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# Procalcitonin-guided initiation of antibiotics in AECOPD inpatients: a multicenter randomized controlled trial



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# Procalcitonin-guided initiation of antibiotics in AECOPD inpatients: a multicenter randomized controlled trial

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## Abstract

**Introduction:** Current antibiotic prescription for acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is generally based on the Anthonisen criteria in The Global Initiative for Chronic Obstructive Pulmonary Disease guideline, that has a potential risk of antibiotics overuse. The dilemma is to identify patients who are most likely to benefit from antibiotics while avoiding unnecessary antibiotic use. Procalcitonin (PCT), a more sensitive and specific biomarker of bacterial infection than other conventional laboratory tests, has the potential to determine those patients in whom antibiotics would be beneficial. It is unclear whether PCT-guided antibiotic therapy is safe and effective for patients hospitalized with AECOPD. The study hypothesis is that PCT-guided antibiotic therapy could reduce the antibiotic prescription rate for AECOPD, compared with the GOLD guideline recommendations, without negatively impacting the treatment success rate.

**Methods and analysis:** In this multicenter, open-label, randomized controlled trial (RCT), we aim to enroll 500 hospitalized patients with AECOPD, that will be randomly assigned to either a PCT-guided group or a GOLD guideline-guided group. The co-primary endpoints are antibiotic prescription rate for AECOPD within 30 days post randomization (superiority design) and treatment success rate at day 30 post randomization (non-inferiority design). The secondary outcomes include: antibiotic prescription rate at day 1 post randomization; hospital antibiotic exposure; length of hospital stay; rate of subsequent exacerbation and hospital readmission; overall mortality within 30 days post randomization; changes in lung function and the score of COPD assessment test (CAT) and modified Medical Research Council (mMRC); and ICU admission rate.

**Ethics and dissemination:** This trial has been approved by the ethic committee of China-Japan Friendship Hospital. The findings of the study will be disseminated in peer-reviewed journals. If the results of the study are positive, PCT-guided antibiotic therapy is likely to change the guidelines for antibiotic recommendations for patients with AECOPD.

**Trial registration number :** ClinicalTrials.gov: NCT04682899

## Strengths and limitations of this study

- The study is a nationwide, multicenter, randomized controlled trial in China with a large sample size.
- The study design conclude two primary outcomes to compare the efficacy and safety between PCT guided antibiotic therapy and current guideline recommendations.
- The present study has the potential to change the current clinical practice regarding the antibiotic prescription recommendations for patients with AECOPD.
- One limitation of the study is open-label. Only outcomes assessor and statisticians are blinded, patients, primary clinicians and laboratory staff are clear to the grouping.

## Introduction

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death in the world, but is projected to be the third by 2020[1]. In China, COPD is the third leading cause of death[2] and the overall prevalence in adults aged 40 years or older has risen from 8.2% (during 2002-04)[3] to 13.7% (during 2012-15)[4]. Additionally, the estimated total number of individuals aged 20 years or older with COPD in 2015 was roughly 100 million in China[4]. Acute exacerbations are the most common reason for hospitalization and death for patients with COPD. The Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guideline[5] notes that exacerbations are mainly triggered by respiratory viral infections, although bacterial infections and environmental factors such as pollution and ambient temperature may also initiate and/or amplify these events. However, for patients with acute exacerbation of COPD (AECOPD) in the USA and Europe, the antibiotic prescription rate was over 85%[6,7], which has a high risk of unnecessary use of antibiotics. Antibiotics overuse wastes medical resources, drives antimicrobial resistance, may cause side effects, negatively affects the microbiome of patients, and distracts from potentially more effective interventions[8].

Identifying AECOPD driven by bacterial infection is necessary prior to antibiotics prescription. As for acute exacerbation driven by viral infections, antibiotic treatment is not expected to be effective[9]. The GOLD guidelines have been recommended antibiotics prescription in patients of Anthonisen I and II[10] with sputum purulence, as well as patients with mechanical ventilation.[11] The GOLD guidelines assume purulence of sputum indicates bacterial infection, however, previous trials have shown it was not a reliable marker for bacterial presence[12,13]. On the basis of guideline recommendations, antibiotic prescription should be implemented on all patients with AECOPD receiving mechanical ventilation. This can obviously lead to overuse of antibiotics, particularly in those with acute exacerbation driven by viral infection or environmental factors. Thus, wide implementation of the antibiotic recommendations from the GOLD guidelines have the potential risk of antibiotic overuse, due to diagnostic difficulty in

distinguishing bacterial infection triggered AECOPD from those driven by other risk factors. Procalcitonin (PCT), a reliable biomarker of bacterial infection, has the potential to guide the prescription of antibiotics. Stolz and colleagues[14] conducted a randomized controlled trial (RCT) to evaluate the efficacy and safety of PCT guidance compared to standard care therapy with antibiotic prescriptions in patients with AECOPD. The study of 208 AECOPD inpatients showed that PCT guidance resulted in reduced antibiotic prescription and exposure compared to standard care therapy, with no difference in secondary outcomes (including success rate, subsequent exacerbation and rehospitalization rates) between the two groups. However, the sample size was calculated according to a single outcome of antibiotic prescription rate from the index exacerbation to the following 6 months and this limited sample size (208 AECOPD inpatients) was insufficiently powered to show whether PCT-guided algorithms do not affect secondary outcomes. Additionally, the recommendation in Stolz's trial for patients with a PCT result between 0.1to 0.25 ng/ml was decided by clinician themselves, which could bring variation for clinicians with different clinical experience. Evidence from our previous study has shown that patients with PCT level less than 0.1 ng/ml did not benefit from the additional antibiotic therapy.[15] PCT guidance, markedly and safely, reduced antibiotic prescriptions or the duration of antibiotic therapy in several previous RCTs conducted in patients with lower respiratory infections[16-18]. However, enrolled patients were not restricted to patients with COPD, but also included patients with community acquired pneumonia, asthma and bronchitis. Due to the lack of confirmatory PCT trials with rigorous methodology for COPD, the current GOLD guideline still recommend antibiotic prescription according to the Anthonisen criteria of 1987[10].

In this protocol, we aim to conduct a multicenter RCT to determine the effect of PCT-guided antibiotic therapy compared to the current GOLD guideline recommendations in patients with AECOPD.

## Methods/design

## Objective

The primary aim is to determine whether PCT-guided antibiotic therapy will reduce the antibiotic prescription rate for AECOPD without negatively impacting the treatment success rate, compared with the GOLD guideline recommendations.

## Design

This is a nationwide, multicenter, open-label, RCT that will be conducted at 10 hospitals in China. Eligible participants will be randomly assigned to either the PCT-guided antibiotic therapy (PCT group) or the GOLD guideline antibiotic recommendations (guideline group) in a ratio of 1:1. Figure 1 shows the flow chart of the trial. We will address this question in terms of co-primary outcome measures: antibiotic prescription rate for AECOPD within 30 days post randomization and the treatment success rate at day 30 post randomization. Between-group differences in antibiotic prescription rates will be investigated for superiority, while differences in treatment success rates for non-inferiority. The study design follows the Standard Protocol Items: Recommendations for Interventional Trials statement recommendations.[19] The items from the trial registration data set are recorded in the online supplementary material 1.

## Population and eligibility criteria

Recruitment will be conducted at the department of the pulmonary and critical care medicine of the 10 tertiary teaching hospitals in China. The detailed information of these hospitals are shown in online supplementary material 2. The inclusion criteria and exclusion criteria are shown in Table 1.

## Ethics and informed consent

The Ethics Committee of China-Japan Friendship Hospital has approved the trial (file number: 2020-87-K51). Written informed consent (online supplementary material 3) will be required from eligible patients at each participating centers, or their legal

representative if they were unable to provide consent.

