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Early Intervention with Tiotropium in Chinese Patients with GOLD Stage I-II Chronic Obstructive Pulmonary Disease (Tie-COPD): a protocol for randomized multicenter clinical trial

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Abstract

Introduction: Owing to high and increasing morbidity and mortality, chronic obstructive pulmonary disease (COPD) has become a major public health problem worldwide. Although the majority of patients with COPD are in the early stages, little attention had been paid to those patients, in particular regarding to early intervention. Tiotropium bromide can significantly relieve symptoms and can reduce the incidence of acute exacerbations of COPD. Therefore, we hypothesize that therapy with tiotropium bromide will also benefit COPD patients with early-stage disease.

Method/analysis: A randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical trial (Tiotropium In Early COPD study, Tie-COPD study) will be conducted to evaluate the efficacy and safety of long-term intervention with tiotropium in COPD patients with early-stage disease. A total number of 800 COPD patients with early stages will be randomized and will receive either tiotropium bromide or matching placebo for two years. Measurements will include FEV₁, health-related quality of life, grade degree of breathlessness related to activities, COPD exacerbations and pharmaco-economic analysis.

Ethics/dissemination: This study has been approved by Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University. The authors will disseminate the findings in peer reviewed publications.

Trial registration: ClinicalTrials.gov (NCT01455129).

Key words: COPD, early intervention, tiotropium, protocol

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ARTICLE SUMMARY

Article focus

Chronic obstructive pulmonary disease is a high morbidity and mortality disease. However, there has been very limited research into the early intervention of COPD.

A randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical trial study is proposed to explore the efficacy of early intervention of COPD.

Key messages

A total number of 800 COPD patients with GOLD stage I-II will be enrolled in.

Intervention with tiotropium or placebo will be conducted for two years to evaluate the efficacy and safety of long-term intervention.

The findings from this study will not only shed new light on the long-term intervention in early-stage COPD patients, but also provide a basis for early detection of COPD patients.

Strengths and limitations of this study

A randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical trial.

A large sample of patients at early stages of the disease who are asymptomatic will be included.

This multi-centre study is only conducted in China and the length of the study is two years.
Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most common respiratory diseases. Using the GOLD (Global Initiative for Chronic Obstructive Lung Disease) standard, the prevalence of COPD may be as high as 4-10% worldwide in adults 40 years and older. [1] Worldwide, there has been increasing morbidity and mortality associated with COPD over the past few decades, and COPD is predicted to rise from the sixth leading cause of death in 1990 to the third in 2020 and to rank as the fifth largest economic burden among diseases worldwide in 2020. [2]

Better medications and more aggressive intervention strategies have been used to manage COPD, but patients at later stages of the disease have shown poor responses to such treatments, associated with high mortality and incidence of re-hospitalization and disability that causes a burden both for the families of patients and for society. [3,4]

Currently, data show that the annual rate of decline in FEV$_1$ in COPD patients with GOLD stage I-II is more rapid than those with GOLD stages III-IV. [5-7] Therefore, we hypothesize that there may be more beneficial effect if the patients receive routine treatment at an earlier stage of the disease.

Tiotropium bromide is the first once-daily long-acting anticholinergic bronchodilator with selective action against M$_3$ receptors on bronchial smooth muscle cells. [8] It has a good safety profile and most of its undesirable effects can be assigned to its anticholinergic properties. [9] Previous studies indicate that tiotropium significantly relieves air flow restrictions in COPD patients and results in improvements in spirometry, dyspnea, exercise tolerance and health-related quality of
life.[6,7] Subgroup analyses of the UPLIFT study indicate that tiotropium was able to reduce the annual decline in FEV$_1$ among GOLD stage II patients and patients who use tiotropium as a first maintenance drug.[7,10] Therefore, it would be of great significance for COPD treatment if we could demonstrate that tiotropium improves lung function, decreases lung function decline and reverses disease progression in patients with early-stage COPD after two years of maintenance treatment. However, there is no large-scale clinical trial on long-term intervention with tiotropium bromide in patients with early-stage COPD (i.e., GOLD stage I-II COPD).

This manuscript outlines the rationale for and reviews the study design of a two-year, randomized, double-blind, placebo controlled, parallel, multicenter clinical trial in China to study early intervention with tiotropium (Tie-COPD).

Methods

Study design

This is a two-year, randomized, double-blind, placebo controlled, parallel, multicenter clinical trial to be conducted in China. Patients with COPD at GOLD stages I and II will be randomized to one of two groups: receiving tiotropium bromide (18µg once daily inhaled) and the other receiving a matching placebo. The amounts of the patients with stage I and stage II will be as close as possible in this whole study.

Because the majority of subjects enrolled are symptom-free or have very slight symptoms, in principle, long-term concomitant application of bronchodilators and other COPD medications with the exception of the drugs under investigation should be avoided during both the screening phase and the treatment phase of the study.
Long-term concomitant medication except for the investigational drugs could be allowed as prescribed if it is clinically necessary or if it has been initiated before the recruitment of the patient in question. For COPD exacerbations, an ipratropium bromide metered dose inhaler (MDI) could be applied if needed, or medical intervention could be applied according to the GOLD guideline for no longer than two weeks.

Recruitment will last for 24 months, with one week of screening, two years of treatment phase and monthly visits in the first month and once every three months thereafter. The data that will be collected at each visit will include a patient diary, a symptom score assessment (mMRC), an assessment of quality of life (CAT, CCQ), results of a physical examination, documentation of adverse events, a record of medication administration, exacerbation, smoking status, documentation of medical expenses, and so on. Any change in smoking status will also be recorded. Pulmonary function tests will be conducted at the first monthly visit and then every six months thereafter. Figure 1 is a trial procedures flow chart.

The primary objective of this trial is to determine the efficacy of treatment using a tiotropium inhalation capsule via HandiHaler device on trough FEV$_1$ after two years of maintenance treatment. Hence, the primary endpoint will be differences from baseline of trough FEV$_1$ at 24 months. Secondary endpoints will include differences in peak FEV$_1$ at 24 months; trough and peak FEV$_1$ at 1, 6, 12 and 18 months; yearly rate of decline in FEV$_1$; FVC and FEV$_1$/FVC (including trough and peak) from one month until completion of the double-blind treatment; quality of life; symptom scores;
frequency, interval, duration and severity of COPD exacerbations; time to first COPD exacerbation; administration of rescue medication; and a cost-effectiveness analysis.

**Population**

A total of 800 COPD patients will be enrolled, and 520 of those subjects are expected to finish the study. The inclusion criteria include a clinical diagnosis of COPD, age between 40 to 85 years, a maximal post-bronchodilator FEV₁/FVC<70% and FEV₁≥50% predicted and the ability to participate in study-related auxiliary examinations. Patients will be excluded if they have had a respiratory infection or an exacerbation in the four weeks prior to screening, frequent use of glucocorticosteroids orally or intravenously (prednisone > 10 mg/d). Patients with a history of asthma, allergic rhinitis, active pulmonary tuberculosis, or who have a blood eosinophil count ≥ 600/mm³ will also be excluded. The presence or absence of reversibility to a bronchodilator will not be an exclusion criterion. All patients will provide written informed consent before participating.

**Procedures**

Regular follow-ups with physical examination and symptom score documentation will be conducted after the first month and then once every three months thereafter. Physical examinations will evaluate general condition, pulse and blood pressure. Any abnormal observation will be recorded in the case report form.

**Spirometry**

Pulmonary function testing will be conducted at the flow-up visit in the first month and then every six months. Pulmonary function testing will be started at...
approximately the same time (±2 hours) on all testing days and will be performed using standardized spirometers, equipment and techniques that conform to American Thoracic Society and European Respiratory Society criteria.[11] Pulmonary function testing will not be conducted within six hours after the use of any short-acting bronchodilators. Spirometry is performed pre- and post- bronchodilator. Salbutamol 400µg will be inhaled 20 minutes prior to conducting reversibility testing. Pulmonary function parameters will include FEV₁, FVC and FEV₁/FVC. Maneuvers are performed in triplicate, although up to five forced expiratory maneuvers are obtained in an effort to achieve three acceptable efforts. The highest acceptable FEV₁ and the highest FVC each obtained on any of three blows meeting the ATS/ERS criteria constitute the data for that test set.[11]

**Exacerbations of COPD**

Information on exacerbations of COPD will be recorded in the patient diary and collected at all visits. A COPD exacerbation is defined as the onset or worsening of at least two of the following symptoms: cough, sputum production, purulent sputum, wheezing and dyspnea lasting for at least 48 hours.[12] The duration of a COPD exacerbation is defined as the number of days from the emergence of the exacerbation event to the termination of treatment for that event. The duration of hospitalization is defined as the days from admission to discharge from the hospital. The interval between COPD exacerbations is defined as the days between the previous exacerbation event and the next event.

Severity of COPD exacerbations are categorized as mild, moderate and severe
according to the following definitions: mild: adding other commonly used COPD medications at home without making out-patient hospital visits or being hospitalized; moderate: resulting in out-patient visits or emergency room visits and modification of a regimen which may include the use of antibiotics and/or systemic glucocorticosteroids; and severe: resulting in hospitalization.

