Clinical Study Protocol

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A Prospective, multicentre, cluster randomised controlled trial to evaluate the impact of the implementation of COPD quality standards in high exacerbation risk patients

------ A COPD Quality Improvement Program（QIP）

Principal Investigator: Prof. Rongchang Chen

Shenzhen People's Hospital

No.1017,Dongmen north road, Luohu district, Shenzhen

Email: chenrc@vip.163.com

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event
COPD	Chronic obstructive pulmonary disease
CRF	Case Report Form
CSR	Clinical Study Report
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroid
ICF	Informed Consent Form
LABA	Long-acting beta2 agonist
LAMA	Long-acting muscarinic antagonist
LSLV	Last Subject Last Visit
OAE	Other Significant Adverse Event
QIP	Quality Improvement Program

Abbreviation or special term	Explanation
QS	Quality Standards
QCI	Quality Control Indicators (QCI)
PI	Principal Investigator
RA	Research Agreement
RSI	Reference Safety Information – reference information for the expectedness of a serious adverse reaction to the IP
SABA	Short-acting beta2 agonist
SAMA	Short-acting muscarinic antagonist
SAE	Serious adverse event

QIP LEXICON OF KEY TERMS

The Quality Improvement Program will be innovative in its development of a central set of "Quality Standards" for COPD care, and in its approach to characterising target patient groups and their clinical management. For consistency in the use of clinical and programme language across the programme, an agreed lexicon of key terms has been summarised below.

Term	Definition
Quality Improvement Programme	The purpose of the Quality Improvement Programme is to improve the management of COPD patients especially those with high exacerbation risk, and to support the adoption of guideline-led clinical decision-making for all COPD patients, with a focus on assessment, therapy, and follow-up of patients with modifiable high-risk COPD.
QIP Cluster Randomised Controlled Trial	The impact of The Quality Improvement Program on COPD outcomes will be evaluated in the subset of patients by a cluster-randomised controlled trial (CRT); tier 2 OR tier 3 level hospitals across China will be the cluster units of randomisation.
COPD exacerbation **(EMR database definition)**	A significant worsening in respiratory symptoms in people with COPD. Either a moderate exacerbation defined as use of systemic corticosteroids and/or antibiotics for at least 3 days; or a severe exacerbation that is an inpatient COPD-related hospitalization or COPD-related death. Exacerbations occurring a minimum of 7 days apart or more will be considered as separate exacerbations.
Diagnosed COPD patient with high exacerbation risk	Patients with COPD who have had 2 or more moderate, or 1 or more severe exacerbations in the last 12 months, AND whose medical record data indicates clearly that there is scope for management optimisation. Patients with frequent exacerbations are at higher future risk of exacerbations. Frequent exacerbations are linked to accelerated lung function decline, greater risk of cardiovascular events and death, and larger healthcare costs. Guidelines state that frequent exacerbators should have their treatment optimised to reduce the risk of future exacerbations and potentially other adverse events. QIP aims to address the management needs of such patients by promoting improved treatment and follow-up.

Patients with scope for management optimisation	High-risk patients who continue to have exacerbations whilst on their current therapy. The intervention will focus on patients whose management may be optimised by correct diagnosis, or where current therapy allows for the addition of at least one inhaled therapy in accordance with GOLD 2022 strategy or national guidelines or where non-pharmacological interventions can be improved.
Quality Standards	The "Chinese Quality Standards of COPD clinical care" (known as the Quality Standards or QS) have been agreed by a panel of 18 experts in COPD, informed by national COPD guideline. There are four evidence-based Quality Standards encompassing identification, clinical assessment, pharmacological and non-pharmacological intervention, and patient follow-up.
Collation of PRO/PRI questionnaire data	At least every 3 months bringing together of PRO/PRI data received during the implementation of the intervention to be used in data analysis and feedback.

RESPONSIBLE PARTIES

Name	Professional title	Role in study	Affiliation	Email address
Chen Rongchang	Professor of Respiratory Medicine	Primary investigator	Shenzhen People's Hospital	chenrc@vip.163.com
Wang Lingwei	Professor of Respiratory Medicine	Sub-investigator	Shenzhen People's Hospital	limey@sina.com
Wang Fengyan	PhD of Respiratory Medicine	Sub-investigator	Guangzhou Institute of Respiratory Diseases	wangfengyan_@126.com
Yang Kai	PhD of Respiratory Medicine	Statistician	Shenzhen People's Hospital	yangkaids@163.com

PROTOCOL SYNOPSIS

A Prospective, multicentre, cluster-randomised controlled trial to evaluate the impact on the implementation of COPD quality standards in exacerbation risk patients
------ A COPD Quality Improvement Program（QIP）

Background and Rationale

Chronic obstructive pulmonary disease (COPD) is currently the most common chronic respiratory disease in China which causes a huge economic and social burden. Acute Exacerbation is a crucial issue that cannot be ignored in the management of COPD. Patients with frequent exacerbations have been found to have greater airflow limitation, a greater symptom burden, increased mortality, and worsen the quality of life (QoL). However, The COPD management of those patients in clinical practice is poor in China. Patients with a low standard of care, lack of regularly pharmacological and non-pharmacological intervention, and insufficient follow-up and disease education in clinical practice.

Objectives and Outcomes

QIP(Quality Improvement Programme) is a COPD quality improvement program in China. The initial step of this program is to set up the Quality Standards(QS) of COPD management in clinical practice, then embed Quality Standards into routine care and uses Quality Control Indicators (QCI)to check the QS implementation. The aim of the QIP program is to standardize COPD management in clinical practice in China, including the standardization of diagnosis, assessment, pharmacological and non-pharmacological intervention, and follow-up. COPD patients can benefit from standardization clinical behaviours, to be identified early, be

accessed comprehensively, and be treated correctly according to guidelines, and with an appropriate follow-up to improve adherence.

The objective of QIP study is to address key gaps in management of patients with high-risk through a targeted quality improvement programme in a healthcare system or practice. The aim is to evaluate the impact of QS implementation on target population compared to usual care in a real-world setting, including but not limited to COPD exacerbation, lung function, quality of life, and treatment pattern.

Primary Objective	**Outcome Measure**
To evaluate the effectiveness of QS implementation on clinically important deterioration (CID)	Time to CID, which is defined as the time from the date of enrolment until the date of the first CID.CID defined as any of the following events: 1) Trough FEV1 decline ⩾100ml 2) CAT increasing ⩾ 2 unit 3) one moderate or severe exacerbation
Secondary Objective:	**Outcome Measure:**
To evaluate the impact of QS implementation on exacerbations, lung function and symptoms in COPD patients	• Annual rate of moderate or severe COPD exacerbation • Annual rate of severe COPD exacerbation • Change from baseline in trough FEV_1 over 48 weeks • Change from baseline in CAT over 48 weeks

To describe COPD management and treatment adherence in QS implementation group and usual care group	• Proportion of patients received inhalation technique review at least once during follow-up period • Proportion of patients received long-acting inhaled medicine with percentage of days covered (PDC)≥ 80% over 48 weeks
To describe intervention group and control group on treatment pattern in stable COPD	• Proportion of prescription of inhaled maintenance medicine at 12, 24, 36, 48 weeks . • Proportion of patients prescribed ICS-containing inhaled maintenance medicine at 12, 24, 36, 48 weeks .

