices used in study and related inspection fees

There is no additional intervention in this study and it will not increase your costs. Inpatient and outpatient routine consultations will not be free. Routine treatments and examinations for other diseases you have combined at the same time will not be free.

(2) Compensation for participating in research

Throughout the study, you only need to visit the site in accordance with the follow-up consultation requirements. There is no additional cost for participating in the study, so no compensation will be made.

(3) Compensation / compensation after damage

The study will not cause additional damage.

8. Subject rights and related considerations

(1) Your rights

You are totally voluntary the study. If you decide not to participate in this study, other treatments you should get will not be affected. If you decide to participate, you will be asked to sign the informed consent form. You have the right to withdraw from the study at any stage of the trial without discrimination or unfair treatment, and your corresponding medical treatment and rights will not be affected.

(2) Related considerations

As a subject, you need to provide true information about your own medical history and current physical condition, tell the research doctor about any discomfort you feel during the study period, do not take restricted drugs and food that the doctor has informed, and tell the research doctor whether you has participated in other study recently or is currently participating in other research.

9.Contact details for information

Your doctor will notify you if there is any important new information during the research that may affect your willingness to continue participating in the study. If you

are interested in your research data or the findings of study, you can ask any questions about the study at any time and get the corresponding answers. Please contact Dr. Jing Zhang at 17898846216.

The ethics committee has reviewed the study, and if you have any questions related to your rights / entitlements, or if you want to reflect the difficulties, dissatisfaction, and anxieties encountered in participating in this study, or if you want to provide comments and suggestions related to this study, please contact the Ethics Committee of Zhongshan Hospital, Fudan University, Tel: 021-64041990 ext. 3257, Email: ec@zs-hospital.sh.cn.

Participant Signature Page

Informed Consent Statement:

I have been informed of the purpose, background, process, risks and benefits of this research. I have enough time and opportunity to ask questions, and I am satisfied with the answers.

I have also been told who to contact when I have questions, want to reflect difficulties, concerns, suggestions for research, or want further information or help with the study.

I have read this informed consent and agree to participate in this study.

I understand that I can choose not to participate in the study and to withdraw from the study at any time during the study process without any reason.

I already know that if my condition gets worse, or if I have serious adverse events, or if my research doctor feels that continuing to participate in the study is not in my best interest, he / she will decide to quit me from the study. Without my consent, the funder or regulator may terminate the study during the study period. If it happens, the

doctor will notify me in time, and the research doctor will discuss my other options with me.

I will get a copy of this informed consent, which contains the signatures of me and the investigator.

Subject Signature: Date:

(Note: If the subject is incapacitated / restricted, the legal representative's signature and signature date are required.)

Legal representative Signature: Date:

(Note: If the subject cannot read the informed consent, an independent witness is required to prove that the researcher has informed the subject of the informed consent. The independent witness's signature and signature date are required.)

Independent Witness Signature: Date:

Investigator Signature: Date:

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	N/A
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
	6b	Explanation for choice of comparators	3-5

Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7-8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-10
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	14
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9-10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	N/A
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	N/A

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The effect of PIFR-based Optimized Inhalation Therapy in Patients Recovering From Acute exacerbation of Chronic Obstructive Pulmonary Disease: protocol of a prospective, multi-center, superiority, randomized controlled trial

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Complete List of Authors:	Hua, Jianlan; Zhongshan Hospital Fudan University, Department of Pulmonary and Critical Care Medicine Zhang, wei; Fudan University, Department of Biostatistics Cao, Hui-fang; Shanghai Jing'an District Central Hospital Du, Chun-ling; Shanghai Qingpu District Central Hospital Ma, Jia-yun; North Branch of Shanghai Ninth People's Hospital Zuo, Yi-hui; Zhongshan Hospital Fudan University, Department of Pulmonary and Critical Care Medicine Zhang, Jing; Zhongshan Hospital Fudan University, Department of Pulmonary and Critical Care Medicine
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Medical education and training, Pharmacology and therapeutics, Research methods
Keywords:	RESPIRATORY MEDICINE (see Thoracic Medicine), Chronic airways disease < THORACIC MEDICINE, MEDICAL EDUCATION & TRAINING

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The effect of PIFR-based Optimized Inhalation Therapy in Patients Recovering From Acute exacerbation of Chronic Obstructive Pulmonary Disease: protocol of a prospective, multi-center, superiority, randomized controlled trial

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Abstract:

Introduction: Acute exacerbation (AE) is a major cause of disease progression and death for patients with Chronic Obstructive Pulmonary Disease (COPD), accounting for a majority of medical expenditures. Correct inhalation therapy is effective in preventing AE attacks. However, inappropriate usages of dry powder inhaler (DPI), partially due to the unrecovered peak inhalation flow rate (PIFR) after AECOPD, result in increased risks of early treatment failure. Therefore, we design a multicenter randomized clinical trial, to determine whether PIFR-based optimized inhalation therapy and training of inhaler usage at discharge could effectively reduce the early treatment failure events.

Methods and analysis: A total of 416 hospitalized patients just recovering from AECOPD will be recruited and be equally randomized into the PIFR group and the control group at a 1:1 ratio. The PIFR group will receive additive support before discharge, including PIFR-guided inhaler choice and education of inhaler usage. PIFR is measure by InCheck DIAL®. In comparison, the control group will only receive inhalers depending on judgments of respiratory physicians. The primary outcome of the study is 30-day treatment failure rate. Other endpoints include PIFR, the error rate of inhalation device use, satisfaction with inhalation devices, 30-day mortality, 90-day mortality, symptoms and life quality of patients and COPD-related treatment costs.