**Randomization and allocation concealment**

Eligible patients will be randomly assigned (1:1) to either the PCT group or the guideline group within 24 hours after hospitalization. The random sequence was generated by a statistician using SAS software, version 9.4 and stored by a manager from the China-Japan friendship hospital, both of them are not involved in the trial. Once an eligible participant is recruited in each center, the site investigator will request a random number by telephone from the manager. The investigator receive the group information based on the random number, and then conducted next step according to trial protocol. The participants, health care providers and laboratory staff are known to the patient allocation. Outcomes assessors and statisticians will be blinded to the study assignment.

**Interventions**

Participants in the PCT group will complete a PCT test within 2 hours after randomization and the results will be sent back to the clinician by laboratory through the internal network of the hospital. The prescribing clinician will use the results of the PCT to help guide their antibiotic prescription decision. Participants in the guideline group will also need to complete a PCT test within 2 hours after randomization, however, the laboratory will save the results and do not sent back to the clinician. The detailed antibiotic recommendations of both groups are shown in Table 2. Other therapies for AECOPD in both groups will be based on the GOLD guideline recommended standard care. All participating centers will be provided the 2020 version of the GOLD guideline.

To ensure the veracity and reliability of results, each center may adopt any one of the following three validated assays to measure the value of PCT: B·R·A·H·M·S PCT sensitive KRYPTOR assay (Thermo Fisher Scientific, Hennigsdorf, Germany), Roche Elecsys B·R·A·H·M·S PCT assay, or the BioMérieux's Vidas B·R·A·H·M·S PCT assay. Each center will perform standard calibration procedures on the instruments and analyze two levels of quality control materials with each sample run. Procedure time for all these assays is less than 30 minutes. Each participating center will have access

to a Kryptor machine, a suitable Vidas or Roche immunoanalyser to expedite the sample analysis and rapidly provide PCT results for guidance in the protocol.

**Outcomes**

Primary endpoints

- Antibiotic prescription rate within 30 days post randomization, expressed as the proportion of patients receiving antibiotics for AECOPD. The objective of antibiotic prescription is to treat AECOPD during hospitalization or after discharge; antibiotics used for other reasons are excluded, such as new urinary tract infection.
- Treatment success rate at day 30 post randomization. Treatment success is defined as cure (a complete resolution of signs and symptoms associated with the exacerbation) or improvement (a resolution or reduction of the symptoms and signs associated with the exacerbation, without new symptoms or signs).[20] Treatment failure is defined as absence of resolution of symptoms and signs; worsening of symptoms and signs; occurrence of new symptoms and signs associated with the primary or with a new infection; or death of any reason after randomization.[20] Face to face consult will be performed on day 30 post randomization.

Secondary endpoints

- Antibiotic prescription rate at day 1 post randomization
- Hospital antibiotic exposure, expressed as the number of days of antibiotic consumed for AECOPD and the proportion of patients receiving antibiotic for AECOPD during hospitalization
- Length of hospital stay, expressed as the number of days of hospitalization
- Rate of subsequent exacerbation, hospital readmission and overall mortality within 30 days post randomization
- Change in lung function, COPD assessment test (CAT)[21] and modified Medical Research Council (mMRC) dyspnea scale[22], expressed as the difference between the baseline of hospital admission and day 30 post randomization.
- ICU admission rate

## Follow-up

The total follow-up period is 30 days post randomization. The follow-up items at multiple time points are shown in Table 3. Notably, we will contact all the eligible participants and ask them to participate a face-to-face interview at each participating center on the day 30 post randomization.

## Adverse events

Choice and duration of antibiotics and other pharmacological treatments including bronchodilators and glucocorticoids in both groups are all based on current guideline recommendations. Study intervention will not change the daily clinical treatment therapy, and consequently will not increase the risk of adverse events. Adverse events will be collected and reported as part of routine follow-up. All events fulfilling the definition of a serious adverse event (SAE), including death, that occur during research period will be reported to the research center expert committee within 24 h post event occurrence.

## Sample size

This study is designed to have sufficient power to detect a 20% reduction from an estimated 70% that consume antibiotics for the AECOPD during the 30 days following randomization. In the Schuetz's RCT to compare PCT guide antibiotic prescription with guideline therapy, subgroup analysis in patients with AECOPD shown that the 30 days prescription rate of guideline group and procalcitonin group was 69.9% and 48.7%, respectively[18]. Detecting a difference in proportions between 0.70 and 0.50 at the 5% significance level with 90% power requires a total 242 participants. Assuming a drop-out rate of 20%, we will need to enroll 302 participants. In addition, we aim to have sufficient power to demonstrate that participants managed with PCT-guided strategy are non-inferior, compared to those managed with guideline recommendations, in terms of treatment success rate at day 30 post randomization. A limited number of studies have reported the success rate at day 30 after randomization in patients with

AECOPD[14,23]. According to prior trials in terms of hospitalized patients with AECOPD, Stolz[14] reported the short-term treatment success rate as 83.9% (from 14 to 21 days post randomization) and Prins[23] determined the treatment failure rate at day 30 after randomization as 20.3%. Based on these data and assuming a treatment success rate of 0.8 at day 30 following randomization , a non-inferior margin of 0.1[24], based on a one-sided significance level of 0.05 and 80% power, would require 396 participants. Again with a drop-out rate of 20%, 495 participants will need to be included. Finally, considering these two primary endpoints, we will aim to recruit 500 participants in total to the study.

**Data collection and management**

An independent clinician from each center, unknown the group information, will collect the data through a prespecified case report form (CRF) at multiple time points. The data filled in the CRF should be accurate, complete, timely and reliable. All centers in our study are qualified by the 'Good Clinical Practice (GCP) training' of the State Food and Drug Administration for compliance in the training. To increase study awareness and protocol adherence, we will convene principle investigator in each center and organize a face-to-face meeting to discuss the study protocol before study initiation. Two experienced data managers from the China-Japan hospital monthly check the CRF of each center, track clinicians' antibiotic prescription decisions in both groups and assess adherence to the protocol. They will ask investigators to resolve any queries identified, record the reasons for non-adherence and provide regular feedback to every center. To solve the potential problems and grantee the quality of research, principle investigator at each center will gather and conduct an online meeting every month. All randomized patients should be followed up until 30 days post randomization.

**Data analysis**

Participants' characteristics and clinical measures will be described by frequencies and percentages, means and standard deviations, or medians and interquartile ranges as

appropriate. There will be no planned interim analysis. All analysis will be based on the ITT population, including all randomized participants. Missing data was considered using multiple imputation. All analyses will be completed using SAS, version 9.4 (SAS Institute).

Primary analysis

- The first primary analysis will aim to compare the rate of antibiotic prescription within 30 days between PCT group and guideline group. A two-sided 95%-confidence interval will be computed for the difference in antibiotic prescription rate for both arms.
- The second primary analysis will compare the difference in proportions of clinical treatment success at day 30 between both groups, relative to a 10% non-inferiority margin, and construct a two-sided 90% confidence interval for the difference in proportions. Non-inferiority will be declared if the lower limit of the confidence interval exceeds -10%.

Secondary analysis

Secondary outcomes will be analyzed in a similar manner to the primary outcomes, with linear, logistic, and Poisson regression models fitted as appropriate. All tests will be two-sided, with *p* value less than 0.05 deemed statistically significant.

**Patient and public involvement**

No patients or public involved in the present study. The results of this study will be published by the investigators in relevant scientific peer-reviewed journals, no matter the study findings.