Quality of life

Quality of life will be assessed at all visits by patients at out-patient visits with designated patient record questionnaires i.e., the COPD assessment test (CAT) and the chronic obstructive pulmonary disease clinical questionnaire (CCQ). The modified British medical research council (mMRC) will be observed and recorded at every visit to evaluate the symptom of dyspnea.

Statistical methods

Sample size has been calculated with regard to the primary endpoint. Patients with mild to moderate COPD (GOLD stage I-II) will form the relevant patient group for this study. From the UPLIFT mega trial it is known that COPD patients with GOLD stage II had an estimated difference of 100 ml in trough FEV\textsubscript{1} after two years (SD 350 ml) between the tiotropium group and the control group.\cite{5,6} Assuming a significance level of 5% and a power of 90% to detect a difference in trough FEV\textsubscript{1}, approximately 260 patients per treatment group will be required. Assuming a 35% patient drop-out rate of patients then 400 patients will need to be randomized to each group. Therefore, the overall sample size required for the study is 800 patients.

Only the primary endpoint will be tested in a confirmatory way. All secondary
endpoints analyses will be exploratory and the results will have to be interpreted in a
descriptive manner. The difference between the two treatment groups in trough FEV$_1$
and peak FEV$_1$ at 1, 6, 12, and 18 months will be compared using an analysis of
variance with repeated measurements. The comparison of annual decline rate in FEV$_1$,
FVC and FEV$_1$/FVC between groups will be analyzed using a random coefficient
regression model with the presumption that efficacy changes linearly with time. The
annual rate of decline will be expressed using the regression coefficient of the model.
The mMRC data will be described and compared by transfer form both before and
after treatment. Repeated measures analysis of variance will be used in the CCQ and
CAT data assessment. The time to first COPD exacerbation will be assessed by
comparison of curves from different treatment groups via Log rank test. The number
of acute exacerbations and hospitalizations or treatments due to COPD will be
compared between two groups using Poisson regression. Time and cost of
hospitalization due to COPD will be described by grouping, and the Wilcoxon
rank-sum test will be applied for inter-group comparison when necessary.

**Ethics and dissemination**

The study is registered at clinicaltrial.gov (NCT01455129). It has been judged by
the medical ethical committee of Ethics Committee of the First Affiliated Hospital of
Guangzhou Medical University. The study findings will be presented at conferences
and will be reported in peer-reviewed journals.

**Discussion**

To date, there is little available evidence on the impact of medication
intervention on the prognosis and relief of lung function decline. This study will be
the first large-scale long-term intervention in patients with early COPD, in particular
the symptom-free COPD patients, aimed at exploring an efficient and safe approach
to attenuate or even reverse the progression of COPD.

Currently, there is no precise definition of early-stage COPD. Previous studies
have included patients with stage 0 COPD, categorizing them as those that need
earlier medical intervention. However, this strategy has not yet been supported by
concrete evidence. It has been recognized that GOLD stage 0 is not equivalent to
early-stage COPD.[13,14] Based on currently available clinical evidence, we define
the early-stage COPD as GOLD stages I-II.

As reported in China, the proportion of patients with GOLD stage I and II (mild
and moderate) COPD is 70.7% of the patient population and most of them are
undertreatment.[4] Although most of these patients, especially those with stage I, have
few symptoms and nearly normal spirometry (i.e., a relatively preserved FEV₁), it has
been found that active small-airway inflammation and significant V_A/Q abnormalities
exist in these patients.[15,16] It is also confirmed that COPD patients with GOLD
stage I have a remarkable loss of small conducting airways when compared with
healthy controls, which may increase peripheral airways resistance.[17] Furthermore,
the rate of decline in FEV₁ is more greatly accelerated in the early stages (Stage I-II)
of COPD than the more severe stages (Stage III-IV), which has been validated in both
the TORCH and the UPLIFT studies.[6,18] That is to say that baseline FEV₁ is an
important covariate of decline of FEV₁. Patients with the lowest FEV₁ had the lowest
rate of decline, and vice versa. The research of Scanlon showed similar result.[19] Therefore, if the decline in FEV$_1$ is faster in the early-stage disease, then early intervention may be both necessary and reasonable in the prevention of progressive pulmonary function decline.

Traditionally, smoking cessation was thought to be the only therapy that could influence mortality and the progression of the disease by reducing the rate of decline of FEV$_1$.[20,21] As pharmacotherapy for COPD has developed in the last decade, outcomes of COPD patients has improved substantially with the availability of long-acting agonists (LABAs), fixed dose combinations of inhaled corticosteroids (ICS) and LABAs, and long-acting muscarinic antagonists (LAMAs). The traditional concept on the basis of ICS research that pharmacotherapy does not affect the progression of COPD[5,22-24] had been challenged by observations from some large clinical trials. Because exacerbations are considered to influence the decline in FEV$_1$,[25,26] some large-scale studies such as TORCH and UPLIFT strongly supported that these pharmaceuticals could affect the progression of COPD by reducing the exacerbation rate. Reduction of the annual rate of decline in FEV$_1$ was discovered in a post hoc analysis of the TORCH study.[26] The annual rate of decline of FEV$_1$ in the three groups, LABAs, ICS and the fixed combination of these drugs decreased, respectively, by 13, 13 and 16 ml when compared with controls.[26] In the UPLIFT study, treatment with tiotropium also hinted at how to slow the decline rate of FEV$_1$ in patients who did not take concomitant medication.[6,10]

Although both the TORCH and UPLIFT studies focused on more severe COPD
patients because of the relatively large numbers of patients with GOLD stage II, they had sufficient power to allow subgroup analysis that supported the efficacy of early intervention. In the TORCH study, it was discovered that the improvement in post-bronchodilator FEV$_1$, reduction in the annual rate of decline of FEV$_1$ and exacerbation rate of patients with GOLD stage II treated with the fixed combination product were slightly but significantly higher than patients in severe stages of disease.[27] Some subgroup analyses from the UPLIFT study also support these concepts. One analysis by Decramer showed that in patients with GOLD stage II, tiotropium not only increased pre-bronchodilator (100-118 ml) and post-bronchodilator FEV$_1$ (52-81 ml) but also reduced the rate of decline in FEV$_1$ compared with controls.[7] Another analysis of the UPLIFT study also suggested that in patients who had not taken any maintenance medication before, treatment with tiotropium not only increased pre-bronchodilator and post-bronchodilator FEV$_1$, improved the health-related quality of life, but also reduced the rate of decline of FEV$_1$ and that approximately 60% of the patients in that subgroup analysis were patients with GOLD stage II disease.[10] A prospective study showing that treatment with 18µg of tiotropium once daily for 12 weeks improved FEV$_1$ and FVC in patients with mild to moderate COPD, when compared with placebo, also supported the concept.[28] This evidence implies that treatment with tiotropium may slow the progression of COPD in its early stages. Tiotropium is most likely beneficial to COPD patients with early stages, as well as to those with disease in the more severe stages.
However, most of these encouraging data have come from subgroup analyses of large, long-term studies, and the outcomes of the subgroup analysis were not the primary outcomes in these studies. Furthermore, most of the patients in the above-mentioned studies were symptomatic patients. Because many COPD patients with early stages are asymptomatic, they could not be representative of the average patients with early-stage disease encountered in general practice. And for long-term treatment of early stage COPD, the cost-effectiveness of treatment is also an important issue, which was not addressed in these studies. Therefore, further longitudinal studies are required to confirm the clinical relevance of these discoveries.

For this reason, the Tie-COPD study is designed. In long-term clinical trials, the most critical methodological challenge is determining the primary outcome variable. Although there are many disadvantages to using FEV$_1$, as it is noninvasive, repeatable and accessible, it has been chosen as the primary outcome variable in the Tie-COPD trial. Premature patient withdrawals must also be considered in trial design and analysis. The discontinuation rate generally increases with study duration in long term trials. Discontinuations are usually higher in the placebo group. The placebo group discontinuation rate in ISOLDE, EUROSCOP and UPLIFT ranged from 30% to 53%.[6,22,23] Therefore, we have estimated a 35% discontinuation rate in our study to ensure that it will be adequately powered to enable evaluation of the primary outcome.

In summary, we speculate that drugs including LAMAs and LABAs could benefit COPD patients with early-stage disease. The Tie-COPD trial will provide an
opportunity to explore the effect of once-daily inhaled tiotropium in COPD patients with early-stage disease. The data gathered will not only shed new light on the long-term intervention with long-acting bronchodilators such as tiotropium in early-stage COPD patients, but also provide a basis for early detection of COPD patients.

Authors’ contributions

Nanshang Zhong, Pixin Ran and Yumin Zhou conceived the original idea for the study. Jinping Zheng, Xiaochen Li, Shuyun Chen participated in the design and supervision of the study. Xiaochen Li wrote the first draft of the manuscript and the final content was developed in collaboration with all authors. All authors saw and approved the final version of the manuscript.

Competing interests

None.