Ethics and dissemination: This trial has been approved by the Ethics Committee of Zhongshan Hospital of Fudan University (B2019-142). Participants will be screened and enrolled from hospitalized patients with AECOPD by clinicians, with no public advertisement for recruitment. After this trial completed, the results will be reported to the public through conference presentations and peer-reviewed journals.

Trial registration: This trial has been registered in ClinicalTrials.gov (NCT04000958).

Strengths and limitations of this study:

1. To our knowledge, this is the first multicenter, randomized trial designed to study the efficacy of PIFR-based inhaler prescription in preventing short-term re-execration in patients recovering from severe acute exacerbation of COPD.

2. InCheck DIAL® is used to measure PIFR and objectively evaluate the capacity of using dry powder inhalers.

3. The inhaler technique will be trained as well to achieve optimal inhalation therapy.

4. Inhalers studied in this trial include Turbuhaler®, Handihaler®, Respimat® and pMDI.

5.The limitation of the study is the single-blind study design, which would yield bias, although blind evaluation is adopted to minimize the bias.

Keywords: chronic obstructive pulmonary disease, acute exacerbation of chronic obstructive pulmonary disease, peak inhalation flow rate, InCheck DIAL®, dry powder inhalers

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a chronic inflammatory disease with the characteristic of irreversible airflow limitation, ranking the 3rd leading cause of death and causing heavy socioeconomic burden worldwide.[1] In China, COPD is also a serious challenge, with the prevalence of 8.6% among adults and high mortality.[2] Direct medical cost of COPD ranged from 72 to 3,565 USD per capita per year, accounting for 33-118% of average annual income of Chinese people.[3] As an important event throughout the course of COPD, acute exacerbation (AE) could accelerate the decline of spirometry and directly cause death, which brings about huge health expenditure[4].

Inhalation drugs is the core pharmaceutical therapy in the management of stable COPD, such as inhaled corticosteroid (ICS), long-acting beta 2 agonists (LABA) and long-acting muscarinic antagonists (LAMA).[5] However, inappropriate usage of inhalers is common in patients with chronic airway diseases, like insufficient inspiratory force and no breath holding (or holding breath for less than 3s)[6,7]. Previous studies showed that errors of inhaler usage were significantly associated with poor outcomes (like frequent exacerbations) and increased medical expenditure.[8] Commonly-used inhalers are classified into four types with different characteristics, including pressure metered dose inhaler (pMDI), dry powder inhalers (DPIs), soft

mist inhalers (SMIs), and nebulizers[9]. The usage of pMDIs is relatively complex, requiring patients to slowly breath in and coordinate many operations to achieve a clinically-effective dose. In comparison, the usage of DPIs is simple, but requires the increase of inspiratory force to overcome internal resistance of the device [10]. Several *in vitro* studies have demonstrated the efficacy of DPI is dependent on the inspiratory flow rate.

When the patient's PIFR is less than a certain threshold required by the DPI device (60 L/min measured at no resistance) [11], the DPI device releases a reduced dose of the drug and generates aerodynamically large drug particles, which is inappropriate to meet the therapeutic needs. Moreover, several studies demonstrated insufficient PIFR in the stable COPD period was associated with poor prognosis, when patients improperly used DPI[12 13]. It should be noted that expiratory flow parameters are not linearly correlated with inspiratory flow rate, suggesting post-bronchodilator forced expiratory volume in one second (FEV_1) is not a suitable predictor of PIFR. Other risk factors for early AECOPD recurrence include age grades, GOLD grades, AE frequency in the previous year, pleural effusion, use of accessory respiratory muscles, noninvasive mechanical ventilation, controlled oxygen therapy and length of hospital stay, while inhaled long-acting β-2-agonists (LABA) and inhaled corticosteroids (ICS) are protection factors[14].

Short-term re-exacerbation is a prominent problem for patients hospitalized for AECOPD with the 30-day re-admission rate of 16-20%. [15 16] Whereas, many patients with COPD do not have enough PIFR to reach the threshold that DPI devices required both in the stable period (nearly 20%)[17] and AE period (based on some small sample studies)[13 18], which influences the effects of inhaled drug on preventing re-AE. Moreover, the assessment of patients' PIFR and ability to use inhaler devices are not integrated into the clinical pathway of discharge for patients hospitalized for AECOPD. Clinicians are still inclined to choose the type of inhalers for patients that they used before admission.

We speculate that the PIFR of patients in the AE recovery period does not return to their baseline levels before AE, and untrained patients are more likely to use the

inhalers incorrectly. Neglect of evaluation of inhalers might result in treatment failure and early re-exacerbation due to ineffective use of inhaled drugs. However, lack of studies demonstrated whether the choice of inhalers based on the PIFR count could reduce the risk of short-term re-exacerbation for patients with AECOPD. Furthermore, although some researches showed that inappropriate use of inhalers was associated with poor prognosis[7,8], it remains unclear whether training patients to correctly use inhalers could reverse poor outcomes.

Therefore, we plan to perform this clinical trial to prospectively determine whether the optimized inhaled drug administration based on PIFR and training patients with InCheck DIAL® could reduce the rate of treatment failure and improve their prognosis for patients hospitalized for AECOPD. Our hypothesis is that AECOPD treatment failure rate is related to improper inhaler selection and missing inhaler use education for patients.

Methods and analysis

Overview

This is a multi-center, single-blind, superiority, randomized clinical trial, in which patients hospitalized for AECOPD are randomly assigned into two groups at a 1:1 ratio: the PIFR group and the control group. Compared with the control group, the PIFR group will receive additive support before discharge, including PIFR-guided inhaler choice and education of inhaler use. The primary outcome is 30-day treatment failure rate. Other endpoints include symptoms and life quality of patients the error rate of inhalation device use, satisfaction with inhalation devices, PIFR, 30-day mortality, 90-day mortality, and COPD-related treatment costs.

