

Procalcitonin-Guided Treatment Regarding Antibiotic Use for Acute COPD Exacerbations (PRECISION): Study Protocol for a Prospective Randomized Controlled Trial.

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Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is a worldwide prevalent disease. It is estimated to be the 3rd leading cause of death worldwide in 2020, and it is also a leading cause of disability-adjusted life years (DALY's). COPD accounts for just over 3% of the total health care budget in the European Union. The majority of these costs are attributed to acute exacerbations of COPD (AECOPD). Given the contribution of exacerbations, it is of paramount importance to improve the current treatment of exacerbations to reduce the burden of disease for patients (mortality and DALY's) and for society (costs). Treatment of AECOPD generally consists of corticosteroids and antibiotics, mostly in one-size fits all fashion. Pulmonary physicians are well aware of overuse of antibiotics, but lack the tools to decide which medication to give. Biomarkers may aid towards a more personalized treatment of AECOPD by identifying which patient would benefit from antibiotics. Procalcitonin (PCT) is the precursor of calcitonin and is released in response to a bacterial infection. PCT levels are minimally raised in viral infections, making it a relative specific diagnostic tool for bacterial infections. Several trials have shown a reduction in antibiotic consumption in AECOPD when using a PCT-guided treatment algorithm. One meta-analysis suggested that PCT-based protocols may be superior to standard care, but the authors stated that appropriately powered confirmatory trials are necessary. The objective of our study is to assess that at hospitalization for a severe AECOPD, PCT-guided treatment to guide antibiotic administration is non-inferior to usual care, in terms of treatment failure at day 30.

Methods: The study is set up as a prospective randomized trial. A total of 693 patients with a severe exacerbation of COPD will be included and randomized between usual care and PCT-guided treatment regarding antibiotic therapy. The primary endpoint will be treatment failure within 30 days after inclusion, the endpoint comprises disease-related mortality and other disease-related adverse events.

Discussion: We believe this trial can add to the currently available evidence with PCT being tested in a clinical setting in a treatment algorithm specifically in COPD with the primary objective being treatment failure.

Trial registration: Netherlands Trial Register. Registration number: NL9122. Date of registration: 24-11-2020. URL of trial registry record: <https://www.trialregister.nl/trial/9122>

Administrative Information

Note

the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see <http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/>).

Title {1}	Procalcitonin-guided treatment regarding antibiotic use for acute COPD exacerbations (PRECISION): study protocol for a prospective randomized controlled trial.
Trial registration {2a and 2b}.	www.trialregister.nl - registration number: NL9122
Protocol version {3}	19-03-2021, version 8
Funding {4}	ZonMW: Care Evaluation and Appropriate Use (ZE&GG)*, Netherlands
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Title {1}	Procalcitonin-guided treatment regarding antibiotic use for acute COPD exacerbations (PRECISION): study protocol for a prospective randomized controlled trial.
Name and contact information for the trial sponsor {5b}	Menno M van der Eerden - Department of Respiratory Medicine, Erasmus Medical Centre, Rotterdam, The Netherlands. Correspondence: m.vandereerden@erasmusmc.nl
Role of sponsor {5c}	ZonMW has participated in the design of the study and has contributed to the study protocol. * The ZE&GG program is a program for evaluation and appropriate use of care launched by the Dutch National Health Care Institute (Zorginstituut Nederland, ZIN) and Netherlands Organization for Health Research and Development (Nederlandse organisatie voor gezondheidsonderzoek en zorginnovatie, ZonMw). The goal is realizing appropriate use of care.

Introduction

Background and rationale {6a}

Chronic obstructive pulmonary disease (COPD) is a prevalent disease, worldwide, and in the Netherlands with approximately 600.000 patients. COPD is estimated to be the 3rd leading cause of death worldwide in 2020 [1–3]. It is also a leading cause of disability-adjusted life years and with increasing prevalence the loss will also increase. The burden on health-care system is therefore impressing: COPD accounts for just over 3% of the total health care budget in the European Union. The majority of these costs are attributed to acute exacerbations of COPD (AECOPD) [3].

Reducing the burden of disease for patients (mortality and disability adjusted life years) and for society (costs) of this leading chronic disease is therefore of paramount importance. Given the contribution of exacerbations both to loss in quality of life and to costs, it is of major importance to improve the current treatment of exacerbations. Treatment of AECOPD generally consists of corticosteroids to reduce airway inflammation and antibiotics to treat bacterial infections, mostly in one-size fits all fashion.

Pulmonary physicians are well aware of overuse of both antibiotics and of prednisolone, but lack the tools to decide which medication to give on in the clinical setting. As a consequence, in the Netherlands 65% of patients hospitalized for COPD receive antibiotics (Landelijk Zorgpad COPD 2018). This overuse is important not only for the costs incurred for giving useless therapy, but there are also major side effects, the more frequent ones being gastrointestinal complaints. Finally, the overuse of antibiotics results in induction of antibiotic resistance, a worldwide grave concern.

Biomarkers may aid towards a more personalized treatment of AECOPD by identifying which patient would benefit from antibiotics. Procalcitonin (PCT) is the precursor of calcitonin and is released in response to a bacterial infection within 6-12 hours by many tissues under stimulation of several cytokines. Procalcitonin levels are minimally raised in viral infections [4], making it a relative specific

diagnostic tool for bacterial infections. Several trials have shown a reduction in antibiotic consumption in AECOPD when using a PCT-guided treatment algorithm [5–8]. One meta-analysis concerning the use of PCT to guide antibiotic administration in AECOPD suggested that PCT-based protocols may be superior to standard care in a mixed group of patients and indications [9]. In this meta-analysis 7 of the 8 included trials, including trials performed by Stolz et al. (Chest 2007), Verduri et al. (PLoS ONE 2015) and Corti et al. (Int J of COPD 2016) recommended starting antibiotic therapy for procalcitonin levels > 0.25ug/L (or 0.25ng/mL), [10–12]. To be able to compare our results to these important international studies we decided to use the same cut-off value. The quality of the data of the meta-analysis was judged low to moderate, necessitating appropriately powered confirmatory trials before recommending introducing such strategies in daily clinical practice [9].

In summary, PCT has not been tested in a clinical setting in a treatment algorithm specifically in COPD with the primary outcome measure being treatment failure.

Objectives {7}

We hypothesize that at hospitalization for a severe acute exacerbation for COPD, biomarker-guided treatment based on the procalcitonin level to guide antibiotic administration is non-inferior to usual care consisting of prednisolone and or antibiotics, which is based on a clinical decision, in terms of treatment failure at day 30.

The secondary objectives are to establish whether a biomarker-guided decision algorithm results in an improvement in quality of life, a decrease in consumption of antibiotics, and a reduction of important side effects.

Trial design {8}

The study is designed as an investigator-initiated, prospective, randomized, usual care controlled, non-inferiority multicenter trial. The allocation ratio will be 1:1. Block-randomisation will be used with randomly alternating blocks of 4 or 6 patients (random permuted block randomisation) and with stratification by center. The patient will not be blinded for the treatment received (prednisolone with or without antibiotic therapy) but the patient will be blinded for the treatment strategy (usual care or PCT-guided treatment). The participating centers will appoint two physicians that will be outcome assessors. The outcome assessors will be blinded for the treatment strategy.

Methods: Participants, Interventions And Outcomes

Study setting {9}

The study will be a multicenter study performed in 8 hospitals in the Netherlands. These centers include 2 academic hospitals (Erasmus Medical Center (Rotterdam) and Radboud University Medical Centre (Nijmegen)) and 6 community-based teaching hospitals (Amphia Hospital (Breda), Franciscus Gasthuis &

Vlietland (Rotterdam), Groene Hart Hospital (Gouda), Isala clinics (Zwolle), OLVG (Amsterdam) and Northwest Hospital Group (Alkmaar)).

Eligibility criteria {10}

Inclusion criteria:

- COPD, according to GOLD 2018 definition [13]
- Indication for hospitalization because of acute severe exacerbation of COPD, as defined by GOLD 2018 and modified Anthonisen criteria [13–15]
- Presence of at least 2 major symptoms of the modified Anthonisen criteria (acute deterioration in sputum volume, sputum purulence and dyspnea) or the presence of 1 major symptom and 1 minor symptom (coughing, wheeze, nasal discharge, sore throat, fever)
- Post-bronchodilator FEV1/FVC < 0,70 and FEV1% < 80%pred. within last 5 years
- At least 40 years
- Smokers or ex-smokers with ≥ 10 packyears
- Written informed consent
- Start of symptoms no more than 5 days before admission

Exclusion criteria:

- Indication for ICU and or non-invasive ventilation < 72h of admission
- Pneumonia, radiologically confirmed
- Sepsis
- Current asthma, or COPD before age 40.
- Clinically relevant heart failure or myocardial ischemia
- Chronic use of immunosuppressants, including prednisolone
- Known bronchiectasis as a primary diagnosis
- Colonisation with Pseudomonas spp. or other micro-organisms in recent cultures (last 60 days) not susceptible to amoxicillin-clavulanic acid
- Pregnancy
- Recent exacerbation (last 28 days)
- Pre-treatment with antibiotics (by general practitioner) during the 5 days prior to admission. Use of maintenance therapy with antibiotics, such as azithromycin is not considered an exclusion criterium.

Who will take informed consent? {26a}

Informed consent will be obtained by the treating physician, a local research nurse or one of the coordinating investigators.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

The patient will be asked to provide consent for collection and use of participant data, which will be stored for 15-20 years, and biological specimens (blood and sputum samples), which will be stored for 5 years. The biological specimens can be used in future studies.

Interventions

Explanation for the choice of comparators {6b}

In this study a PCT-guided treatment strategy regarding antibiotic therapy will be compared to usual care. In the usual care arm it is the physician who makes the (subjective) clinical decision whether the patient needs antibiotic treatment next to the treatment with corticosteroids. In Europe and the USA antibiotics were given in approximately 85% of the patients admitted with an AECOPD [16,17], while it has been estimated that bacterial infections are responsible for 40-50% of the AECOPD [18]. A PCT-based approach is objective and will result in a major change in clinical practice.

Intervention description {11a}

Upon hospitalization for AECOPD, patients will be asked for their informed consent to participate in the study. Participating patients will be randomized to either standard care, or the PCT-guided treatment arm. Subjects in the usual care arm will receive prednisolone with or without antibiotic treatment depending on the physician's decision. Subjects in the PCT-guided treatment arm will receive antibiotic treatment next to prednisolone depending on the concentration of serum procalcitonin measured on the day of admission. A PCT concentration of 0.25ug/L or less means the patient will not receive antibiotics. A PCT concentration of more than 0.25ug/L will result in the patient receiving antibiotic therapy. The antibiotic therapy will be 875/125mg of amoxicillin-clavulanic acid 3 times a day during 5 days. In case of an allergy to beta-lactam antibiotics, the patient will receive 100mg of doxycycline (200mg on the first day) once daily during 5 days.

Criteria for discontinuing or modifying allocated interventions {11b}

When the physician of a participant in the PCT-guided treatment strategy arm decides to start antibiotic therapy in case of a low concentration ($\leq 0.25\text{ug/L}$) of PCT after 48 hours, this will count as reaching one of the secondary outcomes. The patient will be analysed in the intention-to-treat analysis but not in the per-protocol analysis. When the antibiotics are started in the first 48 hours in case of a low serum PCT ($\leq 0.25\text{ug/L}$) the patient will also be analysed in the intention-to-treat analysis but not in the per-protocol analysis.

Strategies to improve adherence to interventions {11c}

During the investigator's meetings we will summarize the currently available literature that states the safety of the use of a PCT-guided strategy. We hope this information will lead to a higher adherence to the PCT-guided treatment protocol.

Relevant concomitant care permitted or prohibited during the trial {11d}

All patients will additionally receive all standard care according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 guideline and the Dutch guideline for the treatment of AECOPD [3,19].

Provisions for post-trial care {30}

An insurance policy has been taken out to be able to compensate those who suffer harm from participating in the trial.

Outcomes {12}

Primary study outcome:

Treatment failure, defined as disease-related mortality, need for endotracheal intubation or vasopressors, renal failure, lung abscess/empyema, development of pneumonia or rehospitalization within 30 days after inclusion.

Explanation:

Studies on PCT in AECOPD performed so far have showed a reduction in antibiotic consumption with a PCT-based strategy. However, before implementing this strategy in clinical practice it is necessary to perform clinical efficacy studies. Until now prospective randomized studies with a primary outcome of treatment failure in AECOPD specifically are lacking. Using treatment failure with the abovementioned parameters will help answer the question whether using a PCT-guided treatment is non-inferior in terms of efficacy and safety. Our key secondary outcome presented below will focus on the patients symptoms, and two other secondary endpoints focus on the quality of life (using the CAT and EXACT questionnaires) making the assessment of the PCT-guided treatment strategy a complete assessment consisting of both hard endpoints and patient reported endpoints.

Length of hospitalization, the percentage of patients treated with antibiotic therapy and the cumulative consumption of antibiotics and prednisolone allow for a comparison of the costs of both strategies. A cost-effectiveness analysis will be performed after completion of the study.

Secondary study outcome:

The key secondary objective is:

- Treatment failure defined as an incomplete resolution of the clinical signs and symptoms associated with the AECOPD at day 30 after inclusion of the study (i.e not reaching the baseline condition prior to the AECOPD) scored using the modified Anthonisen criteria.

The other secondary objectives are:

- Change in Quality of Life from day 1 to day 10, and after 30 days using the COPD Assessment Test (CAT)
- EXACT – Respiratory Symptoms scale (at admission, at day 10 and at day 30 after admission)
- Time to complete resolution of symptoms according to daily symptom diaries evaluating the modified Anthonisen criteria (at admission, day 3, 5, 10 and 30).
- Decision to start antibiotic therapy after an initial opposite decision (after 48 hours)
- Side effects (gastro-intestinal complaints, allergic reactions)
- Cumulative antibiotic consumption
- Cumulative prednisolone consumption
- Length of hospitalization
- Re-exacerbation within 30 days
- Non-Invasive ventilation after 72 hours of admission

Cost-effectiveness analysis (CEA):

- General considerations

Alongside the clinical trial, an economic evaluation will be performed conform the guidelines of the Health Care Institute Netherlands [20]. This evaluation will be conducted from a societal and payer's perspective. When adopting the societal perspective, costs will include 30-day inpatient and outpatient (emergency room, specialist visits) hospital costs, primary care costs (visits to GP and nurse practitioner), medication costs, ambulance costs, productivity costs, informal care costs and travel costs.

- Cost analysis

The resource utilization underlying these costs will be obtained from a combination of sources, including case report forms, hospital administrative systems and a patient's self-reported questionnaire, which is based on an adapted version of the iMTA Medical Consumption Questionnaire (iMCQ) [21]. When adopting the payer's perspective only the costs covered by the Health Insurance Act will be included. Unit costs will be based on reference prices obtained from the costing manual [22]. In a sensitivity analysis we will adjust the unit cost of a hospital day to reflect ward-specific and hospitalization-day-specific costs instead of average costs based on all patients in a hospital. Productivity costs will be based on the Friction Cost method [23].

Savings in health care costs are expected to result from a reduction in antibiotics use, a reduced length of stay and a reduction in the incidence of side-effects from antibiotics. These savings will be compared to the additional costs of adopting the procalcitonin-guided treatment, including the costs of additional lab tests.

- Patient outcome analysis

The difference in total costs between the two groups will be related to the difference in the following outcomes: QALYs, treatment failures and CAT (COPD Assessment Test). This will result in the following incremental cost-effectiveness ratios (ICER): costs per QALY, costs per treatment failure avoided and costs per additional patient with at least one MCID improvement in CAT. The utilities to calculate QALYs will be measured with the EQ-5D-5L with and without the respiratory bolt-on [24]. The ICER's will be estimated using a decision tree model that synthesizes the evidence collected during the clinical trial. The uncertainty around the ICER will be estimated in probabilistic sensitivity analysis, the results of which will be graphically shown in a CE-plane and Cost-Effectiveness Acceptability Curve.

Budget impact analysis (BIA):

- General considerations

A budget impact model to estimate the impact of large-scale implementation of the intervention will be developed. This model will be a transparent cost calculator that includes nation-wide estimates of the size of the COPD population that is hospitalized for exacerbations, scenarios on the proportion and speed of uptake of the procalcitonin-guided AECOPD treatment, and changes in costs as a result of this.

o Cost analysis

These analyses will be conducted in accordance with the ISPOR and Dutch guidelines of ZONMW, for time horizons between 1 and 5 years [25,26].

Participant timeline {13}

	T ₀ /T ₁	T ₃	T ₅	T ₁₀	close-out (T ₃₀)
Initiation procedures:					
Informed consent	X				
Medication history	X				
Vital signs	X				
Check for eligibility	X				
Interventions:					
Sputum collection	X				
Blood sampling, including procalcitonin*	X				
Blood sampling CRP, eosinophils	X	X	X		
Serum for storage	X				
Sputum for storage	X				
Assessments:					
Clinical assessment for treatment failure		X	X	X	X
CAT	X			X	X
E-RS	X			X	X
EQ-5D-5L	X			X	X
iMCQ					X
Randomization	X				
Antibiotic consumption	X	X	X	X	X
Diary cards with modified Anthonisen criteria	X	X	X	X	X
Assessment of adverse effects	X	X	X	X	X

* (PCT will only be reported for the randomised PCT group and not for the usual care group during the study period. The measurement will be performed in the usual care group but this will be blinded until the study ends.))

Sample size {14}

In international literature there is scarce information about the percentages of treatment failure in patients admitted with an AECOPD receiving usual care. Therefore, we have performed a further search on PCT studies with a primary outcome of 30-day treatment failure. In the study by Schuetz et al. [5], who

studied patients with lower respiratory tract infection, 30-day treatment failure was observed in 15.5% of the patients randomised to biomarker-based treatment, as compared to 18.9% in those randomised to usual care. This implies a relative risk of 0.82 in favour of the biomarker-based strategy. The study by Schuetz et al. was designed as a non-inferiority study, using a non-inferiority boundary of 7.5% [5]. In view of these data we decided to design our study as a non-inferior study, whereas we choose a non-inferiority boundary of 5.0%. We based the primary outcome on the study of Huang et al. [27]. The incidence of the primary outcome was 20.4%. Using the relative risk of 0.82 in favour of the PCT-guided treatment group we expect the incidence of the primary outcome to be 16.7% in the PCT-guided treatment group. Then a total sample size of 626 is required (313 per treatment arm) to demonstrate non-inferiority with a power of 80%, and applying a one-sided alpha error of 0.025. We aim to enroll a total of 690 patients, accounting for a 10% drop-out rate.

An interim analysis will be performed at 50% of patient accrual, analyzing the primary outcome and safety data. The safety data consists of observed adverse events and SAE. The non-inferiority design of the study means that a clear disadvantage of the PCT-guided treatment arm or in other words a clear benefit of the usual care arm will lead to discontinuation of the trial. The p-value at the interim analysis will be 0.0054 according to the O'Brien-Fleming method, and the p-value at final analysis will be 0.0492[28]. The safety data consists of observed adverse events and SAE. The change of the p-value at final analysis will lead to an increase of 2 patients per treatment arm. The number of patients per treatment arm will be 315. Using a 10% drop-out rate this will lead to a total number of patients of 693.

Recruitment {15}

Upon hospitalization for AECOPD, all patients will be asked for their informed consent to participate in the study. The benefits of participation will be addressed: possibly less adverse reactions to antibiotics because of lower exposure to antibiotics, less antibiotic resistance and participants help compare a new treatment strategy to usual care, which could help future patients.

Of the 8 participating centers, there are 4 major community-based teaching hospitals, with Isala clinics and Amphia Hospital being the largest in the country. The number of presentations to the emergency ward for AECOPD is high in these centers, e.g. in Isala clinics there are approximately 500 presentations each year.

Assignment of interventions: allocation

Sequence generation {16a}

We will use a computer-generated block-randomization with randomly alternating blocks of 4 or 6 patients (random permuted block randomization) and with stratification by center.

Concealment mechanism {16b}

For randomization, clinical data collection and central data management, Castor® will be used. Castor® is a web-based software tool designed to capture clinical study data. Castor® is hosted by an external party (Castor EDC), which is validated for conducting clinical trials in the Erasmus MC and meets all requirements to be ICH-GCP compliant. The randomization can be performed in Castor, after completion of the eligibility screening using the inclusion and exclusion criteria. Outcome assessors will have accounts that are blinded for the allocation. The randomization will be a random permuted block randomization with randomly alternating blocks of 4 or 6 patients.

Implementation {16c}

The allocation sequence will be randomly generated by Castor®. Patients will be enrolled by local research nurses and the treating physicians. After the randomization procedure in Castor, PCT measurement will be performed for patients randomized to the PCT-guided treatment arm and the treating physician will follow the PCT-guided treatment strategy as discussed earlier.

Assignment of interventions: Blinding

Who will be blinded {17a}

The patient will not be blinded for the treatment received (prednisolone with or without antibiotic therapy) but the patient will be blinded for the treatment strategy (usual care or PCT-guided treatment). The participating centers will appoint two physicians that will be outcome assessors. The outcome assessors will be blinded for the treatment strategy.

Procedure for unblinding if needed {17b}

There are no circumstances under which unblinding will be necessary. When antibiotic treatment is deemed necessary because of deterioration of a patient who was withheld antibiotics on admission the physician can deviate from the protocol and start antibiotic treatment. The unblinding of the allocation is not necessary for this.

Data collection and management

Plans for assessment and collection of outcomes {18a}

For clinical data collection and central data management, Castor® will be used. Castor® is a web-based software tool designed to capture clinical study data. Castor® is hosted by an external party (Castor EDC), which is validated for conducting clinical trials in the Erasmus MC and meets all requirements to be ICH-GCP compliant.

Physicians and research nurses who will participate in enrolling participants and outcome assessors will be trained by the principal investigator and/or coordinating investigator.

Study instruments

- COPD Assessment Test (CAT): The CAT is a simple and widely used, health-related quality of life questionnaire. It consists of 8 items, each with a semantic six-point (from 0 to 5) differential scale. The maximum score is 40 points [29,30]. The CAT is considered to be a reliable and valid instrument that responds to interventions [31]. The minimal clinically important difference (MCID) of the COPD Assessment Test (CAT) is considered to be a decrease of 2 to 3 points (after rehabilitation) according to a recent study [32]. Another group of researchers conducted 3 trials with different groups of COPD patients: patients who underwent rehabilitation, patients who were admitted to the hospital because of an exacerbation and outpatients who were stable found a MCID of 2 points [33]. We will consider a decrease of 2 points as a minimal clinically important difference.
- EXACT-respiratory symptoms (E-RS) scale: The E-RS scale was specifically designed for the use in clinical trials that evaluate the effect of treatment on respiratory symptoms of patients with a COPD exacerbation [34]. It consists of 11 items and is derived from the EXACT, which contains 14 items and is a diary card used in a daily fashion to measure exacerbations of COPD [35]. The definition of symptomatic improvement of the E-RS is RS-total ≥ -2.0 (scale range 0-40) RS-Breathlessness ≥ -1.0 (scale range: 0–17) RS-Cough and Sputum ≥ -0.70 (scale range 0–11) RS-Chest Symptoms ≥ -0.70 (scale range: 0–12) [34].
- Modified Anthonisen criteria diary card: patients will fill in these diary cards at baseline and on day 3, 5, 10 and 30. The card scores the presence of 3 major criteria (worsening dyspnea, increase of sputum volume and increase of sputum purulence) and the presence of 5 minor criteria (cough, fever, sore throat, wheezing, nasal discharge). The diary cards will be sent to the research bureau of the Erasmus MC where the answers will be duplicated in Castor® in preproduced forms. The original diary cards will be stored at the Erasmus MC.
- The iMTA Medical Consumption Questionnaire (iMCQ) is designed to measure the direct costs of medical care used by the patient [36]. The questionnaire is non-disease specific. We used an adapted version of the iMCQ, adding questions of the iPCQ to measure productivity losses as a consequence of the acute COPD exacerbation [37]. The questionnaire will cover only the follow-up period of 30 days used in this trial instead of the usual 90 days used in the questionnaire.
- The EQ-5D-5L is a short questionnaire that can be used to score health-related quality-of-life [24]. It consists of 5 dimensions, with 5 levels of severity. We will use a respiratory bolt-on which adds one question about breathing problems [24]. This question is added to increase the responsiveness of the instrument in patients with chronic respiratory problems such as COPD.

Plans to promote participant retention and complete follow-up {18b}

After signing the informed consent, patients still are allowed to withdraw from the study. Every attempt will be made to collect the primary end-point. Withdrawal by the investigator will mainly be because of safety reasons and mostly constitute a treatment failure.

Patients who are withdrawn from the study will be invited for a follow up visit, and otherwise it will be attempted to collect data on the primary end-points as long as this is within the agreement of the

informed consent.

When a patient discontinues or deviates from the protocol, the outcomes that can be collected are dependent on the timing of the discontinuation or deviation. If, for example, a patient decides to discontinue the study after hospital discharge, the length of hospitalization will still be available for data collection. As stated above, every attempt within the agreement of the informed consent will be made to collect the other outcome data.

Data management {19}

A data management plan (DMP) has been formulated and if necessary can be added as an appendix to the protocol. Relevant sections of the DMP are listed below:

Data entry

Data entry will be done according to Standard Operating Procedures. To ensure the quality there will be regular checks by an objective monitor. The Erasmus MC research code will be followed at all times.

Data coding

After randomization, each patient will be allocated a unique study subject ID. This ID does not include patient identifiers such as date of birth, Patient Hospital number, name or initials. Data collection will strictly be pseudonymized, i.e. based on Subject ID. That is, no identifying data will be collected/ entered in the Database. A patient identification code list, holding the key between subject number and patient identifiers, will be kept at each participating hospital and will not be revealed to the sponsor

Data storage and security

Data will be handled and collected in compliance with ICH-GCP (Good Clinical Practice) and in accordance with prevailing national and international regulations, principles and guidelines such as VSNU code, NFU, WGBO, WMO and GDPR, as well as Erasmus MC policies on clinical trials and data storage and management.

Once the project has ended all data, software codes and research materials, published or unpublished, are managed and securely stored in accordance with VNSU guidelines. The data will be stored for 15 years. Only members of the research team have access to data collected for this study. Arrangements on access to data and results and potential IP generated in this study are made in the consortium agreement. Generated IP will be protected appropriately in consultation with the Erasmus MC technology transfer office.

Confidentiality {27}

Data coding

After randomization, each patient will be allocated a unique study subject ID. This ID does not include patient identifiers such as date of birth, Patient Hospital number, name or initials. Data collection will strictly be pseudonymized, i.e. based on Subject ID. That is, no identifying data will be collected/entered in the Database. A patient identification code list, holding the key between subject number and patient identifiers, will be kept at each participating hospital and will not be revealed to the sponsor

Data storage and security

Once the project has ended all data, software codes and research materials, published or unpublished, are managed and securely stored in accordance with VNSU guidelines. The data will be stored for 15 years.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Sputum and serum samples will be stored for a period of 15 years for future research. Patients will be asked to sign for this in the patient informed consent form. No future research of genetic nature will be conducted. No future molecular research has been planned up to date.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Primary outcome

The primary outcome will be treatment failure within 30 days after inclusion. A non-inferiority margin of 5% will be used to assess non-inferiority. Treatment failure is defined as disease-related mortality, endotracheal intubation, vasopressors, renal failure, lung abscess/empyema, development of pneumonia and hospital readmission within 30 days.

To account for the multicenter effect a logistic mixed effects model will be estimated with centers as random effect and treatment group as fixed effect to analyze the primary outcome. The risk of primary endpoint in the PCT-guided treatment arm versus the usual care treatment arm will be reported with an odds ratio from the logistic model, with a 95% confidence interval. Based on this CI we will determine non-inferiority for the treatment.

Secondary outcome parameters

Skewed data will be analyzed using non-parametric tests. Paired measurements will be analyzed using paired tests.

The quality of life endpoints, using the COPD Assessment Test (CAT) and the EXACT-respiratory symptoms questionnaire, consist of multiple (three) measurements per subject. These measurements are all performed on the same time point (baseline, day 10 and day 30). These endpoints will be scored using the mean score and standard deviation when normally distributed and a median with the inter quartile

range when the data have a skewed distribution. These data will be analyzed with a mixed effects model with random effects for center and patient to account for the extra hierarchical level in the data. The residuals will be evaluated for normality to test the assumptions of the models. In case of violations, transformations will be conducted on the dependent variable.

The unpaired continuous variables will be reported using the mean score and the standard deviation (normal distribution) or the median with the inter quartile range (skewed distribution). These variables will be analyzed using a mixed effects model.

The frequency and percentage will be reported for the categorical (mostly dichotomous) variables. Analysis of these variables will be performed using a logistic mixed-effects model.

The analysis populations upon which the tables and figures will be based will be the per-protocol analysis population.

A concept statistical analysis plan will added as supplementary material.

Interim analyses {21b}

An interim analysis will be performed at 50% of patient accrual, analyzing the primary outcome and safety data. The safety data consists of observed adverse events and SAE. The non-inferiority design of the study means that a clear disadvantage of the PCT-guided treatment arm or in other words a clear benefit of the usual care arm will lead to discontinuation of the trial. The p-value at the interim analysis will be 0.0054 according to the O'Brien-Fleming method, and the p-value at final analysis will be 0.0492 [28]. The safety data consists of observed adverse events and SAE. The change of the p-value at final analysis will lead to an increase of 2 patients per treatment arm. The number of patients per treatment arm will be 315. Using a 10% drop-out rate this will lead to a total number of patients of 693.

A DSMB will assess this interim analysis. The advice(s) of the DSMB will only be sent to the principal investigator of the study. Should the principal investigator decide not to fully implement the advice of the DSMB, the principal investigator will send the advice to the reviewing Ethical Committee (in Dutch: METC), including a note to substantiate why (part of) the advice of the DSMB will not be followed.

Criteria on which the DSMB may decide to terminate the trial prematurely are:

1. Any serious adverse event related to the treatment under investigation has occurred.
2. A clear disadvantage of the PCT-guided treatment arm, exceeding the non-inferiority limit of 5%
3. A significant evidence of benefit of the PCT-guided treatment arm

Methods for additional analyses (e.g. subgroup analyses) {20b}

At this moment we do not have the intention to analyze subgroups. We do not exclude the possibility of

exploratory subgroup analysis but these results can only be presented as summary statistics.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Protocol non-adherence

When a physician decides to prescribe antibiotic therapy even though the patient has a low serum concentration of procalcitonin ($\leq 0.25\mu\text{g/mL}$) this leads to a protocol violation. The patient might recover because of the antibiotic therapy instead of still experiencing symptoms on day 30, which could directly impact the primary endpoint. This subject should not be analyzed in the per-protocol analysis, because of this major protocol deviation/violation.

Early termination of antibiotic therapy, in both groups, could have an impact on the primary endpoint. This could happen when a patient has an initial fast recovery and gets discharged from the hospital without antibiotic therapy after which a relapse of symptoms occurs. We do not expect this to happen more often in one of the two treatment arms, although a high PCT might lead to less frequent discontinuation of the treatment when the patient is discharged in the first 5 days (the antibiotic therapy should be given during 5 days in both groups).

Missing data

After signing the informed consent, patients are still allowed to withdraw from the study. Every attempt will be made to collect the primary end-point. Withdrawal by the investigator will mainly be because of safety reasons and mostly constitute a treatment failure.

The statistical analyst will consider all possible reasons for missing data. If it is safe to assume the data are missing at random (MAR) or missing completely at random (MCAR) we will use multiple imputation for missing values. Sensitivity analyses will be used to investigate the validity of the MAR assumption against missing not at random (MNAR).

Plans to give access to the full protocol, participant level-data and statistical code {31c}

Access to the full protocol, participant level data and the applied statistical codes is only possible with permission of the consortium. Requests for access can be submitted to the consortium, after which the request will be evaluated on its alignment with the original research aims and whether it is admissible under the used PIFs. If the request is in line with the original research aims and is admissible under the used PIFs, appropriate arrangements for access to data and potentially generated results and IP will be made in collaboration with the Erasmus MC technology transfer office. Access will only be given to the specific data required to address the specific request, which means that if access to part of the data is sufficient to address this new request, only the required part of the data will be given insight to. Data will not be transferred, if access to data is granted, this means that the involved researcher(s) will be given access to a secure data platform in which data can be viewed. Data cannot be downloaded or

transferred, unless specifically agreed upon under strict conditions laid down in a data transfer agreement.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

The study is coordinated by the department of pulmonary medicine of Erasmus MC. The department has its own dedicated, highly experienced research bureau, which coordinates, facilitates and manages all clinical studies of the department from day to day. Submission of the protocol and potential amendments for assessment by the medical ethical committee is facilitated by this research bureau. A study coordinator is appointed, who oversees the study in collaboration with a PhD candidate. A dedicated data manager is in charge of data entry and management, and a designated monitor is available to monitor execution and performance of the clinical study at all participating centres. This is overseen by the head of the research bureau on a daily basis. In collaboration with the departments research advisor and legal advisors from Erasmus MC and the ZonMw ZE&GG programme all contractual matters for the study were arranged, such as the consortium agreement and clinical trial agreements with participating centres. This is overseen by the steering committee, consisting of the head of the department of pulmonary medicine and PI dr. Menno van der Eerden, supplemented with prof. dr. Guy Brusselle (departments of public health and pulmonary medicine), dr. Johannes in 't Veen (department of pulmonary medicine) and prof. dr. Eric Boersma, and the consortium members. Monthly meetings are organized between the steering committee, the PhD candidate, the head of the research bureau and the research advisor to discuss progress and practical matters relating to the clinical study. When urgent matters occur, more frequent meetings will be scheduled.

Composition of the data monitoring committee, its role and reporting structure {21a}

Throughout the trial, a trained, BROK-certified and independent monitor will periodically visit each participating site in order to, among other things, randomly check compliance with the protocol, compliance with in- and exclusion criteria, proper implementation and conduct of Informed Consent procedures, Source Data Verification (i.e. cross-check data in Castor® with patient dossier and vice versa) and SAE reporting. Findings will be discussed with the Local Investigator and reported in a standard monitor report that will be shared with and filed by the Sponsor. The monitor will also feed any relevant findings back to the person(s) responsible for data validation (central data management). Data management will be performed according to the data management plan of the clinical study. This data management plan is set up according to institutional policies and is approved by the funding organization ZonMw.

A data monitoring committee is not needed because of the negligible risk for participants according to the NFU Guideline Quality assurance of research involving human subjects [38]. The risk is considered negligible because the medication used in this trial, prednisolone, amoxicillin-clavulanic acid and

doxycycline, are registered in the Netherlands as treatment of choice for an acute COPD exacerbation [19].

Adverse event reporting and harms {22}

AEs, SAEs and SUSARs

Adverse events (AEs):

All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. Common expected adverse events are diarrhoea and gastric complaints.

Severe adverse events (SAEs):

When a SAE is reported spontaneously by the subject or observed by the principal investigator or his staff it will be reported to the coordinating investigator in the ErasmusMC. The coordinating investigator will report the SAEs through the web portal ToetsingOnline to the accredited Medical Research Ethics Committee (MREC) that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reaction. SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

Suspected unexpected serious adverse reactions (SUSARs)

The coordinating investigator in the ErasmusMC will report expedited the following SUSARs through the web portal ToetsingOnline to the MREC:

- SUSARs that have arisen in the clinical trial that was assessed by the MREC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the MREC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the MREC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern. The expedited reporting of SUSARs through the web portal ToetsingOnline is sufficient as notification to the competent authority. The coordinating investigator will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States. The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

Safety reporting

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited MREC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited MREC, except in so far as suspension would jeopardize the subjects' health. The investigator will take care that all subjects are kept informed.

Annual safety report

In addition to the expedited reporting of SUSARs, the coordinating investigator will submit, once a year throughout the clinical trial, a safety report to the accredited MREC, competent authority, and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study, as defined in the protocol.

Frequency and plans for auditing trial conduct {23}

There are no plans for an audit trial conduct at this moment.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Amendments

A 'substantial amendment' is defined as an amendment to the terms of the MREC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;

- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the MREC and to the competent authority. A monthly newsletter will notify the participating centers when a substantial amendment has been submitted. E-mail correspondence will be used when the participating centers should be informed timely (i.e. before the next monthly newsletter).

Non-substantial amendments will not be notified to the accredited MREC and the competent authority, but will be recorded and filed by the sponsor. Examples of non-substantial amendments are typing errors and administrative changes like changes in names, telephone numbers and other contact details of involved persons mentioned in the submitted study documentation.

Dissemination plans {31a}

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited MREC and the Competent Authority.

This study is an investigator-initiated study. Therefore, arrangements concerning the public disclosure and publication between the sponsor and the investigator are not applicable. Results of this study will be disclosed to the public without any restrictions.

Discussion

A recent retrospective study showed no significant benefit of antibiotic therapy on hospital readmissions in patients with AECOPD with a low serum procalcitonin [39]. The authors state that the serum PCT concentration should be added to the 3 major Anthonisen criteria in the GOLD guideline as an important factor in the decision whether or not to start antibiotic therapy in patients with AEOPD.

Lindenauer et al. studied the effect of implementation of PCT testing on the rates of prescription of antibiotics and did not find a difference in the use of antibiotic therapy in patients with AECOPD [40]. Only 5% of patients underwent PCT testing. This could mean that confidence in procalcitonin is still rather low. A beforementioned meta-analysis on the use of PCT-guided treatment in AECOPD stated that confirmatory trials with rigorous methodology are needed to confirm its potential to reduce antibiotic prescription without affecting patient outcomes [9]. With the current study we will prospectively compare the use of a PCT-guided treatment strategy to usual care in an adequately powered randomized trial. The results of the current study will add to the current knowledge on the use of PCT in patients with an acute exacerbation of COPD.

Trial Status

The current trial protocol is version 8, with date 19th March 2021.

The trial is currently recruiting participants.. Recruitment will be expected to be completed in 4 years (May/June 2025).

Abbreviations

AE: adverse event

AECOPD: acute exacerbation of chronic obstructive pulmonary disease

CAT: COPD Assessment Test

COPD: chronic obstructive pulmonary disease

DALY: disability adjusted life year

DMP: data management plan

FEV1: forced expiratory volume in 1 sec

FVC: Forced vital capacity

GOLD: The Global initiative for chronic Obstructive Lung Disease

ICH-GCP: The International Council for Harmonisation - Good Clinical Practice

MAR: missing at random

MCAR: missing completely at random

MCID: minimal clinically important difference

MNAR: missing not at random

MREC: Medical Research Ethics Committee

NFU: Netherlands Federation of University Medical Centres

PCT: procalcitonine

PRECISION: Procalcitonin-guided treatment regarding antibiotic use for acute COPD exacerbations

PROM: patient reported outcome measure

SAE: serious adverse event

SUSAR: suspected unexpected serious adverse reaction

VSNU: Association of research universities in the Netherlands.

WGBO: Dutch Medical Treatment Contracts Act

WMO: Medical Research Involving Human Subjects Act

Declarations

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We would like to thank ZonMW for funding this study. We would also like to thank all the participating members of the research bureau of the Erasmus Medical Centre for their support in the design of this study.

Authors' contributions {31b}

MvS has contributed to the study protocol and is coordinating investigator of the trial and will be including patients in one of the participating centers. JitV has participated in the design of the study and contributed to the study protocol. GB has participated in the design of the study and contributed to the study protocol. JvdB has participated in the design of the study and contributed to the study protocol. MRvM has contributed to the study protocol and will analyze the cost-effectiveness of the PCT-guided treatment. EB was the lead trial methodologist. ME is the principal investigator, and has led the proposal and protocol development. JGJVA has participated in the design of the study and contributed to the study protocol.

Funding {4}

ZonMW: Care Evaluation and Appropriate Use (ZE&GG), Netherlands

Availability of data and materials {29}

Upon granting of this project, a data management plan will be set up based on the FAIR principles, in line with ZonMw guidelines and national and institutional policies. All publications of Erasmus MC are shared in the green route using the 'repub' repository. Publications from this project will be handled according to Erasmus MC policy. In case IP is generated, this will be protected appropriately in consultation with technology transfer office, prior to any form of publication or dissemination.

As is described for access to the full protocol, participant level data and the applied statistical codes, access to generated data, results and/or material is only possible with permission of the consortium. Requests for access can be submitted to the consortium, after which the request will be evaluated on its alignment with the original research aims and whether it is admissible under the used PIFs. If the request is in line with the original research aims and is admissible under the used PIFs, appropriate arrangements

for access to data and potentially generated results and IP will be made in collaboration with the Erasmus MC technology transfer office. Access will only be given to the specific data required to address the specific request, which means that if access to part of the data is sufficient to address this new request, only the required part of the data will be given insight to. Data will not be transferred, if access to data is granted, this means that the involved researcher(s) will be given access to a secure data platform in which data can be viewed. Data cannot be downloaded or transferred, unless specifically agreed upon under strict conditions laid down in a data transfer agreement.

Ethics approval and consent to participate {24}

The study has been approved by the Erasmus Medical Centre Medical Ethics Review Committee (MERC). The registration number of the PRECISION study is MEC 2020-0838/NL.

Upon hospitalization for AECOPD, patients will be notified about the possibility of participation in the study. After giving verbal and written information, with 2 hours to decide, patients will be asked to sign the informed consent form if they wish to participate. Only patients that signed the informed consent will be entered in the study. Subject's written informed consent will be obtained prior to any study-related procedures. At any time patients have the right to withdraw from the study without any consequence for their ongoing treatment.

Consent for publication {32}

Not applicable

Competing interests {28}

The authors declare that they have no competing interests

References

1. Mathers C, Fat DM, Boerma T. The Global Burden of Disease: 2004 Update. Geneva: World Health Organization; 2008.
2. Wedzicha JA, Wilkinson T. Impact of chronic obstructive pulmonary disease exacerbations on patients and payers. *Proc Am Thorac Soc.* 2006;3:218–21.
3. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease [Internet]. 2020 [cited 2021 Mar 31]. Available from: www.goldcopd.org.
4. Linscheid P, Seboek D, Nylen ES, Langer I, Schlatter M, Becker KL, et al. In Vitro and in Vivo Calcitonin I Gene Expression in Parenchymal Cells: A Novel Product of Human Adipose Tissue. *Endocrinology.* 2003;144:5578–84.
5. Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: The ProHOSP randomized controlled trial. *JAMA - J Am Med Assoc.* 2009;302:1059–66.

6. Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: Cluster-randomised, single-blinded intervention trial. *Lancet Elsevier Limited*. 2004;363:600–7.
7. Schuetz P, Müller B, Christ-Crain M, Stolz D, Tamm M, Bouadma L, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections (Review). In: *Cochrane Database Syst Rev*. John Wiley & Sons, Ltd; 2012.
8. Miravittles M, Moragas A, Hernández S, Bayona C, Llor C. Is it possible to identify exacerbations of mild to moderate COPD that do not require antibiotic treatment? *Chest*. American College of Chest Physicians. 2013;144:1571–7.
9. Mathioudakis AG, Chatzimavridou-Grigoriadou V, Corlateanu A, Vestbo J. Procalcitonin to guide antibiotic administration in COPD exacerbations: a meta-analysis. *Eur Respir Rev European Respiratory Society (ERS)*. 2017;26:160073.
10. Stolz D, Christ-Grain M, Bingisser R, Leuppi J, Miedinger D, Müller C, et al. Antibiotic treatment of exacerbations of COPD: A randomized, controlled trial comparing procalcitonin-guidance with standard therapy. *Chest*. 2007;131:9–19.
11. Verduri A, Luppi F, D’Amico R, Balduzzi S, Vicini R, Liverani A, et al. Antibiotic treatment of severe exacerbations of chronic obstructive pulmonary disease with procalcitonin: A randomized noninferiority trial. *PLoS One. Public Library of Science*; 2015;10.
12. Corti C, Fally M, Fabricius-Bjerre A, Mortensen K, Jensen BN, Andreassen HF, et al. Point-of-care procalcitonin test to reduce antibiotic exposure in patients hospitalized with acute exacerbation of COPD. *Int J COPD Dove Medical Press Ltd*. 2016;11:1381–9.
13. GOLD. Global Strategy For The Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease [Internet]. *Glob. Obstr. Lung Dis. GOLD*. 2018 [cited 2021 Mar 31]. Available from: https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf.
14. Trappenburg JCA, Van Deventer AC, Troosters T, Verheij TJM, Schrijvers AJP, Lammers JWJ, et al. The impact of using different symptom-based exacerbation algorithms in patients with COPD. *Eur. Respir. J*. 2011. p. 1260–8.
15. Anthonisen NR, Manfreda J, Warren C, Hershfield E, Harding G, Nelson N. Antibiotic therapy in acute exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med*. 1987;106:196–204.
16. López-Campos JL, Hartl S, Pozo-Rodriguez F, Roberts CM. Antibiotic prescription for COPD exacerbations admitted to hospital: European COPD audit. *PLoS One. Public Library of Science*; 2015;10.
17. Lindenauer PK, Pekow P, Gao S, Crawford AS, Gutierrez B, Benjamin EM. Quality of care for patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med*. 2006;144:894–903.
18. Sethi S, Murphy TF. Infection in the Pathogenesis and Course of Chronic Obstructive Pulmonary Disease [Internet]. 2008. Available from: www.nejm.org.

19. Richtlijndatabase. Diagnostiek en behandeling COPD-longaanval in het ziekenhuis Inhoudsopgave [Internet]. 2017 [cited 2021 Apr 1]. Available from: https://richtlijndatabase.nl/richtlijn/behandeling_copd-longaanval_in_het_ziekenhuis.
20. Zorginstituut Nederland. Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg. 2015 Nov.
21. Bouwmans C, De Jong K, Timman R, Zijlstra-Vlasveld M, Van D Feltz-Cornelis, Tan C. SS, et al. Feasibility, reliability and validity of a questionnaire on healthcare consumption and productivity loss in patients with a psychiatric disorder (TiC-P). *BMC Health Serv Res*. 2013;13.
22. Kanters TA, Bouwmans CAM, Van Der Linden N, Tan SS, Hakkaart-van Roijen L. Update of the Dutch manual for costing studies in health care. *PLoS One*. Public Library of Science; 2017;12.
23. Koopmanschap MA, Rutten FFH, Van Ineveld M, Van Roijen B. L. The friction cost method for measuring indirect costs of disease. *J. Health Econ*. 1995.
24. Hoogendoorn M, Oppe M, Boland MRS, Goossens LMA, Stolk EA, Rutten–van Mólken MPMH. Exploring the Impact of Adding a Respiratory Dimension to the EQ-5D-5L. *Med Decis Mak*. 39: SAGE Publications Inc.; 2019. pp. 393–404.
25. Sullivan SD, Mauskopf JA, Augustovski F, Jaime Caro J, Lee KM, Minchin M, et al. Budget impact analysis - Principles of good practice: Report of the ISPOR 2012 budget impact analysis good practice II task force. *Value Heal*. 2014;17:5–14.
26. ZonMW. Budget Impact Analyses in de praktijk. Leidraad Budget Impact analyse [Internet]. 2020 Feb. Available from: www.facebook.com/zonmwNL.
27. Huang DT, Yealy DM, Filbin MR, Brown AM, Chang CCH, Doi Y, et al. Procalcitonin-guided use of antibiotics for lower respiratory tract infection. *N Engl J Med Massachusetts Medical Society*. 2018;379:236–49.
28. Gogtay N, Thatte U. Principle of Interim Analysis. *J Assoc Physicians Inda*. 2017;65:78–83.
29. Dodd JW, Hogg L, Nolan J, Jefford H, Grant A, Lord VM, et al. The COPD assessment test (CAT): Response to pulmonary rehabilitation. A multicentre, prospective study. *Thorax BMJ Publishing Group*. 2011;66:425–9.
30. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. *Eur Respir J*. 2009;34:648–54.
31. Gupta N, Pinto LM, Morogan A, Bourbeau J. The COPD assessment test: A systematic review. *Eur Respir J European Respiratory Society*. 2014;44:873–84.
32. Smid DE, Franssen FME, Houben-Wilke S, Vanfleteren LEGW, Janssen DJA, Wouters EFM, et al. Responsiveness and MCID Estimates for CAT, CCQ, and HADS in Patients With COPD Undergoing Pulmonary Rehabilitation: A Prospective Analysis. *J Am Med Dir Assoc*. 2017;18:53–8.
33. Kon SSC, Canavan JL, Jones SE, Nolan CM, Clark AL, Dickson MJ, et al. Minimum clinically important difference for the COPD Assessment Test: A prospective analysis. *Lancet Respir Med Lancet Publishing Group*. 2014;2:195–203.

34. Leidy NK, Murray LT, Monz BU, Nelsen L, Goldman M, Jones PW, et al. Measuring respiratory symptoms of COPD: Performance of the EXACT- Respiratory Symptoms Tool (E-RS) in three clinical trials. *Respir Res.* 2014;15:1–10.
35. Leidy NK, Murray LT. Patient-reported Outcome (PRO) measures for clinical trials of COPD: The EXACT and E-RS. *COPD J Chronic Obstr Pulm Dis.* 2013;10:393–8.
36. Bouwmans C, Hakkaart-van Roijen L, Koopmanschap M, Krol M, Severens H, Brouwer W. Handleiding iMTA Medical Cost Questionnaire (iMCQ). Rotterdam; 2013.
37. Bouwmans C, Krol M, Severens H, Koopmanschap M, Brouwer W, Roijen LH Van. The iMTA Productivity Cost Questionnaire: A Standardized Instrument for Measuring and Valuing Health-Related Productivity Losses. *Value Heal.* 18: Elsevier Ltd; 2015. pp. 753–8.
38. NFU. Guideline Quality assurance of research involving human subjects. 2020 Dec.
39. Bremmer DN, Moffa MA, Ma K, Bean HR, Snatchko J, Trienski TL, et al. Acute exacerbations of chronic obstructive pulmonary disease with a low procalcitonin concentration: Impact of antibiotic therapy. *Clin Infect Dis.* Oxford University Press; 2019;68:pp. 725–30.
40. Lindenauer PK, Shieh MS, Stefan MS, Fisher KA, Haessler SD, Pekow PS, et al. Hospital procalcitonin testing and antibiotic treatment of patients admitted for chronic obstructive pulmonary disease exacerbation. *Ann Am Thorac Soc American Thoracic Society.* 2017;14:1779–85.