**Discussion**

AECOPD are important events in the management of COPD because they negatively impact health status, rates of hospitalization and readmission, and disease progression. Over 85% of patients presenting with AECOPD have been prescribed antibiotics in the USA[6] and Europe[7]. However, not all acute exacerbations are driven by bacteria

infection, viral infections and environmental factors are currently main predisposing factors. Current antibiotic prescribing is generally based on the criteria outlined by Anthonisen and colleagues in 1987[10] that includes increased dyspnea, increased sputum volume and increased sputum purulence. The GOLD guideline recommends the use of antibiotics in patients who have all three criteria or, in patients who have two criteria when sputum purulence is one of them, or in patients who require mechanical ventilation. However, whether antibiotic therapy according to Anthonisen criteria will benefit patients is unclear. Some randomized trials have found that only patients with increased sputum purulence benefit from antibiotic therapy with amoxicillin–clavulanate, regardless of the presence or absence of the other two criteria[25,26]. In another randomized trial, doxycycline was not superior to placebo in any Anthonisen criteria–defined subgroup, including among patients with purulent sputum.[27] Thus, Anthonisen criteria have insufficient diagnostic accuracy to predict which patients can safely be managed without antibiotics.

The dilemma is to identify patients who are most likely to benefit from antibiotics while avoiding unnecessary antibiotic use. Procalcitonin, a biomarker of bacterial infection with higher sensitivity and specificity than conventional laboratory tests[28-30], would have the potential to distinguish patients in whom antibiotics would be beneficial and guide their duration of use. Due to the small study populations and multiple subgroups analysis of lower respiratory tract infection in previous studies[14,16-18], it is unclear whether PCT-guided antibiotic therapy is safe and effective for patients with AECOPD. PCT-based protocols may be clinically effective; however, confirmatory trials with rigorous methodology are still required[31].

In our trial, we aim to evaluate whether PCT-guided antibiotic therapy will reduce the antibiotic prescription rate for patients with AECOPD, in comparison to the GOLD guideline recommendations, without negatively impacting the treatment success rate. If the results of the study are positive (i.e. a significant reduction in antibiotic prescribing with no evidence of significant impairment in the treatment success rate),

PCT-guided antibiotic therapy is likely to change the guidelines for antibiotic recommendations for patients with AECOPD.

**Contributors** BC, JW and LH conceived and designed the study. YW and WS provided suggestions for the study design. XG performed the sample size calculation. LH and JW drafted and edited the manuscript. All authors have contributed to the revision of the draft and have read and approved the final version.

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**Disclaimer** The funder had no role in the design of the protocol, the conduction of the trial, or the analyses or reporting of the data.

**Competing interests** None declared.

**Patient consent for publication** Not required

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Table 1. Eligibility criteria

| Inclusion criteria | Exclusion criteria |
|---|---|
| - Hospitalized patients with AECOPD | - Fever, Axillary temperature≥38°C |
| - ≥40 years of age | - Pneumonia identified by X-Ray or CT of the chest |
| - Able to understand and communicate to ensure the completion of the trial | - Severe respiratory failure requiring admittance to ICU |
| | - Concurrent infection at another site (e.g. urinary tract infection) |
| - Voluntary participation and provide written informed consent | - Immunosuppression secondary to chemotherapy, AIDS or malignant tumor of blood system |
| | - Comorbidities requiring corticosteroids (prednisone 30mg/d or equivalent more than 30 days ) |
| | - Invasive mechanical ventilation |
| | - Patients with malignant tumors receiving chemotherapy or radiotherapy |
| | - Pregnancy |
| | - Participation in another clinical trial |
| | - Previously enrollment into the study |
| | - Refuse to attend |

AECOPD: acute exacerbation of chronic obstructive pulmonary disease; CT: computer tomography; ICU: intensive care unit.

Table 2. Antibiotic prescription strategy in both arms

| GOLD guideline-guided antibiotic recommendations | |
|---|---|
| Patients with exacerbations of COPD who have three cardinal symptoms: increase in dyspnea, sputum volume, and sputum purulence; have two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms; or require mechanical ventilation (invasive or noninvasive). | |
| PCT-guided antibiotic regimen | |
| PCT<0.1ng/ml | Strongly discouraged |
| PCT (0.1-0.25ng/ml) and no sputum purulence | discouraged |
| PCT (0.1-0.25ng/ml) and sputum purulence | Recommended |
| PCT>0.25 ng/ml | Strongly recommended |

PCT: procalcitonin; GOLD: The Global Initiative for Chronic Obstructive Pulmonary Disease.

Table 3. Schedule of assessments and data collection

| Assessment | At time of consent | Day 1 (face to face) | Day 3 (face to face) | Day 14 (face to face or telephone) | Day 30 (face to face) |
|---|---|---|---|---|---|
| Assessment of eligibility | × | | | | |
| Written informed consent | × | | | | |
| Basic information | × | | | | |
| Medication history | × | | | | |
| Physical examination | × | | × | | × |
| PCT level | × | | | | |
| CAT score | × | | | | × |
| mMRC score | × | | | | × |
| Antibiotic prescription | × | × | × | × | × |
| Other medicine for AECOPD | × | × | × | × | × |
| Sputum gram staining and culture | × | | | | |
| Lung function | × | | | | × |
| Assessment of therapeutic | | × | × | × | × |
| Adverse effects | × | × | × | × | × |
| Length of hospital stay | | | | | × |
| Mortality | | | | | × |

PCT: procalcitonin; CAT: COPD assessment test; mMRC; modified Medical Research Council.

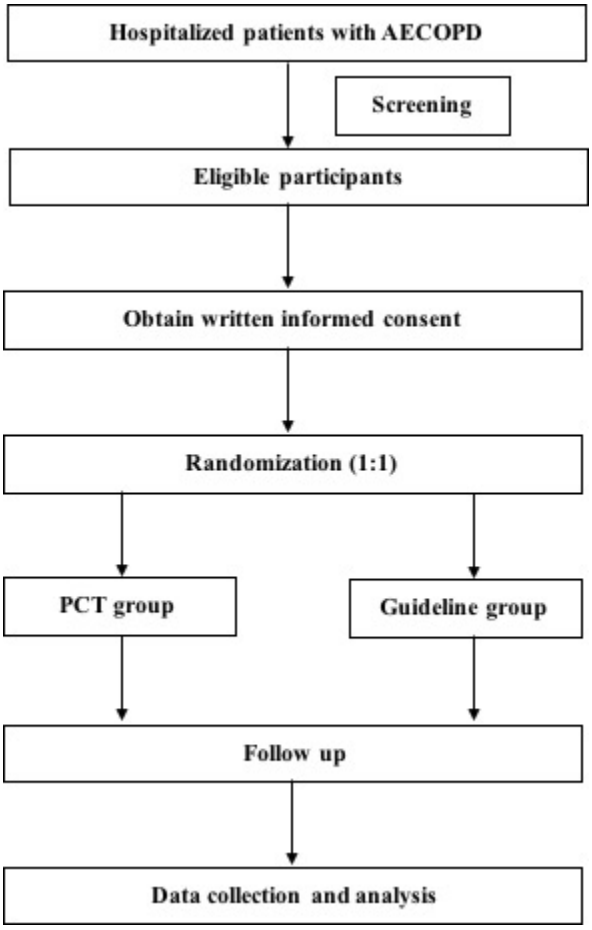


Figure 1 The flow chart of enrolled participants.