The process of patient enrollment, intervention and follow-up of this study are performed at Zhongshan Hospital of Fudan University, Shanghai Jing 'an District Central Hospital, Shanghai Qingpu District Central Hospital and North Branch of Shanghai Ninth People's Hospital in China. The study is expected to last for 2 years.

Recruitment of participants has started since November 2019.

This trial has been approved by the Ethics Committee of Zhongshan Hospital of Fudan University (B2019-142) and registered in ClinicalTrials.gov (NCT04000958).

Inclusion criteria

All the patients with the diagnosis of COPD and hospitalization for AE will be screened. Definitions of COPD and AE are according to the criteria of *Expert Consensus on Acute Exacerbation of Chronic Obstructive Pulmonary Disease in the People's republic of China – 2014 Edition*[4]. Briefly, AECOPD is defined as sudden worsening of respiratory symptoms that require additional treatment (typical manifestations include dyspnea, aggravated cough, increased sputum volume, and/or sputum purulence), which is not explained by normal day-to-day variations and requires additional treatments[4 19].

The subjects will be included if all of the following criteria are met: (1) being 40–80 years old; (2) deteriorated respiratory symptoms being controlled and meeting discharge criteria after 5-7 day standard treatment for AECOPD; (3) having a recorded spirometry measured in the stable period, with post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) <70% and FEV1% predicted value <80%; (4) having signed an informed consent form.

Standard treatment during the hospitalization include atomized or inhaled bronchodilators, broad-spectrum antibiotics and corticosteroids (oral or intravenous glucocorticoid daily equivalent to the 40-50 mg dose of prednisone, or Pulmicort™ 2 mg atomization twice daily).

Discharge criteria are as follows: (1) physician are confident that the patient can manage successfully at home; (2) either LABA and/or LAMA can be used for maintenance with or without ICS, and the frequency of short-acting inhaled β2 receptor agonists is less than every 4 hours; (3) the patient, if previously ambulatory, is able to walk across the room; (4) the patient is able to eat and sleep without frequent awakening due to dyspnea; (5) the patient achieves the clinically-stable

status lasting for 12–24 hours; (6) values of arterial blood gases have been stable for 12–24 hours[4].

Exclusion criteria

Exclusion criteria include:(1) already using home nebulization therapy because of the severe condition; (2) concomitant with asthma, interstitial lung disease, bronchiectasis, pulmonary embolism and other lung diseases; (3) having comorbidities including hypertension, heart diseases, chronic liver and kidney diseases, diabetes, chronic gastrointestinal diseases, malignant tumors and critically ill; (4) suffering from cognitive impairment or not cooperating with the study due to poor mental state; (5) with PIFR less than 20 L/min.

Sample size

We plan to recruit 416 hospitalized patients with AECOPD whose deteriorated symptoms are relieved after 5-7 days of standard therapy. The sample size was calculated using PASS 15.0 Power Analysis and Sample Size Software (2017) (NCSS, LLC. Kaysville, Utah, USA) to ensure the statistical power. Several studies have found that 30-47% patients hospitalized for AECOPD had a PIFR < 60 liters/minute prior to discharge[5 10]. For the control group, 30-day treatment failure rate after hospitalization for AECOPD is approximately 20% according to the literature and our retrospective cohort study [15,16]. However, our preliminary research suggests 30-day treatment failure rate is 10% in the PIFR group. Thus, the expected effect size of superiority is around 10% between two groups. The ratio of number of people in the two groups is 1: 1. A significant two-side *P* value is set as 0.05, and the power is set as 80%. Considering potential dropout risks (5%), 208 patients per group will be recruited, totaling 416 participants.

Study outline

The flow chart of the study design is shown in Figure 1.

The study will recruit 416 patients with AECOPD. After enrollment, the participants are divided into PIFR group and control group at a 1:1 ratio. All the participants in two groups will receive standard treatments for AECOPD described as above during the hospitalized period, and be given the predesigned medications at discharge. At discharge, all the patients will be prescribed with commercial ICS/LABA combination, including either Symbicort turbuhaler® (budesonide/formoterol, 160/4.5 μg *bid*, AstraZeneca AB) or Foster® pressure pMDI (beclomethasone/formoterol, 100/6 μg 2 puff *bid*, Chiesi Farmaceutici S.p.A.). For patients with more respiratory symptoms in the stable period (mMRC ≥2 and CAT≥ 10), Spiriva handihaler® (18μg *qd*) or Spiriva respimat® (2.5μg *qd*, Boehringer IngelheimPharma GmbH & Co.KG) will be given in combination with ICS/LABA.

As for inhalers, participants in the control group will be given DPI or pMDI with a spacer according to the judgment of attending physicians, while participants in the PIFR group will receive education of inhaler use and additive support of evaluation of PIFR at the timepoint of discharge. Attending physicians will show the proper operation of inhalers and correct some common mistakes to patients in the PIFR group.

For PIFR group, PIFR is measured by InCheck DIAL® (Clement Clarke International Ltd, Harlow, UK and Alliance Tech Medical), which is designed to measure inspiratory flow and simulate the "internal resistance" of common inhalers. The numerical values of PIFR provide reference for the attending physicians to guide patients to improve their inspiratory techniques, like increasing or decreasing inspiration forces, which is helpful to achieve a flow rate in consistent with clinical efficacy. The colored 'flow' icons show the clinically effective flow ranges for each different inhaler device. The InCheck DIAL® is accurate to +/− 10% or 10 L/min, and is a low-range inspiratory flow meter (15 to 120 L/min) that has a selectable resistance from high to low, shown by the colored 'flow' icons calibrated to enable the measurement of airflow as if the patient was using certain different inhalers. When

measuring PIFR in this study, we will set the resistance of the InCheck DIAL® to "Zero" and to "Med High" in line with pMDI and turbuhaler®, respectively. Before measuring ，patients are trained to use the InCheck DIAL® correctly. After the PIFR of patients steadily reached the maximum value, the PIFR will be measured for 3 times to make the average as a final result. If PIFR is less than 60 L/min (measured without a resistance), the patients will be given the pMDI with spacer. Otherwise, they will be prescribed with the DPI. Patients using either pMDI or DPI will be taught how to use the device on the spot, and can access to the education video via a WeChat public account at any time.