Funding statement

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Figure 1. Clinical trial design

CAT: COPD assessment test; CCQ: COPD clinical questionnaire; mMRC: modified British medical research council. Patient diary covers daily use of investigational drugs, medication prescribed for COPD exacerbations, contact with healthcare providers, duration of illness and lost working days.

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Early Intervention with Tiotropium in Chinese Patients with GOLD Stages I-II

Chronic Obstructive Pulmonary Disease (Tie-COPD): study protocol for a multicenter, double-blinded, randomized, controlled trial

Xiaochen Li, Yumin Zhou, Shuyun Chen, Jinping Zheng, Nanshan Zhong, Pixin Ran

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Abstract

Introduction: Owing to high and increasing morbidity and mortality, chronic obstructive pulmonary disease (COPD) has become a major public health problem worldwide. Although the majority of patients with COPD are in the early stages, little attention had been paid to them, in particular regarding to early intervention. Tiotropium bromide can significantly relieve symptoms and reduce the incidence of acute exacerbations of COPD. Therefore, we hypothesize that therapy with tiotropium bromide will benefit COPD patients with early-stage disease.

Method/analysis: A randomized, double-blinded, placebo-controlled, parallel-group, multicenter clinical trial (Tiotropium In Early COPD study, Tie-COPD study) is being conducted to evaluate the efficacy and safety of long-term intervention with tiotropium in COPD patients with early-stage disease. A total number of 839 COPD patients who satisfied the eligibility criteria were randomly assigned (1:1) to receive once-daily inhaled capsule of either tiotropium bromide (18µg) or matching placebo for two years. Measurements will include FEV₁, health-related quality of life, grade degree of breathlessness related to activities, COPD exacerbations and pharmaco-economic analysis.

Ethics/dissemination: This study was approved by Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University. Recruitment started in November 2012 and ended in October 2013, with 839 patients randomized. The treatment follow-up of Tie-COPD participants is currently ongoing and is due to finish in November 2015. The authors will disseminate the findings in peer-reviewed
publications, conferences, and seminar presentations.

**Trial registration:** ClinicalTrials.gov (NCT01455129).

**Key words:** COPD, early intervention, tiotropium, protocol

Word count: 3631
ARTICLE SUMMARY

Article focus

Chronic obstructive pulmonary disease is a high morbidity and mortality disease. However, there has been very limited research into the early intervention of COPD.

A randomized, double-blinded, placebo-controlled, parallel-group, multicenter clinical trial study is proposed to explore the efficacy of early intervention of COPD.

Key messages

A total number of 839 COPD patients with GOLD stages I-II have been enrolled.

Intervention with tiotropium or placebo will be conducted for two years to evaluate the efficacy and safety of long-term intervention.

The findings from this study may not only shed new light on the long-term intervention in early-stage COPD patients, but also provide a basis for early detection of COPD patients.

Strengths and limitations of this study

A large sample of patients with early stages of the disease who are asymptomatic have been included in the randomized, double-blinded, placebo-controlled, parallel-group, multicenter clinical trial.

Compliance of participators may challenge the success of the project.
Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most common respiratory diseases. Using the GOLD (Global Initiative for Chronic Obstructive Lung Disease) standard, the prevalence of COPD may be as high as 4-10% worldwide in adults 40 years and older. [1] Worldwide, there has been increasing morbidity and mortality associated with COPD over the past few decades, and COPD is predicted to rise from the sixth leading cause of death in 1990 to the third in 2020 and to rank as the fifth largest economic burden among diseases in 2020. [2]

Better medications and more aggressive intervention strategies have been used to manage COPD, but patients at later stages of the disease have shown poor responses to such treatments, associated with high mortality, incidence of re-hospitalization and disability that causes a burden both for the families of patients and society. [3, 4]

Currently, data show that the annual rate of decline in FEV\textsubscript{1} in COPD patients with GOLD stages I-II is more rapid than those with GOLD stages III-IV. [5-7] The DIMCA study showed that early intervention with fluticasone in subjects with objective signs of obstructive airway disease resulted in significant health gains at relatively low financial cost. [8] Therefore, we hypothesize that there may be more beneficial effect if the patients receive routine treatment at an earlier stage of the disease.

Tiotropium bromide is the first once-daily long-acting anticholinergic bronchodilator with selective action against M\textsubscript{3} receptors on bronchial smooth muscle cells. [8] It has a good safety profile and most of its undesirable effects can be
assigned to its anticholinergic properties.[9] Previous studies indicate that tiotropium significantly relieves air flow restrictions in COPD patients and results in improvements in spirometry, dyspnea, exercise tolerance and health-related quality of life.[6,7] Subgroup analyses of UPLIFT indicate that tiotropium was able to reduce the annual decline in FEV$_1$ among GOLD stage II patients and patients who had not receive any maintenance medication for COPD before enrolled in UPLFT.[7,11]

Therefore, it would be of great significance for COPD treatment if we could demonstrate that tiotropium improves lung function, decreases lung function decline and reverses disease progression in patients with early-stage COPD after long-term intervention with maintenance treatment. However, there is no large-scale clinical trial on long-term intervention with tiotropium bromide in patients with early-stage COPD (i.e., GOLD stages I-II COPD).

On this basis, we designed a trial entitled “Tiotropium in Early Chronic Obstructive Pulmonary Disease Patients in China (Tie-COPD)”. It is a two-year, randomized, double-blinded, placebo controlled, parallel, multicenter clinical trial in China to study early intervention with tiotropium.

**Methods and analysis**

**Study design**

This is a two-year, multicenter double-blinded, RCT of maintenance treatment with once daily tiotropium for patients with early-stage COPD. Screening (visit 0) was undertaken within 7 days before randomization (visit 1) to assess eligibility and collect baseline data. Patients who satisfied the eligibility criteria were randomly
assigned (1:1) to receive tiotropium bromide (18µg once daily inhaled) or placebo.

Patients have an appointment one month after randomization (visit 2), at three months
(visit 3) and then every three months until study drug termination (two years). After
that, a one-month follow-up period is scheduled. The data collected at each visit will
include a patient diary, a symptom score assessment (mMRC), an assessment of
quality of life (CAT, CCQ), results of a physical examination, documentation of
adverse events, a record of medication administration, exacerbation, smoking status,
documentation of medical expenses, and so on. Self-reported smoking status is
recorded at each visit too. Pulmonary function tests will be conducted at the first
monthly visit and then every six months thereafter. Figure 1 is a trial procedures flow
chart.

The primary objective of this trial is to determine the efficacy of treatment using
a once-daily tiotropium inhalation capsule via HandiHaler device on trough FEV$_1$
after two years of maintenance treatment. Hence, the primary endpoint will be
difference of trough FEV$_1$ at 24 months from baseline. Secondary endpoints will
include differences in peak FEV$_1$ at 24 months; trough and peak FEV$_1$ at 1, 6, 12 and
18 months; yearly rate of decline in FEV$_1$, FVC and FEV$_1$/FVC (including trough and
peak) from one month until completion of the double-blinded treatment; quality of life;
symptom scores; frequency, interval, duration and severity of COPD exacerbations;
time to first COPD exacerbation; administration of rescue medication and a
cost-effectiveness analysis.

**Recruitment**
A total of 839 patients with COPD at GOLD stages I and II have been enrolled. The majority of them are symptom-free or have very slight symptoms. Most of them were recruited from community through population survey for COPD. Before recruitment, active smokers were advised to discontinue smoking and were offered a smoking cessation program as counseling sessions, patient education and supportive literature in the survey. After the survey, usually 2-3 months, COPD patients at GOLD stages I and II were recruited, informed about the study and the benefit of smoking cessation again. After obtaining written informed consent, screening (visit 0) was undertaken.

The inclusion criteria include a clinical diagnosis of COPD, presence or absence of respiratory symptoms, age between 40 to 85 years, with or without smoking history, a maximal post-bronchodilator FEV<sub>1</sub>/FVC<sub>1</sub><70% and FEV<sub>1</sub>≥50% predicted and the ability to participate in study-related auxiliary examinations.

Patients will be excluded if they have had a respiratory infection or an exacerbation in the four weeks prior to screening, frequent use of glucocorticosteroids orally or intravenously (prednisone > 10 mg/d). Patients with a history of asthma, allergic rhinitis, active pulmonary tuberculosis, history of pneumonecctomy or who have a blood eosinophil count ≥ 600/mm<sup>3</sup> will also be excluded. The presence or absence of reversibility to a bronchodilator will not be an exclusion criterion.

**Randomization and blinding**

The investigational drug tiotropium bromide capsule (Spiriva) is manufactured and packaged by Boehringer Ingelheim. The department of labeling and packaging
will execute the allocation concealment according to the blind code provided by the statistical participants while the investigators enter the patients and allocate the number in increasing order. Block randomization method will be applied in this trial and the blind code will be generated by statistician from Rundo International Pharmaceuticals Research & Development Co., LTD. with SAS 9.2.2. According to the blind code provided by statistician, the allocation concealment will be completed at labelling place. Emergency envelopes for accidents will be prepared for emergency unblinding and will be retained by investigational sites.