Study design

This is a interventional, cluster-randomized, pragmatic clinical study. A total of 41 hospitals will be selected. Among them, 40 eligible hospitals will be selected across China and randomized (stratified by tier and geographic region) to the intervention group or control group at the ratio of 1:1. In addition, the leading site will be assigned to the intervention group without following the randomization procedure. In the intervention group, QS implementation will be performed. The control group will maintain the current practice. Eligible patients will be recruited in both groups and will be followed up every 12 weeks for 48 weeks.

Study population

The target populations in this study are the diagnosed COPD patients with exacerbation history. Age≥40 years, at least 2 moderate or 1 severe exacerbation in the previous year; or 1 moderate exacerbation in the previous year with FEV1 < 50% predicted value at baseline;.

Those patients currently are symptomatic(CAT⩾10),or have progressive worsening of airflow restriction, and with a scope of optimization in COPD management as judged by physicians.

Intervention

The intervention was delivered at the hospital level. The intervention group will receive QS implementation, including QS training for physicians of respiratory department every 12 weeks; QS implementation check every 12 weeks, and follow-up every 12 weeks, QS-related written COPD clinical procedures will be also suggested to established key QS training requirements are:1) COPD diagnosis and assessment; 2)Therapy prescribed in accordance with national guideline 3)Non-pharmacological interventions; 4)An appropriate follow-up according to QS.

The control group will maintain current practice and follow up every 12 weeks.

Data Sources

The Electronic Data Capture (EDC) system will be used for data collection and query handling. Participating patients will be followed up for at least 48 weeks for data collection. This will include data from the EMR, medical charts, and other sources in healthcare centres in the intervention group and control group. The CAT score will be collected through questionnaire. Patient questionnaire will be collected in CRF by a study staff who will not be involved in recruitment and training.

Assuring Allocated Regimens are Implemented

Unlike traditional clinical trials where there is a near perfect guarantee of the application of the allocated treatment, this real-world cluster-randomized trial may face some barriers in the allocated exposure being applied in hospitals, especially since the intervention is a clinical pathway change. To measure the effective implementation of the intervention, the Quality Control Indicators(QCI) will be regular checked by each site PI who is responsible for the QS implementation of their department.

Statistical methods

Sample Size

A total of 1107 patients will be enrolled in the study(41 clusters, 27 patients in each cluster). With 40(20 per treatment group) clusters randomized at a 1:1 ratio (Intervention group: control group) and a size of 27 individuals per cluster (21 after drop out, assuming 20% drop out), approximately 1080 patients will be enrolled from the 40 randomized hospitals. In addition, the leading site will be assigned to the intervention group without following the randomization procedure and approximately 27 individuals will be enrolled. Whilst, data from the leading site will be excluded from the primary analysis set.

If the true hazard ratio (HR) for the comparison of QS versus Usual Care group in this patient population is 0.70, assuming ICC is 0.079 (ICC of 0.079 was estimated using analysis of variance method based on results from a pilot study[10]), 713 CID events will provide 80% power to demonstrate a statistically significant difference in CID free duration at a 5% 2-sided significance level (this could translate to an increase of median time to CID from 121 days to 172 days), assuming CID free duration is exponentially distributed.

Methods for statistical analyses

Descriptive statistics will be calculated, including n, means, standard deviations, medians, and interquartile ranges for continuous variables and frequency counts and percentages for categorical variables. Percentage will be calculated based on non-missing data unless otherwise specified. Data will be examined for skewness, outliers, and systematic missing data. Transformations will be undertaken as needed. All statistical procedures will be conducted using SAS version 9.4 or later, while graphs may also be produced using R.

The primary outcome measure is time to CID. The primary outcome analysis will be based on FAS, which includes all enrolled subjects among all randomized hospitals who had at least one post-baseline efficacy data assessments. Comparison between treatment groups will be

conducted using a clustered log-rank test at two-sided significance level of 0.05. Kaplan-Meier curve of time to CID will also be presented by treatment group.

Except for comparison of primary outcome measure, all other comparisons will be exploratory while nominal p value might be provided if applicable. Changes from baseline in trough FEV1, CAT over 48 weeks will be analysed using a random effects model. Rate of moderate or severe COPD exacerbation and rate of severe exacerbation will be analysed using random effects Poisson regression. The endpoints of proportion of patients received inhalation technique review at least once during follow-up period, proportion of patients received long-acting inhaled medicine with percentage of days covered (PDC)≥ 80% over 48 weeks, proportion of prescription of inhaled maintenance medicine at each visit, and proportion of patients prescribed COPD-related medicine at each visit will be summarised. Descriptive statistics for these endpoints will be presented by treatment group.

Sensitivity analysis will be conducted among all enrolled subjects who had at least one post-baseline efficacy data assessments.

INTRODUCTION

1. BACKGROUND AND RATIONALE

1.1 Background

Chronic obstructive pulmonary disease (COPD) is currently the most common chronic respiratory disease in China, with a high prevalence of 13.7% (Wang C et al. 2018) and it is also the third leading cause of death (Stanaway J D et al. 2019), which causes a huge economic and social burden. Patients with exacerbation history or high symptom burden will have higher future risk of exacerbations, accelerated lung function decline, greater risk of cardiovascular events and higher mortality rates (Jones, R. C. M. et al. 2014, Kostikas, K. et al. 2020, Larsson, K. et al. 2019, Donaldson, G. C. et al. 2010, Kunisaki, K. M. et al. 2018).

But because the symptom of COPD is not typical and the public disease awareness is low, the diagnosis and treatment of COPD are seriously inadequate in China, there is only 5.9% of patients had ever been tested by spirometry in the history and 11.7% were taking treatments for COPD (Fang L et al. 2018). Therefore, the current management of COPD patients is poor, with low standard of care, a lack of regular pharmacological and non-pharmacological intervention, insufficient follow-up and disease education in the Chinese COPD clinical practice even in those high risk patients.

A pilot study of COPD management status in Guangdong province shows that only 28% of COPD patients received long-acting inhaled maintenance medication, 2.9% of smoking patients received smoking cessation intervention, and only 7.4% of patients received documented disease education in real world(Qiu Chen et al. 2019). The pilot study showed that in China, the standardized management of COPD is poor, we have a huge opportunity to improve the status.

1.2 Rationale

Due to the lack of quality control standards for the standardized management of COPD in China, Quality Standards (QS) has been published in 2022. The Quality Standards aims to

standardize COPD management in clinical practice in China, including diagnosis, assessment, pharmacological and non-pharmacological intervention, and follow-up. According to the COPD guideline and previous study (Ferrone M et al. 2019, Chen X R C et al. 2021), patients can benefit from standardized clinical behaviours, to be identified early, to be accessed comprehensively, to be treated correctly according to guidelines, and with appropriate follow-up to improve adherence.

The QIP study focuses on improving disease management of COPD patients who have a history of exacerbation, and with a scope to optimize their current COPD management according to medical history record. Acute exacerbation is a crucial issue that cannot be ignored in the management of COPD. COPD diagnosed patients with frequent exacerbation have been found to have more severe airflow limitation, heavier symptom burden, increased mortality rate, and worse quality of life (QoL) (Soler-Cataluna J J et al. 2005, Kerkhof M, et al. 2019, Le Rouzic O et al. 2018, Donaldson G C et al. 2002). These patients are at a higher risk of future events(such as exacerbations, hospital admission, or death) but there is an opportunity to modify that risk and improve outcomes through thorough standardized patient management.

The QIP study aims to evaluate the impact of QS implementation on target patients in intervention group (receive QS implementation) compared to control group(maintain current practice) in a real-world setting, including but not limited to exacerbation, lung function, quality of life, and treatment pattern.

