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PROTOCOL TITLE

Antibiotic stewardship through CRP-guided antibiotic treatment for patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD)

Protocol Number

AECOPD-WAI-21200182

Version 1.1

Date

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Contents

1. List of Abbreviations

AE	Adverse event
A&E	Accident and Emergency
AECOPD	Acute Exacerbation of Chronic Obstructive Pulmonary Disease
AIDS	Acquired immunodeficiency syndrome
BA	blood agar
CCQ	Clinical COPD Questionnaire (Appendix 1)
CI	Confidence Interval
COPD	Chronic obstructive pulmonary disease
CONSORT	Consolidated Standards of Reporting Trials
CRP	C-reactive protein
CRQ-SAS	Chronic Respiratory Disease Questionnaire, self-administered, standardized (Appendix 2)
ED	Emergency Department
EQ-5D	EuroQoL 5-dimension
EQ-5D-5L	EuroQoL 5-dimension 5-level (Appendix 3)
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HA	Hospital Authority
HOKLAS	Hong Kong Laboratory Accreditation Scheme
ICU	Intensive Care Unit
IQR	Interquartile range
ISO	International Organization for Standardization
ITT	Intention-to-treat
MALDI-ToF-MS	Matrix Assisted Laser Desorption Ionising Time of Flight Mass Spectrometry
NEWS2	National Early Warning Score 2
PCT	Procalcitonin
OR	Odds ratio
QALY	Quality-adjusted life year
QMH	Queen Mary Hospital
RCT	Randomized Controlled Trial
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
UTI	Urinary Tract Infection

2. Study Summary

Title	Antibiotic stewardship through CRP-guided antibiotic treatment for patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD)
Short Title	Antibiotic stewardship in AECOPD
Protocol Number	AECOPD-WAI-21200182
Methodology	Patient-level, multi-centre, single-blind, open-label, randomized, combined superiority (antibiotic duration) and non-inferiority (COPD health status) trial.
Study Duration	36 months
Study Centre	Multiple centres
Objectives	To determine whether the addition of serial CRP levels (with advice on interpretation) to usual care for managing AECOPD leads to a reduction in antibiotic exposure (defined as the total number of antibiotic days by Day 28) for AECOPD without negatively impacting on COPD health status, compared with usual care alone.
Number of Subjects	N=1,184
Diagnosis and Main Inclusion Criteria	1. Being diagnosed with active AECOPD; AND 2. Known COPD in their medical records; AND 3. Age 40 years or older; AND 4. Able to provide informed consent in Cantonese, Mandarin, or English; AND 5. Able to complete the questionnaires during the study period
Participation Duration	One year
Interventions	The intervention group will be recommended to test for CRP at randomization and every day during the stay. Antibiotics are considered for discontinuation when CRP reduces below 5mg/dL, on top of existing clinical judgment. The control group will not be tested for CRP and antibiotics will be discontinued according to clinical judgment.
Main outcome measures and study instruments	The antibiotic exposure (total number of antibiotic days) and recovery in terms of COPD health status (Clinical COPD Questionnaire total scores) within 28 days from randomization. The secondary outcomes include prevalence of potentially pathogenic bacteria and commensal organisms and their proportion of drug-resistant strain, antibiotics prescribed and total antibiotics consumption (doses), adverse effects potentially attributable to antibiotics prescribed for the exacerbation, general health status, disease-specific, health-related quality of life over time measured using the CRQ-SAS (dyspnoea, fatigue, emotion function, mastery and total scores) and costs (total HA cost) and cost-effectiveness.
Statistical Methodology	- Baseline subject characteristics: descriptive statistics. - COPD-related health status, general health status, and duration of antibiotics: Fisher exact tests. - Adverse effects and number of events: Chi squared tests. - Between-group difference, CCQ score, and EQ-5D: Students' t-test. - Group comparison for categorical variables: Fisher 's Exact test - All analyses will be performed using Stata software - For missing data handling: multiple imputation methods. - Cost evaluations: the healthcare provider using standard methods. - Cost-effectiveness analysis during the RCT: ITT principle. - Health economic outcomes: QALY.

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4. Introduction

Multiple small successes against antimicrobial resistance are urgently needed. The Global Action Plan in 2015 reiterated the importance of tackling antimicrobial abuse and bacterial resistance, which is jeopardizing our ability to manage infectious diseases.[1] Antimicrobial resistance is predicted to cause catastrophic economic impacts in the next 10 years by putting 24 million people into extreme poverty, and will lead to an estimated 10 million deaths annually by 2050.[2] Evidence has shown that an extended course of antibiotics is by no means superior to a shorter one.[3] The over-prescription of broad-spectrum antibiotics in both hospitals and primary care has become a global concern and has driven initiatives to safeguard patient safety through the responsible use of antibiotics as treatments and prophylaxis. In our recent analysis, 55% of pathogenic bacteria identified in sputum culture from AECOPD patients in Hong Kong has demonstrated resistance to at least one antibiotic. (A Wai, personal communication) Even relatively small changes in prescribing are likely to have beneficial effects on resistance at a population level.[4]

There is a need for improved decision-making for antibiotic prescription in AECOPD. International Guideline (GOLD strategy)[5] recommends empirical broad-spectrum antibiotics covering common respiratory pathogens for acute management,[5] based on self-reported subjective AECOPD features, and the risk of bacterial infection. Evidence for the optimal duration of antibiotic treatment is unclear.[6] Antibiotics are reportedly used in 87% of AECOPD patients in US, [7] 74% in UK,[8] and 96% in Hong Kong (A Wai, Personal communication). AECOPD contributes 21,000 episodes of local hospital admission and readmission in 2019 (A Wai, personal communication). AECOPD is triggered by infectious and non-infectious precipitants, although 30% are undetermined.[9] Bacterial infection accounts for only 35%-57% among the infected. Inappropriate antibiotic usage may increase the risks of adverse events such as *Clostridioides difficile* colitis.[10] Moreover, this confers a predisposition to airway colonization by multidrug-resistant bacteria, increasing COPD patients' risk of carrying resistant organisms in their lungs and then exacerbation or progression of pneumonia.[10] We have found that 55% of pathogenic bacteria identified from sputum culture among AECOPD patients were resistant to 1 or more antibiotics. (A Wai, personal communication)

C-Reactive Protein (CRP) may help physicians make more appropriate antibiotic decisions. C-Reactive Protein (CRP) is an acute-phase reactant secreted by the liver in response to bacterial infections. It is synthesized within 4 to 6 hours after tissue injury/inflammation, and levels double every 8 hours, peaking at about 36 hours.[11] CRP is significantly elevated in patients with bacterial infection, representing better treatment effect with antibiotics at elevated CRP values.[12] CRP has been shown to be highly selective for AECOPD and it has excellent diagnostic accuracy when interpreted together with AECOPD symptomatology.[13] Elevated CRPs (>5 mg/dL) in hospitalised AECOPD patients are

associated with chest infections, implying a treatment role for antibiotics in this group. Yet antibiotics did not offer higher benefit over placebo among those with normal CRP level.[14]

Work done by others

CRP-guided antibiotic prescription is effective and safe. In hospitalised AECOPD patients with CRP-guided prescriptions (antibiotic treatment if CRP ⩾50 mg/L, i.e. 5mg/dL) versus a control group with standard GOLD treatment fewer patients in the CRP group were prescribed with antibiotics compared to the GOLD group (31.7% versus 46.2%, p=0.028; adjusted odds ratio (OR) 0.178, 95% CI 0.077–0.411, p=0.029), without a significant difference in the treatment effects between both groups. Yet, the discontinuation of antibiotics in both groups was guided by clinical judgment. The 30-day treatment failure rate was nearly equal in CRP and control groups (44.5% vs. 45.5%, p=0.881), the time to next exacerbation was comparable (32 days vs. 28 days, p=0.713), and the length of hospital stay was also similar (7 days vs. 6 days, p=0.206). On day 30, there was no difference in the symptoms score and quality of life, and no serious adverse events were detected.

CRP-guided antibiotic discontinuation is also safe. Whether antibiotic therapy with CRP-guided duration or fixed 7-day duration were clinically non-inferior to fixed 14-day duration in patients with uncomplicated gram-negative bacteraemia was determined in a multicentre trial involved 504 adults.[15] The main outcome was the rate of clinical failure at 30 days, which was 2.4% in CRP-guided patients who experienced recurrent bacteraemia, local suppurative complications, distant complications, re-initiation of antibiotic therapy due to clinical deterioration, or any-cause mortality, compared with a failure rate of 6.6% in the 7-day group and 5.5% in the 14-day group. The CRP-guided treatment met the 10% margin for inferiority.

Work done by us

The team is experienced to conduct trials on antibiotic stewardship with AECOPD. Butler *et al.* studied whether point-of-care CRP laboratory testing could be used to safely guide (and perhaps reduce) antibiotic prescribing for AECOPD in primary care practices in the UK.[16] In this multi-centre, open-label, randomised controlled trial, 653 AECOPD patients were randomised to either the CRP-guided treatment group or the usual (GOLD strategy) care group.[5] The results showed that patients in the CRP group reported less antibiotic use within 28 days of randomisation (57.0% vs. 77.4%, adjusted OR 0.31, 95% CI 0.20 to 0.47) and mildly lower (better) clinical COPD questionnaire scores at 2 weeks (adjusted mean difference −0.19 points, 90% CI −0.33 to −0.05). Antibiotics were prescribed less frequently at the initial consultation in the CRP-guided group compared with the usual care group (47.7% vs. 69.7%, adjusted OR 0.31, 95% CI 0.21 to 0.45). There was no evidence of harm to patients, including no differences in diagnosis of pneumonia at the 4-week follow-up and no differences in adverse events related to antibiotics. Both Prins *et al.* and this study provide evidence of the

benefits of CRP-guided antibiotic prescription in regard to less antibiotic use, and non-inferiority on the clinical outcomes in AECOPD patients including 30-day treatment failure, length of stay, symptoms score, diagnosis of pneumonia, quality of life, and adverse events.

In the previous study antibiotics were found to be prescribed in 33% of patients who had low CRP levels, even though guidance indicated that antibiotics likely would not be of benefit.[16] Patient factors such as expectations for antibiotics, access to antibiotics before consultation with the clinician, and lack of clear guidelines can influence clinicians' antibiotics prescribing behaviour for acute respiratory symptoms. Previous reports also suggested that risk aversion and long turnaround time for CRP resulted in driving them to prescribe antibiotics.[17]

Local situation has been well studied. Hui (co-applicant) and Ko (our collaborator) found that an infectious aetiology could be established in only 48.7% of the AECOPD patients.[18] 40.8% of sputum culture was positive. The commonest bacteria identified were Streptococcus pneumoniae, Pseudomonas aeruginosa, and Haemophilus influenzae.

A&E is an ideal location to start antibiotic stewardship for AECOPD. Prior work has also been conducted by our team in Hong Kong to ensure the significance of the problem, the feasibility of data collection, and the preliminary results relevant to AECOPD patients with available CRP levels. 21,129 patients were admitted to emergency medicine wards and medical wards through A&E in 2019 (mean age 79 years (IQR 71-86)). Elevated CRP was associated with doubled odds ratio of ICU admission or death (Odds ratio 2.06, 95%CI 1.75 – 2.43). Analysis reveals that 96% of patients with a normal CRP were given antibiotics. Among those with normal CRP, unadjusted statistics suggested those without antibiotics did not have lower odds ratios for deterioration requiring ICU admission and for death ($p<0.01$) (**Appendix 4, Table 1**). Overall, AECOPD patients were prescribed antibiotics for a mean of 9.4 days (SD 10.3) but the mean duration of an elevated CRP was 6.4 days (SD 6.8). There is an opportunity to shorten antimicrobial regimen for some AECOPD patients. Further details of the results can be found in **Appendix 4, Figure 1 and Figure 2**. As personalised antibiotic treatments may reduce healthcare resource utilisation, we sought to determine the optimal antibiotics therapy duration for AECOPD patients based on clinical decision-making and CRP results.

Research Gaps

1. **Antibiotic stewardship involves both appropriate prescription and timely discontinuation of an antibiotic treatment. Limited evidence informs antibiotic prescription practice for AECOPD in A&E. Information on CRP-guided antibiotic discontinuation is absent.**
2. **Previous studies with hospitalized AECOPD patients with severe symptoms and severe outcomes was insufficient in power.**

3. **Cost-effectiveness analyses on CRP-guided antibiotic treatment in AECOPD patients are lacking.**

5. Aims and Objectives of the study

5.1 Clinical Question

In adult AECOPD patients in Emergency Departments, does CRP-guided antibiotic treatment, compared with usual care, lead to shorter antibiotic duration without negatively impact on clinical COPD-health status?

5.2 Aims and Hypotheses to be Tested:

This study seeks to establish whether serial CRP level guided clinical judgment can safely and cost-effectively be used to better target antibiotic treatment (include both treatment and discontinuation) for AECOPD in emergency departments to those that are most likely to benefit, so that overall antibiotic exposure duration is decreased without compromising COPD-related health status.

The **primary objective** is to determine whether the addition of a serial CRP levels to usual care for AECOPD leads to shorter antibiotic duration,

The **co-primary objective** is to determine whether the addition of a serial CRP levels to usual care for AECOPD is non-inferior to usual care alone, on COPD health status as measured by CCQ

The **secondary objectives** are the effectiveness of the addition of serial CRP levels to usual care in AECOPD patients on:

- General health status as measured by EQ-5D-5L
- Adverse effects of antibiotics
- Cost-effectiveness of individualised CRP-guided antibiotic treatments.

Primary and secondary objectives and outcome measures are listed in **Appendix 5**.

We **hypothesise** that:

(i) **antibiotic duration** (defined as 'the number of days of antibiotic treatment') in 28 days among AECOPD patients will be significantly lower for **CRP-guided antibiotic treatment (including prescription and discontinuation)** than usual care

(ii) **COPD health status** as measured by the Clinical COPD Questionnaire (CCQ) has no statistically significant difference between two groups;

(iii) general health status of AECOPD patients as measured by EQ-5D-5L will not be significantly different between the two groups

(iv) adverse effects of antibiotic treatment in AECOPD patients will not be significantly different between the two groups

(v) CRP-guided antibiotic treatment will be more cost-effective than usual care

6. Study design

6.1 Design

Patient-level, multi-centre, single-blind, open-label, randomized, combined superiority (antibiotic duration) and non-inferiority (COPD health status) trial.

6.2 Study sites

Eligible patients will be recruited via the A&E and relevant departments (e. g. medical wards) of 8 hospitals in 5 hospital clusters in Hong Kong.

6.3 Subjects recruitment

Eligible patients will be recruited via the A&E of 8 hospitals in 5 hospital clusters in Hong Kong. Patients will be screened on arrival in A&E for inclusion and exclusion criteria. Delegated trained personnel will explain the study to the potential subjects and obtain their written consent before joining the study.

6.4 Selection of Subjects

6.4.1 The inclusion criterion:

The inclusion criteria are ALL of the below:

1. Being diagnosed with active AECOPD (AECOPD is defined as an event in the natural course of a disease characterized by a change in baseline dyspnoea, cough, and/or sputum that is beyond the normal day-to-day variations with acute onset, which may warrant a change in regular medication in patients with underlying COPD).[5]
2. Known COPD in their medical records.
3. Age 40 years or older.
4. Able to provide informed consent in Cantonese, Mandarin, or English
5. Able to complete the questionnaires during the study period (i.e. 6 months after randomisation)

6.4.2 The exclusion criteria:

Patients will be excluded if any ONE of the following are present:

1. Pre-treatment with systemic corticosteroids for the present exacerbation.

2. Pre-treatment with any antibiotics for the present exacerbation, any concurrent infection or prophylaxis.
3. Known clinical stroke in past 6 months
4. Patients with high suspicion of active AECOPD mimics:
    1) Pneumonia
    2) Congestive heart failure
    3) Bronchiectasis
    4) Pulmonary embolism
    5) Pneumothorax
    6) Atrial fibrillation / flutter
5. Lung comorbidities:
    1) Cystic fibrosis
    2) Tuberculosis
    3) Unresolved lung malignancy
6. Progression or new radiographic abnormalities on the chest X-ray.
7. Immunodeficiency disorders such as AIDS, humoral immune defect, ciliary dysfunction etc., and the use of immunosuppressive drugs for more than 28 days.
8. Active inflammatory condition (e.g. flare up of rheumatoid arthritis, gout or polymyalgia rheumatica) or concurrent infection at another site (e.g. UTI, cellulitis) that is likely to produce a systemic response
9. Currently pregnant
10. NEWS2 score[19] of ≥3

6.5 Intervention

This is a two-arm, open, single-blind, single-centred, individually randomised controlled trial involving emergency physicians in ED. This trial will evaluate the addition of serial CRP levels to usual care to guide antibiotics management decisions for patients presenting in ED with AECOPD, which is the first in the world. Patients presenting with AECOPD will be randomised to clinical management based on usual care alone or usual care with the addition of a serial CRP levels.

Control arm

Patients in the control arm will be treated with usual care (GOLD initiative). No CRP would be measured.

Intervention arm

Training in CRP interpretation will help to guide decisions about the use of antibiotic treatment for AECOPD. All serum CRP tests will be conducted by the local pathology laboratory in each

participating hospital. These laboratories have been accredited by Hong Kong Laboratory Accreditation Scheme (HOKLAS) based on ISO standards.

The attending doctor will use the CRP level to inform their decision to continue antibiotics around 3 hours from blood taking. These doctors will be provided pre-study training on CRP interpretation.

Every day from randomization, serum CRP testing will be encouraged to take. Once CRP has declined to <5mg/dL and the patient has remained afebrile for past 48 hours, antibiotic treatment will be reviewed for discontinuation. Otherwise, antibiotic treatment will be continued. A switch on the administration route, or a change of antibiotics due to adverse effect, allergy, or suggestion from culture result, is permitted according to in-patient physician's decisions. CRP will continue to be monitored daily upon discharge from that hospital (up to 28 days).

6.6 Procedures

Patients This trial will be taken place in the emergency departments and wards from 5 hospitals in 5 hospital clusters in Hong Kong.

6.6.1 Subject Eligibility assessment

An attending emergency physician who assesses and cares the patient with active AECOPD shall assess the eligibility for recruitment. That patient will be eligible for the trial if inclusion criteria are fulfilled, without any exclusion criteria. After consent, that patient will be given a participant identity code as the identifier in the trial.

6.6.2 Randomization

Patients will be randomized at ED (Day 1). They are randomised in a 1:1 ratio to receive either usual care alone (control), or usual care with addition of CRP trend monitoring for discontinuation of antibiotics. The randomization sequence will be centralised. Computer-generated and randomly permuted blocks allocations will be used. Exacerbation classification suggested by GOLD Initiative is adopted as a minimisation variable so that balance is achieved with respect to differing levels of COPD exacerbation severity.

6.6.3 Allocation concealment and blinding

Once the subjects sign the consent form, the research nurse will open an opaque, sealed envelope to assign the patients in a 1:1 ratio into the two different groups: (1) intervention arm: usual care (GOLD strategy) with addition of serial CRP levels or (2) control arm: usual care (GOLD strategy) only. The outcome assessors (who will be the research nurses) and data analysts will be blinded throughout the study. The A&E / ward physicians cannot be blinded as they will follow our protocol for ordering serum CRP testing and for antibiotic

treatments for patients in the intervention group. All staff involved in the recruitment, consent, data collection and clinical evaluation will be trained with a standard Good Clinical Practice (GCP)-compatible programme, which covers the aims and rationale of this trial, the management of AECOPD recommended in GOLD initiative, and the interpretation of CRP results. A diagram detailing the data collection time points for intervention group and control group is shown in Appendix 5. A participant flow diagram is available at Appendix 6. The CONSORT diagram is listed as Appendix 7.

6.6.4 Communication with Receiving Ward Staffs

Participants in the study may transfer to another departments after treatment/ care in A&E. The following communication would be conducted:

- A handover note that informs the receiving ward staffs about patients' enrolment to the trial, group assignment, and previous treatments given in A&E. The note would also suggest the investigations for the receiving ward staffs.
- Telephone handover about intervention group and investigations of the study, and treatments given in A&E to ward.

6.6.5 Data collection

Trained physicians and nurses may help patient recruitment and data collection in busy emergency departments.

6.6.6 Procedure

The attending emergency physician who sees the patient will report the duration of AECOPD symptoms, medication history, and physical findings (temperature, pulse, oxygen saturation, respiratory rate, abnormal lung sounds and peak expiratory flow rate before and after bronchodilators). The patient was treated according to GOLD initiative, including bronchodilator, and systemic steroid. A sputum sample, a throat swab sample (for bacterial culture) and a nasopharyngeal swab (for respiratory virus – pneumonia panel) are collected. The attending physician will assess and record the sputum colour using the Bronkotest chart (Appendix 8). That patient will be interviewed for CCQ an EQ-5D-5L questionnaire.

Patients randomised to the intervention group will be recommended to have CRP tested and the result will be recorded in the proforma. Medication (including antibiotics) prescription and other management plan will be recorded.

Trial team members will collect healthcare service utilization data, spirometry result, laboratory results and antibiotics prescribed for 12 months before randomization.

6.6.7 Microbiological assessment

Sputum, throat swab and nasopharyngeal swab samples, which are obtained in the initial encounter and in week-4 follow up, are sent to local hospital laboratories. Sputum sample is not necessarily available, depending on the symptomatology.

All samples will be prepared and tested according to hospital standard operation procedure. Bacteria found in the sputum sample will be identified using the Matrix Assisted Laser Desorption Ionising Time of Flight Mass Spectrometry (MALDI-ToF-MS) and semi-quantitative counts recorded. The throat swab for bacterial culture & sensitivity should be collected using sterile swabs and placed into Amies transport medium (+/- charcoal). A sheep blood agar plate (BA) is inoculated and incubated at 35 – 37℃ for 20 - 24h in 5 – 10% CO_2. Nasopharyngeal swab sample is collected with flexible wire shaft swab and transported in viral transport media. The sample will be tested for RT-PCR for respiratory viruses.

6.6.8 Follow Up

The trial team will aim to contact all participants through telephone call, or audio / video call with instant messaging software and application service such as WhatsApp, WeChat, or Instant Messenger, every week after randomization to follow up CCQ and EQ-5D questionnaires. The patient will be met on video call at 4-weeks post randomization. A copy of Chronic Respiratory Disease Questionnaire, self-administered, standardized (CRQ-SAS) and EQ-5D will be sent to patients for completion and return at 6 months.

Week 1 & Week 3

Follow-up call for *week 1 and 3* (±1 working day): The patient will be interviewed for the symptomatology, CCQ and EQ-5D questionnaires.

Week 4

Clinical follow up at *week 4* (±2 working days) by research clinician for medication consumption, adverse effects, sick leave, diagnosis of pneumonia since the initial encounter, any further CRP tests since the initial encounter, health care consultations, CCQ and EQ-5D. The patient will be required to return to the emergency department to undergo fresh sputum collection, throat swab and nasopharyngeal swab anytime during the day of weekdays before end of week 5. The colour of the sputum specimen will be examined. If the patient defaults the follow up at week 4, the team will contact the patient again and collect as many data items as possible. If the patient is unable to present, follow up call will be performed.

Month 6

At *6-months* post randomisation, the trial team member will examine the patient's medical record for any spirometry results, prescription, and healthcare service utilization. The patient will also be sent a copy of CRQ-SAS and EQ-5D then for self-completion. A text reminder message will be sent through with instant messaging software and application service application. Defaulted patients will be called for interview to collect their responses.

7. Assessment of Efficacy

Mean antibiotic duration (in days) within 28-days for AECOPD after randomization.

8. Assessment of Safety

Adverse Event

Events fulfilling the definition of a serious adverse event (SAE), including death, emergency hospitalization for conditions other than AECOPD, life-threatening medical conditions, (required preventive intervention for) disability or permanent damage, or other serious medical events that occur between randomization and 4-week post randomization will be reported to the trial team as soon as it is detected.

9. Statistics and Data Analysis

Trained physicians and nurses will help with patient recruitment and data collection in the busy emergency departments.

Baseline subject characteristics will be reported using descriptive statistics such as percentage, medians, and interquartile ranges. COPD-related health status, general health status, and duration of antibiotics use will be compared among groups by Fisher exact tests. Adverse effects and number of events in the intervention group compared to control group will be noted and compared by Chi squared tests.

To estimate the between-group difference on primary outcome of antibiotic duration, two sample T test will be used to the analysis. The other continuous variables including the co-primary outcome (CCQ score) and secondary outcome (EQ-5D) will be analyzed in the same manner.

Fisher 's Exact test will be used to make group comparison for categorical variables such as COPD Severity (GOLD grading), COPD exacerbation severity (Anthonisen criteria) and microbiological pathogen. All available data will be summarized descriptively by tables and figures. All analyses will be performed using Stata software (version 16 or updated version) and considered significant at $p<0.05$.

For missing data handling, multiple imputation methods will be used to assess the sensitivity of primary outcome results to missing data. Assuming at random, generalised linear models will used for the multiple imputations.

Cost evaluations of the intervention group versus control group among AECOPD patients attending EDs will be conducted according to the healthcare provider using standard methods. For the cost-effectiveness analysis during the RCT, empirical data from RCT will be used to estimate the effects and proportions of antibiotic use in each group following the ITT principle within the trial period. An ingredient approach will be used to estimate the cost of the individualised CRP-guided groups including antibiotics, CRP testing, and culture testing. The healthcare resource use with respect to length of hospital stay in the general ward, intensive care unit, and high dependency unit, and investigations, procedures, vasopressors, and drugs will be measured for all patients in the two groups. The EQ-5D-5L utility scores at baseline and at the follow-up assessments will be used to estimate quality-adjusted life years (QALY) using the area under the receiver operating characteristic curve approach. Health economic outcomes will be assessed as incremental cost-effectiveness ratios in the form of incremental cost per incremental QALY gained from the intervention relative to the control group over the trial period. Both deterministic and probabilistic sensitivity analyses will be conducted to test the robustness and uncertainty in the costs and health economic outcomes.

10. Outcomes and measures

Based on our Co-I's prior experience [20], co-primary outcomes will be proposed in this study because including both antimicrobial use and patients' relevant clinical outcomes can ensure adequate power and effect size to simultaneously answer both research questions.

The primary outcome is mean antibiotic duration (in days) within 28-days for AECOPD after randomization, measured at the end of each week, using audio/video call until 28 days post randomization. Medication record is also reviewed at 4-weeks post randomization to capture prescription of antibiotics related or unrelated to AECOPD.

The co-primary outcome is the CCQ score which will be collected via audio/video call at 14 days, as this is the time most AECOPD patients recover and helps inform if that patient is suffering from delayed recovery. The CCQ is a patient-centred health status measure that has been well validated and is widely used in patients with COPD.[21]

Secondary outcome measures include adverse effects potentially attributable to antibiotics prescribed for the exacerbation, general health status measured by EuroQol-5D (EQ-5D),

Costs (total HA cost) and cost-effectiveness, Disease-specific, health-related quality of life over time measured using the CRQ-SAS (dyspnoea, fatigue, emotion function, mastery and total scores).

11. Direct Access to Source Data/ Documents

The investigators and the research assistants in the research team will be responsible for data collection of the project. The investigators will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s), providing direct access to source data and documents.

12. Ethics

The trial will be conducted in accordance with the principles originating in the Declaration of Helsinki, and those in Good Clinical Practice. After patients (or relatives/legal representatives) are assessed as suitable for the Trial, all subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form is submitted with the protocol for review and approval by the Institutional Review Board (IRB) for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent. The trial will be conducted in accordance with the information and consent forms.

13. Data Handling and Record Keeping

We will collect baseline and follow up data as appropriate. The principal investigator will be responsible for data safekeeping. We will use a bespoke case report form and an audit trail to ensure that the data captured are consistent, reliable and fully compliant with Good Clinical Practice/regulatory requirements. Information about study subjects will be kept confidential, and managed according to the laws of the Hong Kong Special Administrative Region and, in particular, the Personal Data (Privacy) Ordinance, Cap 486. The name, address or any other identifying information will not be passed on to anyone and data will be assigned an anonymous identification code. The hospital inpatient and specialist clinic outpatient paper medical records are retained for six years and general outpatient paper medical records are kept for three years after the last follow up of a patient. Radiological films are stored only for one to four years. These documents should be retained for a longer period if required.

14. Financing and Insurance

The study would apply for the Health and Medical Research Fund (HMRF).

The study would apply for HKU Master Clinical Trial Insurance Policy.

15. Publication Policy

The research findings will be published in international peer reviewed journals and reports. Individual subjects will not be directly identifiable from the results.

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Appendix 1

Clinical COPD Questionnaire

Patient number:_____
Date:_____

Clinical COPD questionnaire

Please circle the number of the response that best describes how you have been feeling during the past week
(Only one response for each question)

On average, during the past week, how often did you feel:	never	hardly ever	a few times	several times	many times	a great many times	almost all the time
1. Short of breath at rest?	0	1	2	3	4	5	6
2. Short of breath doing physical activities?	0	1	2	3	4	5	6
3. Concerned about getting a cold or your breathing getting worse?	0	1	2	3	4	5	6
4. Depressed (down) because of your breathing problems?	0	1	2	3	4	5	6
In general, during the past week, how much of the time:							
5. Did you cough?	0	1	2	3	4	5	6
6. Did you produce phlegm?	0	1	2	3	4	5	6
On average, during the past week, how limited were you in these activities because of your breathing problems:	**not limited at all**	**very slightly limited**	**slightly limited**	**moderately limited**	**very limited**	**extremely limited**	**totally limited/or unable to do**
7. Strenuous physical activities (such as climbing stairs, hurrying, doing sports)?	0	1	2	3	4	5	6
8. Moderate physical activities (such as walking, housework, carrying things)?	0	1	2	3	4	5	6
9. Daily activities at home (such as dressing, washing yourself)?	0	1	2	3	4	5	6
10. Social activities (such as talking, being with children, visiting friends/ relatives)?	0	1	2	3	4	5	6

Appendix 2

CRQ-SAS

Short version of the Chronic Respiratory Disease Questionnaire Self-Administered Standardized (CRQ-SAS 17)	
Factor 1: **DYSPNEA**	Taking care of your basic needs, such as bathing, showering, eating, or dressing (item 2)
	Walking (item 3)
	Performing chores, such as housework, shopping or grocery shopping (item 4)
	Participating in social activities, such as meeting with family, friends (item 5)
Factor 2: **EMOTIONAL FUNCTIONING**	How much of the time have you felt frustrated or impatient? (item 6)
	How much of the time did you feel upset, worried, or depressed? (item 12)
	How much of the time did you feel relaxed and free of tension? (item 14)
	How much of the time have you felt discouraged or down in the dumps? (item 16)
	How happy, satisfied, or pleased have you been with your personal life? (item 18)
	How often have you felt restless, tense, or uptight? (item 20)
Factor 3: **DISEASE CONTROL**	How often did you have a feeling of fear or panic when you had difficulty getting your breath? (item 7)
	How much of the time did you feel very confident and sure that you could deal with your respiratory problem? (item 10)
	How often did you feel upset or scared when you had difficulty getting your breath? (item 19)
Factor 4: **FATIGUE**	How tired have you felt? (item 8)
	How much energy have you had? (item 11)
	How often have you felt low in energy? (item 15)
	How often have you felt worn out or sluggish? (item 17)

CRQ-SAS: Chronic Respiratory Disease Questionnaire Self-Administered Standardized.

Source: Wijkstra P, TenVergert E, Van Altena R, Otten V, et al. Reliability and validity of the Chronic Respiratory Questionnaire (CRQ). Thorax. 1994; 49(5):465-7.

Appendix 3

EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY
I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE
I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)
I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT
I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION
I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

Source: HERDMAN, Michael, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research, 2011, 20.10: 1727-1736.

Appendix 4

Prior work on AECOPD in Hong Kong

Table 1 Outcomes of AECOPD patients

	No Antibiotics		Antibiotics				
	Not ICU / death	ICU / death	Not ICU / death	ICU / death	Total	p-value	OR (95%CI)
Normal CRP	200	2	4898	318	5418	0.001	0.15 (0.02, 0.57)
High CRP	12	0	2422	312	2746	0.382	0 (0, 2.49)

Figure 1 Density graph for duration of CRP elevation for AECOPD patients by different pathogens

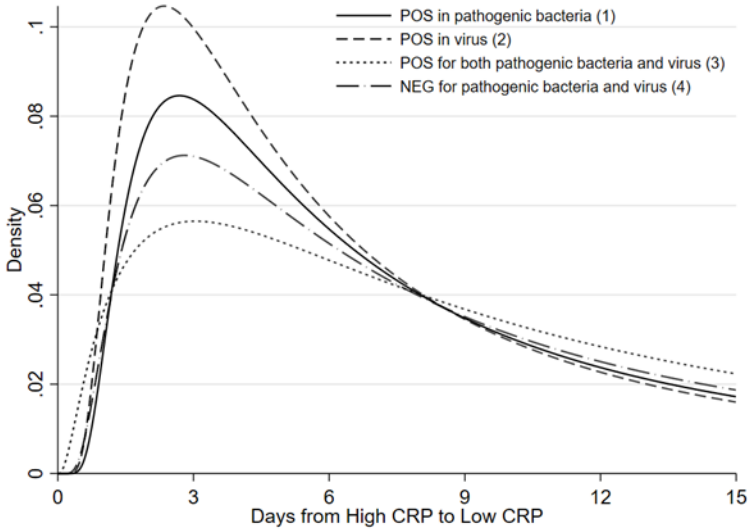
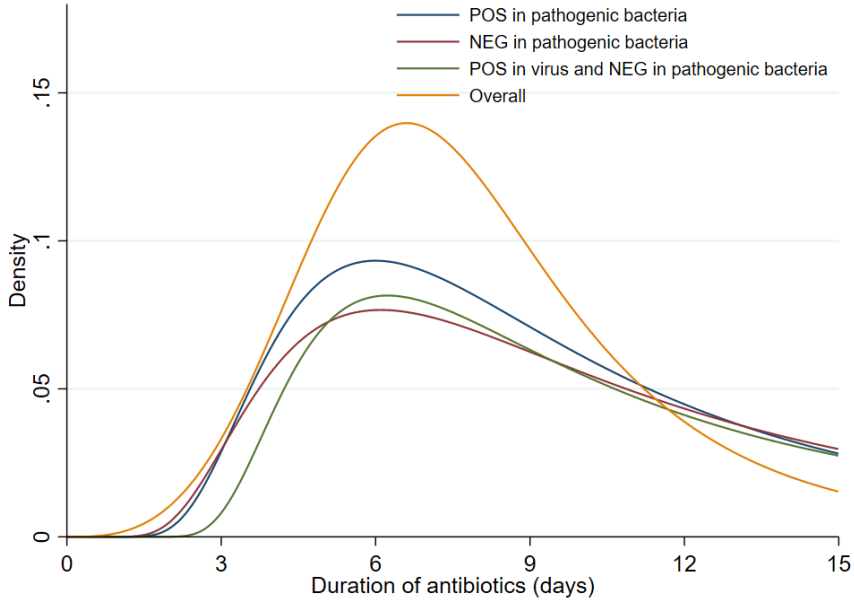


Figure 2 Density graph for duration of antibiotics for AECOPD patients by different pathogens



Appendix 5

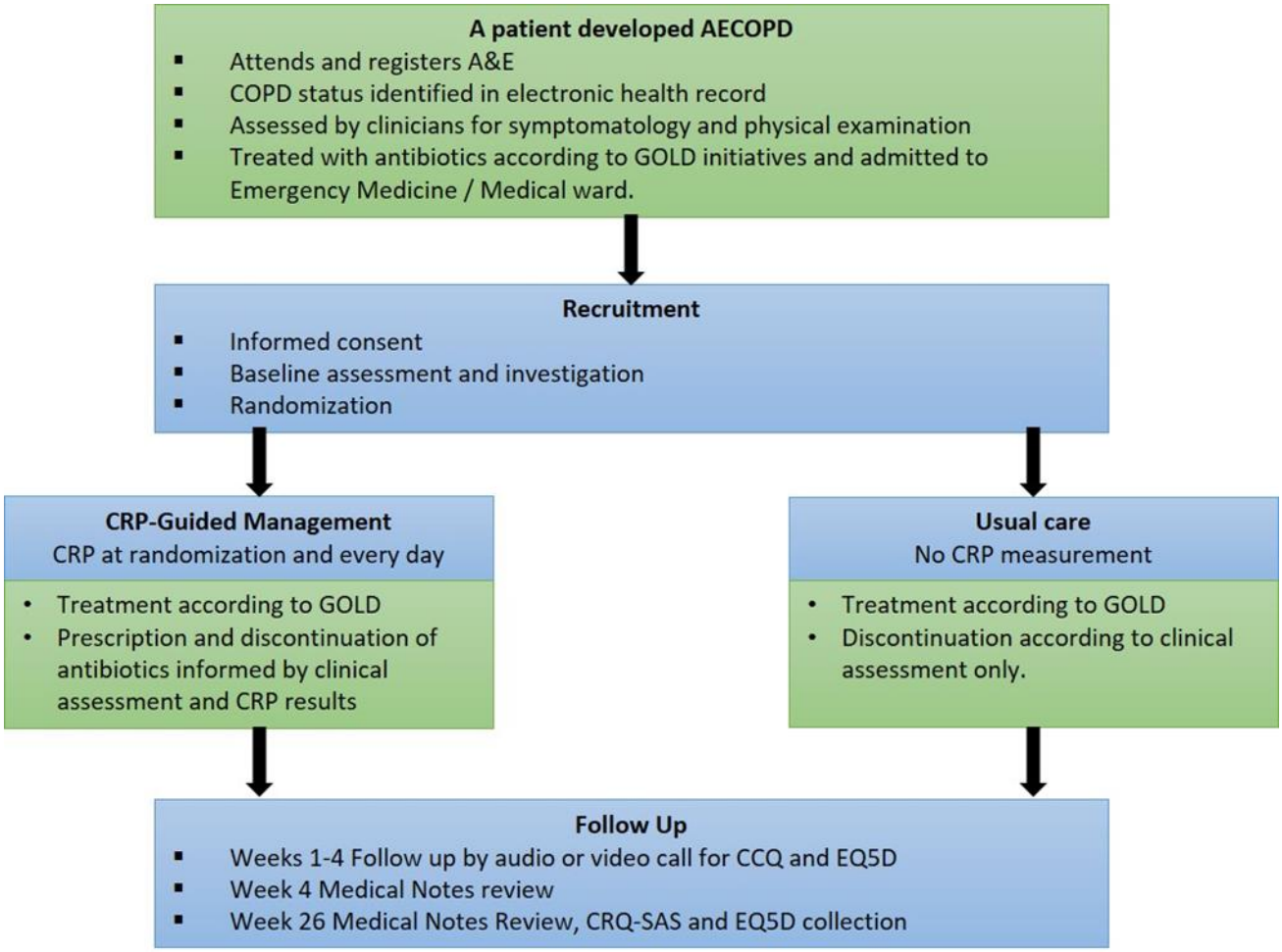
Primary and secondary objectives and outcome measures.

	Objective	Outcome measures	Time point of evaluation (from Randomization)
Primary	To determine whether the addition of a serial CRP levels (with advice on interpretation) to usual care for managing AECOPD leads to a reduction in antibiotic exposure for AECOPD compared to usual care alone.	Antibiotic duration	4 week
Primary	To determine whether the addition of a serial CRP levels (with advice on interpretation) to usual care for managing AECOPD leads to a reduction in antibiotic exposure for AECOPD without negatively impacting on COPD health status compared to usual care alone.	Recovery in terms of COPD health status as assessed using the Clinical COPD Questionnaire (CCQ) total scores	2 week
Secondary	To evaluate the effect of serial CRP levels for AECOPD in emergency department on:	Prevalence of potentially pathogenic bacteria cultured from sputum at 4 weeks and the proportion of bacteria that are resistant	4-week
		Prevalence of commensal organisms cultured from sputum at 4 weeks and the proportion of bacteria that are resistant	4-week
		Adverse effects potentially attributable to antibiotics prescribed for the exacerbation	Weekly for 4 weeks
		All-cause antibiotic consumption	During the first 4 weeks post randomisation
		Antibiotic prescribing	At index consultation & 4-week
		Use of other COPD treatments including orally administered steroids	4-week
		General health status measured by EuroQol-5D (EQ-5D)	Weekly for 4 weeks
		Primary and secondary care consultations, including hospitalisations	4-week & 6-month
		Costs (total HA cost) and cost-effectiveness	6 month
		Incidence of pneumonia (measured by patient and medical record)	4-week & 6-momnth
		Disease-specific, health-related quality of life over time measured using the CRQ-SAS (dyspnoea, fatigue, emotion function, mastery and total scores)	6-month

Key: AECOPD acute exacerbation of chronic obstructive pulmonary disease, CCQ Clinical COPD Questionnaire, CRP C-reactive protein point-of-care test, CRQ-SAS Chronic Respiratory Disease Questionnaire, self-administered, standardised

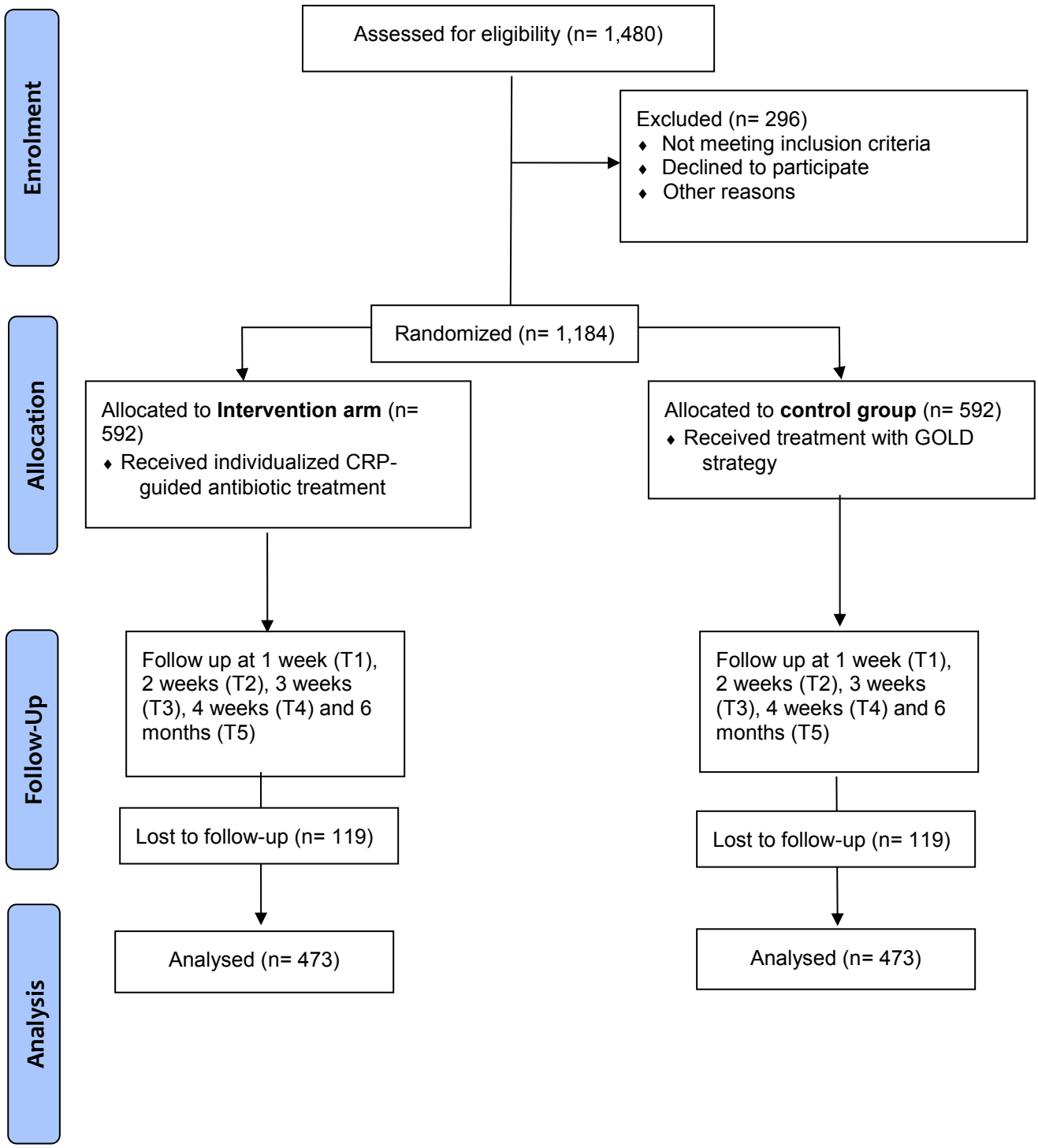
Appendix 6

Participant Flow Diagram



Appendix 7

CONSORT 2010 Flow Diagram

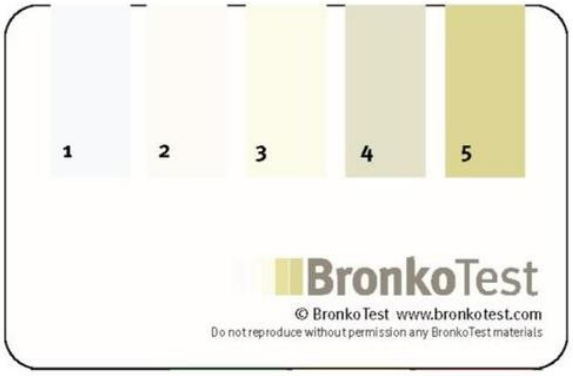


Appendix 8

BRONKOTEST

ERS

Evaluation of sputum colour



- **Sputum purulence correlates with presence of bacteria and favourable effect of antibiotics**

european respiratory society every breath counts

Source: https://www.ersnet.org