**Concomitant medication and treatment**

Because the majority of subjects enrolled are symptom-free or have very slight symptoms, in principle, long-term concomitant application of bronchodilators and other COPD medications with the exception of the drugs under investigation should be avoided during both the screening phase and the treatment phase of the study. Long-term concomitant medication except for the investigational drugs could be allowed as prescribed if it is clinically necessary or if it has been initiated before the recruitment of the patient in question. For COPD exacerbations, an ipratropium bromide metered dose inhaler (MDI) could be applied if needed, or medical intervention could be applied according to the GOLD guideline for no longer than two weeks.

**Measures**

Regular follow-ups with physical examination and symptom score documentation will be conducted after the first month and then once every three
months thereafter. Any abnormal observation will be recorded in the case report form. Self-reported smoking status is also recorded at each visit. Patient diary will be dispensed at the former visit and retrieved at the latter visit. The diary should be reviewed by the investigator together with the patient. In case any adverse event or exacerbation is defined by investigator, relevant documentation should be made in the case report form. The patient diary should cover daily used investigational drugs, medication prescribed for COPD exacerbation (rescue drugs, antitussives, expectorants, inhaled corticosteroids and antibiotics), contacting health care providers, duration of illness and lost working days.

**Spirometry**

Pulmonary function testing will be conducted at the flow-up visit in the first month and then every six months. Pulmonary function testing will be started at approximately the same time (±2 hours) on all testing days and will be performed using standardized spirometers, equipment and techniques that conform to American Thoracic Society and European Respiratory Society criteria.[12] Pulmonary function testing will not be conducted within six hours after the use of any short-acting bronchodilators. Spirometry is performed pre- and post- bronchodilator. Salbutamol 400µg will be inhaled 20 minutes prior to conducting reversibility testing. Pulmonary function parameters will include FEV$_1$, FVC and FEV$_1$/FVC. Maneuvers are performed in triplicate, although up to five forced expiratory maneuvers are obtained in an effort to achieve three acceptable efforts. The highest acceptable FEV$_1$ and the highest FVC each obtained on any of three blows meeting the ATS/ERS criteria.
constitute the data for that test set.[12]

Exacerbations of COPD

Information on exacerbations of COPD will be recorded in the patient diary and collected at all visits. A COPD exacerbation is defined as the onset or worsening of at least two of the following symptoms: cough, sputum production, purulent sputum, wheezing and dyspnea lasting for at least 48 hours.[13] The duration of a COPD exacerbation is defined as the number of days from the emergence of the exacerbation event to the termination of treatment for that event. The duration of hospitalization is defined as the days from admission to discharge from the hospital. The interval between COPD exacerbations is defined as the days between the previous exacerbation event and the next event.

Severity of COPD exacerbations are categorized as mild, moderate and severe according to the following definitions: mild: adding other commonly used COPD medications at home without making out-patient hospital visits or being hospitalized; moderate: resulting in out-patient visits or emergency room visits and modification of a regimen which may include the use of antibiotics and/or systemic glucocorticosteroids; and severe: resulting in hospitalization.[14]

Quality of life

Quality of life will be assessed at all visits by patients at out-patient visits with designated patient record questionnaires, the COPD assessment test (CAT) and the chronic obstructive pulmonary disease clinical questionnaire (CCQ). The modified British medical research council (mMRC) will be observed and recorded at every visit.
to evaluate the symptom of dyspnea.

**Quality control**

The principal investigator at each site is responsible for the inspection of the compliance to the protocol in terms of study conduction, accurate and timely data documentation in the CRF by investigators. The investigator/institution will permit trial-related monitoring, auditing, IRB / IEC review and regulatory inspection and will be providing relevant inspectors with direct access to all related source data/documents. The principal investigator should ensure adequate training and updated information or notifications have been delivered to study relevant personnel including physicians and nurses. Data from the study will be documented in the CRFs at the termination of the study and then entered into database with blinded design for data checking and reviewing. All of the documents relevant to patient information should be kept in the database and kept confidential according to relevant laws and regulations. The quantity of retrieved investigational drug (capsules) should be recorded in the case report form. Administration of 80%-120% of the predicted use of investigational drug will be considered to be good compliance.

**Statistical methods**

Sample size has been calculated with regard to the primary endpoint. Patients with mild to moderate COPD (GOLD stages I-II) will form the relevant patient group for this study. From the UPLIFT mega trial it is known that COPD patients with GOLD stage II had an estimated difference of 100 ml in trough FEV\(_1\) after two years (SD 350 ml) between the tiotropium and control group.\[5,6\] Assuming a significance
level of 5% and a power of 90% to detect a difference in trough FEV$_1$, approximately 260 patients per treatment group will be required. Assuming a 35% patient drop-out rate of patients then 400 patients will need to be randomized to each group.\[15\] Therefore, the overall sample size required for the study is 800 patients.

Only the primary endpoint will be tested in a confirmatory way. All secondary endpoints analyses will be exploratory and the results will have to be interpreted in a descriptive manner. The difference between the two treatment groups in trough FEV$_1$ and peak FEV$_1$ at 1, 6, 12, and 18 months will be compared using an analysis of variance with repeated measurements. The comparison of annual decline rate in FEV$_1$, FVC and FEV$_1$/FVC between groups will be analyzed using a random coefficient regression model with the presumption that efficacy changes linearly with time. The annual rate of decline will be expressed using the regression coefficient of the model. The mMRC data will be described and compared by transfer form both before and after treatment. Repeated measures analysis of variance will be used in the CCQ and CAT data assessment. The time to first COPD exacerbation will be assessed by comparison of curves from different treatment groups via Log rank test. Group description will be applied in the assessment of interval, duration, and severity of COPD exacerbations. The application of rescue medication will be analyzed with Fisher exact test, while further describe the relief related information such as frequency of drug use. The number of acute exacerbations and severe acute exacerbations will be compared between two groups with the use of Poisson regression with correction for treatment exposure and overdispersion. Time and cost
of hospitalization due to COPD will be described by grouping, and the Wilcoxon
rank-sum test will be applied for inter-group comparison when necessary. The
analysis plan will be specified in detail in a separately prepared Statistical Analysis
Plan (SAP) prior to database lock.

Ethics and dissemination

The study was registered at clinicaltrial.gov (NCT01455129). It was approved by
the medical ethical committee of Ethics Committee of the First Affiliated Hospital of
Guangzhou Medical University. Recruitment into the Tie-COPD trial started in
November 2011 and ended in October 2013, with 839 patients (104% of target
enrolment) randomized, one third of which are patients with GOLD stage I. The
treatment follow-up of tiotropium is currently ongoing and the last trial visit of the
last participants is due to take place in November 2015. The study findings will be
presented at conferences and will be reported in peer-reviewed journals.

Discussion

To date, there is little available evidence on the impact of medication
intervention on the prognosis and relief of lung function decline. This study will be
the first large-scale long-term intervention in patients with early COPD, in particular
the symptom-free COPD patients, aimed at exploring an efficient and safe approach
to attenuate or even reverse the progression of COPD.

Currently, there is no precise definition of early-stage COPD. Previous studies
have included patients with stage 0 COPD, categorizing them as those that need
earlier medical intervention. However, this strategy has not yet been supported by
concrete evidence. It has been recognized that GOLD stage 0 is not equivalent to early-stage COPD.[16,17] Based on currently available clinical evidence, we define the early-stage COPD as GOLD stages I-II.

As reported in China, the proportion of patients with GOLD stages I and II (mild and moderate) COPD is 70.7% of the patient population and most of them are undertreated.[4] Although most of these patients, especially those with stage I, have few symptoms and nearly normal spirometry (i.e., a relatively preserved FEV₁), it has been found that active small-airway inflammation and significant Vₐ/Q abnormalities existed in these patients.[18-20] It has also been confirmed that COPD patients with GOLD stage I have a remarkable loss of small conducting airways when compared with healthy controls, which may increase peripheral airways resistance.[21] Furthermore, the rate of decline in FEV₁ is more greatly accelerated in the early stages (Stage I-II) of COPD than the more severe stages (Stage III-IV), which has been validated in both the TORCH and the UPLIFT studies.[6,22] That is to say that patients with the lowest FEV₁ had the lowest rate of decline, and vice versa. The research of Scanlon showed similar result.[23] Therefore, if the decline in FEV₁ is faster in the early-stage disease, then early intervention may be both necessary and reasonable in the prevention of progressive pulmonary function decline.