2. OBJECTIVES

QIP study aims to evaluate the impact of QS implementation through patient outcome. The objective needs to be addressed in a real-world setting to demonstrate the true benefit of QS implementation on target population compared with control group.

2.1 Primary objective

Primary Objective	**Outcome Measure**
To evaluate the effectiveness of QS implementation on clinically important deterioration (CID)	Time to CID, which is defined as the time from the date of enrolment until the date of the first CID. CID is defined as any of the following events: 1) Trough FEV1 decline ⩾100ml 2) CAT increasing ⩾ 2 unit 3) one moderate or severe exacerbation

2.2 Secondary objectives

Secondary Objective:	**Outcome Measure:**
To evaluate the impact of QS implementation on exacerbations, lung function and symptoms in COPD patients	• Annual rate of moderate or severe exacerbation • Annual rate of severe exacerbation • Change from baseline in trough FEV_1 over 48 weeks • Change from baseline in CAT over 48 weeks

To describe COPD management and treatment adherence in QS implementation group and usual care group	• Proportion of patients received inhalation technique review at least once during follow-up period • Proportion of patients received long-acting inhaled medicine with percentage of days covered (PDC)≥ 80% over 48 weeks
To describe treatment pattern in stable COPD for intervention group and control group	• Proportion of prescription of inhaled maintenance medicine at 12, 24, 36, 48 weeks • Proportion of patients prescribed ICS-containing inhaled maintenance medicine at 12, 24, 36, 48 weeks.

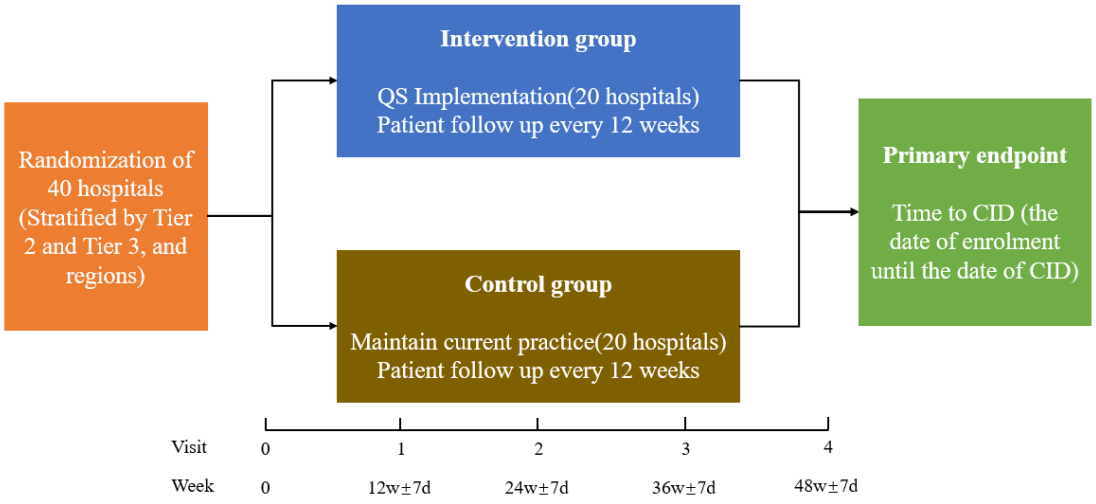
3. METHODOLOGY

3.1 Study Design

This is a interventional, cluster-randomized, pragmatic clinical study. Totally, there are 41 sites will be selected across China, It is worth mentioning that leading site will directly enter the intervention group, mainly be in charge of supervising and managing the QS implementation in the sites of intervention group. The rest 40 sites will be randomized (stratified by tier levels and geographic region) to the intervention group or control group at the ratio of 1:1. In the intervention group, QS implementation will be performed, and will be checked every 12 weeks. The control group will maintain the current practice. Eligible patients will be recruited and followed up every 12 weeks for 48 weeks.

Eligible consented patients will be enrolled consecutively to minimize selection bias (see section 3.3.2 and section 3.3.3 for inclusion and exclusion criteria).

Figure 1. study schematic



Leading site will directly enter the intervention group, and will recruit at least 27 patients, supervises and manages the QS implementation in the sites of intervention group.

3.2 Intervention

The QIP study is based on implementation of the Quality Standards into routine care, supported by data collection and analysis as core components. Figure 2 is a visual representation of QS, with the centre of the figure describing the components needed to implement the Quality Standards into practice. All components in bold text in Figure 2 are core components for the study and should be implemented by independent sites.

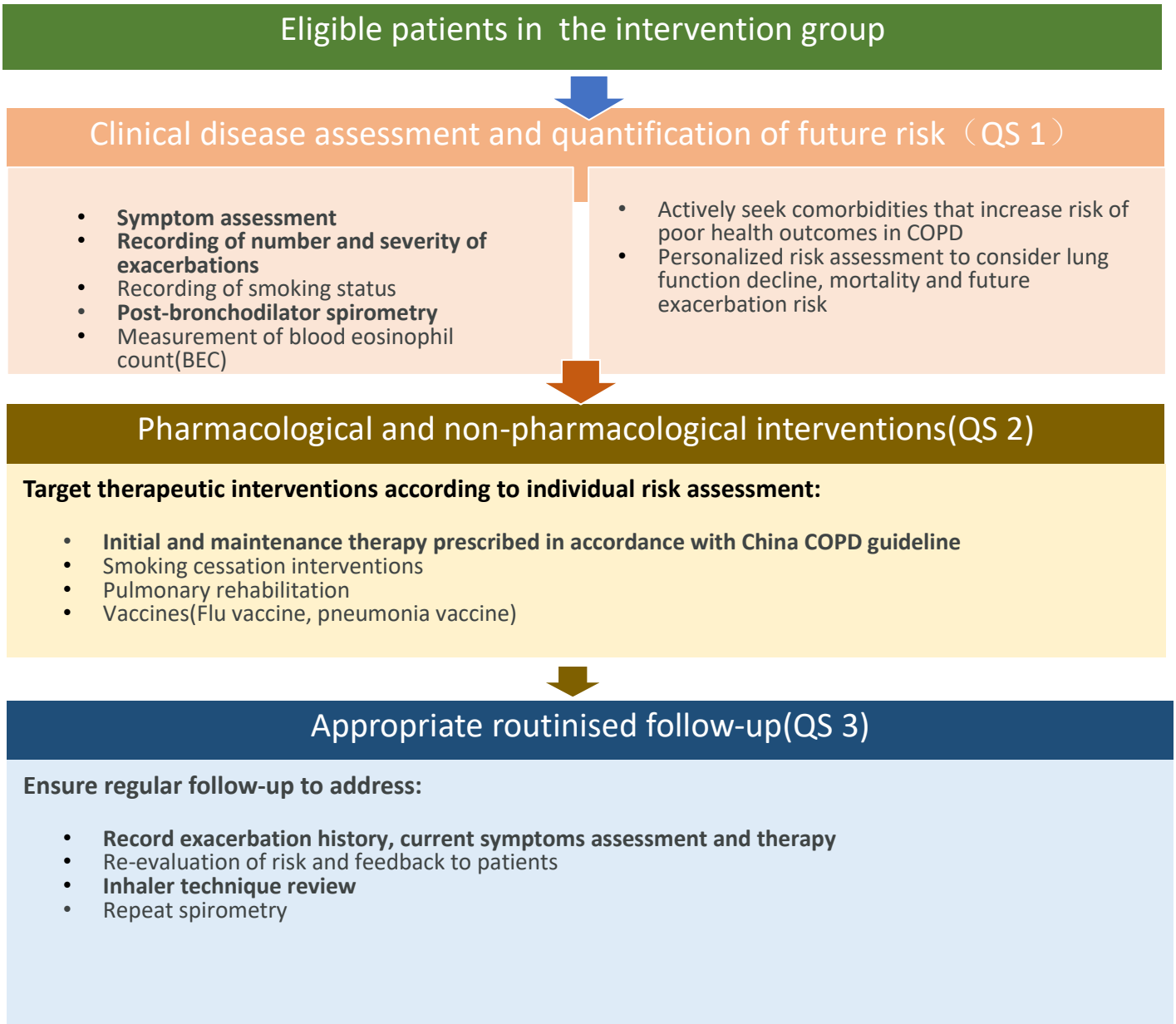
3.2.1 Quality Standards

The "Chinese Quality Standards of COPD Clinical Care" (known as the Quality Standards or QS) have been agreed by a panel of 17 experts in COPD, also involved by national COPD guideline. The Quality Standards aim to provide a framework of quality improvement efforts in COPD patients. There are three evidence-based Quality Standards encompassing clinical assessment, pharmacological and non-pharmacological intervention, and patient follow-up which are outlined in Figure 2.