Moreover, the InCheck DIAL® is also a training device of inhalation muscles, which helps to improve patients' ability to use inhalers. When used for the training of inspiratory muscles, the resistance threshold of InCheckDIAL® is set according to the types of inhalers used by the patient.

Study step

Researchers collect baseline information from participants on the day of enrollment and give interventions to COPD patients recovering from AE at the timepoint of discharge. After discharge, all the participants will be followed up for 3 months and asked for 2 separate visits at 1 and 3 month.

Table 1 shows the requirements of data collection for each visit. Baseline information in the stable period is listed as follows: demographics, clinical characteristics, evaluation of respiratory symptoms and quality of life in the stable phase, PIFR, chest imaging (X-ray or computed tomography) and echocardiography or electrocardiogram in the stable phase. Demographics includes age, gender, age, height, weight, ethnicity, occupation(number of years of work), marital status, family address, etc. Clinical characteristics includes past disease history, history of drug sensitivity, history of vaccination, family disease history, current medical history, comorbidities, medications, etc. Respiratory symptoms are assessed by the modified

Medical Research Council (mMRC) dyspnea scale and the COPD Assessment Test (CAT) score for the patients and quality of life is evaluated by St.George's Respiratory Questionnaire(SGRQ) scale. In addition, PIFR and routine laboratory tests for AE patients (e.g. blood routine, C-reactive protein, liver and kidney function, blood electrolytes, B-type natriuretic peptide, D-dimer) were also recorded.

At the 1-month and 3-month, patients are required to have an outpatient department visit to assess the effects of intervention and collect some data, including CAT score, mMRC score, SGRQ score, PIFR, spirometry, the error rate of inhalation device use, satisfaction with inhalation devices, and COPD-related medications. To reinforce the adherence, patients and their relatives will be contacted by telephone to confirm the dates of evaluation in advance. If the patient is inconvenient to come to the hospital, researchers will collect the above information from the patient as much as possible via phone.

Outcomes

The primary endpoint is 30-day treatment failure rate of AECOPD. Treatment failure means AECOPD recurrence resulting in an emergency visit, admission, or need for intensified medication.

Secondary outcomes include PIFR, the error rate of inhalation device use, satisfaction with inhalation devices, 30-day mortality, 90-day mortality, symptoms and life quality of patients and COPD-related treatment costs.

Patient's satisfaction with inhalation devices will be assessed by the Feeling of Satisfaction with Inhaler (FSI-10) questionnaire. The FSI-10 questionnaire is supposed to be completed by patients themselves, which has been widely applied to assess patients' opinions about inhalers in terms of ease of use, portability, and usability[20].The symptoms of patients are evaluated by the CAT scale and mMRC scale. The patients' quality of life are evaluated by SGRQ scale.

PIFR is measured by InCheck DIAL® (Clement Clarke International Ltd, Harlow,

UK and Alliance Tech Medical) under the guidance of respiratory physicians. Some common errors in the usage of different inhalation devices are described in Table 2[6 7].

Randomization and blinding

The participants will be assigned into two groups at a 1:1 ratio using random number table generated by IBM SPSS statistics 23 (SPSS Inc, Chicago, IL). The randomization process was performed by an independent researcher who will not participate in other research procedures. To maximize the objectivity and reliability of our study, single-blind and allocation concealment are adopted. Sealed envelopes containing an allocation number are distributed to attending physicians in advance to achieve allocation concealment, and they will not know the allocation group until giving intervention. Other researchers responsible for data collection and follow-up are not informed of which group the patient has been assigned to. Patients and their relatives are blinded to allocation during the whole process, and are only informed that they participate in a study of COPD discharge plan. In addition, statistical analysis will be performed by an independent statistician, who will also be blinded to the group labels.

Statistical analysis

1. Statistical analysis datasets

- Modified intent-to-treat set (MITTS)

Subjects that have undergone randomization and interventions, and carry out primary endpoint evaluation.

- Safety set (SS)

Subjects that are randomized, undergo the intervention, and with safety evaluation data.

2. Statistical analysis methods

Statistical analyses will be performed using IBM SPSS statistics 22 (SPSS Inc, Chicago, IL). Continuous variables are described as mean (standard deviation) or

median (interquartile range), while categorical variables are described as frequency and percentage. A two-tailed *P* value < 0.05 is considered as statistical significance. Student's t-tests or Mann-Whitney test, depending on normality and homogeneity of variance, was used to compare continuous variables between two groups, including PIFR, CAT score, mMRC score, SGRQ score and COPD-related treatment costs. For discrete variables, such as 30-day treatment failure rate, the error rate of inhalation device use, satisfaction with inhalation devices, 30-day mortality and 90-day mortality, Chi-Quared ($\chi 2$) Test, Fisher's exact test or CMH $\chi 2$ test will be applied for comparison. To rule out the influence of confounding factors and identify optimal subpopulation, subgroup analysis will be performed based on previous exacerbation history and GOLD grades.

Patient and public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination of our research. The results will be available to the public if necessary.