103x162mm (72 x 72 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | 2 |
| Protocol version | 3 | Date and version identifier | 20200101-Version1.0 |
| Funding | 4 | Sources and types of financial, material, and other support | 13 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1,13 |
| | 5b | Name and contact information for the trial sponsor | 13 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 13 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 10 |

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

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 9,10 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 6 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 7 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 7 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 7 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 7 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 7 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 10 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 10 |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 10 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 10,11 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 10,11 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 10,11 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 10 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 10 |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 9 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | NA |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 6 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 6 |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 6 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | 6 |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 10 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 13 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 13 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | Supplementary file 3 |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 13 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | 13 |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 13 |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | Supplementary file 3 |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | NA |

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

Supplementary material 2. The details of hospitals participating in this trial

| Hospital | Province, City | Location in China | Teaching hospital | Grade of hospital |
|---|---|---|---|---|
| China-Japan Friendship Hospital | Beijing | North | Yes | Tertiary |
| Beijing Luhe Hospital, capital medical University | Beijing | North | Yes | Tertiary |
| Daxing Hospital Affiliated to Capital Medical University | Beijing | North | Yes | Tertiary |
| Qingdao Municipal Hospital | Shandong | East | Yes | Tertiary |
| Linzi district People's hospital | Shandong | East | Yes | Tertiary |
| First Hospital of Shanxi Medical University | Shanxi | North | Yes | Tertiary |
| Hebei Provincial General Hospital | Hebei | North | Yes | Tertiary |
| First Affiliated Hospital of Guangxi Medical University | Guangxi | South | Yes | Tertiary |
| Xiangtan Central Hospital | Hunan | Central | Yes | Tertiary |
| First Affiliated Hospital of Wenzhou Medical University | Zhejiang | East | Yes | Tertiary |

Definition of Secondary and Tertiary hospital in China: The Secondary hospital is defined as a hospital providing medical, prevention, health care and rehabilitation services to multiple communities (with a radius of population more than 100,000 peoples); the Tertiary hospital is defined as a hospital providing medical service to the whole country beyond cities and provinces, with comprehensive medical, teaching and research ability.

# Informed Consent Form· Notice for Participants

Dear Mr/Ms _____:

You (/ your family) are currently hospitalized with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). You are invited to attend a clinical study of AECOPD. Please read the following information as carefully as possible before you decide whether or not to participate in this study. It will help you understand the value and significance, the procedures and duration, as well as the possible benefits, discomfort and risks of participating in this study. If you want, you can also discuss it with your relatives, friends, or consult your doctor to help you make the decision. If you have any question, please do not hesitate to contact the doctor.

## 1. Background and objective

### 1.1 Background

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death in the world, but is projected to be the third by 2020. Acute exacerbations are the most common reason for hospitalization and death for patients with COPD. Not all patients with AECOPD would benefit from antibiotic therapy. Antibiotics overuse wastes medical resources, drives antimicrobial resistance, may cause side effects, negatively affects the microbiome of patients, and distracts from potentially more effective interventions. The GOLD guidelines have been recommended antibiotics prescription in patients of Anthonisen I and II with sputum purulence, as well as patients with mechanical ventilation, which has potential risk in overuse of antibiotics. Procalcitonin (PCT), a reliable biomarker of bacterial infection, has the potential to guide the prescription of antibiotics. In order to evaluate the efficacy of PCT to guide antibiotic management in patients with AECOPD, we aim to perform this multicenter, blind, randomized, controlled clinical trial.

### 1.2 Objective

This study aim to determine whether PCT-guided antibiotic therapy will reduce the antibiotic prescription rate for AECOPD without negatively impacting the treatment success rate, compared with the GOLD guideline recommendations.

**2. Research method**

This study has been approved by the Medical Ethics Committee of China-Japan Friendship Hospital. This is a multicenter, randomized, controlled clinical trial which will be conducted in 10 tertiary general hospitals including China-Japan Friendship Hospital, and plans to recruit 500 eligible hospitalized patients with AECOPD to participate voluntarily.

Eligible participants will be randomly assigned to either the PCT-guided antibiotic therapy (PCT group) or the GOLD guideline antibiotic recommendations (guideline group) in a ratio of 1:1. The selection of different groups will not affect the routine treatment for you.

This study will record your personal and disease-related information, including medical history (such as vital signs), routine medical and laboratory examination results. In order to objectively evaluate the changes of your condition, you will be inquired in varying time points (screening period, day1, day 3, day 14 and day 30 after randomization) and the changes will be recorded. The follow-up will continue until day 30 after randomization.

The above routine treatment and medical examinations are all necessary for the clinical treatment of patients with AECOPD. This study does not involve any special examinations or treatment, nor add extra burden on patients.

**3. Participants' Responsibility**

During the study period, you (/your family) are required to follow the study protocol and undergoing the follow-up by your investigators about your (/your family) outcome.

4. **Participants' Right**

You (/your family) are voluntary to participate in this study. You should not feel any pressure to participate. You have the rights to refuse to attend this study, or at any time inform the investigator to request withdrawal from the study without any discrimination or retaliation. Your data will not be included in the study and any medical treatment. Your benefits will not be affected.

You can keep track of the information and progress of this research. If you have any questions about the study, or if you feel any discomfort during the research, or if the

study involves your rights, you can always consult the investigators. If you have any complaints, please contact the ethics committee of your hospital.

**5. The possible benefits during the study**

You, people and society will probably benefit from this study, such as the potential avoidance of antibiotics use, and it may be helpful for other patients with similar condition. Treatment and related medical examinations will be performed according to the routine protocol of GOLD guideline regardless of your participation in this study. Investigators will follow up your health condition until day 30 after randomization, regardless you stay in hospital or not, and give you careful guidance.

**6. The possible risks during the study**

The routine therapy for AECOPD is based on the GOLD guideline. A previous study has shown that recommending not antibiotic therapy for patients with PCT level less than 0.1ng/ml do not occur adverse outcome. If any adverse event occurs in this study, the Medical Experts Committee will identify whether it is related to the study. If the damage is related to the study, the cost of treatment and relevant economic compensation will be provided according to the provisions of China's "Good Clinical Practice (GCP).

**7. Participants personal privacy protection**

If you (/your family) decide to participate in the study, your personal data in the study are confidential. In all medical records of this study, your name will be replaced by a Pinyin abbreviation. Your medical records and information will be kept in the hospital, only the investigator, research authority department, and ethics committee will be approved to access them. Any public report about the results of this study will not disclose your personal identity.

You (/your family) can choose not to attend this study, or to withdraw at any time without any discrimination or retaliation, and your medical treatment and benefits will not be affected.

Your (/your family's) participation in this study is voluntary. You (/your family) can keep track of the relevant information. If you have any questions related to this research,

or you have a research-related injury, or have questions about the Participants' rights and interests, you can contact the investigator any time.

In the case of an emergency, please contact the investigator:

Contact phone number:

# Participants' informed consent form

I have read the introduction of this trial and have the opportunity to discuss and ask questions with my doctor about this trial. All my questions were answered satisfactorily. I know the risks and benefits of participating in this trial, and I understand that participating in this trial is voluntary. I inquired about the details of the trial and all the relevant questions were answered. At the same time, my family and I have plenty of time to consider, but also a clear understanding of the following:

1. I can consult my doctor for more information at any time.
2. All my personal information is confidential; my privacy and right to know will be kept confidential.
3. I can withdraw from this trial at any time without discrimination or retaliation, and medical treatment will not be affected.
4. I agree that investigators, research authorities and ethics committees should consult my medical records after approval.
5. I will get a signed and dated copy of the informed consent.

I decided to agree to participate in this trial and try to comply with the doctor's advice.

Participant or legal representative signature: Signature date:

Contact phone number:

The relationship between the signer and the subject:

I confirm that I have accurately explained to the subject the details of the trial, including its rights, possible benefits and risks, and answered all questions.

The participant volunteered to participate in the trial and had given a signed copy of the informed consent.