Figure 2 also shows where the target populations link with the Quality Standards and provides a broad outline of how the study flows.

The study targets patients who have a confirmed COPD diagnosis and with high-risk of future events. Patients are scheduled for clinical disease assessment using the components described in QS 1 (section 3.2.2.2.a). Pharmacological and non-pharmacological interventions are then initiated based on the information obtained during disease assessment (QS 2, section 3.2.2.2.b). Depending on the intervention required, follow-up and patient review is carried out using QS for those whose COPD is not stable or controlled (QS 3, section 3.2.2.2.c). The follow-up recommendations then ensure patients are regularly reviewed and reassessed to improve the quality of patient care and management.

Figure 2. Key components of Quality Standards for target population and process



3.2.2 QS implementation

Quality Standard has core components and requirements that must be implemented in order to translate it into practice, and these are described in section 3.2.2.2.

3.2.2.1 Translating the Quality Standards into practice

The intended pathway and interlinking of the Quality Standards during implementation of the QS is shown in Figure 2. Different hospitals may differ, however, to translate the Quality Standards into practice the following requirements must be adhered to. Where acceptable, options to modify these components to suit each hospital needs are provided.

a) QS 1:Assessment of disease and quantification of future risk

Eligible patients following the QS 1 assessment process goes on to have a thorough clinical assessment to characterise their disease status. This clinical assessment will also consider the patient's risk of future exacerbations, cardiac events and mortality.

Assessment of disease

- **Symptom assessment** to be performed during follow-up period.
    - The COPD Assessment Test (CAT) (Jones et al. 2009, Jones et al. 2012) score (Appendix 2)(developed to quantify symptom burden in COPD using a concise and simple set of questions) is the core symptom assessment method in the QS. It is referred to frequently in COPD guidelines and is used to help guide treatment.
    - Symptom assessment should be performed at least every 12weeks, but may be performed more frequently depending on frequency of patient review and disease stability.

- **Exacerbation Risk** Number and severity of exacerbations since previous review to be recorded in EMR.

Quantification of future risk

- **Comorbidities** including osteoporosis, diabetes mellitus, gastroesophageal reflux disease (GERD), anxiety and depression to be actively sought and managed.

- **Risk prediction** QS will be used to quantify risk of future events and/or mortality. Details regarding specific risk score methods used should be documented and available for sharing with the QC team where possible.

    - Information resulting from risk assessment to be conveyed to patient when felt to be beneficial by healthcare provider.

b) QS 2: Pharmacological and non-pharmacological interventions

Following thorough assessment, QS 2 focuses on ensuring patients receive therapy and intervention in line with their risk and clinical parameters. The focus in QS 2 is to identify opportunities to increase or alter treatment such that health outcomes are improved. The following list of pharmacological and non-pharmacological interventions are core components of the QS and should be routinely applied.

- **Initial therapy for newly diagnosed** patients to be based on China COPD guideline classification and recommendations

- **Modification of therapy** for high-risk patients to be made in accordance with current China COPD guideline follow-up pharmacological treatment algorithms, utilizing information obtained during assessment. The focus is on inhaled maintenance therapy, other COPD therapies to be evaluated in accordance with China COPD guideline.

- **Smoking cessation intervention(s)** such as referral to smoking cessation services and prescription of pharmacotherapy for smoking cessation to be offered at initial assessment and subsequent review as required.

- **Pulmonary rehabilitation** according to need and physician's recommendation.
- **Vaccination** pneumococcal and influenza vaccines will be recommended.

c) QS 3: Appropriate follow-up

COPD is a chronic disease and effort to optimise management must continue beyond initial assessment or diagnosis in the provision of regular multi-faceted follow-up consultations.

- **Medication and symptom review** must involve the recording of current therapy, medication adherence, exacerbation history since previous review and current symptoms.
- **Inhaler technique** to be reviewed at least once during study period and corrections in technique made as necessary.
- **Spirometry** performed for monitoring purposes and to detect those with rapid decline in FEV1 (defined as more than 40ml per year (Vestbo J et al. 2011)).

3.2.2.2 Quality Control (QC) team

Implementation of QS requires input from some clinical staffs of participating hospitals.

The QC team members are recommended to be directors of respiratory departments from participating hospitals and should familiarise themselves with the Quality Standards and core QS components(Figure 2).

The QC team responsibilities include:

- Coordination of overall delivery of the QS
- Facilitate understanding of the overall project objectives and rationale
- Ensure the site-level delivery of QS education and training
- Assess the site-level QS implementation and quality
- Collect feedback of physicians from respiratory departments from participating hospitals

- Regular check implementation performance and review implementation process. This may be achieved by a sub-group in the team who are responsible for ongoing assessment of the programme, and for making recommendations for modifications where necessary.

The QS training will be performed every 3 months by the QC team, the initial one will be a comprehensive face-to-face training and with a full test before sites launch. And the training content of next 3 times during study period will be determined based on the assessment and feedback of implementation sites.

The control group will maintain their usual care. COPD usual care is decided by the physician based on the clinical practice.

Patients in both groups will be trained of exacerbation identification.

3.2.2.3 Quality Control indicators

The Quality Control Indicators (QCI) are linked to the Quality Standards described in Figure 2 , reflecting the physicians' standardized behaviours to manage the COPD populations. The Quality Control Indicators(QCI) should be checked by QC team every 3 months.

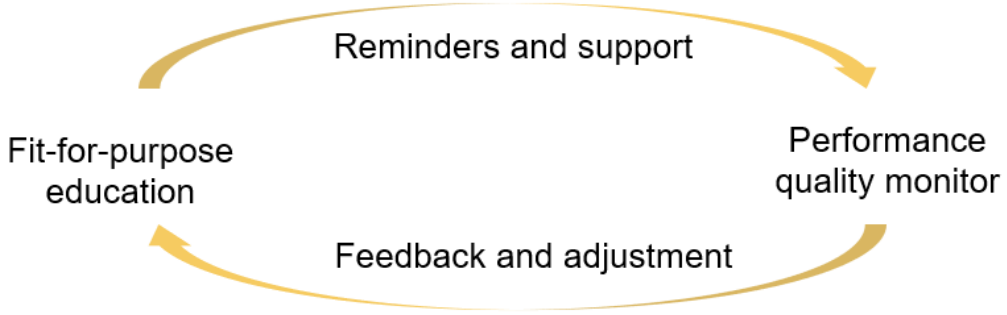
The checking items including % of patients receiving inhalation therapy, non-pharmaceutical treatment , exacerbations treatment, % of patients who had been given the COPD disease education during visit, etc. the details showed in Appendix 1.