Ethics and dissemination

This trial has been approved by the Ethics Committee of Zhongshan Hospital of Fudan University (B2019-142). In this study, diagnosis and treatment will be performed in accordance with the routine management of COPD. Neither Additional drug intervention nor invasive examination and charges will be needed. Therefore, the study is relatively safe with minimal additional risks. Participants will be screened and recruited from hospitalized patients by physicians, with no public advertisement for recruitment. All participants will be supposed to sign an informed consent. A blank copy of the original consent form is provided and shown as a supplementary document. All information of participants will be kept private and will not be provided to any company or institution. The results will be disseminated through

peer-reviewed journals and conference presentations.

Discussion

DPI drug delivery depends on the inherent resistance of the inhaler and the PIFR of the patient. PIFR value is determined by an individual's subjective effort as well as his/her respiratory muscle force, which may be decreased in patients with COPD due to airway stenosis, lung hyperinflation, hypoxemia, and muscle wasting. As a breath-actuated inhaler, DPI requires patients to create enough turbulent forces to disaggregate the powder into respirable particles which can reach the lower respiratory tract. Patients with a relatively high PIFR (> 60 L/min) enable DPIs to release a sufficient amount of powder and disaggregate the drug to achieve sufficient drug deposition in the lung.

Sharma and colleagues reported that 31.7% of hospitalized patients for AECOPD had PIFR less than 60 L/min at the timepoint of discharge [10]. Patients with a PIFR less than 60 L/min have been considered not be able to effectively inhale medications using a DPI into their lower respiratory tracts, while a PIFR less than 30 L/min was insufficient[21 22]. For lack of availability of long-acting bronchodilators with pMDI, most Chinese clinicians routinely prescribe DPIs to the patients recovering from AECOPD without measuring their values of PIFR. Inappropriate inhaler selection may result in treatment failure of AECOPD. To our knowledge, it remains unclear whether treatment failure rate is negatively related to improper inhaler description. A suitable inspiratory flow rate helps to improve the treatment efficacy. In addition to appropriate inhaler selection, participants in PIFR group also receive inhaler training to help them master the correct inhalation method.

Our research has proposed to measure PIFR of patients recovering from AECOPD by InCheck DIAL® to guide the choice of inhalers and the training of inhalation techniques. The aim of this study is to determine whether treatment failure rate of patients just recovering from AECOPD could be reduced by the optimized inhalation

therapy based on PIFR which is measured against the simulated airway resistance. We anticipate that the positive results of this study will provide evidence for improving discharge protocols of AECOPD by including PIFR evaluation.

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Figure legends : Figure 1. The flow chart of the study. The process of patient's screening, recruitment, intervention, visits and data processing are described in the figure. V0, V1, V2, and V3 are time points to collect data. AECOPD: acute exacerbation of chronic obstructive disease; PIFR: peak inspiratory flow rate.

Contributors: JLH and JZ planned the study. WZ planned the Statistical analysis methods. All authors contributed to design and development of the trail (JLH, JZ, WZ, HFC, CLD, JYM and YHZ). JLH drafted the manuscript. JZ , HFC, CLD, JYM and YHZ contributed to revised the manuscript. All authors read and approved the final manuscript.

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Table 1. Data collected at each visit

	V0	*V1*	*V2*	*V3*
	Hospitalization±1 day	At the time of discharge (meet discharge standards)	1 month after discharge	3 month after discharge
Basic Information	√			
Information of COPD at stable phase	√			
Blood routine	√	√		
Liver and kidney function	√	√		
Electrolyte	√	√		
C-reactive protein	√	√		
procalcitonin	√	√		
brain natriuretic peptide	√	√		
D-dimer 、 Fibrinogen	√	√		
cardiac troponin T	√	√		
CAT score	√	√	√	√
mMRC	√	√	√	√
SGRQ		√	√	√
Drug for COPD	Stable phase	AE phase	Stable phase	Stable phase
PIFR		PIFR√	PIFR√	PIFR√

Prognosis			√	√
Pulmonary function		√	√	√
Echocardiography at stable phase				
CT at stable phase				
CT at AE phase				
Error of inhaler use			√	√
Satisfaction with the inhaler			√	√
Daily cost of COPD related treatment			√	√

Abbreviations: CAT, the COPD Assessment Test; mMRC, the modified Medical Research Council dyspnea scale; SGRQ, St.George's Respiratory Questionnaire; PIFR, eak inhalation flow rate.

Table 2. **Common errors in the usage of different inhalation devices**

Turbuhaler®	**Handihaler®/Accuhaler®**	**pMDI**	**Respimat®**
Cover is not removed or not covered properly.	Cover is not removed or not covered properly.	Cover is not removed or not covered properly.	Cover is not removed or not covered properly.
Dose is reduced due to patients shaking or tilt the device during preparation.	-		The device is not installed correctly before use.
Device is not held upright.	-	Device is not held upright.	-
Patient does not twist grip at the base or twist around and then back until click is heard.	-	-	Patient dose not turn the device toward the arrow in the label until it clicks.
Inhalation force is insufficient.	Inhalation force is insufficient.	Patient dose not inhale deeply and slowly.	Patient dose not inhale deeply and slowly.
Patient does not tilt his/her head to make his/her chin	Patient does not hold his/her head in a vertical position.	Patient does not tilt his/her head to make his/her chin	Patient dose not point the inhaler toward the back

slightly upturned.		slightly upturned.	of throat.
Patient does not exhale to empty the lung before the next inhalation.	Patient does not exhale to empty the lung before the next inhalation.	Patient does not exhale to empty the lung before the next inhalation.	Patient does not exhale to empty the lung before the next inhalation.
-	Patient does not turn his/her head away from device's mouthpiece before exhalation.	Patient exhales into the device before the next inhalation.	Patient covers the air entries while inhaling.
Patient does not seal the mouthpiece with his/her lips.	The patient did not place the mouthpiece in his/her mouth nor closed his/her lips.	Patient does not seal the mouthpiece with his/her lips.	Patient does not seal the mouthpiece with his/her lips.
NA	NA	Patients does not inhale them in sync with the drug releasing.	Patients does not inhale them in sync with the drug releasing.
Patient does not hold breath (or hold breath less than 3s).	Patient does not hold breath (or hold breath less than 3s).	Patient does not hold breath (or hold breath less than 3s).	Patient does not hold breath (or hold breath less than 10s).
Patient does not cover the lid and wait for 30-60 seconds for the second dose.	Patient dose not dispose of the capsule and cover the lid on the device.	Patient does not exhale and wait for 30-60 seconds before the second puff.	Patient dose not inhale twice to achieve the total daily dosage.