Investigator signature: Signature date:

Contact phone number:

BMJ Open

# Procalcitonin-guided initiation of antibiotics in AECOPD inpatients: study protocol for a multicenter randomized controlled trial

| | |
|---|---|
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# Procalcitonin-guided initiation of antibiotics in AECOPD inpatients: study protocol for a multicenter randomized controlled trial

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## Abstract

**Introduction:** Current antibiotic prescription for acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is generally based on the Anthonisen criteria in The Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guideline, that has a potential risk of antibiotics overuse. The dilemma is to identify patients who are most likely to benefit from antibiotics while avoiding unnecessary antibiotic use. Procalcitonin (PCT), a more sensitive and specific biomarker of bacterial infection than other conventional laboratory tests, has the potential to determine those patients in whom antibiotics would be beneficial. It is unclear whether PCT-guided antibiotic therapy is safe and effective for patients hospitalized with AECOPD. The study hypothesis is that PCT-guided antibiotic therapy could reduce the antibiotic prescription rate for AECOPD, compared with the GOLD guideline recommendations, without negatively impacting the treatment success rate.

**Methods and analysis:** In this multicenter, open-label, randomized controlled trial, we aim to enroll 500 hospitalized patients with AECOPD, that will be randomly assigned to either a PCT-guided group or a GOLD guideline-guided group. The co-primary endpoints are antibiotic prescription rate for AECOPD within 30 days post randomization and treatment success rate at day 30 post randomization. The secondary outcomes include: antibiotic prescription rate at day 1 post randomization; hospital antibiotic exposure; length of hospital stay; rate of subsequent exacerbation and hospital readmission; overall mortality within 30 days post randomization; changes in lung function and the score of COPD assessment test and modified Medical Research Council (mMRC); and rate of intensive care unit admission.

**Ethics and dissemination:** This trial has been approved by the ethic committee of China-Japan Friendship Hospital. The findings of the study will be disseminated in peer-reviewed journals. If the results of the study are positive, PCT-guided antibiotic therapy is likely to change the guidelines for antibiotic recommendations for patients with AECOPD.

**Trial registration number :** ClinicalTrials.gov: NCT04682899

## Strengths and limitations of this study

- This is a nationwide, multicenter, randomized controlled trial in China.
- The study design conclude two primary outcomes regarding safety and effectivity.
- The study encompasses multiple clinically related secondary outcomes.
- The study has a sample size large enough to provide high-quality evidence to evaluate the safety and effectivity of PCT in patients with AECOPD.
- One limitation of the study is that patients, primary clinicians and laboratory staff are clear to the grouping, only outcomes assessor and statisticians are blinded.

## Introduction

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death in the world, but is projected to be the third by 2020[1]. In China, COPD is the third leading cause of death[2] and the overall prevalence in adults aged 40 years or older has risen from 8.2% (during 2002-04)[3] to 13.7% (during 2012-15)[4]. Acute exacerbations are the most common reason for hospitalization and death for patients with COPD. The Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guideline notes that exacerbations of COPD are mainly triggered by respiratory viral infections,[5] however, a very high proportion of patients with acute exacerbation of COPD (AECOPD) received antibiotic treatment. The prescription rate of antibiotics for inpatients with AECOPD in the United States, Europe, and China all exceeds 85%[6-8]. This brings a high risk of unnecessary use of antibiotics. Antibiotics overuse wastes medical resources, drives antimicrobial resistance, may cause side effects, negatively affects the microbiome of patients, and distracts from potentially more effective interventions[9].

The current GOLD guidelines recommended antibiotics prescription in patients of Anthonisen I and II[10] with sputum purulence, as well as patients with mechanical ventilation.[11] The GOLD guidelines assume purulence of sputum indicates bacterial infection, however, previous trials have shown it was not a reliable marker for bacterial presence[12,13]. On the basis of guideline recommendations, antibiotic prescription should be implemented on all patients with AECOPD receiving mechanical ventilation. This can obviously lead to overuse of antibiotics, particularly in those with acute exacerbation driven by viral infection or environmental factors. Thus, wide implementation of the antibiotic recommendations from the GOLD guidelines have the potential risk of antibiotic overuse.

Identifying AECOPD driven by bacterial infection is necessary prior to antibiotics prescription. Procalcitonin (PCT), a reliable biomarker of bacterial infection, has the potential to guide the prescription of antibiotics. Several randomized controlled trials

(RCTs) have explored the effect of PCT on guiding antibiotic therapy in patients with lower respiratory infections[14-16] and especially patients with AECOPD[17]. Given the limitations of these studies, whether PCT-guided antibiotic therapy will safely and effectively bring clinical benefit for AECOPD was unclear. PCT guidance, markedly and safely, reduced antibiotic prescriptions or the duration of antibiotic therapy in patients with lower respiratory infections[14-16]. However, enrolled patients were not restricted to patients with COPD, but also included patients with community acquired pneumonia, asthma and bronchitis. A RCT study of 208 inpatients with AECOPD showed that PCT guidance resulted in reduced antibiotic prescription and exposure compared to standard care therapy, with no difference in secondary outcomes (including success rate, subsequent exacerbation and rehospitalization rates) between the two groups.[17] However, the sample size was calculated according to a single outcome of antibiotic prescription rate and this limited sample size (208 AECOPD inpatients) was insufficiently powered to show whether PCT-guided algorithms do not affect secondary outcomes. Due to the lack of confirmatory PCT trials with rigorous methodology for COPD, the current GOLD guideline still recommend antibiotic prescription according to the Anthonisen criteria of 1987[10].

Evidence from our previous study has shown that patients with AECOPD and with a PCT level less than 0.1 ng/ml did not benefit from the additional antibiotic therapy.[18] In this protocol, we aim to conduct a multicenter RCT to determine the effect of PCT-guided antibiotic therapy compared to the current GOLD guideline recommendations in patients with AECOPD.

## Methods/design

### Objective

The primary aim is to determine whether PCT-guided antibiotic therapy will reduce the antibiotic prescription rate for AECOPD without negatively impacting the treatment success rate, compared with the GOLD guideline recommendations.

## Design

This is a nationwide, multicenter, open-label, RCT that will be conducted at 10 hospitals in China. Eligible participants will be randomly assigned to either the PCT-guided antibiotic therapy (PCT group) or the GOLD guideline antibiotic recommendations (guideline group) in a ratio of 1:1. Figure 1 shows the flow chart of the trial. We will address this question in terms of co-primary outcome measures: antibiotic prescription rate for AECOPD within 30 days post randomization and the treatment success rate at day 30 post randomization. Between-group differences in antibiotic prescription rates will be investigated for superiority, while differences in treatment success rates for non-inferiority. The study design follows the Standard Protocol Items: Recommendations for Interventional Trials statement recommendations.[19] The items from the trial registration data set are recorded in the online supplementary material 1.

## Population and eligibility criteria

Recruitment will be conducted at the department of the pulmonary and critical care medicine of the 10 tertiary teaching hospitals in China. The detailed information of these hospitals are shown in online supplementary material 2. The inclusion criteria and exclusion criteria are shown in Table 1. In the context of preventing and controlling COVID-19 pandemic, wearing a mask in whole people in China increase the difficulty of recruitment of eligible patients with AECOPD. According to the current recruitment speed, approximately 30 patients were enrolled into the study every month in 10 centers. We estimate that recruitment duration will last until April 2022.

## Ethics and informed consent

The Ethics Committee of China-Japan Friendship Hospital has approved the trial (file number: 2020-87-K51). Written informed consent (online supplementary material 3) will be required from eligible patients at each participating centers, or their legal representative if they were unable to provide consent.

**Randomization and allocation concealment**

Eligible patients will be randomly assigned (1:1) to either the PCT group or the guideline group within 24 hours after hospitalization. The random sequence was generated by a statistician using SAS software, version 9.4 and stored by a manager from the China-Japan friendship hospital, both of them are not involved in the trial. Once an eligible participant is recruited in each center, the site investigator will request a random number by telephone from the manager. The investigator receive the group information based on the random number, and then conducted next step according to trial protocol. The participants, health care providers and laboratory staff are known to the patient allocation. Outcomes assessors and statisticians will be blinded to the study assignment.