QC team could make modifications of training content according to the QCI assessment and feedback where necessary.

3.2.3 Monitor progress and sustain improvement

QS has to be practiced in the intervention group, thus a crucial part of the programme for implementing sites is the cyclical review of the implementation process and outcomes achieved throughout the program. This iterative process(Figure 3) is used to identify on-going opportunities for program enhancement and make the necessary modifications to existing approaches that will continuously improve patient outcomes.

Figure 3. QS education and improvement process



3.2.4 Data source(s)

The Electronic Data Capture (EDC) system will be used for data collection and query handling. Participating patients will be followed up for at least 48 weeks for data collection. This will include data from the EMR, medical charts, and other sources in healthcare centres in the intervention group and control group. CAT score will be collected through questionnaire. Patient questionnaire will be collected in CRF by a study staff who will not be involved in recruitment and training.

3.3 Study Population

3.3.1 Hospital selection criteria

Totally 41 hospitals across China will be included, and 40 hospitals will be allocated via cluster-randomization to the intervention or control groups (20 hospitals*2). Leading site will directly enter the intervention group, mainly be in charge of supervising and managing the QS implementation in the sites of intervention group. So a total of 41 hospitals should meet the following criteria will be considered for inclusion in this study:

- Tier 2 or tier 3 hospitals.
- Equip with standardized spirometers and technicians meeting ATS criteria.
- No implementation of QS or similar programs before study entry.
- Have established department of Pulmonary and Critical Care Medicine, emergency unit, and the corresponding wards.

- Availability of COPD maintenance inhaled medicines (at least one mono , one dual, and one triple inhaled therapy should be available) recommended by the China COPD guideline.

3.3.2 Inclusion criteria

Patients are eligible to be included in the study if all of the following criteria apply:

- Diagnosed with COPD
- Aged 40 years or older
- CAT≥10
- With exacerbation history:
  - at least 2 moderate or 1 severe exacerbation in the previous year;
  - or 1 moderate exacerbation in the previous year with FEV1 <50% predicted value at baseline;
- Must able to sign the informed consent form

3.3.3 Exclusion criteria

Patients will be excluded from this study if any of the following exclusion criteria apply:

- Patients on triple therapy at baseline with a LAMA, LABA, and inhaled corticosteroid (ICS) combination (Including open triple and fix-dose triple)
- Significant diseases or conditions other than COPD, which, in the opinion of the Investigator, may put the subject at risk because of participation in the study or may influence either the results of the study or the subject's ability to participate in the study
- Patients who are currently involved in any other interventional studies

3.3.4 Subject enrolment

Potentially eligible patients will be screened, investigators should keep a record of subjects who screened for this study. Patients who meet the inclusion criteria will be enrolled. Investigators should keep a record of subjects who entered this study.

The Investigators will:

- Obtain signed informed consent from the potential subject or their guardian/legal representative before any study specific procedures are performed.
- Assign potential subject a unique enrolment number.
- Determine subject eligibility. See Section 3.2.2 and Section 3.2.3

3.3.5 Procedures for handling incorrectly enrolled subjects

Subjects who are enrolled, but subsequently found not to meet the eligibility criteria must be withdrawn from the study. The investigator(s) should record the detailed reasons .

3.4 Criteria for withdrawal

3.4.1 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time, without prejudice to further intervention.

If a subject withdraws from participation in the study, then his/her enrolment code cannot be reused. Withdrawn subjects will not be replaced. Reason of withdrawal will be recorded.

4. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

4.1 Efficacy assessments

The primary endpoint is time to CID, time to CID is defined as the time from the date of enrolment until the date of CID, and CID is defined as the occurrence of any of the following events:

- trough FEV1 decline ≥100ml or
- CAT increase ≥ 2 unit or
- one moderate or severe exacerbation

4.1.1 Pulmonary Function Tests

All study staff responsible for performing pulmonary function testing should receive standardized training and obtain the qualification certification. All technicians are required to demonstrate proficiency in the use of the equipment and the ability to perform technically acceptable PFTs (ATS criteria, Miller, 2005) prior to performing testing on study subjects. It should be avoided to conduct lung function testing within 6 hours after the use of any short-acting bronchodilators. Ventolin pMDI 400μg will be inhaled 20 minutes prior to the conduction of reversibility testing.

Lung function test should be assessed at visit 0,visit 1, visit 2,visit 3, and visit 4. Patients do not need to have spirometry at visit 0 if they have lung function test report in 4 weeks before visit 0.

The trough value for FEV1 at Weeks 12, 24, 36, 48 visit is the pre-dose (prior to taking the morning dose of maintenance treatment) and pre-bronchodilator assessment at that visit.

4.1.2 COPD Exacerbations

A COPD exacerbation will be defined as change in the subject's usual COPD symptoms that lasts 2 or more days, is beyond normal day-to-day variation, is acute in onset, and may warrant a change in regular medication.

4.1.2.1 COPD Exacerbation Severity

Each COPD exacerbation will be categorized based on severity as follows:

Moderate: Worsening symptoms of COPD that require treatment with oral/systemic corticosteroids and/or antibiotics.

Severe: Worsening symptoms of COPD that require treatment with in-patient hospitalization.

4.1.3 COPD Assessment Test (CAT)

The COPD Assessment Test (Jones et al. 2009, Jones et al. 2012) is a validated, short and simple patient completed questionnaire which has been developed for use in routine clinical practice to measure the health status of patients with COPD. The CAT is an 8-item questionnaire suitable for completion by all patients diagnosed with COPD. When completing the questionnaire, subjects rate their experience on a 6-point scale, ranging from 0 (maximum impairment) to 5 (no impairment) with a scoring range of 0-40. Higher scores indicate greater disease impact. The CAT score will describe the burden and symptomatic impact of COPD in subjects enrolled in the study and will be used to determine subject eligibility to participate in the study.

Subjects will complete the CAT (Refer to Appendix 2) at visit 0,visit 1, visit 2,visit 3, and visit 4.

4.1.4 Patients questionnaire

A patient questionnaire (Appendix 3) will be specifically designed for this study to check the behaviours of physicians in the intervention group. This questionnaire aims to confirm whether the subjects have received the inhaler device usage education, COPD-related disease education, smoking education and advice, and the vaccine advice. Patients questionnaire will perform at the end of every visit.

4.2 Treatment pattern and compliance variables

4.2.1 Treatment pattern

Stable COPD treatment pattern will be described by maintenance treatment(long-acting inhaled medicine prescription and oral medicine prescription) using the following categories. Number of prescription records with each of the following categories will be tracked and reported.

- LAMA (long-acting muscarinic antagonist, e.g. Tiotropium)
- LABA (long-acting beta2-agonist, e.g. Formoterol, Indacaterol, Salmeterol, etc.)
- ICS+LABA (Inhaled corticosteroids + LABA combinations)
- LABA+LAMA
- ICS+LABA+LAMA
- Methylxanthines (long-acting/short-acting)
- SABA (Short-acting inhaled beta2-agonists) or SAMA (short-acting muscarinic antagonist)
- Oral systemic corticosteroids
- Traditional Chinese Medicines
- Antibiotics
- Others(Antitussive/Mucolytics/cough-mucolytics)

4.2.2 Compliance

Treatment compliance will be based upon a percentage of days covered (PDC) calculation of for long-acting inhaled maintenance medication. The PDC will be a measure obtained through the ratio of the cumulative days of drug use and the length of the observation period, expressed as %.

Patients were deemed to be adherent if their PDC was ≥ 80% and not adherent if their PDC was <80% over the post-index observation period.

5. STATISTICAL ANALYSIS PLAN

5.1 Populations for Analyses

The FAS analysis set is all enrolled subjects among all randomized hospitals who had at least one post-baseline efficacy data assessments. The FAS set will be the primary analysis set in the study.

5.2 Sample size

A total of 1107 patients will be enrolled in the study(41 clusters, 27 patients in each cluster). With 40(20 per treatment group) clusters randomized at a 1:1 ratio (Intervention group: control group) and a size of 27 individuals per cluster (21 after drop out, assuming 20% drop out), approximately 1080 patients will be enrolled from the 40 randomized hospitals. In addition, the leading site will be assigned to the intervention group without following the randomization procedure and approximately 27 individuals will be enrolled. Whilst, data from the leading site will be excluded from the primary analysis set. The hypotheses are:

$$H_0\colon S_1(t) = S_2(t) \quad for\ all\ t$$

$$H_1\colon S_1(t) \neq S_2(t) \quad for\ some\ t$$

If the hazard ratio (HR) for the comparison of QS versus usual care in this patient population is 0.70, assuming ICC is 0.079, 713CID events will provide 80% power to demonstrate a statistically significant difference at a 5% 2-sided significance level (this could translate to an increase of median time to CID from 121 days to 172 days), assuming CID free duration is exponentially distributed.

5.3 Methods for statistical analyses

5.3.1 General Considerations

The statistical analysis plan (SAP) will be finalised prior to data base lock (DBL) and it will include a more technical and detailed description of the statistical analyses described in this section. As randomisation was at the hospital (cluster) level, appropriate statistical methods to account for the clustering effect will be used in the analysis.

Descriptive statistics will be calculated, including n, means, standard deviations, medians, and interquartile ranges for continuous variables and frequency counts and percentages for categorical variables. Percentage will be calculated based on non-missing data unless otherwise specified.

Unless otherwise specified, analyses of change from baseline to a particular time point will be based on the measurement available at that time point. Missing data will be assumed missing at random or missing completely at random. In general, no imputation will be applied unless otherwise specified.

5.3.2 Analysis of the primary variable (s)

The primary outcome measure is time to CID, which is defined as from enrolment to CID. CID is defined as the first occurrence of any following events over study follow-up:

- ≥ 100 mL decrease in pre-dose trough FEV1
- One moderate-to-severe COPD exacerbation occurring after enrolment
- ≥ 2-unit increase in CAT total score

Patients who are CID free and alive at the time of analysis will be censored at the date of their last follow-up assessments. Patients who died prior to CID will be censored at the date of death. Patients who withdrew from the study without experiencing an event will be censored at the date of withdrawal.

Time to CID will be analysed using a clustered log-rank test for generation of the p-value and using Breslow approach for handling ties. Hazard Ratio and regarding 95% CI will also be presented. Statistical testing will be conducted at significance level of 0.05.

For each treatment group, time to CID will be summarized using K-M (Kaplan-Meier) method and K-M curves will also be presented.

5.3.3 Analysis of the secondary variable(s)

Change from baseline in trough FEV1, CAT over 48 weeks and rate of moderate/severe and severe COPD exacerbation

Change from baseline in trough FEV1, CAT over 48 weeks will be analysed using a random effects model. The model is planned to take clusters as random intercept term, with covariates including but not limited to: tier of hospital, geographic regions, COPD exacerbation history at baseline, CAT at baseline, trough FEV1 at baseline, etc. For the covariance structure within subject, the unstructured (UN), Toeplitz (TOEP), first-order autoregressive (AR(1)) or compound symmetric (CS) covariance structure will be used. The unstructured (UN) covariance will be used firstly. If there is convergence problem under current covariance structure, the latter structure will be used as the order presented above until no convergence problem. Estimated effect size (mean difference between the two treatment groups) and regarding 95% confidence interval will be provided, while nominal p-value will also be presented as appropriate.

Rate of moderate or severe COPD exacerbation and severe COPD exacerbation will be analysed using random effects Poisson regression. Chronic obstructive pulmonary disease exacerbations will be considered separate events provided that 7 or more days are between the recorded stop date of the earlier event and start date of the latter. Time at risk of experiencing an exacerbation will be used as an offset variable in the model. The model might include but not limited to below covariates: tier of hospital at baseline, geographic regions, baseline COPD exacerbation history, baseline CAT and baseline trough FEV1. Estimated relative risk with 95% confidence interval will be provided where nominal p-value will be presented as appropriate as well.

Proportion of patients received at least once inhalation technique review, proportion of patients received long-acting inhaled medicine with percentage of days covered (PDC)≥ 80% over 48 weeks and treatment pattern in intervention group and control group

The other secondary outcome measures are:

Proportion of patients received inhalation technique review at least once during follow-up period, where denominator will be number of patients with available record in FAS at 12weeks/24weeks/36weeks/48weeks.

Proportion of patients received long-acting inhaled medicine with percentage of days covered (PDC)≥ 80% over 48 weeks, where denominator will be based on patients with long-acting inhaled medicine records at baseline or through the study follow-up.

Proportion of patients prescribed inhaled maintenance medicine at 12 weeks/24 weeks/36 weeks/48 weeks and proportion of patients prescribed COPD-related medicine at 12 weeks/24 weeks/36 weeks/48 weeks will be derived based on number of patients with available records respectively.

All above four outcome measures will be summarized using descriptive statistics by treatment group.

5.3.4 Sensitivity analysis

Sensitivity analysis will be conducted among all enrolled subjects who had at least one post-baseline efficacy data assessments.

5.4 Bias

5.4.1 Methods to Minimise Bias

Potential sources of bias come from differences between hospitals, which includes participation in different tiers and different geographic regions, differences in the capability of COPD management exist between the same tier hospital in different cities. There may be a selection bias that occurs because the hospitals need to meet the inclusion criteria in order to participate in the study. However, clustered randomization, with every attempt to balance the

hospital tiers and geographic regions within each group, will somewhat equalize these medical centers across both study groups, to mitigate this bias. Additionally, an extra backup hospital will be selected in each strata to minimize selection bias. If a hospital withdraw from the study after randomization, the backup hospital in the corresponding strata will replace it.

Periodic collection of relevant data in the control group will improve the compliance of patients, to a certain extent, that will affect the HCP's attention to patients. However, an independent team（a nurse from each site who will not be involved in recruitment and training） will be supposed to collect data in both groups to reduce and to balance the influence between data collection and the purpose for the study.

Potential cross-contamination across groups from patients transfer to different hospitals. In order to reduce contamination, the QIP study will choose 8 hospitals in each region. Hospitals will be selected from five regions of the whole country, namely, east, west, north, south and central. In addition, it will be emphasized in ICF and try to encourage patients to seek care at the study hospital if they need.

5.4.2 Adjustment for Multiple Comparisons

Only the analysis of primary outcome measure will be formal statistical testing with full portion of the alpha (0.05) assigned. All other comparisons will be exploratory and p-values will be nominal.

6. STUDY PLAN AND TIMING OF PROCEDURES

6.1 Study plan

Table 1. Schedule of Activities for Patients

Procedure	Follow up period				
Visit	0 (enrolment)	1	2	3	4
Week	0	12	24	36	48

Day	0	90 (±7d)	168 (±7d)	252 (±7d)	336 (±7d)
Informed consent	X				
Inclusion/exclusion criteria	X				
Demographics	X				
Smoking status [a]	X	X	X	X	X
Medical history/COPD history [b]	X				
Concomitant Medications	X	X	X	X	X
Physical examination [c]	X				
Comorbidities [d]	X	X	X	X	X
Exacerbations	X	X	X	X	X
BEC/FENO (if available)[e]	X	X	X	X	X
Spirometry Test[f](not required in V0 if patients have lung function report in 1 month before enrollment)	X	X	X	X	X
CAT	X	X	X	X	X
COPD pharmacological treatments [g]	X	X	X	X	X
COPD non-pharmacological treatments [h]	X	X	X	X	X
Patient Questionnaire [i]	X	X	X	X	X

Notes:
a. Smoking status include current smoker or former smoker or stopping smoking or restarting smoking, smoking pack-years.
b. Medical history/COPD history include all medical history details, family history of COPD, and COPD exacerbations in the last 12 months.
c. A complete physical examination will be performed at Visit 0.
d. Comorbidities includes new diagnosed comorbidities after enrollment period.
e. BEC, blood eosinophil count
f. At Visit 0, both pre-bronchodilator and post-bronchodilator spirometry will be conducted. At Visit 1 through Visit 4, perform pre-bronchodilator (30 minute prior to taking morning dose of maintenance treatment drugs). Spirometry test should be performed after withholding rescue albuterol for ⩾6 hours at all visits.
g. COPD pharmacological treatments information include any COPD related drugs that the patient used within 4 weeks before enrolment and during the whole study in stable COPD periods.
h. COPD non-pharmacological treatments information include any non-pharmacological treatments(pulmonary rehabilitation, pneumococcal and influenza vaccines, smoking cession intervention, oxygen therapy) within 4 weeks before enrolment and during the whole study.
i. Patient Questionnaire include information of whether the patients receive the inhaler device usage education and review, smoke cession education, and COPD disease education or not.

6.2 Procedure

6.2.1 Enrolment period

At Visit 0, patients who met all of the inclusion criteria and none of the exclusion criteria will be enrolled. At this visit, as showing in table 1, the investigator will obtain baseline data, including demographics, medical/surgical history, COPD exacerbation history in the previous

year, smoking status, COPD-related medication, comorbidities, clinical laboratory tests, physical examination etc.

The patients' latest spirometry data before visit 0 and the spirometry data obtained at Visit 0 should be confirmed for the inclusion criterion. If the previous spirometry data is not available, the pulmonary function test should be performed first. Re-screening is not allowed for patients who do not meet the spirometry criteria at Visit 0.

6.2.2 follow-up period

Patients will return to the study hospital every 12 weeks for the on-site visit.

During on-site visits, in the intervention group, patients should be reassessed for the attainment of treatment goals and identification of any barriers to successful treatment. Following a review of the patient's response to treatment initiation, adjustments in pharmacological treatment may be needed. The following content needs to be strengthened during this period:

- Review of symptoms(CAT score) and Exacerbations.
- Assess the inhaler technique and adherence and non-pharmacological interventions.
- Adjust the inhaler device and pharmacological interventions.
- Smoke cession education and COPD disease education.

During on-site visits, in the control group, there is just data collection every 12 weeks according to the study plan as showing in table 1.

The purpose of the Patient Questionnaire (Appendix 3) in this study is to confirm whether the physician review the inhaler device usage, give the patients smoke cession education and COPD-related disease education. The Patient Questionnaire should be collected at the end of every on-site visit. If the patient is unable to read the Patient Questionnaire clearly due to vision problems, the study staff should read the contents to the patient clearly but cannot explain them.

Patients in both groups will be encouraged to come back to study hospital once they have COPD related conditions or symptoms worsening. If in emergency case they choose to visit the hospitals other than study hospital, they should report it to study physician or study staffs once it's possible. In case there're data generated from other hospitals that needed to be collected as per this protocol, the data and supportive document (medical record, prescription etc.) will be required on next on-site visit.

7. STUDY AND DATA MANAGEMENT

7.1 Training of study site personnel

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

7.1.1 Research Agreement(s)

The Principal Investigator should comply with all the terms, conditions, and obligations of the Research Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Research Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Research Agreement shall prevail.

7.1.2 Archiving of study documents

The investigator follows the principles outlined in the Research Agreement (RA).

Study files. Investigator will organise and retain all study-related documents. Principal Investigator (or the person designated by the principal investigator to be responsible for the quality control of this study) will regularly check the file to ensure that all relevant documents are retained. The contents of the file may be audited/inspected by Funding provider's auditor -or IRB.

Period of record retention. The study sites will retain the essential documents specified in the ICH GCP (e.g., source document such as medical records, contract, signed consent form). Essential documents should be retained at the study site for at least 15 years following completion of the study, or per regulatory obligations if longer, and thereafter destroyed only after agreement with investigator. However, this is not always applied to those that are not preservable such as blood samples. In the event of any inconsistency between the above-mentioned contents and the contract with the study site, the contract shall prevail. These documents should be retained for a longer period however if needed by investigator, and the specific period and method of retention will be separately discussed between the study site and investigator. Investigator should notify the head of the study site in writing when the study related records are no longer needed. The records should be managed by a responsible person appointed by the head of the study site.

7.1.3 Deviation from the clinical study protocol

The Investigator(s) must not deviate from or make any changes to the protocol without documented agreement between the Principal Investigator or the IRB approval based on its deliberations. However, this shall not apply to cases where the deviation or change is necessary to avoid an immediate hazard to the subjects or for other compelling medical reasons, or where the changes involve only logistical or administrative aspects of the clinical study (e.g., changes to the organisation/structure of the study site, the name/department name of the study site, the address or phone number of the study site , the job title of the Investigator, and monitors).

The Investigator(s) should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to the subjects or for other medically compelling reason, the Investigator should prepare and submit the records explaining the reasons thereof to the head of study site and retain a copy of the records.

The Investigator(s) may deviate from or make a change to the protocol without documented agreement between the Principal Investigator or the IRB approval, only in the event of a

medical emergency, e.g., it is only way to avoid an immediate hazard to the subjects. In such case, the Principal Investigator must notify details of the deviation or change, the reason, and a proposed revision in the protocol if required, to the head of the study site and IRB as soon as possible, in order to obtain their approval. A certificate of approval should be obtained.

7.2 Data management

Investigator(s) will collect the patients' data and enter data into the EDC. CRFs will be archived at the investigator's site. Investigator will check and collect the CRFs periodically. When data have been entered, reviewed and edited, the data will be locked to prevent further editing. Investigator(s) should ensure the quality of collected data.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practice of China, applicable regulatory requirements and the Sponsor policy on Bioethics and Human Biological Samples.

The Investigator is responsible for ensuring that this protocol, the site's ICF, and any other information that will be presented to potential subjects are reviewed and approved by the appropriate IRB/IEC. The Investigator agrees to allow the IRB/IEC direct access to all relevant documents. The IRB/IEC must be constituted in accordance with all applicable regulatory requirements.

8.2 Subject data protection

The Informed Consent Form will explain that:

- Study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation.

- Patient data will be maintaining confidentiality in accordance with national data legislation
- For data verification purposes, a regulatory authority, an IRB may require direct access to parts of the hospital or practice source records relevant to the study, including subjects' medical history
- All data computer processed by investigator will be identified by study code and enrolment code.
- It would be emphasized that if patients need to seek health care during the study out of visit period, they are recommended to come to the hospital that they enrolled in.

8.3 Ethics review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing.

The Ethics Committee should approve all advertising used to recruit subjects for the study.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

8.4 Informed consent

The Principal Investigator (s) will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study

- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by IRB/ Ethics Committee.

8.5 Changes to the protocol and informed consent form

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee before implementation. Local requirements are to be followed for revised protocols.

If regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

8.6 Audits and inspections

Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements.

8.7 Collection and Reporting of Adverse Events/Adverse Drug Reactions

For this study, there is no requirement for the patients to use an special investigate medicine, and there is no any safety endpoint. Then no pro-active safety data collection will be taken place. The investigator is responsible for reporting adverse events to regulatory authorities according to China related regulation, i.e. "Provisions for Adverse Drug Reaction Reporting and Monitoring (Order No.81 of the Ministry of Health)".

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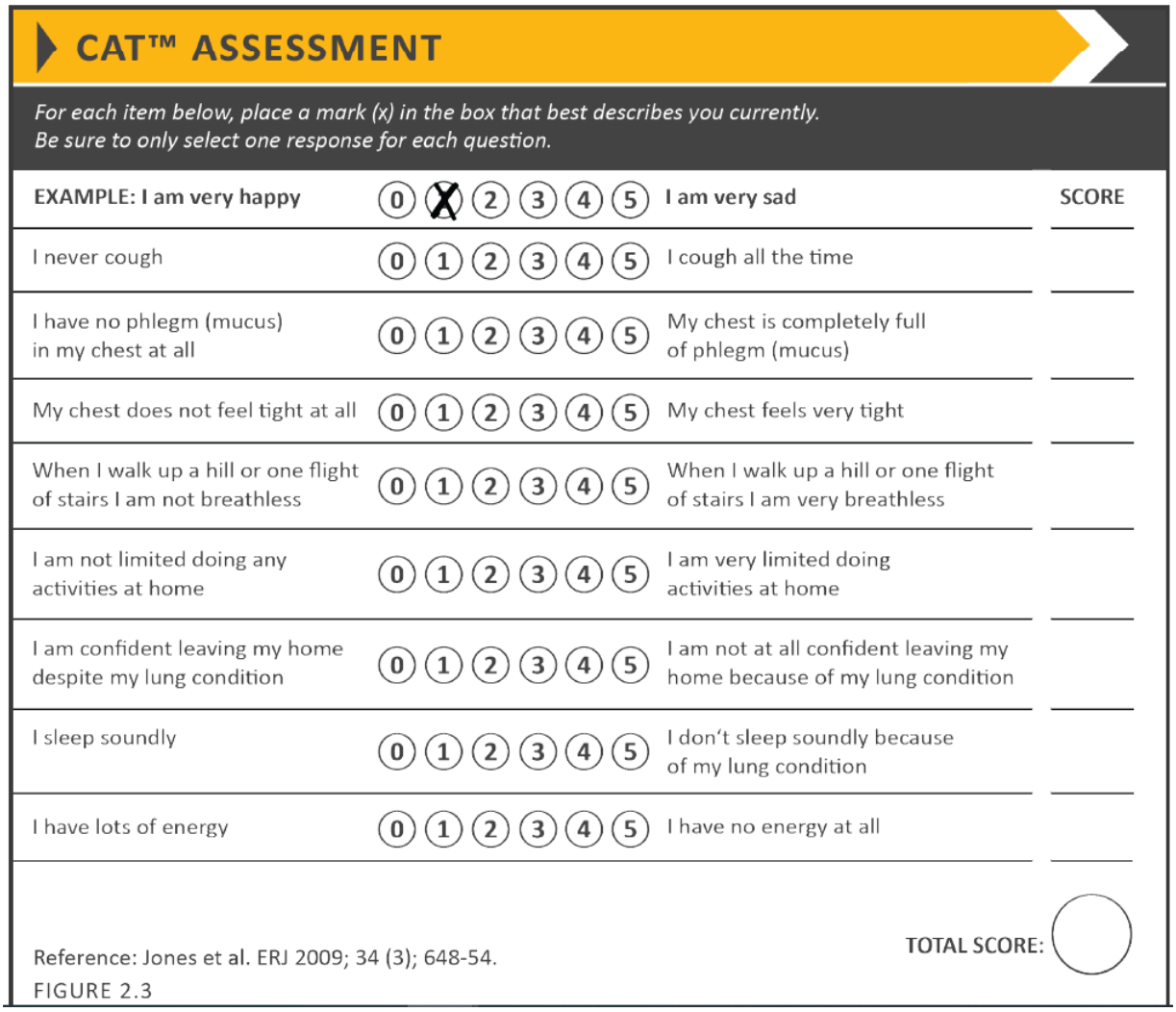
APPENDICES

Appendix 1 **Quality Control Indicators**

Key items of QS		**Quality Control Indicators(QCI)**	**Check time point(s)**
Treatment		% receiving inhalation therapy	every 3 months
		% receiving non-pharmaceutical treatment	
		% of exacerbations(only in respiratory department) treated with: a) OCS and antibiotics b) OCS only c) Antibiotics only	every 3 months
Follow-up	COPD-related Education	% of patients who had been given the COPD disease education during visit.	every 3 months
		% of patients who had been given the smoking cessation education and advice during visit.	
		% of patients who had been given the inhaler technique education when initial treatment, or post-AECOPD ,or change a new inhaler.	
		% with documented inhaler technique review in last 12 months	
		% of patients who had been given patient vaccine advice during visit.	

Appendix 2 **COPD Assessment Test (CAT）**



CAT™ ASSESSMENT

For each item below, place a mark (x) in the box that best describes you currently.
Be sure to only select one response for each question.

EXAMPLE: I am very happy	0	X	2	3	4	5	**I am very sad**
I never cough	0	1	2	3	4	5	I cough all the time
I have no phlegm (mucus) in my chest at all	0	1	2	3	4	5	My chest is completely full of phlegm (mucus)
My chest does not feel tight at all	0	1	2	3	4	5	My chest feels very tight
When I walk up a hill or one flight of stairs I am not breathless	0	1	2	3	4	5	When I walk up a hill or one flight of stairs I am very breathless
I am not limited doing any activities at home	0	1	2	3	4	5	I am very limited doing activities at home
I am confident leaving my home despite my lung condition	0	1	2	3	4	5	I am not at all confident leaving my home because of my lung condition
I sleep soundly	0	1	2	3	4	5	I don't sleep soundly because of my lung condition
I have lots of energy	0	1	2	3	4	5	I have no energy at all

SCORE

Reference: Jones et al. ERJ 2009; 34 (3); 648-54.

TOTAL SCORE:

FIGURE 2.3

Note: Total Scores range 0-40. The COPD influence on subjects: 1stage (mild): 0-10 points; 2 stage (moderate): 11-20 points; 3 stage (severe):21-30 points; 4 stage (very severe):31-40 points.

APPENDIX 3 **Patient Questionnaire**

Patient Questionnaire	
Instructions: The goal of this questionnaire is only to observe whether you have had received the education of COPD disease, smoke cession, the inhaler device usage from the physician during your every visit.	
1	(In case you're using an inhaler) Did your doctor check the inhaler device you currently use?
	□ Yes □ No
2	(In case you haven't use any inhalers before or change a new inhaler device this time) Did your doctor teach you how to use the inhaler device?
	□ Yes □ No
3	Did your doctor suggest you to give up smoking or any advice to have smoke cession?
	□ Yes □ No
4	Did your doctor teach you any COPD disease knowledge or any advice on how to manage your disease by yourself ?
	□ Yes □ No
5	Did your doctor give you any advice to get pneumonia vaccine or flu vaccine?
	□ Yes □ No