Traditionally, smoking cessation was thought to be the only therapy that could influence mortality and the progression of the disease by reducing the rate of decline of FEV₁.[24,25] As pharmacotherapy for COPD has developed in the last decade, outcomes of COPD patients have improved substantially with the availability of
long-acting agonists (LABAs), fixed dose combinations of inhaled corticosteroids (ICS) and LABAs, and long-acting muscarinic antagonists (LAMAs). The traditional concept on the basis of ICS research that pharmacotherapy does not affect the progression of COPD[5,26-28] had been challenged by observations from some large clinical trials. Because exacerbations are considered to influence the decline in FEV₁,[29,30] some large-scale studies such as TORCH and UPLIFT strongly supported that these pharmaceuticals could affect the progression of COPD by reducing the exacerbation rate. Reduction of the annual rate of decline in FEV₁ was discovered in a post hoc analysis of the TORCH study.[30] The annual rate of decline of FEV₁ in the three groups, LABAs, ICS and the fixed combination of these drugs decreased, respectively, by 13,13 and 16 ml when compared with controls.[30] In the UPLIFT study, treatment with tiotropium also hinted at how to slow the decline rate of FEV₁ in patients who did not take concomitant medication.[6,11]

Although both the TORCH and UPLIFT studies focused on more severe COPD patients, because of the relatively large numbers of patients with GOLD stage II, they had sufficient power to allow subgroup analysis that supported the efficacy of early intervention. In the TORCH study, it was discovered that the improvement in post-bronchodilator FEV₁, reduction in the annual rate of decline of FEV₁ and exacerbation rate of patients with GOLD stage II treated with the fixed combination product were slightly but significantly higher than patients in severe stages of disease.[31] Some subgroup analyses from the UPLIFT study also support these concepts. One analysis by Decramer showed that in patients with GOLD stage II,
tiotropium not only increased pre-bronchodilator (100-118 ml) and post-bronchodilator FEV$_1$ (52-81 ml) but also reduced the rate of decline in FEV$_1$ compared with controls.[7] Another analysis of the UPLIFT study also suggested that in patients who had not taken any maintenance medication before, treatment with tiotropium not only increased pre- and post-bronchodilator FEV$_1$, improved the health-related quality of life, but also reduced the rate of decline of FEV$_1$ and that approximately 60% of the patients in that subgroup analysis were patients with GOLD stage II disease.[11] A prospective study showing that treatment with 18µg of tiotropium once daily for 12 weeks improved FEV$_1$ and FVC in patients with mild to moderate COPD, when compared with placebo, also supported the concept.[32] This evidence implies that treatment with tiotropium may slow the progression of COPD in its early stages. Tiotropium is most likely beneficial to COPD patients with early stages, as well as to those with disease in the more severe stages.

However, most of these encouraging data have come from subgroup analyses of large, long-term studies, and the outcomes of the subgroup analysis were not the primary outcomes in these studies. Furthermore, most of the patients in the above-mentioned studies were symptomatic patients. Because many COPD patients with early stages are asymptomatic, they could not be representative of the average patients with early-stage disease encountered in general practice. And for long-term treatment of early-stage COPD, the cost-effectiveness of treatment is also an important issue, which was not addressed in these studies. Therefore, further longitudinal studies are required to confirm the clinical relevance of these discoveries.
For this reason, Tie-COPD study is designed. In long-term clinical trials, the most critical methodological challenge is determining the primary outcome variable. Although there are many disadvantages to using FEV\textsubscript{1}, as it is noninvasive, repeatable and accessible, it has been chosen as the primary outcome variable in the Tie-COPD trial. Premature patient withdrawals must also be considered in trial design and analysis. The discontinuation rate generally increases with study duration in long-term trials. Discontinuations are usually higher in the placebo group. The placebo group discontinuation rate in ISOLDE, EUROSCOP and UPLIFT ranged from 30% to 53%.[6,26,27] As with the protocol of UPLIFT, we have estimated a 35% discontinuation rate in our study to ensure that it will be adequately powered to enable evaluation of the primary outcome.[15] In order to reduce the drop-out rate, we will conduct scheduled health education for patients, including smoking cessation, benefit of early intervention and health consultation, etc. Meanwhile, we will establish a good relationship with the participants, and supervise them through unscheduled telephone follow-up.

The majority of subjects enrolled are symptom-free or have very slight symptoms, and the mere presence of respiratory symptoms or a gradually reduced lung function is insufficient reason for patients to seek medical help.[33] So, most of the patients came from population screening for COPD in community. In the population survey, we had suggested the active smokers to discontinue smoking and offered a smoking cessation program. After the survey, patients who satisfied the eligibility criteria were recruited. They will be advised to quick smoking at each visit.
However, in order to avoid the confounding effects of smoking cessation, we will not provide special smoking cessation intervention. According to Hurst J, up to 22% of patients in GOLD stage II can be considered frequent exacerbations.[34] So, there were still some moderate COPD patients with history of exacerbations from hospital enrolled in the study. They may not at present be identified for interventions to reduce exacerbations and may get more benefit from the intervention.

In summary, Tie-COPD trial will provide an opportunity to explore the effect of once-daily inhaled tiotropium in COPD patients with early-stage disease. The data gathered may not only shed new light on the long-term intervention with long-acting bronchodilators such as tiotropium in early-stage COPD patients, but also provide a basis for early detection of COPD patients. At present, recruitment of patients has been completed. Results are anticipated in 2016.
Authors’ contributions

Nanshang Zhong, Pixin Ran and Yumin Zhou conceived the original idea for the study. Jinping Zheng, Xiaochen Li, Shuyun Chen participated in the design and supervision of the study. Xiaochen Li wrote the first draft of the manuscript and the final content was developed in collaboration with all authors. All authors saw and approved the final version of the manuscript.

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Competing interests

None.

Funding statement

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Early Intervention with Tiotropium in Chinese Patients with GOLD Stage I-II Chronic Obstructive Pulmonary Disease (Tie-COPD): a study protocol for a multicenter, double-blinded, randomized, multicenter clinical controlled trial

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Abstract

Introduction: Owing to high and increasing morbidity and mortality, chronic obstructive pulmonary disease (COPD) has become a major public health problem worldwide. Although the majority of patients with COPD are in the early stages, little attention had been paid to those patients, in particular regarding to early intervention. Tiotropium bromide can significantly relieve symptoms and reduce the incidence of acute exacerbations of COPD. Therefore, we hypothesize that therapy with tiotropium bromide will also benefit COPD patients with early-stage disease.

Method/analysis: A randomized, double-blinded, placebo-controlled, parallel-group, multicenter clinical trial (Tiotropium In Early COPD study, Tie-COPD study) will be conducted to evaluate the efficacy and safety of long-term intervention with tiotropium in COPD patients with early-stage disease. A total number of 839 COPD patients with early stages who satisfied the eligibility criteria will be randomized and will receive either tiotropium bromide or matching placebo for two years, were randomly assigned (1:1) to receive once-daily inhaled capsule of either tiotropium bromide (18µg) or matching placebo for two years. Measurements will include FEV1, health-related quality of life, grade degree of breathlessness related to activities, COPD exacerbations and pharmaco-economic analysis.

Ethics/dissemination: This study has been approved by Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University. Recruitment started in November 2012 and ended in October 2013, with 839 patients randomized. The...
Treatment follow-up of Tie-COPD participants is currently ongoing and is due to finish in November 2015. The authors will disseminate the findings in peer-reviewed publications, conferences, and seminar presentations.

Trial registration: ClinicalTrials.gov (NCT01455129).

Key words: COPD, early intervention, tiotropium, protocol

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ARTICLE SUMMARY

Article focus

Chronic obstructive pulmonary disease is a high morbidity and mortality disease. However, there has been very limited research into the early intervention of COPD.

A randomized, double-blinded, placebo-controlled, parallel-group, multicenter clinical trial study is proposed to explore the efficacy of early intervention of COPD.

Key messages

A total number of 800-839 COPD patients with GOLD stages I-II will have been enrolled in.

Intervention with tiotropium or placebo will be conducted for two years to evaluate the efficacy and safety of long-term intervention.

The findings from this study may not only shed new light on the long-term intervention in early-stage COPD patients, but also provide a basis for early detection of COPD patients.

Strengths and limitations of this study

A randomized, double-blind, placebo controlled, parallel-group, multicenter clinical trial.

A large sample of patients with early stages of the disease who are asymptomatic have been included in the randomized, double-blinded, placebo-controlled, parallel-group, multicenter clinical trial.

This multi-centre study is only conducted in China and the length of the study is two years. Compliance of participants may challenge the success of the project.
Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most common respiratory diseases. Using the GOLD (Global Initiative for Chronic Obstructive Lung Disease) standard, the prevalence of COPD may be as high as 4-10% worldwide in adults 40 years and older.[1] Worldwide, there has been increasing morbidity and mortality associated with COPD over the past few decades, and COPD is predicted to rise from the sixth leading cause of death in 1990 to the third in 2020 and to rank as the fifth largest economic burden among diseases worldwide in 2020.[2]

Better medications and more aggressive intervention strategies have been used to manage COPD, but patients at later stages of the disease have shown poor responses to such treatments, associated with high mortality and incidence of re-hospitalization and disability that causes a burden both for the families of patients and for society.[3,4] Currently, data show that the annual rate of decline in FEV1 in COPD patients with GOLD stages I-II is more rapid than those with GOLD stages III-IV.[5-7] The DIMCA study showed that early intervention with fluticasone in subjects with objective signs of obstructive airway disease resulted in significant health gains at relatively low financial cost.[8] Therefore, we hypothesize that there may be more beneficial effect if the patients receive routine treatment at an earlier stage of the disease.