**Interventions**

Participants in the PCT group will complete a PCT test within 2 hours after randomization and the results will be sent back to the clinician by laboratory through the internal network of the hospital. The prescribing clinician will use the results of the PCT to help guide their antibiotic prescription decision. Participants in the guideline group will also need to complete a PCT test within 2 hours after randomization, however, the laboratory will save the results and do not sent back to the clinician. The detailed antibiotic recommendations of both groups are shown in Table 2. Other therapies for AECOPD in both groups will be based on the GOLD guideline recommended standard care. All participating centers will be provided the 2020 version of the GOLD guideline.

To ensure the veracity and reliability of results, each center may adopt any one of the following three validated assays to measure the value of PCT: B·R·A·H·M·S PCT sensitive KRYPTOR assay (Thermo Fisher Scientific, Hennigsdorf, Germany), Roche Elecsys B·R·A·H·M·S PCT assay, or the BioMérieux's Vidas B·R·A·H·M·S PCT assay. The direct measuring range of B·R·A·H·M·S PCT sensitive KRYPTOR assay is from 0.02-50 ng/ml, and the Functional Assay Sensitivity (FAS) is 0.06 ng/ml, which is 3-fold to 10-fold above normal mean values.[17,20] The direct measuring range of Roche

Elecsys B·R·A·H·M·S PCT assay is from 0.02-100 ng/ml, and the FAS is 0.06 ng/ml.[20] The direct of measuring range of BioMérieux's Vidas B·R·A·H·M·S PCT assay is 0.05-200 ng/ml, and the FAS is 0.09 ng/ml.[20] Each center will perform standard calibration procedures on the instruments and analyze two levels of quality control materials with each sample run. Procedure time for all these assays is less than 30 minutes. Each participating center will have access to a Kryptor machine, a suitable Vidas or Roche immunoanalyser to expedite the sample analysis and rapidly provide PCT results for guidance in the protocol.

**Outcomes**

Primary endpoints

- Antibiotic prescription rate within 30 days post randomization, expressed as the proportion of patients receiving antibiotics for AECOPD. The objective of antibiotic prescription is to treat AECOPD during hospitalization or after discharge; antibiotics used for other reasons are excluded, such as new urinary tract infection.
- Treatment success rate at day 30 post randomization. Treatment success is defined as cure (a complete resolution of signs and symptoms associated with the exacerbation) or improvement (a resolution or reduction of the symptoms and signs associated with the exacerbation, without new symptoms or signs).[21] Treatment failure is defined as absence of resolution of symptoms and signs; worsening of symptoms and signs; occurrence of new symptoms and signs associated with the primary or with a new infection; or death of any reason after randomization.[21] Face to face consult will be performed on day 30 post randomization.

Secondary endpoints

- Antibiotic prescription rate at day 1 post randomization
- Hospital antibiotic exposure, expressed as the number of days of antibiotic consumed for AECOPD and the proportion of patients receiving antibiotic for AECOPD during hospitalization
- Length of hospital stay, expressed as the number of days of hospitalization
- Rate of subsequent exacerbation, hospital readmission and overall mortality within

30 days post randomization

- Change in lung function, COPD assessment test (CAT)[22] and modified Medical Research Council (mMRC) dyspnea scale[23], expressed as the difference between the baseline of hospital admission and day 30 post randomization.
- ICU admission rate

**Follow-up**

The total follow-up period is 30 days post randomization. The follow-up items at multiple time points are shown in Table 3. Notably, we will contact all the eligible participants and ask them to participate a face-to-face interview at each participating center on the day 30 post randomization.

**Adverse events**

Choice and duration of antibiotics and other pharmacological treatments including bronchodilators and glucocorticoids in both groups are all based on current guideline recommendations. Study intervention will not change the daily clinical treatment therapy, and consequently will not increase the risk of adverse events. Adverse events will be collected and reported as part of routine follow-up. All events fulfilling the definition of a serious adverse event (SAE), including death, that occur during research period will be reported to the research center expert committee within 24 h post event occurrence.

**Sample size**

This study is designed to have sufficient power to detect a 20% reduction from an estimated 70% that consume antibiotics for the AECOPD during the 30 days following randomization. In the Schuetz's RCT to compare PCT guide antibiotic prescription with guideline therapy, subgroup analysis in patients with AECOPD shown that the 30 days prescription rate of guideline group and procalcitonin group was 69.9% and 48.7%, respectively[16]. Detecting a difference in proportions between 0.70 and 0.50 at the 5%

significance level with 90% power requires a total 242 participants. Assuming a drop-out rate of 20%, we will need to enroll 302 participants. In addition, we aim to have sufficient power to demonstrate that participants managed with PCT-guided strategy are non-inferior, compared to those managed with guideline recommendations, in terms of treatment success rate at day 30 post randomization. A limited number of studies have reported the success rate at day 30 after randomization in patients with AECOPD[17,24]. According to prior trials in terms of hospitalized patients with AECOPD, Stolz[17] reported the short-term treatment success rate as 83.9% (from 14 to 21 days post randomization) and Prins[24] determined the treatment failure rate at day 30 after randomization as 20.3%. Based on these data and assuming a treatment success rate of 0.8 at day 30 following randomization , a non-inferior margin of 0.1[25], based on a one-sided significance level of 0.05 and 80% power, would require 396 participants. Again with a drop-out rate of 20%, 495 participants will need to be included. Finally, considering these two primary endpoints, we will aim to recruit 500 participants in total to the study.

**Data collection and management**

An independent clinician from each center, unknown the group information, will collect the data through a prespecified case report form (CRF) at multiple time points. The data filled in the CRF should be accurate, complete, timely and reliable. All centers in our study are qualified by the 'Good Clinical Practice (GCP) training' of the State Food and Drug Administration for compliance in the training. To increase study awareness and protocol adherence, we will convene principle investigator in each center and organize a face-to-face meeting to discuss the study protocol before study initiation. Two experienced data managers from the China-Japan hospital biweekly check the CRF of each center, track clinicians' antibiotic prescription decisions in both groups and assess adherence to the protocol. They will ask investigators to resolve any queries identified, record the reasons for non-adherence and provide regular feedback to every center. To solve the potential problems and grantee the quality of research, principle investigator at each center will gather and conduct an online meeting every month. All

randomized patients should be followed up until 30 days post randomization.

**Data analysis**

Participants' characteristics and clinical measures will be described by frequencies and percentages, means and standard deviations, or medians and interquartile ranges as appropriate. There will be no planned interim analysis. All analysis will be based on the ITT population, including all randomized participants. Missing data was considered using multiple imputation. All analyses will be completed using SAS, version 9.4 (SAS Institute).

Primary analysis

- The first primary analysis will aim to compare the rate of antibiotic prescription within 30 days between PCT group and guideline group. A two-sided 95%-confidence interval will be computed for the difference in antibiotic prescription rate for both arms.
- The second primary analysis will compare the difference in proportions of clinical treatment success at day 30 between both groups, relative to a 10% non-inferiority margin, and construct a two-sided 90% confidence interval for the difference in proportions. Non-inferiority will be declared if the lower limit of the confidence interval exceeds -10%.

Secondary analysis

Secondary outcomes will be analyzed in a similar manner to the primary outcomes, with linear, logistic, and Poisson regression models fitted as appropriate. All tests will be two-sided, with *p* value less than 0.05 deemed statistically significant.

**Patient and public involvement**

No patients or public involved in the present study. The results of this study will be published by the investigators in relevant scientific peer-reviewed journals, no matter the study findings.

## Ethics and dissemination

This trial has been approved by the ethic committee of China-Japan Friendship Hospital (file number: 2020-87-K51). The findings of the study will be published by the investigators in relevant scientific peer-reviewed journals. Once published, the data in our study will be available to other researchers upon reasonable request and with the permission of researcher committee.

