Supplementary

Real-world Effectiveness Study of Guideline-Directed COPD STANDARDized Management in Patients with Chronic Obstructive Pulmonary Disease: a Cluster Randomized Trial Design

Strengthened training and Central quality control

Before study initiation, but after treatment group allocation, training materials will be distributed to local investigators. Except that SM interventions training is just delivered to hospitals in the SM group, trainings on the study procedures, such as pulmonary function testing, 6-minute walking test (6MWT), data entry into electronic data capture (EDC), will be provided to hospitals in both groups. Local investigators practice 6MWT and send videos of their practice to the steering committee for central review. Spirometry reports are required at least three qualified measurements and curves to assess the quality of testing. Advanced pulmonary specialists in tertiary hospitals will act as quality coordinators, who will visit the secondary hospitals to give clinical guidance according to a checklist crafted by steering committee. The frequency of guidance differs between the two groups. In the UC group, the tertiary hospital pulmonary specialists will review the pulmonary function testing, 6MWT and other assessments at first patient enrollment and every 6 months during follow-up. In the SM group, besides the assessments, they will review the delivery of the planned interventions. Pulmonary specialists' visits are scheduled at the first patient enrollment and every 2-3 months afterward. Site monitor visits will be conducted by an independent CRA to review study procedures and verify source data. Throughout the study, repeated training and central quality control will be provided.

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After enrolling 3-5 patients per site, the steering committee will visit the site to verify the eligibility of enrolled patients by reviewing medical records. A face-to-face strengthened training on the study protocol and operating procedures will be delivered. Local investigators (physicians, nurses, and administrators) will be invited to attend the training workshop. Key operating procedures will be stressed in this face-to-face meeting, aiming to improve adherence to study procedures and better understanding of the protocol.

A web-based data capture system is developed for data quality audit and feedback. Value ranges, logic checks and warnings against missing data are predefined. Once outliers, erroneous, or incomplete data are identified, queries are automatically sent to local investigators (physicians or nurses). The investigators will respond to each inquiry by checking original files and determine any necessary corrections, if necessary, modify original files with written documentation of changes, and finally close the queried item. The EDC system will also monitor study progress at each site and send electronic messages to investigators and patients to remind them of the coming visits. Throughout the study, investigators' access to data and activities undertaken in the system will be regulated based on their privileges.

Additionally, centralized reviews will be performed to assure quality of key data, such as endpoints and spirometry tests. Independent specialists who are not involved in the study adjudicate exacerbation events and the severity via reviewing medical records on patients' hospital visits and healthcare-seeking behaviors. Trained technicians will perform quality-assured post-bronchodilator spirometry and reports are evaluated centrally by qualified readers with experience in spirometry testing.

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Standardized Management

In order to standardize the management for stable COPD in SM group, an integrated intervention encompassing the following aspects will be delivered:

(1) Inhaler use and maintenance therapy

Long-acting muscarinic antagonists (LAMAs), long-acting beta$_2$-agonist (LABA), inhaled corticosteroids (ICS), short-acting antimuscarinics (SAMAs), and short-acting beta$_2$-agonists (SABA) will be prescribed, as indicated. For patients newly diagnosed with COPD or never used inhalers regularly before, including those who used inhalers previously but have stopped, inhaled medicine will be prescribed at baseline as their initial treatment. Exacerbation history and respiratory symptoms are combined to determine the regimen, with pneumonia and other comorbidities taken into consideration. For patients who have been previously diagnosed with COPD and already taken inhalers regularly, their response to this treatment will be assessed and if it judged to be inadequate, physicians will first evaluate the patient's use of their inhaler device, identify possible causes of poor response, and adjust their treatment regimen accordingly (Figure S1A). Normally, a one-month course of medicine is prescribed as per health policies in China. At the follow visit, physicians will review the patient's responses to their initial therapy and leave it unchanged, escalate or de-escalate (Figure S1B). Given the key role of proper inhalation technique, direct observation of inhaler technique and re-education will be delivered to ensure patients proper use of inhalers at each visit. A check of inhaler technique and adherence will be performed before modifying the treatment. The choice of inhalers and devices will depend on patients' morbid conditions, responses, and inhaled drugs provided in the hospital. Information on pharmacological therapy and inhalation techniques are

collected every three months (Table S2). If a patient misses a scheduled visit, nurses will remind them via messaging or phone.

(2) Long-term follow-up and symptom monitoring

Nurses in each hospital will administer the CAT and mMRC assessments every 3 months during the 12-month follow-up (Table S1). Physicians will review patients' respiratory symptoms (dyspnea, cough, wheeze, and sputum) and assess their symptom control and comorbidities (pneumonia, tuberculosis, non-tuberculosis mycobacteria, allergic rhinitis) for maintenance therapy prescription.

(3) Annual pulmonary function testing

Patients in the SM group will undergo post-bronchodilator spirometry at baseline and 12 months. Trained technicians perform tests that meet American Thoracic Society standards [1,2].

(4) Strengthened COPD education

To improve early recognition and self-management of exacerbations, patients and family caregivers will be motivated to engage in education sessions conducted by trained nurses, starting on the day of enrollment, and at each clinic visit. This will include information about COPD, including causes, symptoms, importance of long-term inhaler use and maintenance therapy, prevention and management of acute exacerbation. A total of seven education sessions will be delivered to enable patients to manage their diseases. Patients will have a quiz at the end of each session to test whether their knowledge needs to be strengthened (Figure S2).

(5) Behavioral modification

Patients will be encouraged to use non-pharmacological treatments, including smoking cessation, pulmonary rehabilitation, vaccination, and other favorable behaviors [3]. For patients who are active smokers, smoking cessation counseling will be provided mainly using 5R and 5A principles. As smoking cessation can help retard COPD progression [4], the counseling is repeated until patients quit smoking or the end of 12-month follow-up (Figure S3). Rehabilitation programs will also be prescribed to maintain patients' physical activity. These will be culturally appropriate. Patients will receive supervised breathing training including diaphragmatic and pursed lip breathing and a walking program regimen. Patients will be encouraged to perform breathing exercise twice daily with 5 minutes for each. They will also be encouraged to learn baduanjin, a Chinese traditional health-promoting exercise that can improve clinical outcomes in COPD patients[5]. Patients who have practiced baduanjin will be encouraged to perform it each day. 2) Walking program will be personalized based on their 6-minute walking distance (6MWD) and blood oxygen saturation, both of which will be evaluated at baseline and 12 months. Oxygen saturation will be measured before and at the end of 6MWD to obtain saturation at rest and saturation at activity. If patients present no hypoxemia, with oxygen saturation ≥90% at rest and oxygen saturation ≥85% during activity, home-based aerobic exercise regimen of 30-minute walking will be prescribed. The 30-minute walking distance is recommended to be multiplication of 6MWD and 5 and 85%. For example, if patient walks 400 meters in the 6MWD test and has no hypoxemia, he/she would be recommended to walk for at least 30 minutes and the distance would be 400 x 5 x 85%, which equates to 1700 meters. If patients present with hypoxemia, use of an oxygen delivery device will be recommended. At the end of the rehabilitation program, patients will be encouraged to

maintain physically active throughout the study (Figure S4). Influenza and pneumococcal vaccination will be recommended if patients are not vaccinated at each visit until patients get vaccinated or the end of follow-up. Some patients may still be advised to be re-vaccinated if they have exceeded the vaccination time interval, specifically, longer than 1 year for influenza or 5 years for pneumococcal vaccination (Figure S5).

A web-based interactive EDC is developed for correct delivery of the SM interventions. Key procedures and reminders are embedded into the system. When patients' information is entered into the EDC, individualized advice will be presented interactively to help physicians prescribe appropriate inhalers for patients and help nurses provide non-pharmacological part of SM interventions. Three kinds of pocket card are also designed with key messages or tips for physicians to prescribe inhalers, for nurses to provide education and for patients to adopt favorable lifestyle, respectively. EDC and pocket-cards are aimed to ensure COPD delivered in a standardized way (Figure S6). Compliance to visits will be assessed to determine whether patients are receptive to SM in real-world clinical setting. To enhance adherence and reduce the burden on local investigators' existing workload, patients will receive the education component of the program in a group online, or when they return clinics to refill their medicine.

Intervention modifications and discontinuations

Patients in SM group will discontinue the interventions if they refuse to use inhaler medicine and do not receive the non-pharmacological interventions from baseline and the following visit. Patients in both groups who are lost-to-follow-up for two

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consecutive visits, have ≥80% visits outside visit window, or unexpected death after baseline and before the first follow-up will also be withdrawn early from the study.

Retention plan

To reduce loss to follow-up, we developed a retention strategy that includes, but is not limited to: providing financial reimbursement for round-trip fares between hospital and home at each face-to-face encounter, confirm patients' contact information at each visit, give test results back to patients, e.g., spirometry testing, blood routine tests, 6-minute walking test. To ensure patients' long-term follow up, we will select hospitals that serve a relative stable population. Patients who are residents living nearby will be recruited as potentially eligible patients. For patients who remain lost to follow-up, we will record their reasons for attrition to determine the pattern of missing data.

Confidentiality

Confidentiality of patient information will be kept throughout the study. Data collected in the study will be stored into the EDC and backed up periodically. No ancillary information or biological specimens will be collected from patients during study period. When pre-screening potentially eligible patients, local investigators record their names, identification code and contact number if they are willing to participate. Written informed consent will be obtained before screening and any data collection.

Data Management Plan

A secure, web-based EDC system has been developed to manage data. Site investigators will use the EDC to enter data, with automatic checks for value ranges, logical mistakes and missingness. Source data, such as medical records, recordings, will be reviewed by an independent CRA to verify data accuracy. The QA team will manage data queries by reviewing audit trails for tracing data manipulation in the EDC system. Spirometry data will be sent to the steering committee for central review.

Analysis plan

For the primary analysis, to account for within-cluster correlation in each hospital, a generalized linear mixed model will be applied to estimate the effect of standardized management versus usual care on annual moderate-to-severe exacerbations, assuming a negative binomial distribution with logarithm of follow-up time as an offset variable and hospitals as random effect. Adjustment will be made for covariates, including demographic information, exacerbation rate in the previous 12 months, disease severity, and geographical location of hospitals. The incidence rate obtained from the model is the annual moderate-to-severe exacerbation rate in this study. In analyses for secondary objectives, readmission within short-term and long-term periods and length of stay will be compared. Cost in the health service use will be used for cost-effectiveness/utility assessment of standardized management in reducing exacerbation and improving life quality. Changes in lung function, respiratory symptoms, health status, exercise tolerance, patients' self-management and mortality reduction will be evaluated. Moreover, patients' adherence to regimen and safety events are also analyzed for the feasibility and safety assessment of standardized management in clinical setting. The safety events in two arms will be described in

tabulation.

If patients withdraw prematurely, all data on their exacerbations, health status, healthcare cost, and lung function available at the time of withdrawal will be included for analysis. There is no multiplicity adjustment for effect comparisons. All analyses of secondary and other supplementary outcomes are considered exploratory. Statistical analyses will be performed based on the pre-defined analysis plan in SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

We will perform subgroup analyses to evaluate the effect of standardized management in patients whose characteristics may affect the primary outcome (COPD-related hospitalizations/ emergency visits and/or moderate exacerbations). Considering exacerbation history is a commonly recognized predictor for COPD exacerbation, we will conduct subgroup analysis based on patients' exacerbation history in previous one year. The study patients have a broad spectrum of disease severity. We will perform subgroup analysis according to ratio of post-bronchodilator FEV_1 to predicted normal values, e.g., <50% and ≥50%, or <30%, ≥30% to <50%, ≥50% to <80%, ≥80% predicted. Baseline eosinophil count might be used as another factor for subgroup analysis.

Data collection will begin with the first patient recruitment until completing the last patient's follow-up. Four datasets will be analyzed: (1) Screened patient set, which comprises all individuals providing informed consent and undergoing screening at baseline. We will compare patients enrolled and those with screen failure to assess selection bias. (2) Intention-to-Treat (ITT)/Modified ITT: ITT dataset consists of

patients enrolled into the hospitals regardless of withdrawals, lost to follow-up or cross-overs between groups during follow-up. Of note, we select hospitals from each county or district to ensure each hospital is located apart from each other to reduce the cross-overs of patients between SM and UC groups. Patients will be analyzed according to their initial hospital group at baseline. Modified ITT is a subset of ITT that excludes patients who are eligible initially but become ineligible after enrollment, such as patients who never receive interventions assigned to the hospital. (3) Per protocol set includes all patients who receive study interventions as hospital randomized and have good compliance without major protocol deviations.

Patients with complete data at baseline and at least at 12 months are included for analyses. Missing key information at baseline (e.g., age, gender, exacerbation history in prior one year, lung function, et al) or missing data on exacerbation events during follow-up are considered as invalid.

Interim analysis of safety events will be performed by an independent statistician blindly when all patients finish the 6-month visits. An independent data monitoring committee (IDMC) will be unblinded and access to the interim results. They operate independently from the investigators, being authorized to access to adverse events, demography and other relevant information. Based on the interim analyses, IDMC reports to the study's principal investigators and might confidentially suggest some modifications of the study on an ongoing basis if it is safe to continue the study.

Safety events, including adverse events and serious adverse events that occur during follow up, will be assessed. Adverse events, an untoward medical occurrence in

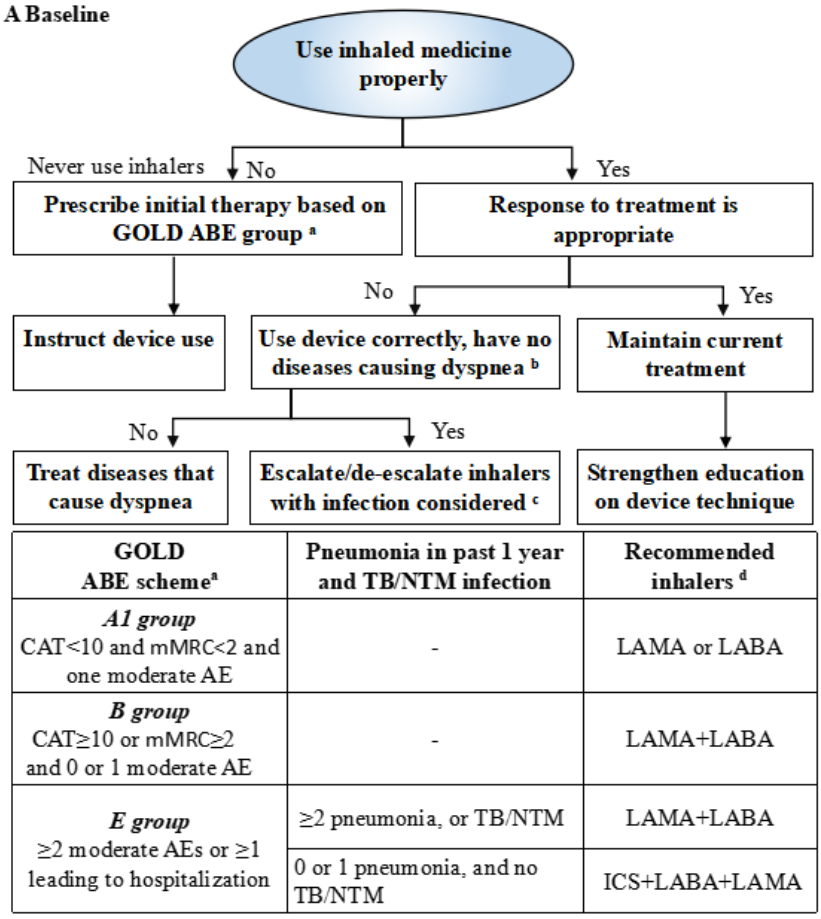
patients, do not necessarily have a causal relationship with Standardized management. All adverse events will be reported in an adverse event form by physicians in secondary hospitals.

Ancillary and post-trial care

Patients with COPD suffering other concomitant diseases such as cardiovascular diseases, diabetes, venous thromboembolism, gastroesophageal reflux are permitted to receive relevant concomitant care and treatments during the study. This study has purchased trial insurance to cover for non-negligent harm to patients during the study and claims pursued through the courts. In this study, SM interventions will be delivered to SM hospitals whilst routine care is provided in the UC hospitals. Should the SM interventions be proven effective in preventing exacerbation, SM interventions will be rolled out to hospitals in the UC group to effectively manage patients after completion of the study, with the anticipation to improve health and reduce COPD-related burden in patients with COPD nationwide.

Dissemination policy

The study primary findings will be released to local physicians, nurses, and administrators in the participating hospitals via reporting at closing conference. Abstracts will be submitted to academic conferences to publicize the main results to researchers in chronic respiratory diseases field. Investigators that meet the authorship requirements of ICMJE guideline will be listed as coauthors in the publications. The full protocol can be accessed by contacting principal investigators on reasonable requests.



GOLD ABE scheme[a]	Pneumonia in past 1 year and TB/NTM infection	Recommended inhalers [d]
A1 group CAT<10 and mMRC<2 and one moderate AE	-	LAMA or LABA
B group CAT≥10 or mMRC≥2 and 0 or 1 moderate AE	-	LAMA+LABA
E group ≥2 moderate AEs or ≥1 leading to hospitalization	≥2 pneumonia, or TB/NTM	LAMA+LABA
	0 or 1 pneumonia, and no TB/NTM	ICS+LABA+LAMA

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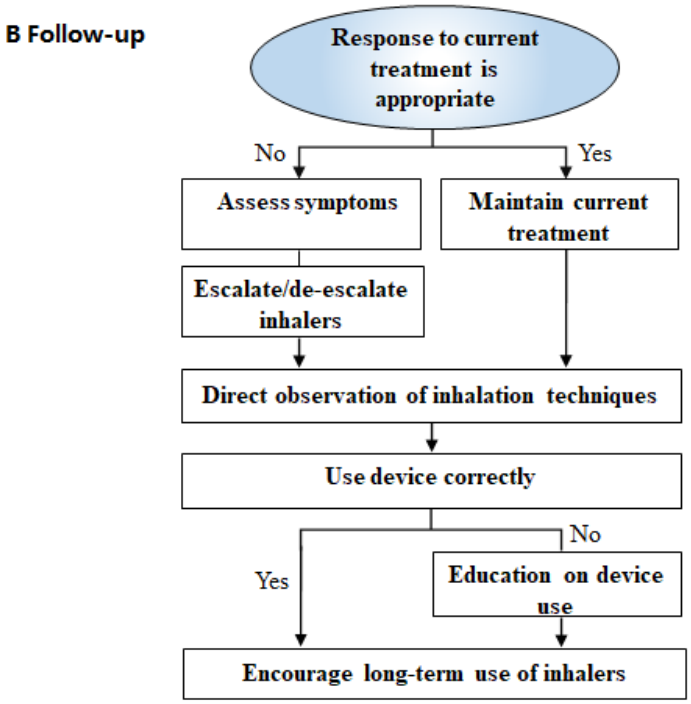

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Figure S1. Pharmacological management at baseline and during follow-up

[a] Patients with COPD who are symptomatic or have exacerbation risk are enrolled in this study. As per GOLD guideline, patients are grouped into A1, B or E. Group A1 refers to patients who have CAT<10, mMRC<2 and have one moderate exacerbation in prior 12 months. Group B refers to patients who have CAT ≥10 or mMRC ≥2 and no or one moderate exacerbation in prior 12 months. Group E refers to patients who have two moderate exacerbations or once been admitted to hospitals in prior 12 months. Initial therapy will be prescribed based on their CAT, mMRC and infection comorbidities.

[b] Besides AE, some other diseases can also cause dyspnea in COPD patients, such as pneumonia, pulmonary embolism, pneumothorax, cardiac insufficiency, and arrhythmia.

[c] Pneumonia history in past one month, tuberculosis or nontuberculous mycobacteria, and allergic rhinitis are considered when adjusting inhalers.

[d] Monotherapy (LAMA or LABA) is recommended for patients in group A1. If long-acting inhalers are not available in secondary hospitals, short acting inhalers such as SABA or SAMA may be prescribed instead. Combination therapy of LABA and LAMA is recommended for patients in group B. Combinations of long-acting inhalers and short acting inhalers may be considered, such as LABA+SAMA, LAMA+SABA when one of the long-acting inhaler (LABA or LAMA) is not available in the hospitals. For patients in group E, pneumonia and TB/NTM infection are taken into consideration. Combination therapy of LABA and LAMA is recommended for patients who have recurrent pneumonia (≥2 pneumonia) in past one year or have TB/NTM. If patients do not have such infection history, ICS-contained therapy is recommended. Of note, if patients comorbid with asthma,

ICS-contained therapy is recommended.

GOLD=Global Initiative for Chronic Obstructive Lung Disease, mMRC=modified British Medical Research Council, CAT=COPD Assessment Test, AE=Acute exacerbation, TB=tuberculosis, NTM=Nontuberculous mycobacteria, LAMA=Long-acting B2 Agonists, LABA=Long-acting muscarinic antagonist, ICS=Inhaled corticosteroid

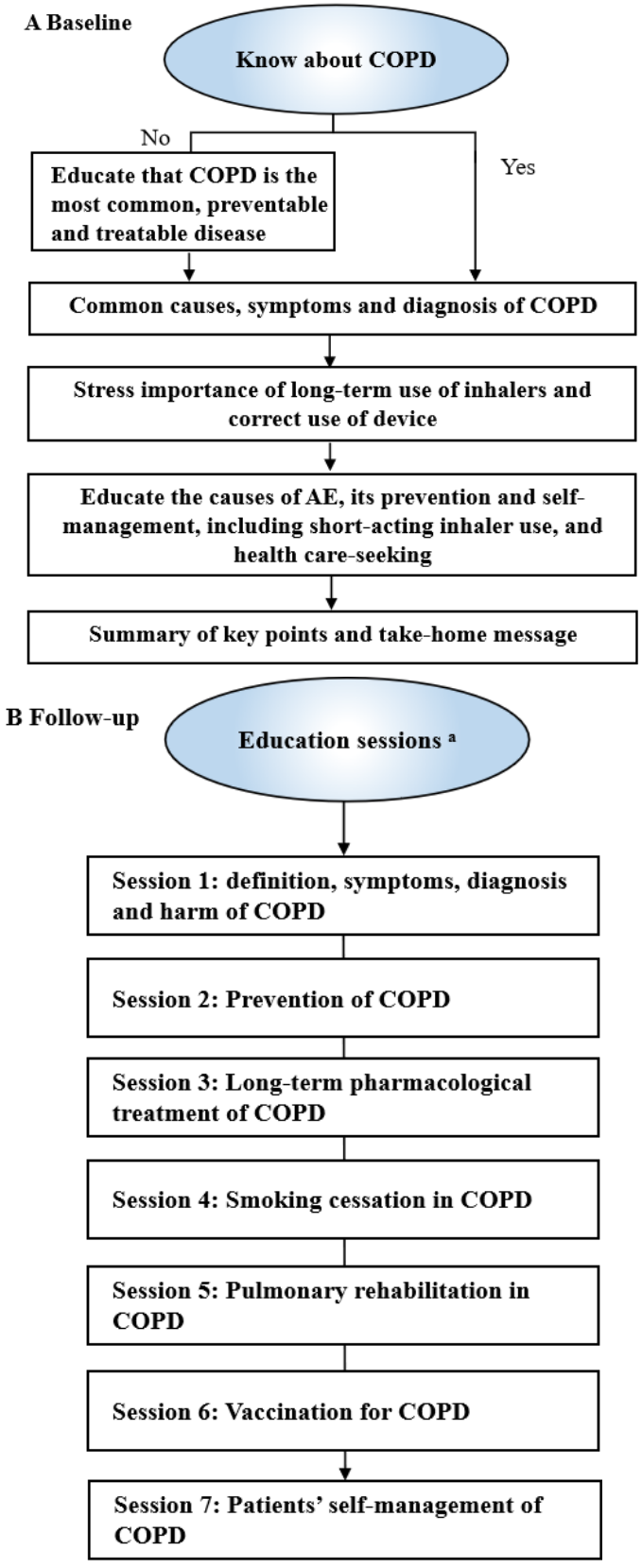
A Baseline
Know about COPD
No
Yes
Educate that COPD is the most common, preventable and treatable disease
Common causes, symptoms and diagnosis of COPD
Stress importance of long-term use of inhalers and correct use of device
Educate the causes of AE, its prevention and self-management, including short-acting inhaler use, and health care-seeking
Summary of key points and take-home message
B Follow-up
Education sessions a
Session 1: definition, symptoms, diagnosis and harm of COPD
Session 2: Prevention of COPD
Session 3: Long-term pharmacological treatment of COPD
Session 4: Smoking cessation in COPD
Session 5: Pulmonary rehabilitation in COPD
Session 6: Vaccination for COPD
Session 7: Patients' self-management of COPD

Figure S2. Strengthened COPD education at baseline and during follow-up

[a] Patients have a quiz to test whether they grasp the key messages after each education session. Answers and interpretations will be provided after completing the quiz.

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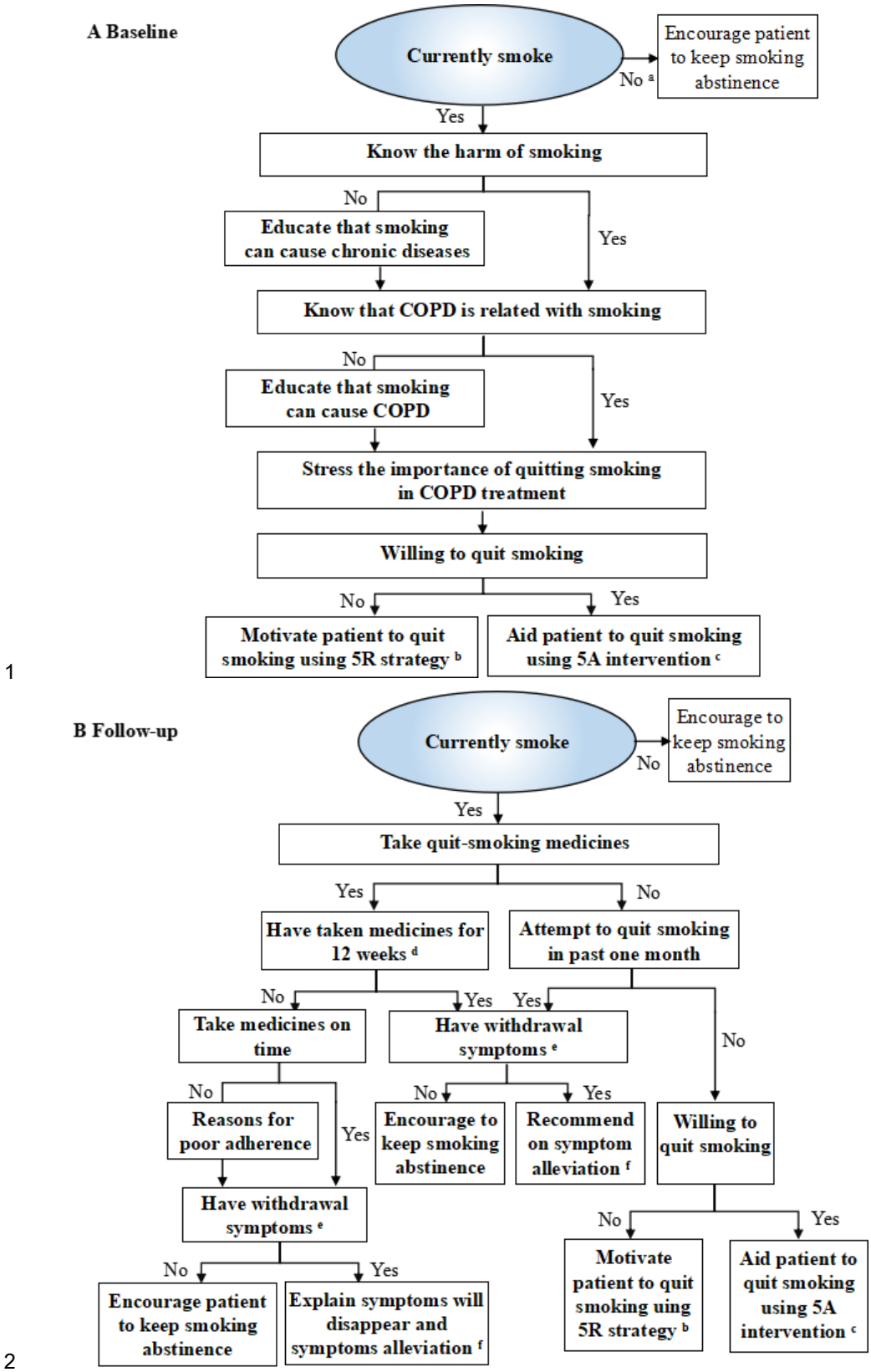

A Baseline
Currently smoke
No [a]
Encourage patient to keep smoking abstinence
Yes
Know the harm of smoking
No
Educate that smoking can cause chronic diseases
Yes
Know that COPD is related with smoking
No
Educate that smoking can cause COPD
Yes
Stress the importance of quitting smoking in COPD treatment
Willing to quit smoking
No
Yes
Motivate patient to quit smoking using 5R strategy [b]
Aid patient to quit smoking using 5A intervention [c]
B Follow-up
Currently smoke
No
Encourage to keep smoking abstinence
Yes
Take quit-smoking medicines
Yes
No
Have taken medicines for 12 weeks [d]
Attempt to quit smoking in past one month
No
Yes
Yes
Take medicines on time
Have withdrawal symptoms [e]
No
Reasons for poor adherence
Yes
No
Encourage to keep smoking abstinence
Yes
Recommend on symptom alleviation [f]
Willing to quit smoking
Have withdrawal symptoms [e]
No
Yes
Motivate patient to quit smoking uing 5R strategy [b]
Aid patient to quit smoking using 5A intervention [c]
No
Yes
Encourage patient to keep smoking abstinence
Explain symptoms will disappear and symptoms alleviation [f]

Figure S3. Smoking cessation counseling at baseline and during follow-up

[a] Patients who do not currently smoke including never smokers and former smokers who have quitted smoking.

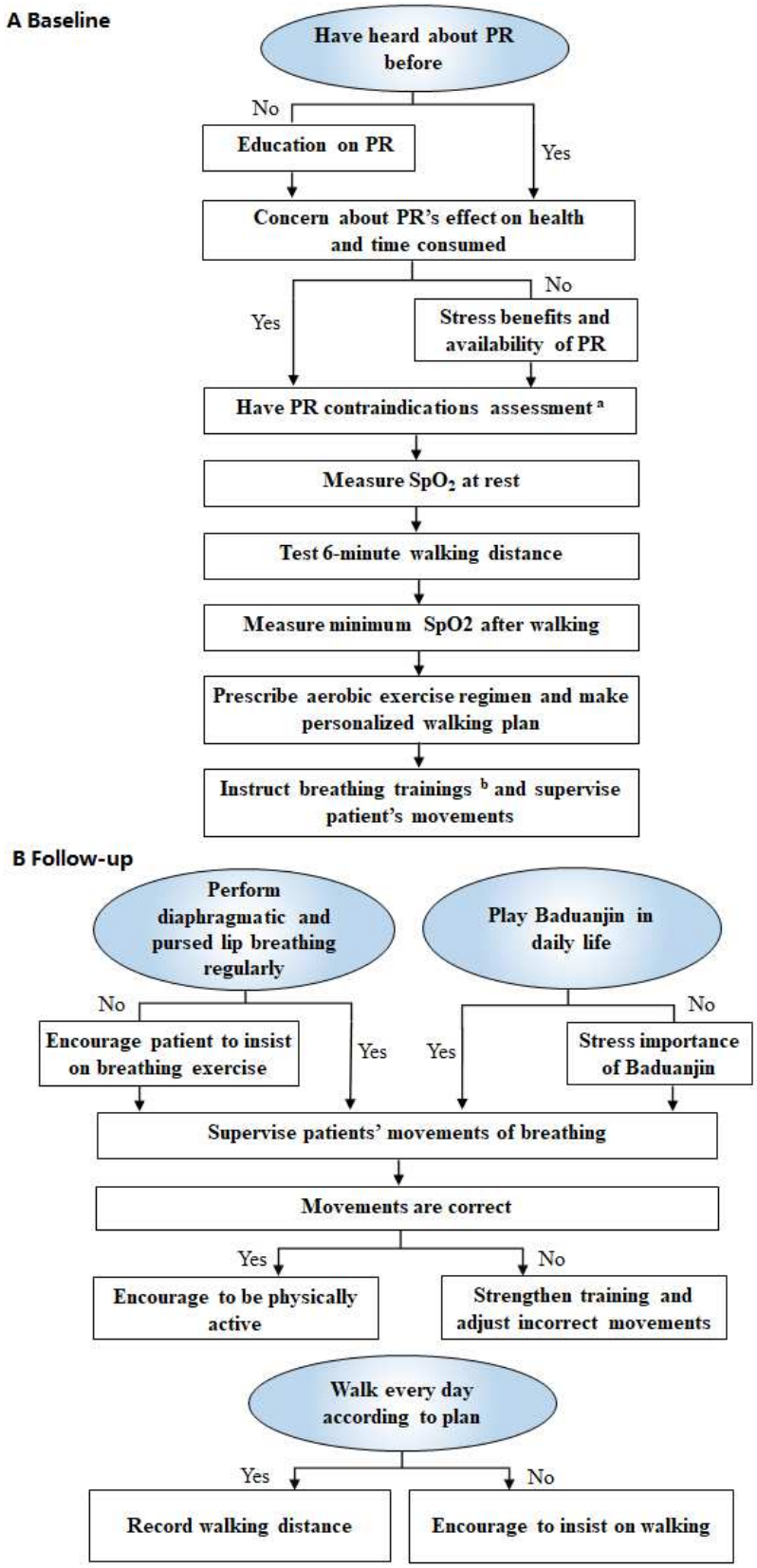
[b] 5R strategy is Relevance, Risk, Rewards, Roadblocks, and Repetition

[c] 5A strategy is Ask, Advise, Assess, Assist and Arrange.

[d] Quit-smoking medications need to be taken for 12 weeks

[e] Withdrawal symptoms in smokers are normally urges or cravings to smoke, having a hard time to concentrate or trouble sleeping, feeling irritated, jumpy, hungrier, anxious, or depressed.

[f] As for smokers with withdrawal symptoms, they are recommended to take deep breath, drink water, listen to music or do others to relieve their eagerness to smoke.


A Baseline
Have heard about PR before
No
Education on PR
Yes
Concern about PR's effect on health and time consumed
No
Yes
Stress benefits and availability of PR
Have PR contraindications assessment [a]
Measure SpO_2 at rest
Test 6-minute walking distance
Measure minimum SpO2 after walking
Prescribe aerobic exercise regimen and make personalized walking plan
Instruct breathing trainings [b] and supervise patient's movements
B Follow-up
Perform diaphragmatic and pursed lip breathing regularly
Play Baduanjin in daily life
No
Encourage patient to insist on breathing exercise
Yes
Yes
No
Stress importance of Baduanjin
Supervise patients' movements of breathing
Movements are correct
Yes
No
Encourage to be physically active
Strengthen training and adjust incorrect movements
Walk every day according to plan
Yes
No
Record walking distance
Encourage to insist on walking

1

Figure S4. Pulmonary rehabilitation at baseline and during follow-up

[a] If patients have pulmonary rehabilitation contraindications, they would not take 6-minute walking test and not be prescribed exercise regimen.

[b] Breathing trainings in this study include diaphragmatic and pursed lip breathing

PR=Pulmonary Rehabilitation, SpO_2=Oxygen saturation

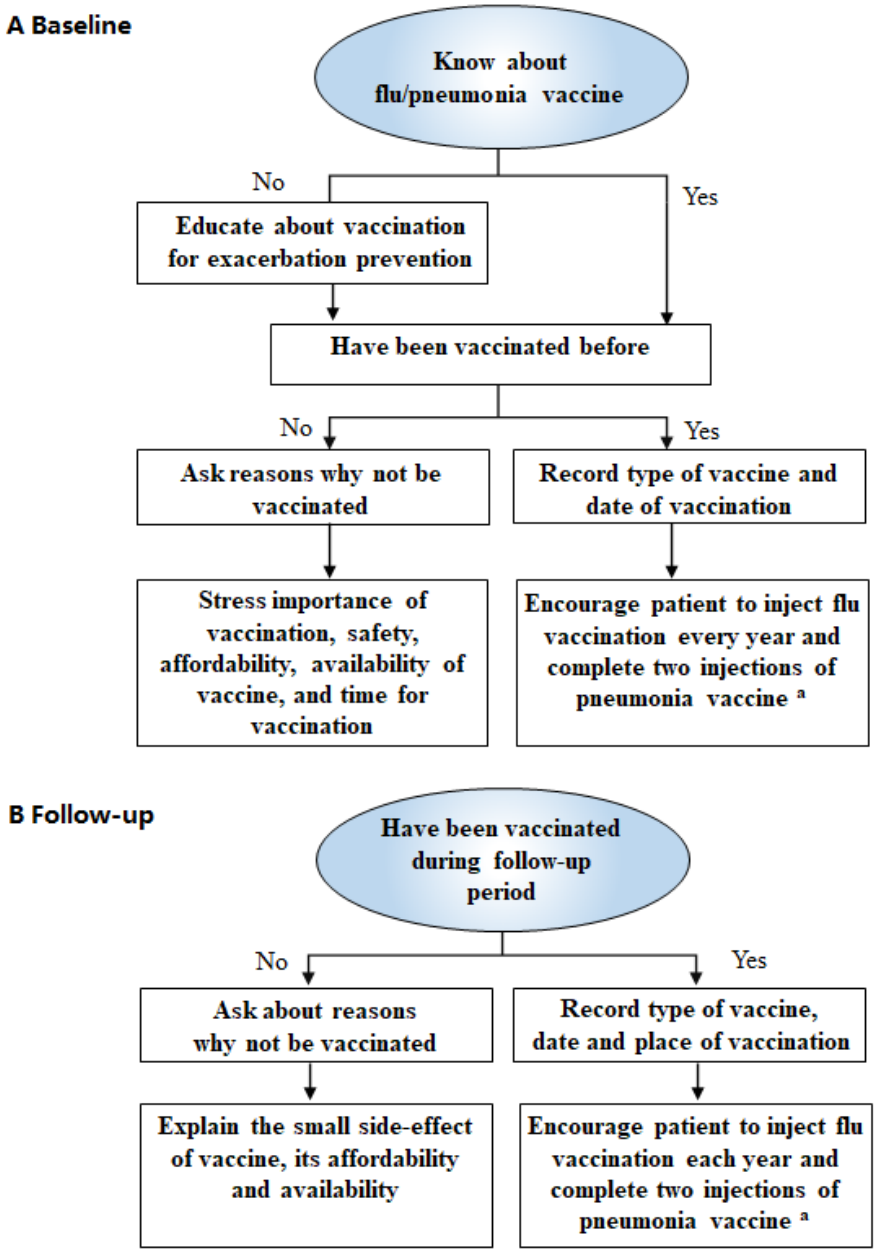


Figure S5. Vaccination encouragement at baseline and during follow-up

[a] Flu vaccine is recommended to be injected once every year and pneumococcal vaccination should be injected twice in life with an interval of 5 years.

Figure S6. Pocket-cards are designed to help the delivery of interventions in SM group: A for physicians; B for nurses, and C for patients

Table S1. Interventions delivered over study period

Group	Doers, visits and places	Baseline	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12
		Clinic	**Clinic/Phone**	**Clinic/Phone**	**Clinic**	**Clinic**	**Clinic**	**Clinic**
SM	Physicians	(1) Prescribe inhalers as initial treatment for non-inhaler users/irregular users and prescribe maintain therapy for regular users. (2) Observe patients' inhaler techniques and re-educate patients where needed. (3) Provide smoking cessation counseling	Refill/adjust inhalers to maintain therapy	Refill/adjust inhalers to maintain therapy	Refill/adjust inhalers to maintain therapy	Refill/adjust inhalers to maintain therapy Identify HRU occurring between baseline and 6 months	Refill/adjust inhalers to maintain therapy	Refill/adjust inhalers to maintain therapy Identify HRU occurring between 6 months and 12 months
	Nurses /technicians	Provide patient education, pulmonary rehabilitation (PR) training, and vaccination encouragement	Non-pharmacological part [a]	Non-pharmacological part [b]	Non-pharmacological part [c]	Non-pharmacological part [d]	Non-pharmacological part [e]	Non-pharmacological part [f]
		Baseline assessments: PFT, 6MWT, CAT, mMRC, SGRQ-C and others			Monitor symptoms by assessing CAT/mMRC	Monitor symptoms by assessing CAT/mMRC	Monitor symptoms by assessing CAT/mMRC	12-month assessments: PFT, 6MWT, CAT, mMRC, sGRQ-C and others

UC	**Doers and places**	**Clinic**		**Phone**		**Clinic**
	Physicians and nurses	Baseline assessments: PFT, 6MWT, CAT, mMRC, SGRQ-C and others	Collect information on patients' care seeking behaviors only when patients contact investigators. No interventions are delivered to interrupt the usual care	Identify HRU occurring between baseline and 6 months	Collect information on patients' care seeking behaviors only when patients contact investigators	Identify HRU occurring between 6 months and 12 months
						12-month assessments: PFT, 6MWT, CAT, mMRC, SGRQ-C and others

SM=Standardized management, UC=Usual care, HRU= Healthcare resource utilization, PR=Pulmonary Rehabilitation, PFT=Pulmonary function test, 6MWT=6-minute walking test, CAT= COPD assessment test, mMRC= Modified British medical research council, SGRQ-C= Saint George Respiratory Questionnaire for COPD

[a] Non-pharmacological part includes: strengthen inhaler techniques, 1st and 2nd education session, PR training, including breathing trainings and encouraging daily walk according to walking program, vaccination encouragement, and smoking cessation for active smokers

[b] Non-pharmacological part includes: strengthen inhaler techniques, 3rd and 4th education session and repeat the key messages of 1st-2nd education session, PR training, including breathing trainings and encouraging daily walk according to walking program, vaccination encouragement, and smoking cessation for active smokers

[c] Non-pharmacological part includes: strengthen inhaler techniques, 5th-6th education session and repeat the key messages of 1st-4th education session, PR training, including breathing trainings and encouraging daily walk according to walking program, vaccination encouragement, and

smoking cessation for active smokers

[d] Non-pharmacological part includes: strengthen inhaler techniques, 7th education session and repeat key messages of 1st-6th education session, PR training, including breathing trainings and encouraging daily walk according to walking program, vaccination encouragement, and smoking cessation for active smokers

[e] Non-pharmacological part includes: strengthen inhaler techniques, repeat key messages of 1st-7th education session, PR training, including breathing trainings and encouraging daily walk according to walking program, vaccination encouragement, and smoking cessation for active smokers

[f] Non-pharmacological part includes: strengthen inhaler techniques, repeat key messages of 1st-7th education session, PR training, including breathing trainings and encouraging daily walk according to walking program, vaccination encouragement, and smoking cessation for active smokers

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Table S2. Study schedule

Events & Time	Hospital allocation -30 days	Patient screening and Enrollment Visit 0 (Baseline)	Follow-up			
			Visit 3 (Month 3)	Visit 6 (Month 6)	Visit 9 (Month 9)	Visit 12 (Month 12)
Patient visit type		SM: Clinic visit UC: Clinic visit	SM: Clinic visit	SM: Clinic visit UC: By phone	SM: Clinic visit	SM: Clinic visit UC: Clinic visit
Hospital assessment and randomization						
Hospital invitation, assessment, and written informed consent	x					
Potential patient prescreening	x					
Hospital randomization and disclosure	x					
Patient eligibility assessment and enrollment						
Written informed consent of patients		x				
Baseline characteristics		x				
Patient screening and enrollment using in-/exclusion criteria		x				
Assessing respiratory symptoms to exclude patient experiencing exacerbation at screening phase		x				

Events & Time	Hospital allocation -30 days	Patient screening and Enrollment Visit 0 (Baseline)	Follow-up			
			Visit 3 (Month 3)	Visit 6 (Month 6)	Visit 9 (Month 9)	Visit 12 (Month 12)
Exacerbation and hospitalization history in previously diagnosed COPD patients		x				
Reviewing CT image to exclude patients who have obvious lung structure destruction due to severe bronchiectasis, pneumoconiosis, interstitial lung disease, pulmonary tuberculosis, or other diseases.		x				
Pregnancy, breastfeeding or potential pregnancy in female participants		x				
Standardized management (SM) of COPD in SM group						
Routine blood testing		x				
Initial treatment with exacerbation history, respiratory symptoms and comorbidities taken into consideration		x				
Inhaler use for maintenance therapy during follow-up (maintenance therapy after initial treatment) [a]			x	x	x	x

Events & Time	Hospital allocation -30 days	Patient screening and Enrollment Visit 0 (Baseline)	Follow-up			
			Visit 3 (Month 3)	Visit 6 (Month 6)	Visit 9 (Month 9)	Visit 12 (Month 12)
Inhaler technique assessment and strengthened instructions on techniques of using inhaler during follow-up [a]		x	x	x	x	x
Symptoms monitoring in SM group						
CAT		x	x	x	x	x
Dyspnea-mMRC		x	x	x	x	x
Health status-SGRQ-C		x				x
Quality of life measured by EQ-5D-5L		x				x
Self-efficacy measurement		x				x
Exacerbation event				x		x
Routine spirometry testing for lung function in SM group		x				x
Six-minute walking distance test		x				x
Anxiety and depression assessment		x				x
Education and strengthened education session for patients [a]		x	x	x	x	x

Events & Time	Hospital allocation -30 days	Patient screening and Enrollment Visit 0 (Baseline)	Follow-up			
			Visit 3 (Month 3)	Visit 6 (Month 6)	Visit 9 (Month 9)	Visit 12 (Month 12)
Training on patients' self-management [a]		x	x	x	x	x
Influenza/Pneumococcal vaccination encouragement [b]		x	x	x	x	x
Smoking cessation counseling and smoking status [a]		x	x	x	x	x
Pulmonary rehabilitation training [a]		x	x	x	x	x
Usual care (UC) in control group						
Usual care according to local clinical practice [c]		x				
Routine blood testing		x				
Inhaler use for initial treatment		x				
Inhaler use during follow-up (maintenance therapy after initial treatment) [d]				x		x
Inhaler technique assessment		x				x
Symptoms evaluation in control group						
CAT		x				x
Dyspnea-mMRC		x				x

Events & Time	Hospital allocation -30 days	Patient screening and Enrollment Visit 0 (Baseline)	Follow-up			
			Visit 3 (Month 3)	Visit 6 (Month 6)	Visit 9 (Month 9)	Visit 12 (Month 12)
Health status-SGRQ-C		x				x
Quality of life measured by EQ-5D-5L		x				x
Self-efficacy measurement		x				x
Exacerbation events				x		x
Spirometry testing for lung function in control group		x				x
Six-minute walking distance test		x				x
Anxiety and depression assessment		x				x
Routine education session for patients [e]		x				
Outcome assessments						
Moderate exacerbations (oral antibiotics and/or oral or nebulized glucocorticoids use) and severe exacerbations (hospitalizations or emergency visits) tracked by electronic medical record in local hospitals [f]				x		x

Events & Time	Hospital allocation -30 days	Patient screening and Enrollment Visit 0 (Baseline)	Follow-up			
			Visit 3 (Month 3)	Visit 6 (Month 6)	Visit 9 (Month 9)	Visit 12 (Month 12)
Length of stay in hospitalized patients ascertained by electronic medical records in local hospitals [g]				x		x
COPD-related healthcare cost at clinic visits and during hospitalization [g]				x		x
Adherence to treatment and adoption of favorable lifestyle [h]				x		x
Medicine refilling & follow up [i]				x		x
Safety assessments [j]				x		x

Note: x means that data will be collected at the Visit

[a] In SM group, patient education sessions, with each session focused on inhaler technique assessment and instruction, training on self-management, influenza/pneumococcal vaccination encouragement, smoking cessation counseling and pulmonary rehabilitation training will be conducted when patients come back to clinics for maintenance prescription or online in a group of patients.

[b] At baseline, patients will be asked whether they are vaccinated or not. If vaccinated, types of vaccine and injection time will be recorded electronically and do not need to be collected in the following visits. Some patients may still be advised for new injections if his/her last

injection exceeds the time interval of vaccination, for instance, more than 1 year for influenza or 5 years for pneumococcal vaccination. For patients who are not vaccinated, they will be advised to inject influenza or pneumococcal vaccination and encouraged to get injection at each visit until they get vaccination or the end of the 12-month follow-up, whatever occurs first.

[c] According to baseline survey on routine COPD care in clinical practice, COPD patients are not regularly followed up.

[d] In the usual care group, we will not interrupt physicians' prescriptions or remind patients to visit physicians for maintenance therapy during the 12-month intervention period. The local investigators just record patients' health care seeking behaviors when they contact the investigators. Exacerbation events, the primary outcome, are collected at 6 months over the phone and 12 months at clinics to prevent recall bias and minimize interruption into the usual care.

[e] To obtain patients' self-reported exacerbation in both arms, patients and caregivers in control group will only be informed of signs and symptoms of an exacerbation at baseline, with no further interventions assigned by researchers during the 12-month follow up. The education sessions will be at the discretion of physicians and done as usual.

[f] Exacerbation events are collected at clinic visits or by phone every six months during follow-up. Moderate and severe exacerbations will be assessed and ascertained by tracking electronic medical records in local hospitals at 6 and 12 months. Pulmonologists who are unaware of hospital assignments and interventions will adjudicate exacerbation events.

[g] The length of stay and direct economic costs during hospitalization will be ascertained by reviewing electronic medical records. Healthcare costs in clinic visits will also be retrieved from electronic medical records.

[h] In SM group, adherence to regimen includes taking medicine as required, attending education sessions, breathing exercises, and smoking cessation counseling in smokers to improve self-management of COPD. Clinic attendance rate is calculated as ratio of clinic visits to total expected visits. Adherence to non-pharmacological treatment is quantified as proportion of individuals adopting health behaviors. In both groups, inhaler medication compliance will be assessed from the unused medication and used medication reported by patient and/or families, measured as ratio of days of inhaler use according to the required usage to the total expected days.

[i] Medicine refilling & follow up: in both groups, patients' compliance with inhalers prescription and refilling will be evaluated every 6 months. Electronic medical records will be reviewed to ascertain patients' clinic visits and inhaler prescription. Meantime, the lost to follow-up for this study will be evaluated as well. For patients who do not visit as scheduled, the responsible physicians or nurses will contact patients or families by phone calls. If patients remain unavailable during the visiting window (visiting date ±7 days), the responsible researchers will document the dates of missed visits and reasons. Patients who miss all the remaining visits until the end of 12 months are considered lost to follow-up. The number of designated clinic/phone visits that have been done will be summarized to assess patients' compliance with follow-up in each group.

[j] Safety will be assessed by collecting adverse events that might be attributed to the study interventions or other causes. Chest X-Rays will be sourced for radiographically-confirmed pneumonia. Any discontinuation or withdrawal from study due to adverse events will be collected. When half of patients complete the 6-month follow-up, data will be pooled for the IDMC to evaluate safety.

Dong F, *et al. BMJ Open Respir Res* 2025; 12:e002768. doi: 10.1136/bmjresp-2024-002768

Table S3. Items from World Health Organization Trial Registration Data Set

Data category	Information
Primary Registry and Trial Identifying Number	ClinicalTrials.gov NCT04664491
Date of Registration in Primary Registry	December 11, 2020
Secondary Identifying Numbers	-
Sources of Monetary or Material Support	GlaxoSmithKline
Primary Sponsor	China-Japan Friendship Hospital
Secondary Sponsor(s)	-
Contact for Public Queries	copdstandardstudy@163.com
Contact for Scientific Queries	Dr.Ting Yang, copdstandardstudy@163.com, 010-84206408,Yinghua East road 2 Chaoyang District Beijing, China-Japan Friendship Hospital
Public Title	Real-world Effectiveness Study of Guideline-Directed COPD STANDARDized Management in Patients with Chronic Obstructive Pulmonary Disease: a Cluster Randomized Trial Design
Scientific Title	Real-world Effectiveness Study of Guideline-Directed COPD STANDARDized Management in Patients with Chronic Obstructive Pulmonary Disease: a Cluster Randomized Trial Design

Countries of Recruitment	China
Health Condition(s) or Problem(s) Studied	Chronic obstructive pulmonary disease; Exacerbation
Intervention(s)	Guideline-directed standardized management of COPD Usual care for COPD routinely provided in clinical practice
Key Inclusion and Exclusion Criteria	Inclusion criteria: aged ⩾40 years, post-bronchodilator FEV1/FVC <70%,baseline CAT score ⩾10 or history of exacerbation in previous 12 months with any use of oral antibiotics and/or oral or nebulized corticosteroids for increased cough, sputum and dyspnea, or exacerbation requiring hospitalization/ emergency admission, local residents who live nearby and can be followed up throughout study period, written informed consent Exclusion Criteria: pregnancy, breastfeeding, or potential pregnancy, primary diagnosis of asthma, having severe cognitive dysfunction, severely ill with less than 12-month life expectancy, patients with alcohol abuse history, have participated in similar trials or are undergoing other clinical trials, refuses or unable to give informed consent, plan to move, contraindicated to maintenance medicine, unstable cardiovascular conditions, relative contraindications to spirometry, comorbid lung disease including bronchiectasis and tuberculosis, or undergoing anti-tuberculosis treatment, recent exacerbation treated with antibiotics and/or oral or nebulized corticosteroids within 30 days prior to enrolment, exacerbation

	requiring emergency admission or hospitalization within 30 days prior to enrolment.
Study Type	Interventional study Allocation: randomized; parallel assignment; open-label, cluster randomized pragmatic trial Primary purpose: prevention Allocation concealment: group allocation is blinded to investigators who are responsible for patient enrollment. Sequence generation: an independent statistician generates random sequence and keeps hospital allocation separately
Date of First Enrollment	First enrollment of pilot study is February 2023; First enrollment of the nationwide study is October, 2023
Sample Size	3456
Recruitment Status	Recruiting
Primary Outcome(s)	Annual rate of moderate-to-severe exacerbation
Key Secondary Outcomes	Exacerbation-related admissions, and time to first moderate/severe exacerbation; COPD-related hospitalization, readmissions, and mortality; direct medical costs of exacerbations
Ethics Review	The pilot study is approved by China-Japan Friendship Hospital Ethics committee on September 23, 2020; The study nationwide is approved by the ethical committee on September 25, 2023

Completion date	The last subject last visit will be 2026
Summary Results	-
IPD sharing statement	Deidentified participant data supporting the conclusion of this study will be available from corresponding author on reasonable request

Appendices

Appendix 1: SPIRIT checklist

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 4
	2b	All items from the World Health Organization Trial Registration Data Set	Supplementary page 35-38
Protocol version	3	Date and version identifier	Page 31
Funding	4	Sources and types of financial, material, and other support	Page 29
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Pages 1-2, 29
	5b	Name and contact information for the trial sponsor	Page 29
	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	Page 29
	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)	Page 31-33

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	Page 6-7
	6b	Explanation for choice of comparators	Page 8
Objectives	7	Specific objectives or hypotheses	Page 7-8
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)	Page 8-9
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	Page 8-9, 32
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)	Page 9-10, 25-26
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 11-13, Supplementary page 3-6
	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)	Supplementary page 6-7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 12-13, Supplementary page 6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Supplementary page 11

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	Page 14-15
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)	Supplementary page 26-34
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	Page 17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 27-28
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	Page 13-14
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	Page 13-14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 13-14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 14

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	Supplementary page 8, 25-33
	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	Supplementary page 7
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	Supplementary page 2, 8
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	Supplementary page 8-11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Supplementary page 9
	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)	Supplementary page 9-10

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	Page 33
	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	Page 33, Supplementary page 10

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	Supplementary page 10-11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 27-28, Supplementary page 1-2
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 10, 23
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)	Page 31
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 10, 23
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Supplementary page 7
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	Supplementary page 7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 29
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	Page 23
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	Supplementary page 11

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	Supplementary page 11
	31b	Authorship eligibility guidelines and any intended use of professional writers	Supplementary page 11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 23, Supplementary page 11
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary page 45-47
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	Supplementary page 7

*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.

Appendix2: Informed consent form for patients in SM group

知情同意书

受试者须知页

方案名称：中国基层慢阻肺规范化管理效果评价研究
主要研究者：
申办者：中日友好医院
资助者：

尊敬的受试者：

您被邀请参加_中国基层慢阻肺规范化管理效果评价研究_，该项研究由中日友好医院提供支持。请仔细阅读本知情同意书并慎重做出是否参加本项研究的决定。参加这项研究完全是您自主的选择。作为受试者，您必须在加入临床研究前给出您的书面同意书。当您的研究医生或者研究人员和您讨论知情同意书的时候，您可以让他/她给您解释您看不明白的地方。我们鼓励您在做出参与此项研究的决定之前，和您的家人及朋友进行充分讨论。您有权拒绝参加本研究，也可随时退出研究，且不会受到处罚，也不会失去您应有的权利。若您正在参加别的研究，请告知您的研究医生或者研究人员。本研究的背景、目的、研究过程及其他重要信息如下：

一、 研究背景

1、研究意义

慢性阻塞性肺疾病（简称"慢阻肺"）是我国最常见的慢性呼吸系统疾病，患病率和死亡率高且疾病负担重。全国有近 1 亿名慢阻肺患者，众多的慢阻肺患者在疾病发展过程中易出现急性加重，会导致呼吸功能受损、病情恶化、甚至死亡，增加社会和个人的疾病负担。亟需一种有效和规范的疾病管理策略来减少急性加重的发生、改善生命质量和避免疾病所致的过早死亡。目前，慢阻肺管理主要在社区基层医疗机构开展，提高基层慢阻肺的规范化管理能力将有助于提升我国慢阻肺防治水平。

2、国内外研究现状及发展动态分析

慢阻肺患者在疾病发展过程易出现病情加重，这会严重影响患者的健康状况，导致生活质量下降甚至死亡。同时，慢阻肺疾病负担沉重，导致频繁的住院或急诊，给个人和社会带来巨大的社会和经济负担。有效降低慢阻肺急性加重的发生是慢阻肺管理的主要目标，以减少慢阻肺相关医疗资源的使用和疾病负担。

目前，指南建议通过维持治疗（例如吸入长效β_2激动剂（LABA），长效抗胆碱能药物（LAMA），吸入糖皮质激素（ICS））和非药物干预措施（常规随访，症状监测，患者教育，戒烟，接种疫苗，康复等）改善慢阻肺管理和减少急性加重。在我国，慢阻肺的管理主要集中在二级医院、社区医院和乡镇医院，因为慢阻肺是一种慢性呼吸系统疾病，患者出院后的自我管理，包括监测和管理其症状和体征，对长期的疾病管理至关重要。社区干预是慢阻肺管理和预防的最佳方式，提高基层医疗机构慢阻肺规范化管理水平至关重要。

然而，在临床实践中，尤其在基层机构，指南推荐的慢阻肺管理策略未能得到很好的实施，慢阻肺管理现状不容乐观。在本研究团队前期调查中，初级医师对规范化慢阻肺管理的认识较低。他们对肺功能测试（Pulmonary function testing, PFT）知之甚少，对肺功能检测不足。部分慢阻肺患者被漏诊，甚至被误诊为哮喘性支气管炎或慢性支气管炎。基层医师较少为患者开吸入药物用于慢阻肺治疗。上述慢阻肺管理不足的现状是受到诸多因素的影响，包括慢阻肺具有隐匿性的疾病特征、医疗人员对慢阻肺的诊断和治疗认识不足、设备缺乏(如氧气设备，CT，PFT)，以及目前我国基本公共卫生服务政策等原因使得吸入性药物未能在基层被充分利用。为了解决以上问题，亟需在基层进行慢阻肺患者的规范管理，包括 PFT 的培训、合理用药、患者自我管理、教育等。目前，在实际的临床实践中，这些指南推荐的措施是否能有效地改善患者的预后，尚不清楚。

因此，我们将开展一项多中心、结局评估者盲法、平行、整群随机临床试验，评估在我国基层医疗机构基于指南实施的规范化疾病管理在减少慢阻肺加重方面的可行性和效果。

3、本项目立项的理论依据

GOLD2020 以及中国慢性阻塞性肺疾病诊治指南中均对慢阻肺诊治进行了基于临床数据的推荐，在中国的基层医疗机构，缺乏根据指南指导的方案对慢阻肺患者进行规范治疗管理，不利于慢阻肺患者预后以及降低疾病负担。本研究拟在中国真实世界中对基层医疗机构的慢阻肺患者，依据指南实施规范化治疗，探讨与目前常规治疗相比，对降低慢阻肺患者急性加重发生、急性加重入院的效果。

二、 研究目的

本研究的目的是评估在基层医疗机构实施基于指南建议指导的慢阻肺规范化管理效果，降低慢阻肺患者 12 个月期间中度（口服糖皮质和/或抗生素的使用）和重度（住院/急诊就诊）急性加重发生率。

三、研究过程

1. 多少人将参与这项研究？

有 3456 人将在 96 个不同医疗机构参与本项研究，每家医疗机构 36 人。

2. 研究步骤

如果您同意参加本研究，请您签署这份知情同意书。

在您入选研究前，医生将询问、记录您的病史。之后您将会接收到规范管理。

您将接受医生遵循GOLD 2020和中国基层慢性阻塞性肺疾病诊治指南中的建议进行疾病管理。包含以下内容：（1）初次治疗后的维持治疗。初始治疗是在基线（入组时）开具的吸入药物。维持治疗是指初始治疗后长期使用的吸入药物（LABA，LAMA或ICS）；（2）长期随访和症状常规监测，研究期间共随访12个月，每3个月随访1次，监测呼吸症状；（3）定期进行肺功能检查（PFT）以监测肺功能水平的变化情况；（4）加强慢阻肺教育；（5）行为改变，例如：鼓励进行流感/肺炎球菌疫苗接种，戒烟辅导，呼吸运动训练。

3. 这项研究会持续多久？

本研究会持续12个月。随访从入组开始至研究结束，共12个月。

您可以在任何时间选择退出研究而不会失去您本应获得的任何利益。然而，如果在研究途中您决定退出本研究，我们鼓励您先和您的医生商议。如果您出现严重的不良事件，或者您的研究医生觉得继续参加研究不符合您的最佳利益，他/她会决定让您退出研究。申办者或者监管机构也可能在研究期间终止研究。但您的退出不会影响您的正常医疗待遇与权益不受影响。

如果您因为任何原因从研究中退出，您可能被询问有关您参加研究的情况。如果医生认为需要，您也可能被要求进行实验室检查和体格检查。

4. 研究中收集的信息

本研究收集的主要信息为急性加重事件，包括加重次数、首次加重时间和首次加重的严重程度。此外，还会收集再入院和住院次数、治疗花费、症状、肺功能、生活质量。您还需要提供研究期间所有因慢阻肺就诊或住院治疗的病历。您的研究信息将被录入电子数据平台，平台设有密码，只有有权限的医生才能获取您的信息。对您进行的问卷调查及其他相关的诊治信息将被统一妥善保管，确保您的信息不会外泄。研究医生将使用您的研究数据仅用于医学研究。研究过程将全程录音，研究过程包含预筛选阶段需电话谈知情同意的过程、正式筛选入组和随访等与研究相关的过程，录音的音频仅用于本研究的过程和数据质控。为便于12个月长期随访，数据系统收集您姓名和联系电话用于系统发送短信提醒您随访。

四、风险与受益

1. 参加本研究的风险是什么？

参加本研究可能给您带来的风险如下。您应该和您的研究医生，或者您愿意，与您平日照看您的医生讨论一下这些风险。

本研究不会带来风险。然而，可能随访时小部分行肺功能检查过程中会有一些不适，检查医生会全程评估以确保您安全。在规范管理组，您的医生会鼓励但不强迫您进行流感/肺炎球菌疫苗接种、戒烟辅导、呼吸运动训练等，您可以根据您自己情况进行选择。若您选择进行疫苗接种，会有疫苗相关的不良反应，医生会跟您提前告知。若您选择进行戒烟，戒烟过程中会出现戒断症状等不适，医生会全程予以指导。

如果在研究期间您出现任何不适，或病情发生新的变化，或任何意外情况，不管是否与研究有关，均应及时通知您的医生，他/她将对此作出判断并给与适当的医疗处理。在研究中任何时刻，您都可以退出本研究。

您在研究期间需要按时到医院随访，做一些检查，这将会占用您的一些时间，也可能给您造成麻烦或带来不方便。

2. 参加研究有什么受益？

直接受益：如果您同意参加本研究，您将有可能获得直接的医疗受益。随访期间您将会获得免费的肺功能检查及相关问卷评估。您将在研究期间获得良好的医疗服务，会得到医生的妥善照顾及治疗。医生会详细记录您的情况，您会与医生保持长期联系，这将对您非常有益处。

潜在受益：本研究可能会延缓肺功能下降，减少急性加重次数，改善生活质量，对疾病自我管理能力提升。我们希望从您参与的本研究中得到的信息在将来能够使您或与您病情相同的病人获益。

五、备选的治疗方案

本研究提供常规的疾病管理和基于指南的疾病规范管理模式，常规管理将根据研究当地医院现行临床实践进行常规管理。规范化管理组将按照GOLD 2020和中国基层慢性阻塞性肺病诊治指南中的建议进行疾病管理。

六、研究结果的使用和个人信息的保密

在您和其他受试者的理解和协助下，通过本项目研究的结果可能会在医学杂志上发表，但是我们会按照法律的要求为您的研究记录保密。研究受试者的个人信息将受到严格保密，除非应相关法律要求，您个人信息不会被泄露。必要时，政府管理部门和医院伦理委员会及其它相关研究人员可以按规定查阅您的资料。

七、关于研究费用及相关补偿

1. 研究所用的药物/器械及相关检查费用

随访时肺功能检查及相关问卷评估费用由申办方免费提供。对于您同时合并的其他疾病所需的常规治疗和检查，将不在免费的范围之内。

2. 参加研究的补偿

为参与本研究所花费的开支（如您的交通费），您将得到补偿。每次随访您将得到伍拾元人民币补偿，研究期间随访次数共5次。补偿总费用将根据研究结束后您的实际随访次数确定。

3. 发生损伤后的补偿/赔偿

如果发生与该项研究相关的损伤，您可以获得由研究单位提供的免费治疗，并按中国有关法律进行补偿/赔偿。申办方已经为本项临床研究购买临床试验责任保险。

八、受试者的权利和相关注意事项

1. 您的权利

在参加研究的整个过程中，您都是自愿的。如果您决定不参加本研究，也不会影响您应该得到的其他治疗。如果您决定参加，会要求您在这份书面知情同意书上签字。您有权在试验的任何阶段随时退出试验而不会遭到歧视或受到不公平的待遇，您相应医疗待遇与权益不受影响。

2. 注意事项

作为受试者，您需要提供有关自身病史和当前身体状况的真实情况；告诉研究医生自己在本次研究期间所发现的任何不适；不得服用医生已告知的受限制药物、食物等；告诉研究医生自己最近是否参与其他研究，或目前正参与其他研究。本研究过程中因质控需要，可能会对您和您医生的谈话进行录音和(或)录像，录音和录像只用于质控过程，不作其他用途。

九、获知信息的相关联系方式

如果在研究过程中有任何重要的新信息，可能影响您继续参加研究的意愿时，您的医生将会及时通知您。如果您对自己的研究数据，或研究结束后您希望知道本研究的发现。您可以在任何时间提出有关本项研究的任何问题，并得到相应的解答，请通过电话_____与_____联系。

伦理委员会已经审查通过该研究，如果您有与自身权利/权益相关的任何问题，或者您想反映参与本研究过程中遭遇的困难、不满和忧虑，或者想提供与本研究有关的意见和建议，请联系中日友好医院伦理委员会，联系电话：010-84206250，电子邮件：zryyec@126.com。

受试者签字页

知情同意声明：

我已被告知此项研究的目的、背景、过程、风险及获益等情况。我有足够的时间和机会进行提问，问题的答复我很满意。

我也被告知，当我有问题、想反映困难、顾虑、对研究的建议，或想进一步获得信息，或为研究提供帮助时，应当与谁联系。

我已经阅读这份知情同意书，并且同意参加本研究。

我知道我可以选择不参加此项研究，或在研究期间的任何时候无需任何理由退出本研究。

我已知道如果我的状况更差了，或者我出现严重的不良事件，或者我的研究医生觉得继续参加研究不符合我的最佳利益，他/她会决定让我退出研究。无需征得我的同意，资助方或者监管机构也可能在研究期间终止研究。如果发生该情况，医生将及时通知我，研究医生也会与我讨论我的其他选择。

我将得到这份知情同意书的副本，上面包含我和研究者的签名。

受试者签名：_____ 日期：_____

（注：如果受试者无行为能力/限制行为能力时，则需法定代理人签名和签署日期）

受试者联系方式：_____

法定代理人签字：_____ 日期：_____

（注：如果受试者不能阅读该知情同意书时，则需一名独立见证人证明研究者已将知情同意书的所有内容告知了受试者，独立见证人需签名和签署日期）

法定代理人联系方式：_____

独立见证人签字：_____ 日期：_____

独立见证人联系方式：_____

研究者签名：_____ 日期：_____

研究者联系方式：_____

Appendix 3: The TIDieR (Template for Intervention Description and Replication) Checklist

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.	Page 8	_____
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	Page 11	_____
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	Page 11-13, Supplementary Page 3-6	_____
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	Supplementary page 23-25 (Table S1)	_____
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	Supplementary page 1-2, 23-25	_____

		(Table S1)	
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	Supplementary page 3-4, 26-34 (Table S2)	_____
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	Supplementary page 26-34 (Table S2)	_____
	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	Supplementary page 23-34 (Table S1-S2)	_____
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	Supplementary page 3-6, Figure S1-S5	_____
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why,	N/A. This will	_____

	when, and how).	be described after the study is completed	
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	Supplementary page 6, page 33 (Table S2)	_____
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	N/A. This will be described after the study is completed	_____

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see

www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

Reference

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