Tiotropium bromide is the first once-daily long-acting anticholinergic bronchodilator with selective action against M3 receptors on bronchial smooth muscle cells.[8] It has a good safety profile and most of its undesirable effects can be
assigned to its anticholinergic properties.[9] Previous studies indicate that tiotropium significantly relieves air flow restrictions in COPD patients and results in improvements in spirometry, dyspnea, exercise tolerance and health-related quality of life.[6,7] Subgroup analyses of the UPLIFT study indicate that tiotropium was able to reduce the annual decline in FEV$_1$ among GOLD stage II patients and patients who use tiotropium as a first maintenance drug had not receive any maintenance medication for COPD before enrolled in UPLFT.[7,4011]

Therefore, it would be of great significance for COPD treatment if we could demonstrate that tiotropium improves lung function, decreases lung function decline and reverses disease progression in patients with early-stage COPD after two years of long-term intervention with maintenance treatment. However, there is no large-scale clinical trial on long-term intervention with tiotropium bromide in patients with early-stage COPD (i.e., GOLD stages I-II COPD).

On this basis, we designed a trial entitled “Tiotropium in Early Chronic Obstructive Pulmonary Disease Patients in China (Tie-COPD)”. This manuscript outlines the rationale for and reviews the study design of a two-year, randomized, double-blind, placebo-controlled, parallel, multicenter clinical trial in China to study early intervention with tiotropium (Tie-COPD). It is a two-year, randomized, double-blinded, placebo controlled, parallel, multicenter clinical trial in China to study early intervention with tiotropium.

Methods and analysis

Study design
This is a two-year, multicenter randomized, double-blinded, placebo-controlled, parallel, multicenter clinical trial RCT to be conducted in China of maintenance treatment with once daily tiotropium for patients with early-stage COPD. Screening (visit 0) was undertaken within 7 days before randomization (visit 1) to assess eligibility and collect baseline data. Patients who satisfied the eligibility criteria were randomly assigned (1:1) to receive tiotropium bromide (18µg once daily inhaled) or placebo. Patients have an appointment one month after randomization (visit 2), at three months (visit 3) and then every three months until study drug termination (two years). After that, a one-month follow-up period is scheduled. The data collected at each visit will include a patient diary, a symptom score assessment (mMRC), an assessment of quality of life (CAT, CCQ), results of a physical examination, documentation of adverse events, a record of medication administration, exacerbation, smoking status, documentation of medical expenses, and so on. Self-reported smoking status is recorded at each visit too. Pulmonary function tests will be conducted at the first monthly visit and then every six months thereafter. Figure 1 is a trial procedures flow chart.

Patients with COPD at GOLD stages I and II will be randomized to one of two groups: receiving tiotropium bromide (18µg once daily inhaled) and the other receiving a matching placebo. The amounts of the patients with stage I and stage II will be as close as possible in this whole study.

Because the majority of subjects enrolled are symptom-free or have very slight symptoms, in principle, long-term concomitant application of bronchodilators and...
other COPD medications with the exception of the drugs under investigation should be avoided during both the screening phase and the treatment phase of the study. Long-term concomitant medication except for the investigational drugs could be allowed as prescribed if it is clinically necessary or if it has been initiated before the recruitment of the patient in question. For COPD exacerbations, an ipratropium bromide metered dose inhaler (MDI) could be applied if needed, or medical intervention could be applied according to the GOLD guideline for no longer than two weeks.

Recruitment will last for 24 months, with one week of screening, two years of treatment phase and monthly visits in the first month and once every three months thereafter. The data that will be collected at each visit will include a patient diary, a symptom score assessment (mMRC), an assessment of quality of life (CAT, CCQ), results of a physical examination, documentation of adverse events, a record of medication administration, exacerbation, smoking status, documentation of medical expenses, and so on. Any change in smoking status will also be recorded. Pulmonary function tests will be conducted at the first monthly visit and then every six months thereafter. Figure 1 is a trial procedures flow chart.

The primary objective of this trial is to determine the efficacy of treatment using a once-daily tiotropium inhalation capsule via HandiHaler device on trough FEV₁ after two years of maintenance treatment. Hence, the primary endpoint will be differences from baseline of trough FEV₁ at 24 months from baseline. Secondary endpoints will include differences in peak FEV₁ at 24 months; trough and peak FEV₁
at 1, 6, 12 and 18 months; yearly rate of decline in FEV\textsubscript{1}, FVC and FEV\textsubscript{1}/FVC (including trough and peak) from one month until completion of the double-blinded treatment; quality of life; symptom scores; frequency, interval, duration and severity of COPD exacerbations; time to first COPD exacerbation; administration of rescue medication; and a cost-effectiveness analysis.

**Population Recruitment**

A total of 839 patients with COPD at GOLD stages I and II have been enrolled. The majority of them are symptom-free or have very slight symptoms. Most of them were recruited from community through population survey for COPD. Before recruitment, active smokers were advised to discontinue smoking and were offered a smoking cessation program as counseling sessions, patient education and supportive literature in the survey. After the survey, usually 2-3 months, COPD patients at GOLD stages I and II were recruited, informed about the study and the benefit of smoking cessation again. After obtaining written informed consent, screening (visit 0) was undertaken.

A total of 800 COPD patients will be enrolled, and 520 of those subjects are expected to finish the study. The inclusion criteria include a clinical diagnosis of COPD, presence or absence of respiratory symptoms, age between 40 to 85 years, with or without smoking history, a maximal post-bronchodilator FEV\textsubscript{1}/FVC<70% and FEV\textsubscript{1}≥50% predicted and the ability to participate in study-related auxiliary examinations.

Patients will be excluded if they have had a respiratory infection or an
exacerbation in the four weeks prior to screening, frequent use of glucocorticosteroids orally or intravenously (prednisone > 10 mg/d). Patients with a history of asthma, allergic rhinitis, active pulmonary tuberculosis, history of pneumonectomy or who have a blood eosinophil count ≥ 600/mm$^3$ will also be excluded. The presence or absence of reversibility to a bronchodilator will not be an exclusion criterion. All patients will provide written informed consent before participating.

**Randomization and blinding**

The investigational drug tiotropium bromide capsule (Spiriva) is manufactured and packaged by Boehringer Ingelheim. The department of labeling and packaging will execute the allocation concealment according to the blind code provided by the statistical participants while the investigators enter the patients and allocate the number in increasing order. Block randomization method will be applied in this trial and the blind code will be generated by statistician from Rundo International Pharmaceuticals Research & Development Co., LTD. with SAS 9.2.2. According to the blind code provided by statistician, the allocation concealment will be completed at labelling place. Emergency envelopes for accidents will be prepared for emergency unblinding and will be retained by investigational sites.

**Concomitant medication and treatment**

Because the majority of subjects enrolled are symptom-free or have very slight symptoms, in principle, long-term concomitant application of bronchodilators and other COPD medications with the exception of the drugs under investigation should be avoided during both the screening phase and the treatment phase of the study.
Long-term concomitant medication except for the investigational drugs could be allowed as prescribed if it is clinically necessary or if it has been initiated before the recruitment of the patient in question. For COPD exacerbations, an ipratropium bromide metered dose inhaler (MDI) could be applied if needed, or medical intervention could be applied according to the GOLD guideline for no longer than two weeks.

**Procedures/Measures**

Regular follow-ups with physical examination and symptom score documentation will be conducted after the first month and then once every three months thereafter. Physical examinations will evaluate general condition, pulse and blood pressure. Any abnormal observation will be recorded in the case report form.

Self-reported smoking status is also recorded at each visit. Patient diary will be dispensed at the former visit and retrieved at the latter visit. The diary should be reviewed by the investigator together with the patient. In case any adverse event or exacerbation is defined by investigator, relevant documentation should be made in the case report form. The patient diary should cover daily used investigational drugs, medication prescribed for COPD exacerbation (rescue drugs, antitussives, expectorants, inhaled corticosteroids and antibiotics), contacting health care providers, duration of illness and lost working days.

**Spirometry**

Pulmonary function testing will be conducted at the flow-up visit in the first month and then every six months. Pulmonary function testing will be started at
approximately the same time (±2 hours) on all testing days and will be performed using standardized spirometers, equipment and techniques that conform to American Thoracic Society and European Respiratory Society criteria. Pulmonary function testing will not be conducted within six hours after the use of any short-acting bronchodilators. Spirometry is performed pre- and post- bronchodilator. Salbutamol 400µg will be inhaled 20 minutes prior to conducting reversibility testing. Pulmonary function parameters will include FEV₁, FVC and FEV₁/FVC. Maneuvers are performed in triplicate, although up to five forced expiratory maneuvers are obtained in an effort to achieve three acceptable efforts. The highest acceptable FEV₁ and the highest FVC each obtained on any of three blows meeting the ATS/ERS criteria constitute the data for that test set.

Exacerbations of COPD

Information on exacerbations of COPD will be recorded in the patient diary and collected at all visits. A COPD exacerbation is defined as the onset or worsening of at least two of the following symptoms: cough, sputum production, purulent sputum, wheezing and dyspnea lasting for at least 48 hours. The duration of a COPD exacerbation is defined as the number of days from the emergence of the exacerbation event to the termination of treatment for that event. The duration of hospitalization is defined as the days from admission to discharge from the hospital. The interval between COPD exacerbations is defined as the days between the previous exacerbation event and the next event.

Severity of COPD exacerbations are categorized as mild, moderate and severe
according to the following definitions: mild: adding other commonly used COPD medications at home without making out-patient hospital visits or being hospitalized; moderate: resulting in out-patient visits or emergency room visits and modification of a regimen which may include the use of antibiotics and/or systemic glucocorticosteroids; and severe: resulting in hospitalization.[14]

Quality of life

Quality of life will be assessed at all visits by patients at out-patient visits with designated patient record questionnaires i.e., the COPD assessment test (CAT) and the chronic obstructive pulmonary disease clinical questionnaire (CCQ). The modified British medical research council (mMRC) will be observed and recorded at every visit to evaluate the symptom of dyspnea.

Quality control

The principal investigator at each site is responsible for the inspection of the compliance to the protocol in terms of study conduction, accurate and timely data documentation in the CRF by investigators. The investigator/institution will permit trial-related monitoring, auditing, IRB / IEC review and regulatory inspection and will be providing relevant inspectors with direct access to all related source data/documents. The principal investigator should ensure adequate training and updated information or notifications have been delivered to study relevant personnel including physicians and nurses. Data from the study will be documented in the CRFs at the termination of the study and then entered into database with blinded design for data checking and reviewing. All of the documents relevant to patient information...
should be kept in the database and kept confidential according to relevant laws and regulations. The quantity of retrieved investigational drug (capsules) should be recorded in the case report form. Administration of 80%-120% of the predicted use of investigational drug will be considered to be good compliance.

Statistical methods

Sample size has been calculated with regard to the primary endpoint. Patients with mild to moderate COPD (GOLD stages I-II) will form the relevant patient group for this study. From the UPLIFT mega trial it is known that COPD patients with GOLD stage II had an estimated difference of 100 ml in trough FEV$_1$ after two years (SD 350 ml) between the tiotropium group and the control group.[5,6] Assuming a significance level of 5% and a power of 90% to detect a difference in trough FEV$_1$, approximately 260 patients per treatment group will be required. Assuming a 35% patient drop-out rate of patients then 400 patients will need to be randomized to each group.[15] Therefore, the overall sample size required for the study is 800 patients.

Only the primary endpoint will be tested in a confirmatory way. All secondary endpoints analyses will be exploratory and the results will have to be interpreted in a descriptive manner. The difference between the two treatment groups in trough FEV$_1$ and peak FEV$_1$ at 1, 6, 12, and 18 months will be compared using an analysis of variance with repeated measurements. The comparison of annual decline rate in FEV$_1$, FVC and FEV$_1$/FVC between groups will be analyzed using a random coefficient regression model with the presumption that efficacy changes linearly with time. The annual rate of decline will be expressed using the regression coefficient of the model.
The mMRC data will be described and compared by transfer form both before and after treatment. Repeated measures analysis of variance will be used in the CCQ and CAT data assessment. The time to first COPD exacerbation will be assessed by comparison of curves from different treatment groups via Log rank test. Group description will be applied in the assessment of interval, duration, and severity of COPD exacerbations. The application of rescue medication will be analyzed with Fisher exact test, while further describe the relief related information such as frequency of drug use. The number of acute exacerbations and severe acute exacerbations will be compared between two groups with the use of Poisson regression with correction for treatment exposure and overdispersion. The number of acute exacerbations and hospitalizations or treatments due to COPD will be compared between two groups using Poisson regression. Time and cost of hospitalization due to COPD will be described by grouping, and the Wilcoxon rank-sum test will be applied for inter-group comparison when necessary. The analysis plan will be specified in detail in a separately prepared Statistical Analysis Plan (SAP) prior to database lock.

**Ethics and dissemination**

The study was registered at clinicaltrial.gov (NCT01455129). It has been judged approved by the medical ethical committee of Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University. Recruitment into the Tie-COPD trial started in November 2011 and ended in October 2013, with 839 patients (104% of target enrolment) randomized, one third of which are patients with GOLD stage I. The treatment follow-up of tiotropium is currently ongoing and the last
The trial visit of the last participants is due to take place in November 2015. The study findings will be presented at conferences and will be reported in peer-reviewed journals.

**Discussion**

To date, there is little available evidence on the impact of medication intervention on the prognosis and relief of lung function decline. This study will be the first large-scale long-term intervention in patients with early COPD, in particular the symptom-free COPD patients, aimed at exploring an efficient and safe approach to attenuate or even reverse the progression of COPD.

Currently, there is no precise definition of early-stage COPD. Previous studies have included patients with stage 0 COPD, categorizing them as those that need earlier medical intervention. However, this strategy has not yet been supported by concrete evidence. It has been recognized that GOLD stage 0 is not equivalent to early-stage COPD.\[13,14,16,17\] Based on currently available clinical evidence, we define the early-stage COPD as GOLD stages I-II.

As reported in China, the proportion of patients with GOLD stages I and II (mild and moderate) COPD is 70.7% of the patient population and most of them are undertreated.\[4\] Although most of these patients, especially those with stage I, have few symptoms and nearly normal spirometry (i.e., a relatively preserved \( FEV_1 \)), it has been found that active small-airway inflammation and significant \( V_A/Q \) abnormalities existed in these patients.\[15,16,18,20\] It has also been confirmed that COPD patients with GOLD stage I have a remarkable loss of small conducting
airways when compared with healthy controls, which may increase peripheral airways resistance.[17] Furthermore, the rate of decline in FEV$_1$ is more greatly accelerated in the early stages (Stage I-II) of COPD than the more severe stages (Stage III-IV), which has been validated in both the TORCH and the UPLIFT studies.[6,18] That is to say that patients baseline FEV$_1$ is an important covariate of decline of FEV$_1$. Patients with the lowest FEV$_1$ had the lowest rate of decline, and vice versa. The research of Scanlon showed similar result.[19] Therefore, if the decline in FEV$_1$ is faster in the early-stage disease, then early intervention may be both necessary and reasonable in the prevention of progressive pulmonary function decline.

Traditionally, smoking cessation was thought to be the only therapy that could influence mortality and the progression of the disease by reducing the rate of decline of FEV$_1$.[20,21,24,25] As pharmacotherapy for COPD has developed in the last decade, outcomes of COPD patients have improved substantially with the availability of long-acting agonists (LABAs), fixed dose combinations of inhaled corticosteroids (ICS) and LABAs, and long-acting muscarinic antagonists (LAMAs). The traditional concept on the basis of ICS research that pharmacotherapy does not affect the progression of COPD[5,22-24,26-28] had been challenged by observations from some large clinical trials. Because exacerbations are considered to influence the decline in FEV$_1$, some large-scale studies such as TORCH and UPLIFT strongly supported that these pharmaceuticals could affect the progression of COPD by reducing the exacerbation rate. Reduction of the annual rate of decline in FEV$_1$ was discovered in a post hoc analysis of the TORCH study.[26] The annual rate of
decline of FEV₁ in the three groups, LABAs, ICS and the fixed combination of these
drugs decreased, respectively, by 13,13 and 16 ml when compared with
controls.[2630] In the UPLIFT study, treatment with tiotropium also hinted at how to
slow the decline rate of FEV₁ in patients who did not take concomitant
medication.[6,1011]

Although both the TORCH and UPLIFT studies focused on more severe COPD
patients, because of the relatively large numbers of patients with GOLD stage II, they
had sufficient power to allow subgroup analysis that supported the efficacy of early
intervention. In the TORCH study, it was discovered that the improvement in
post-bronchodilator FEV₁, reduction in the annual rate of decline of FEV₁ and
exacerbation rate of patients with GOLD stage II treated with the fixed combination
product were slightly but significantly higher than patients in severe stages of
disease.[2731] Some subgroup analyses from the UPLIFT study also support these
concepts. One analysis by Decramer showed that in patients with GOLD stage II,
tiotropium not only increased pre-bronchodilator (100-118 ml) and
post-bronchodilator FEV₁ (52-81 ml) but also reduced the rate of decline in FEV₁
compared with controls.[7] Another analysis of the UPLIFT study also suggested that
in patients who had not taken any maintenance medication before, treatment with
tiotropium not only increased pre-bronchodilator and post-bronchodilator FEV₁,
improved the health-related quality of life, but also reduced the rate of decline of
FEV₁ and that approximately 60% of the patients in that subgroup analysis were
patients with GOLD stage II disease.[1011] A prospective study showing that
treatment with 18µg of tiotropium once daily for 12 weeks improved FEV\textsubscript{1} and FVC in patients with mild to moderate COPD, when compared with placebo, also supported the concept.\cite{28,32} This evidence implies that treatment with tiotropium may slow the progression of COPD in its early stages. Tiotropium is most likely beneficial to COPD patients with early stages, as well as to those with disease in the more severe stages.

However, most of these encouraging data have come from subgroup analyses of large, long-term studies, and the outcomes of the subgroup analysis were not the primary outcomes in these studies. Furthermore, most of the patients in the above-mentioned studies were symptomatic patients. Because many COPD patients with early stages are asymptomatic, they could not be representative of the average patients with early-stage disease encountered in general practice. And for long-term treatment of early-stage COPD, the cost-effectiveness of treatment is also an important issue, which was not addressed in these studies. Therefore, further longitudinal studies are required to confirm the clinical relevance of these discoveries.