## Discussion

AECOPD are important events in the management of COPD because they negatively impact health status, rates of hospitalization and readmission, and disease progression. Over 85% of patients presenting with AECOPD have been prescribed antibiotics in the USA[6] and Europe[7]. However, not all acute exacerbations are driven by bacteria infection, viral infections and environmental factors are currently main predisposing factors. Current antibiotic prescribing is generally based on the criteria outlined by Anthonisen and colleagues in 1987[10] that includes increased dyspnea, increased sputum volume and increased sputum purulence. The GOLD guideline recommends the use of antibiotics in patients who have all three criteria or, in patients who have two criteria when sputum purulence is one of them, or in patients who require mechanical ventilation. However, whether antibiotic therapy according to Anthonisen criteria will benefit patients is unclear. Some randomized trials have found that only patients with increased sputum purulence benefit from antibiotic therapy with amoxicillin–clavulanate, regardless of the presence or absence of the other two criteria[26,27]. In another randomized trial, doxycycline was not superior to placebo in any Anthonisen criteria–defined subgroup, including among patients with purulent sputum.[28] Thus, Anthonisen criteria have insufficient diagnostic accuracy to predict which patients can safely be managed without antibiotics.

The dilemma is to identify patients who are most likely to benefit from antibiotics while avoiding unnecessary antibiotic use. Procalcitonin, a biomarker of bacterial infection

with higher sensitivity and specificity than conventional laboratory tests[29-31], would have the potential to distinguish patients in whom antibiotics would be beneficial and guide their duration of use. Due to the small study populations and multiple subgroups analysis of lower respiratory tract infection in previous studies[14-17], it is unclear whether PCT-guided antibiotic therapy is safe and effective for patients with AECOPD. PCT-based protocols may be clinically effective; however, confirmatory trials with rigorous methodology are still required[32].

In our trial, we aim to evaluate whether PCT-guided antibiotic therapy will reduce the antibiotic prescription rate for patients with AECOPD, in comparison to the GOLD guideline recommendations, without negatively impacting the treatment success rate. If the results of the study are positive (i.e. a significant reduction in antibiotic prescribing with no evidence of significant impairment in the treatment success rate), PCT-guided antibiotic therapy is likely to change the guidelines for antibiotic recommendations for patients with AECOPD.

**Contributors** BC, JW and LH conceived and designed the study. YW and WS provided suggestions for the study design. XG performed the sample size calculation. LH and JW drafted and edited the manuscript. All authors have contributed to the revision of the draft and have read and approved the final version.

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**Disclaimer** The funder had no role in the design of the protocol, the conduction of the trial, or the analyses or reporting of the data.

**Competing interests** None declared.

**Patient consent for publication** Not required

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Table 1. Eligibility criteria

| Inclusion criteria | Exclusion criteria |
|---|---|
| - Hospitalized patients with AECOPD* | - Fever, Axillary temperature≥38°C |
| - ≥40 years of age | - Pneumonia identified by X-Ray or CT of the chest |
| - Able to understand and communicate to ensure the completion of the trial | - Severe respiratory failure requiring admittance to ICU |
| - Voluntary participation and provide written informed consent | - Concurrent infection at another site (e.g. urinary tract infection) |
| | - Immunosuppression secondary to chemotherapy, AIDS or malignant tumor of blood system |
| | - Comorbidities requiring corticosteroids (at least prednisone 30mg/d or equivalent more than 30 days ) |
| | - Invasive mechanical ventilation |
| | - Patients with malignant tumors receiving chemotherapy or radiotherapy |
| | - Pregnancy |
| | - Participation in another clinical trial |
| | - Previously enrollment into the study |
| | - Refuse to attend |

AECOPD: acute exacerbation of chronic obstructive pulmonary disease; CT: computer tomography; ICU: intensive care unit.

* The diagnostic criteria for AECOPD is based on the recommendation in GOLD guideline.[5]

Table 2. Antibiotic prescription strategy in both arms

| GOLD guideline-guided antibiotic recommendations | |
|---|---|
| Patients with exacerbations of COPD who have three cardinal symptoms: increase in dyspnea, sputum volume, and sputum purulence; have two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms; or require mechanical ventilation (invasive or noninvasive). | |
| PCT-guided antibiotic regimen | |
| PCT<0.1ng/ml | Strongly discouraged |
| PCT (0.1-0.25ng/ml) and no sputum purulence | discouraged |
| PCT (0.1-0.25ng/ml) and sputum purulence | Recommended |
| PCT>0.25 ng/ml | Strongly recommended |

PCT: procalcitonin; GOLD: The Global Initiative for Chronic Obstructive Pulmonary Disease.

Table 3. Schedule of assessments and data collection

| Assessment | At time of consent | Day 1 (face to face) | Day 3 (face to face) | Day 14 (face to face or telephone) | Day 30 (face to face) |
|---|---|---|---|---|---|
| Assessment of eligibility | × | | | | |
| Written informed consent | × | | | | |
| Basic information | × | | | | |
| Medication history | × | | | | |
| Physical examination | × | | × | | × |
| PCT level | × | | | | |
| CAT score | × | | | | × |
| mMRC score | × | | | | × |
| Antibiotic prescription | × | × | × | × | × |
| Other medicine for AECOPD | × | × | × | × | × |
| Sputum gram staining and culture | × | | | | |
| Lung function | × | | | | × |
| Assessment of therapeutic | | × | × | × | × |
| Adverse effects | × | × | × | × | × |
| Length of hospital stay | | | | | × |
| Mortality | | | | | × |

PCT: procalcitonin; CAT: COPD assessment test; mMRC; modified Medical Research Council.

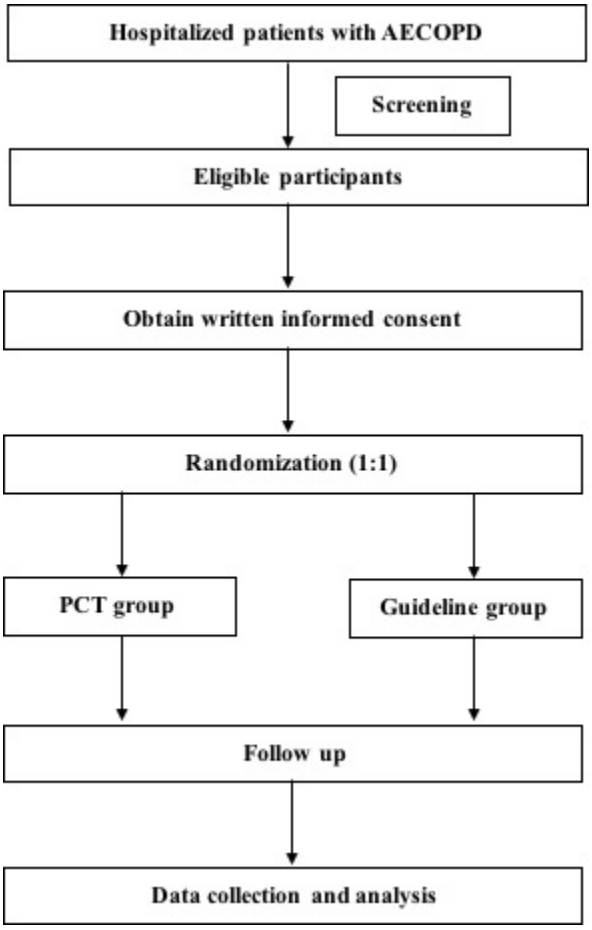


Figure 1 The flow chart of enrolled participants.