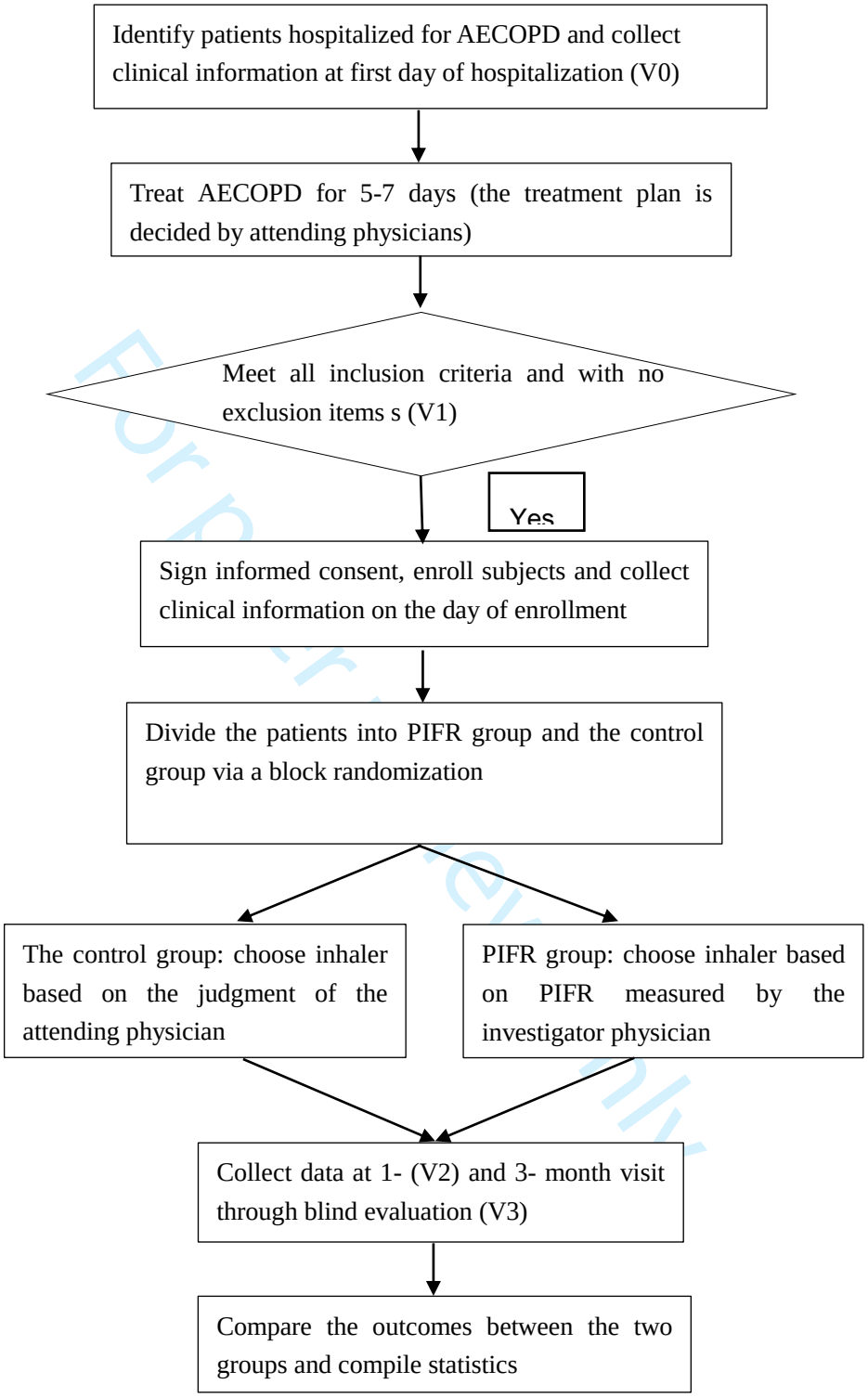

Figure 1. The flow chart of the study. The process of patient's screening, recruitment, intervention, visits and data processing are described in the figure. V0, V1, V2, and V3 are time points to collect data. AECOPD: acute exacerbation of chronic obstructive disease; PIFR: peak inspiratory flow rate.

Informed consent

Participant Information Page

Project Title: Optimized Inhalation Therapy Based on Peak Inspiratory Flow Rates Measured Against the Simulated Resistance in Patients Recovering From Acute Exacerbation of Chronic Obstructive Pulmonary Disease: a Randomized Trial

Principal investigator: Jing Zhang

Sponsor: Zhongshan Hospital, Fudan University

Dear participant:

You are invited to participate in a clinical study of Optimized Inhalation Therapy Based on Peak Inspiratory Flow Rates Measured Against the Simulated Resistance in Patients Recovering From Acute Exacerbation of Chronic Obstructive Pulmonary Disease, supported by Zhongshan Hospital, Fudan University. Please read this informed consent carefully and make a careful decision on whether to participate in this study. Participation in this research is entirely your autonomous choice. As a subject, you need to give your written consent before joining the clinical study. When your research doctor or researcher discusses your informed consent with you, you can ask him / her to explain to you what you don't understand. We encourage you to discuss this thoroughly with your family and friends before making a decision to participate in this research. You have the right to refuse to participate in the study and to withdraw from the study at any time without penalty and without losing your rights. If you are participating in another study, please inform your research doctor or researcher. The background, purpose, research process and other important information of this research are as follows:

1. Background

Chronic obstructive pulmonary disease (COPD) is a common, multiple, highly disabling and highly lethal respiratory disease. Epidemiological surveys in different

periods in China have suggested that COPD has caused a heavy burden of disease. The prevalence of people over 40 years of age is as high as 8.2-13.7%, and it is on the rise. The number of disabled and deadly people caused by COPD exceeds 5 million and 1.28 million each year respectively. Expenditure for patients with advanced COPD accounts for 40% of household income. Therefore, the prevention and treatment of COPD is an important part of Chinese current health undertakings.

Inhalation therapy directly affects the lungs, which has the advantages of rapid onset, excellent curative effect, and good safety. It has an irreplaceable clinical status and is the first-line basic treatment method for COPD. There are three main types of inhalation devices: aerosols, dry powder inhalers (DPI) and miniature nebulizers. Aerosols are divided into pressure metered dose inhaler (pMDI), pMDI and spacers, new pMDI, soft mist inhaler (SMI) and so on. Different inhalation devices have different requirements on the hand and mouth coordination and inhalation ability of patients, and their use methods also have their own characteristics. Research results at home and abroad show that some patients with severe COPD are unable to effectively inhale DPI due to suboptimal lung function. In addition, 28% -68% of patients are unable to benefit from prescription drugs due to improper use of inhalers. Quite a few patients have poor adherence to inhalation therapy, and they have stopped their medication or used irregularly when their symptoms have improved slightly. Therefore, the key to improving the standardization and efficacy of inhalation therapy is: (1) how to choose the most suitable inhaler for patients; (2) how to improve the patients' capacity to use inhalers; (3) how to improve patients' compliance.

In response to these problems, we have designed an optimized inhalation treatment plan, which mainly includes 3 innovative measures and process improvements: (1) selecting the most suitable inhalers for patients based on peak inspiratory flow rates (PIFR), (2) the prescription was made after training and evaluation of the inhalation device, (3) The WeChat public account will regularly push the inhaler using videos and remind patients to take medication regularly to improve the accuracy and standardization of patients' medication.

2. Study purpose

The aim of this study is to determine whether the optimized inhalation therapy based PIFR can reduce the rate of treatment failure in patients recovering from AECOPD and improve patients' prognosis. Errors in inhaler use and quality of life are also to be evaluated.

3. Study outline

(1) How many patients will participate in this study?

This study is a multi-center and approximately 250 people will participate in the study at our hospital.

(2) Study steps

If you agree to participate in this study, please sign this informed consent form. Before you are enrolled in the study, the doctor will ask, record your medical history, and collect information about your previous relevant examinations. We hope that you can truthfully and fully report your medical history and condition to your doctor in order to accurately evaluate your condition and determine whether you are suitable to participate in this study.

After determining that you will participate in this study, the doctor will assign you into the control or optimized group using a random envelope method. The control group will be treated and followed up according to the prescription drugs and devices of Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2019 Report. The optimized group will be given the appropriate inhaler based on their PIFR, and will be evaluated and trained their ability to use the inhalers before prescription. After the prescription, the WeChat public account will also be used to remind the medication regularly and provide patient education.

You will be needed to complete a total of 3 visits, including 2 on-site visits (i.e. baseline visits and 1-month visit), and 1 telephone visits (3-month visit).

The baseline visit was completed on the day of enrollment, including: (1) Basic information: ① Demographic data, including age, gender, age, height, weight, ethnicity,

occupation (years of work), marital status, region, etc. ②General clinical data, including past disease history, drug susceptibility history, vaccination history, family history, current disease history, comorbidities and medication. (2) Evaluation of respiratory symptoms and quality of life: ① the COPD Assessment Test (CAT) Scale, the modified Medical Research Council (mMRC) dyspnea scale; ② St.George's Respiratory Questionnaire(SGRQ) scale. (3) 6-minute walking distance; (4) Survey of satisfaction with inhalers; (5) Measurement of pulmonary ventilation function; (6) Types and dosages of COPD-related drugs.

1-month on-site visit includes: (1) Evaluation of respiratory symptoms and quality of life: ① the COPD Assessment Test (CAT) Scale, the modified Medical Research Council (mMRC) dyspnea scale; ② St.George's Respiratory Questionnaire(SGRQ) scale. (2) Survey of satisfaction with inhalation devices; (3) the error rates of inhaler use; (4) Measurement of pulmonary ventilation function; (5) Acute exacerbation conditions of patients; (6) Types and dosages of COPD-related drugs.

3-month telephone visit includes: (1) Evaluation of respiratory symptoms: the COPD Assessment Test (CAT) Scale the modified Medical Research Council (mMRC) dyspnea scale; (2)the error rates of inhaler use; (3) Acute exacerbation conditions of patients; (4) Types and dosages of COPD-related drugs.

The inspections required during the visit are all based on the clinical needs of regular diagnosis and treatment. There is no need to take additional specimens, which will not increase your burden and risk outside of routine medical treatment.

(3) How long will this study last?

It took 3 months from enrollment to the end of observation. You can opt out of the study at any time without losing any benefits you would have received. However, if you decide to withdraw from the study during the study, we encourage you to discuss it with your doctor first. If you have a serious adverse event, or if your research doctor feels that continuing to participate in the study is not in your best interest, he / she will decide to withdraw you from the study. The sponsor or regulator may also terminate the study during the study period. Your withdrawal will not affect your normal medical treatment and rights.

If you withdraw from the study for any reason, you may be asked about your participation condition in the study. If your doctor thinks it is necessary, you may also be asked to perform laboratory tests and physical examinations.

(4) Information and biological specimens collected during study

This study will collect your basic clinical information, relevant questionnaire information, and information about your condition changes. No extra invasive biological specimen collection will be performed.

The clinical information and samples will be coded by subject numbers and stored in the Department of Respiratory Medicine, Zhongshan Hospital, Fudan University. They will be destroyed after the publish of study and data analysis.

4.Risks and benefits

(1) What are the risks of participating in this study?

The risks that you may take from participating in this study are as follows. You can discuss these risks with your research doctor if you prefer.

During the study, you may have some, all, or none of these adverse events (adverse medical events after the patient or clinical trial subject receives a test product such as a drug / medical device), risks, discomfort, inconvenience, such as:

① There is no additional operation and medication, which will not affect the normal diagnosis and treatment, and will not increase the medical risks other than the normal diagnosis and treatment.

② Participation in this research may involve risks in information security. We will do our best to protect your information from leakage. Some of the questions we ask you in this study may make you feel uncomfortable. You can refuse to answer such questions, and you can rest at any time during the study process. You can also withdraw from the study at any time during the study.

If you experience any discomfort or a new change in your condition or any unexpected condition during the study, whether or not it is related to the study, you should promptly notify your doctor, who will make a judgment and give appropriate

medical treatment.

During the study, you need to be followed up to the hospital on time and do some examinations. It will take some of your time and may cause some trouble or inconvenience.

(2) What are the benefits of participating in the study?

Immediate Benefit: If you agree to participate in this study, you will receive follow-up and free medical counseling for your disease during the study.

Potential benefits: This study may contribute to the improvement of the treatment methods of COPD, and your contribution to the medical cause is very meaningful. We hope that the information you get from this study will benefit you or another patient same as your condition in the future.

5. Alternative treatment options

No alternative treatment options.

6. Use of study results and confidentiality of personal information

All your information during the study is strictly confidential. Only relevant personnel can view your medical records so that they can check the accuracy of the information collected and ensure that the study proceeds normally. Any electronically transmitted information will be renamed to ensure the confidentiality of the information. Information on all computers will be protected with a password. Results of the study may be reported at medical conferences and published in scientific journals. However, no personally identifiable information will be used.

With your and other subjects' understanding and assistance, the results of the research through this project may be published in medical journals, but we will keep your research records confidential as required by law. The personal information of the study subjects will be kept strictly confidential, and your personal information will not be disclosed unless required by relevant laws. When necessary, government administrations, hospital ethics committees, and other relevant researchers can review your data as required.

7. Study costs and related compensation

(1) Drugs / devices used in study and related inspection fees

There is no additional intervention in this study and it will not increase your costs. Inpatient and outpatient routine consultations will not be free. Routine treatments and examinations for other diseases you have combined at the same time will not be free.

(2) Compensation for participating in research

Throughout the study, you only need to visit the site in accordance with the follow-up consultation requirements. There is no additional cost for participating in the study, so no compensation will be made.

(3) Compensation / compensation after damage

The study will not cause additional damage.

8. Subject rights and related considerations

(1) Your rights

You are totally voluntary the study. If you decide not to participate in this study, other treatments you should get will not be affected. If you decide to participate, you will be asked to sign the informed consent form. You have the right to withdraw from the study at any stage of the trial without discrimination or unfair treatment, and your corresponding medical treatment and rights will not be affected.

(2) Related considerations

As a subject, you need to provide true information about your own medical history and current physical condition, tell the research doctor about any discomfort you feel during the study period, do not take restricted drugs and food that the doctor has informed, and tell the research doctor whether you has participated in other study recently or is currently participating in other research.

9.Contact details for information

Your doctor will notify you if there is any important new information during the research that may affect your willingness to continue participating in the study. If you

are interested in your research data or the findings of study, you can ask any questions about the study at any time and get the corresponding answers. Please contact Dr. Jing Zhang at 17898846216.

The ethics committee has reviewed the study, and if you have any questions related to your rights / entitlements, or if you want to reflect the difficulties, dissatisfaction, and anxieties encountered in participating in this study, or if you want to provide comments and suggestions related to this study, please contact the Ethics Committee of Zhongshan Hospital, Fudan University, Tel: 021-64041990 ext. 3257, Email: ec@zs-hospital.sh.cn.

Participant Signature Page

Informed Consent Statement:

I have been informed of the purpose, background, process, risks and benefits of this research. I have enough time and opportunity to ask questions, and I am satisfied with the answers.

I have also been told who to contact when I have questions, want to reflect difficulties, concerns, suggestions for research, or want further information or help with the study.

I have read this informed consent and agree to participate in this study.

I understand that I can choose not to participate in the study and to withdraw from the study at any time during the study process without any reason.

I already know that if my condition gets worse, or if I have serious adverse events, or if my research doctor feels that continuing to participate in the study is not in my best interest, he / she will decide to quit me from the study. Without my consent, the funder or regulator may terminate the study during the study period. If it happens, the

doctor will notify me in time, and the research doctor will discuss my other options with me.

I will get a copy of this informed consent, which contains the signatures of me and the investigator.

Subject Signature: Date:

(Note: If the subject is incapacitated / restricted, the legal representative's signature and signature date are required.)

Legal representative Signature: Date:

(Note: If the subject cannot read the informed consent, an independent witness is required to prove that the researcher has informed the subject of the informed consent. The independent witness's signature and signature date are required.)

Independent Witness Signature: Date:

Investigator Signature: Date:

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Reported on page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	N/A
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
	6b	Explanation for choice of comparators	3-5

Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7-8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-10
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	14
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9-10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	N/A
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	N/A

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.