For this reason, the Tie-COPD study is designed. In long-term clinical trials, the most critical methodological challenge is determining the primary outcome variable. Although there are many disadvantages to using FEV\textsubscript{1}, as it is noninvasive, repeatable and accessible, it has been chosen as the primary outcome variable in the Tie-COPD trial. Premature patient withdrawals must also be considered in trial design and analysis. The discontinuation rate generally increases with study duration in long-term trials. Discontinuations are usually higher in the placebo group. The
placebo group discontinuation rate in ISOLDE, EUROSCOP and UPLIFT ranged from 30% to 53%.[6,226,227] Therefore, as with the protocol of UPLIFT, we have estimated a 35% discontinuation rate in our study to ensure that it will be adequately powered to enable evaluation of the primary outcome.[15] In order to reduce the drop-out rate, we will conduct scheduled health education for patients, including smoking cessation, benefit of early intervention and health consultation, etc. Meanwhile, we will establish a good relationship with the participants, and supervise them through unscheduled telephone follow-up.

The majority of subjects enrolled are symptom-free or have very slight symptoms, and the mere presence of respiratory symptoms or a gradually reduced lung function is insufficient reason for patients to seek medical help.[33] So, most of the patients came from population screening for COPD in community. In the population survey, we had suggested the active smokers to discontinue smoking and offered a smoking cessation program. After the survey, patients who satisfied the eligibility criteria were recruited. They will be advised to quick smoking at each visit. However, in order to avoid the confounding effects of smoking cessation, we will not provide special smoking cessation intervention. According to Hurst J, up to 22% of patients in GOLD stage II can be considered frequent exacerbations.[34] So, there were still some moderate COPD patients with history of exacerbations from hospital enrolled in the study. They may not at present be identified for interventions to reduce exacerbations and may get more benefit from the intervention.
In summary, we speculate that drugs including LAMAs and LABAs could benefit COPD patients with early-stage disease. The Tie-COPD trial will provide an opportunity to explore the effect of once-daily inhaled tiotropium in COPD patients with early-stage disease. The data gathered will may not only shed new light on the long-term intervention with long-acting bronchodilators such as tiotropium in early-stage COPD patients, but also provide a basis for early detection of COPD patients. At present, recruitment of patients has been completed. Results are anticipated in 2016.

Authors’ contributions
Nanshang Zhong, Pixin Ran and Yumin Zhou conceived the original idea for the study. Jinping Zheng, Xiaochen Li, Shuyun Chen participated in the design and supervision of the study. Xiaochen Li wrote the first draft of the manuscript and the final content was developed in collaboration with all authors. All authors saw and approved the final version of the manuscript.

Acknowledgements
The Tie-COPD trial would like to thank Paul Chen (Medical advisor, respiratory Medical affairs manager of Boehringer Ingelheim Int’l Trading Co., Ltd) and Tong Ming (Clinical Research Manager of Rundo International Pharmaceuticals Research & Development Co., Ltd) for their time and input.

Competing interests
None.

Funding statement

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mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 1999;353(9167):1819-23


Figure 1. Clinical trial design

CAT: COPD Assessment test; CCQ: COPD clinical questionnaire; mMRC: modified British medical research council. Patient diary covers daily used investigational drugs, medication prescribed for COPD exacerbations, contacting health care providers, duration of illness and lost working days.

168x103mm (300 x 300 DPI)
Table 1. Concomitant medication and treatment

<table>
<thead>
<tr>
<th>Concomitant medication and treatment that should be avoided&lt;sup&gt;*1&lt;/sup&gt;</th>
<th>Concomitant medication and treatment that could only be used when the original administration and dosage has not been changed&lt;sup&gt;*2&lt;/sup&gt;</th>
<th>Concomitant medication and treatment that could only be used when exacerbation occurs&lt;sup&gt;*3&lt;/sup&gt;</th>
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</thead>
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<tr>
<td>Intravenous or oral application of glucocorticosteroids</td>
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<td>●&lt;sup&gt;*4&lt;/sup&gt;</td>
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<td>Bronchodilators · anticholinergics</td>
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<td>Bronchodilators · β&lt;sub&gt;2&lt;/sub&gt; agonists · xanthines</td>
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<td>Antibiotics</td>
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<td>Expectorants and antitussives</td>
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<tr>
<td>Respiratory rehabilitation</td>
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<td>Non-specific immunomodulator</td>
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<tr>
<td>Long-term oxygen therapy</td>
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<td>●&lt;sup&gt;*4&lt;/sup&gt;</td>
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</tbody>
</table>

<sup>*1</sup>: Long-term use during screening and treatment phase should be avoided.

<sup>*2</sup>: In principle, long-term concomitant medication will be allowed with the original administration and dosage in case it has been initiated before the recruitment. The name, dosage, administration method of the medication and the rationale of its application should be recorded in the case report form. If the administration and dosage is changed, the reason of relevant adjustment should also be recorded on the case report form.

<sup>*3</sup>: Concomitant medication will only be allowed when exacerbation occurs. The name, dosage, administration method of the medication and the rationale of its application should be recorded in the case report form.

<sup>*4</sup>: Concomitant medication will be allowed with limitation, i.e. duration of no more than 2 weeks in general.
### Table 2. Flow chart

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<td>Retrieval of investigational drugs and compliance assessment</td>
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<td>Training on use of inhaler</td>
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<td>Concomitant medication administration</td>
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<td>Blood and urine routine examination, blood chemistry examinations, chest X-ray, electrocardiogram</td>
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</table>
Margin of V1 to V11: ±7 days.

Related auxiliary examinations in recent 3 months can also be used as substitute, and be redone if necessary. The latest results should be used for decision making. Blood chemistry examinations include hepatic function (ALT, AST, TBIL), renal function (Scr, BUN) and blood sugar (fasting).
CONSORT 2010 checklist of information to include when reporting a randomised trial*

<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Item No</th>
<th>Checklist item</th>
<th>Reported on page No</th>
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<td>1a</td>
<td>Identification as a randomised trial in the title</td>
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<td>Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)</td>
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<td>Introduction</td>
<td>2a</td>
<td>Scientific background and explanation of rationale</td>
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<td>2b</td>
<td>Specific objectives or hypotheses</td>
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<td>Methods</td>
<td>3a</td>
<td>Description of trial design (such as parallel, factorial) including allocation ratio</td>
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<td>3b</td>
<td>Important changes to methods after trial commencement (such as eligibility criteria), with reasons</td>
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<td>Participants</td>
<td>4a</td>
<td>Eligibility criteria for participants</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>4b</td>
<td>Settings and locations where the data were collected</td>
<td>6-14</td>
</tr>
<tr>
<td>Interventions</td>
<td>5</td>
<td>The interventions for each group with sufficient details to allow replication, including how and when they were actually administered</td>
<td>6-9</td>
</tr>
<tr>
<td>Outcomes</td>
<td>6a</td>
<td>Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed</td>
<td>7-11</td>
</tr>
<tr>
<td></td>
<td>6b</td>
<td>Any changes to trial outcomes after the trial commenced, with reasons</td>
<td>NA</td>
</tr>
<tr>
<td>Sample size</td>
<td>7a</td>
<td>How sample size was determined</td>
<td>12-13</td>
</tr>
<tr>
<td></td>
<td>7b</td>
<td>When applicable, explanation of any interim analyses and stopping guidelines</td>
<td>NA</td>
</tr>
<tr>
<td>Randomisation:</td>
<td>8a</td>
<td>Method used to generate the random allocation sequence</td>
<td>8-9</td>
</tr>
<tr>
<td>Sequence generation</td>
<td>8b</td>
<td>Type of randomisation; details of any restriction (such as blocking and block size)</td>
<td>8-9</td>
</tr>
<tr>
<td>Allocation</td>
<td>9</td>
<td>Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned</td>
<td>8-9</td>
</tr>
<tr>
<td>Allocation concealment mechanism</td>
<td>10</td>
<td>Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions</td>
<td>8-9,11</td>
</tr>
<tr>
<td>Blinding</td>
<td>11a</td>
<td>If done, who was blinded after assignment to interventions (for example, participants, care providers, those</td>
<td>8-9</td>
</tr>
<tr>
<td>Item</td>
<td>Description</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>-------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11b</td>
<td>If relevant, description of the similarity of interventions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12a</td>
<td>Statistical methods used to compare groups for primary and secondary outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12b</td>
<td>Methods for additional analyses, such as subgroup analyses and adjusted analyses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13a</td>
<td>For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13b</td>
<td>For each group, losses and exclusions after randomisation, together with reasons</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14a</td>
<td>Dates defining the periods of recruitment and follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14b</td>
<td>Why the trial ended or was stopped</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>A table showing baseline demographic and clinical characteristics for each group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17a</td>
<td>For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17b</td>
<td>For binary outcomes, presentation of both absolute and relative effect sizes is recommended</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Generalisability (external validity, applicability) of the trial findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Registration number and name of trial registry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Where the full trial protocol can be accessed, if available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Sources of funding and other support (such as supply of drugs), role of funders</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.