103x162mm (72 x 72 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | 2 |
| Protocol version | 3 | Date and version identifier | 20200101-Version1.0 |
| Funding | 4 | Sources and types of financial, material, and other support | 13 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1,13 |
| | 5b | Name and contact information for the trial sponsor | 13 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 13 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 10 |

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

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 9,10 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 6 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 7 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 7 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 7 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 7 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 7 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 10 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 10 |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 10 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 10,11 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 10,11 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 10,11 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 10 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 10 |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 9 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | NA |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 6 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 6 |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 6 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | 6 |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 10 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 13 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 13 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | Supplementary file 3 |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 13 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | 13 |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 13 |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | Supplementary file 3 |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | NA |

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

Supplementary material 2. The details of hospitals participating in this trial

| Hospital | Province, City | Location in China | Teaching hospital | Grade of hospital |
|---|---|---|---|---|
| China-Japan Friendship Hospital | Beijing | North | Yes | Tertiary |
| Beijing Luhe Hospital, capital medical University | Beijing | North | Yes | Tertiary |
| Daxing Hospital Affiliated to Capital Medical University | Beijing | North | Yes | Tertiary |
| Qingdao Municipal Hospital | Shandong | East | Yes | Tertiary |
| Linzi district People's hospital | Shandong | East | Yes | Tertiary |
| First Hospital of Shanxi Medical University | Shanxi | North | Yes | Tertiary |
| Hebei Provincial General Hospital | Hebei | North | Yes | Tertiary |
| First Affiliated Hospital of Guangxi Medical University | Guangxi | South | Yes | Tertiary |
| Xiangtan Central Hospital | Hunan | Central | Yes | Tertiary |
| First Affiliated Hospital of Wenzhou Medical University | Zhejiang | East | Yes | Tertiary |

Definition of Secondary and Tertiary hospital in China: The Secondary hospital is defined as a hospital providing medical, prevention, health care and rehabilitation services to multiple communities (with a radius of population more than 100,000 peoples); the Tertiary hospital is defined as a hospital providing medical service to the whole country beyond cities and provinces, with comprehensive medical, teaching and research ability.

# Informed Consent Form· Notice for Participants

Dear Mr/Ms _____:

You (/ your family) are currently hospitalized with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). You are invited to attend a clinical study of AECOPD. Please read the following information as carefully as possible before you decide whether or not to participate in this study. It will help you understand the value and significance, the procedures and duration, as well as the possible benefits, discomfort and risks of participating in this study. If you want, you can also discuss it with your relatives, friends, or consult your doctor to help you make the decision. If you have any question, please do not hesitate to contact the doctor.

## 1. Background and objective

### 1.1 Background

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death in the world, but is projected to be the third by 2020. Acute exacerbations are the most common reason for hospitalization and death for patients with COPD. Not all patients with AECOPD would benefit from antibiotic therapy. Antibiotics overuse wastes medical resources, drives antimicrobial resistance, may cause side effects, negatively affects the microbiome of patients, and distracts from potentially more effective interventions. The GOLD guidelines have been recommended antibiotics prescription in patients of Anthonisen I and II with sputum purulence, as well as patients with mechanical ventilation, which has potential risk in overuse of antibiotics. Procalcitonin (PCT), a reliable biomarker of bacterial infection, has the potential to guide the prescription of antibiotics. In order to evaluate the efficacy of PCT to guide antibiotic management in patients with AECOPD, we aim to perform this multicenter, blind, randomized, controlled clinical trial.

### 1.2 Objective

This study aim to determine whether PCT-guided antibiotic therapy will reduce the antibiotic prescription rate for AECOPD without negatively impacting the treatment success rate, compared with the GOLD guideline recommendations.

**2. Research method**

This study has been approved by the Medical Ethics Committee of China-Japan Friendship Hospital. This is a multicenter, randomized, controlled clinical trial which will be conducted in 10 tertiary general hospitals including China-Japan Friendship Hospital, and plans to recruit 500 eligible hospitalized patients with AECOPD to participate voluntarily.

Eligible participants will be randomly assigned to either the PCT-guided antibiotic therapy (PCT group) or the GOLD guideline antibiotic recommendations (guideline group) in a ratio of 1:1. The selection of different groups will not affect the routine treatment for you.

This study will record your personal and disease-related information, including medical history (such as vital signs), routine medical and laboratory examination results. In order to objectively evaluate the changes of your condition, you will be inquired in varying time points (screening period, day1, day 3, day 14 and day 30 after randomization) and the changes will be recorded. The follow-up will continue until day 30 after randomization.

The above routine treatment and medical examinations are all necessary for the clinical treatment of patients with AECOPD. This study does not involve any special examinations or treatment, nor add extra burden on patients.

**3. Participants' Responsibility**

During the study period, you (/your family) are required to follow the study protocol and undergoing the follow-up by your investigators about your (/your family) outcome.

4. **Participants' Right**

You (/your family) are voluntary to participate in this study. You should not feel any pressure to participate. You have the rights to refuse to attend this study, or at any time inform the investigator to request withdrawal from the study without any discrimination or retaliation. Your data will not be included in the study and any medical treatment. Your benefits will not be affected.

You can keep track of the information and progress of this research. If you have any questions about the study, or if you feel any discomfort during the research, or if the

study involves your rights, you can always consult the investigators. If you have any complaints, please contact the ethics committee of your hospital.

**5. The possible benefits during the study**

You, people and society will probably benefit from this study, such as the potential avoidance of antibiotics use, and it may be helpful for other patients with similar condition. Treatment and related medical examinations will be performed according to the routine protocol of GOLD guideline regardless of your participation in this study. Investigators will follow up your health condition until day 30 after randomization, regardless you stay in hospital or not, and give you careful guidance.

**6. The possible risks during the study**

The routine therapy for AECOPD is based on the GOLD guideline. A previous study has shown that recommending not antibiotic therapy for patients with PCT level less than 0.1ng/ml do not occur adverse outcome. If any adverse event occurs in this study, the Medical Experts Committee will identify whether it is related to the study. If the damage is related to the study, the cost of treatment and relevant economic compensation will be provided according to the provisions of China's "Good Clinical Practice (GCP).

**7. Participants personal privacy protection**

If you (/your family) decide to participate in the study, your personal data in the study are confidential. In all medical records of this study, your name will be replaced by a Pinyin abbreviation. Your medical records and information will be kept in the hospital, only the investigator, research authority department, and ethics committee will be approved to access them. Any public report about the results of this study will not disclose your personal identity.

You (/your family) can choose not to attend this study, or to withdraw at any time without any discrimination or retaliation, and your medical treatment and benefits will not be affected.

Your (/your family's) participation in this study is voluntary. You (/your family) can keep track of the relevant information. If you have any questions related to this research,

or you have a research-related injury, or have questions about the Participants' rights and interests, you can contact the investigator any time.

In the case of an emergency, please contact the investigator:

Contact phone number:

# Participants' informed consent form

I have read the introduction of this trial and have the opportunity to discuss and ask questions with my doctor about this trial. All my questions were answered satisfactorily. I know the risks and benefits of participating in this trial, and I understand that participating in this trial is voluntary. I inquired about the details of the trial and all the relevant questions were answered. At the same time, my family and I have plenty of time to consider, but also a clear understanding of the following:

1. I can consult my doctor for more information at any time.
2. All my personal information is confidential; my privacy and right to know will be kept confidential.
3. I can withdraw from this trial at any time without discrimination or retaliation, and medical treatment will not be affected.
4. I agree that investigators, research authorities and ethics committees should consult my medical records after approval.
5. I will get a signed and dated copy of the informed consent.

I decided to agree to participate in this trial and try to comply with the doctor's advice.

Participant or legal representative signature: Signature date:

Contact phone number:

The relationship between the signer and the subject:

I confirm that I have accurately explained to the subject the details of the trial, including its rights, possible benefits and risks, and answered all questions.

The participant volunteered to participate in the trial and had given a signed copy of the informed consent.

Investigator signature: Signature date:

Contact phone number: