Statistical Analysis Plan

We would like to acknowledge the Cambridge University Hospitals Clinical Trials Unit for the development of the template (version CCTU/TPLV2), which was modified by the Michigan Institute for Clinical & Health Research (MICHR).

TRIAL FULL TITLE	Procalcitonin-guided treatment regarding antibiotic use for acute COPD exacerbations: a prospective randomised controlled trial (PRECISION)
SAP VERSION	1.3 (CONCEPT)
SAP VERSION DATE	28-09-2021
TRIAL STATISTICIAN	Sara Baart, Eric Boersma
Protocol Version (SAP associated with)	Version 28-09-2021
TRIAL PRINCIPAL INVESTIGATOR	M.M. van der Eerden
SAP AUTHOR(s)	M.L. van Schaik
NCT number	[NCT ID not yet assigned]

1 SAP Signatures

I give my approval for the attached SAP entitled PRECISION study, dated 28-09-2021, version 1.3

Statistician (Author)
Name:

Signature: _____

Date: _____

Statistician Reviewer (As applicable)
Name:

Signature: _____

Date: _____

Principal Investigator
Name:

Signature: _____

Date: _____

2 Table of Contents

3 Abbreviations and Definitions

AE	Adverse Event
AECOPD	Acute Exacerbation of COPD
CRF	Case Report Form
COPD	Chronic Obstructive Pulmonary Disease
DSMB	Data Safety Monitoring Board
IMP	Investigational Medical Product

IQR	Interquartile range
PCT	Procalcitonin
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SUSAR	Suspected unexpected serious adverse event

4 Introduction

4.1 Preface

Chronic obstructive pulmonary disease (COPD) is a prevalent disease, worldwide, and in the Netherlands with approximately 600.000 patients. COPD is currently the 4th leading cause of death worldwide and it is estimated to be the 3rd leading cause in 2020 [1–3]. It is also a leading cause of disability-adjusted life years. 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) [4]. 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. 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 levels are minimally raised in viral infections, making it a relative specific diagnostic tool for bacterial infections [5]. Several trials have shown a reduction in antibiotic consumption in AECOPD when using a PCT-guided treatment algorithm [6–9]. PCT has not been tested in a clinical setting in a treatment algorithm specifically in COPD with the primary outcome measure being treatment failure

4.2 Scope of the analyses

The primary objective of this study is to show that at hospitalization for a severe exacerbation of COPD, PCT-guided treatment regarding antibiotic use is non-inferior to usual care consisting of prednisolone and or antibiotics, in terms of treatment failure at day 30 for patients hospitalized because of an acute exacerbation of COPD (AECOPD). Treatment failure is 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).

5 Study Objectives and Endpoints

5.1 Study Objectives

We hypothesize that at hospitalization for a severe acute exacerbation for COPD, biomarker-guided treatment based on 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 that 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.

5.2 Endpoints

The primary objective of this study is to show that at hospitalization for a severe exacerbation of COPD, PCT-guided treatment regarding antibiotic use is non-inferior to usual care consisting of prednisolone and or antibiotics, in terms of treatment failure at day 30 for patients hospitalized because of an acute exacerbation of COPD (AECOPD). Treatment failure is defined as disease-related mortality, endotracheal intubation, vasopressors, renal failure, lung abcess/empyema, pneumonia development or hospital readmission within 30 days after inclusion of the study.

The secondary objectives of this study are to assess the following secondary endpoints:

- 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.
- Change in Quality of Life on day 1, 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
- Start of antibiotic therapy after an initial opposite decision (after 48 hours)
- Non-Invasive ventilation after 72 hours of admission
- Length of hospitalization
- Re-exacerbation within 30 days
- Side effects (gastro-intestinal complaints, allergic reactions)
- Cumulative antibiotic consumption
- Cumulative prednisolone consumption

6 Study Methods

6.1 General Study Design and Plan

- Study design: prospective, randomized-controlled trial. Patients will be randomized to biomarker-guided treatment (based on blood procalcitonin level) or to usual care. In the usual care arm, and in the biomarker guided-arm in case of high (> 0.25ug/L) procalcitonin, patients will receive amoxicillin-clavulanic acid.
- Type of Comparison: non-inferiority.
- Type of control(s): usual care
- Level and method of blinding (e.g. double-blind): The patient and the outcome assessor will be blinded for the allocated treatment strategy. Two independent physicians will be selected per center to be the outcome assessors. The patient will not be blinded for the treatment itself (prednisolone with or without antibiotic therapy).
- Method of treatment assignment: We will use a block-randomisation with randomly alternating blocks of 4 and 6 patients (random permuted block randomisation). The randomisation will be stratified per center.
- At what point in time subjects are randomized relative to treatments, events and study periods: Upon presentation at the emergency department, patients will be clinically

judged for in- and exclusion criteria, among which indication for hospitalization. When eligible the patient will be notified about the study. When the patient is interested in participating, the patient information form will be discussed by the treating physician. The participation being voluntarily and the opportunity to discontinue participation will be made clear by the treating physician. Informed consent will be requested with at least two hours of time to decide

- Sequence and duration of all study periods: screening will occur on the first day of admission as decribed above, baseline characteristics will be collected within 24 hours of admission, active treatment will be 5 days, follow-up will be 30 days.

6.2 Inclusion-Exclusion Criteria and General Study Population

Inclusion criteria

- COPD, according to GOLD 2018 definition [10]
- Indication for hospitalization because of acute severe exacerbation of COPD, as defined by GOLD 2018 and modified Anthonisen criteria [10–12]
- 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) [11]
- 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 (bronchopathy is not an exclusion criterium)
- 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 exlusion criterium.

6.3 Randomization and Blinding

Upon presentation at the emergency department, patients will be clinically judged for in- and exclusion criteria, among which indication for hospitalization. When eligible the patient will be notified about the study. When the patient is interested in participating, the patient information form will be discussed by the treating physician. The participation being voluntarily and the opportunity to discontinue participation will be made clear by the treating physician. Informed consent will be requested with at least two hours of time to decide. Randomisation will occur by a computer-based program. We will use a block-randomisation with randomly alternating blocks of 4 and 6 patients and with stratification by center. The outcome assessors at day 30 will be blinded for the treatment arm. Two independent physicians will be selected per center to be the outcome assessors. The patient will also be blinded for the treatment strategy (usual care or PCT-guided), but not for the received treatment (antibiotics or no antibiotics next to prednisolone).

6.4 Study Assessments

Visit	Baseline	Day 3	Day 5	Day 10	Day 30
Informed consent	x				
Medication history	x				
Vital signs	x				
Check for eligibility	x				
Sputum collection	x				
Blood sampling, including procalcitonin*	x				
Blood samples for CRP, eosinophils	x	x	x		
Serum for storage	x				
Sputum for storage	x				
Modified Anthonisen criteria	x	x	x	x	x
Clinical assessment for treatment failure		x	x	x	x
CAT	x			x	x
EXACT-RS	x			x	x
EQ-5D-5L + resp. bolt-on	x			x	x
iMCQ (adapted version)					x
Randomization	x				
Antibiotic consumption	x	x	x	x	x
Prednisolone consumption	x	x	x	x	x
Diary cards according to modified	x	x	x	x	x

Anthonisen criteria					
Assesment of adverse effects/events	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.)

Analysis Time Windows

Visit (target day)	Lower bound (days)	Upper bound (days)
Baseline (0)	N/A	N/A
Day 3	N/A	N/A
Day 5	N/A	N/A
Day 10	9	11
Day 30	28	32

This section will go beyond the description of variables provided in the protocol in that it will list and describe all important study variables from a statistical perspective. The description of each variable should include:

- Modified Anthonisen criteria
    - Items are measured on with 3 optional answers where the first option = no deterioration, the second is slightly worse and the third option = much worse.

- EXACT respiratory symptoms questionnaire
    - Comprised of 11 questions about respiratory symptoms common for patients with COPD
    - Items are measured on a 0-3 or 0-4 ordered categorical scale for which a 0 = not at all, 1 = slightly or rarely or a little (depending on the question), 2 =moderately, 3 = severely or quite a bit, and 4 = extremely
    - The answer scales slightly differ depending on the question, for example breathlessness is scored on 0-3 ordered categorical scale for which a 0 = unaware of breathlessness, 1 = breathless during strenuous activity, 2= breathless during light activity, 3= breathless when washing or dressing, or present when resting

- COPD assessment test (CAT)
    - Comprised of 8 items to assess the impact of COPD on patients quality of life.
    - Items are measured on a 0-5 ordered categorical scale for which 0 = never experience this symptom to 5 = experience this symptom continuously

7 Sample Size

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. [6], 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%. 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. [13]. 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.

8 General Analysis Considerations

8.1 Timing of Analyses

Give details here of when, or under what criteria, the final analyses will be performed. Give details of what data cleaning and locking processes must take place to comply with standard operating procedure (SOP) specifications. For example:

- The final analysis will be performed when 693 subjects have completed the follow-up of 30 days, after which the database will be locked.

8.2 Analysis Populations

(ICH E3; 9.7.1, 11.4.2.5. ICH E9; 5.2)

8.2.1 Full Analysis Population (or Intention to Treat or Modified Intention to Treat)

- All subjects who were randomized and who took at least one dose of study drug.

8.2.2 Per Protocol Population

- All subjects who:
  - met all inclusion/exclusion criteria,
  - attained a sufficient compliance to the treatment received, treatment with prednisolone and/or antibiotics, when prescribed on admission for at least 5 days,
  - did not present serious deviations from the protocol.

8.2.3 Safety Population

- All subjects who received any study treatment (including control) but excluding subjects who drop out prior to receiving any treatment.

The analysis of all the efficacy variables will be performed on both the ITT and the PP populations in order to assess the robustness of the findings from the ITT population.
All the demographic and baseline patients' characteristics and safety outcomes will be analysed using the ITT population.
All efficacy variables will be analysed for ITT and the PPS, and the PP population will be considered the primary population for assessing efficacy.

8.3 Covariates and Subgroups

(ICH E3; 9.7.1, 11.4.2.1. ICH E9; 5.7)
As mentioned above, patients will be randomized. This will remove the effect of possible confounders.

The randomization and treatment allocation will be stratified by center. We will use alternating blocks of 4 and 6 patients which will lead to a maximum imbalance of 3 participants per center. We consider this to be an acceptable amount of imbalance.
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.

8.3.1 Multi-center Studies

(ICH E3;9.7.1, 11.4.2.4. ICH E9; 3.2)
We will adjust for center using random center-effects, this allows treatment effect to be different between centers. The combining of centers is necessary to be able to include the large number of patients needed according to our power analysis. Performing the same research in one center would lead to a much longer duration of the trial. The maximum number of patients recruited in one center in one year was estimated to be around 40, this would mean the trial would take up to more than 15 years before all of the 678 patients are included. The combining of centers also allows for testing the PCT-guided strategy in a variety of settings, and this will lead to a greater generalizability of the results.

8.4 Missing Data

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.

The statistical analyst will consider all possible reasons for missing data. If it is safe to assume that 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).

8.5 Interim Analyses and Data Monitoring (as applicable)

An interim analysis will be performed at 50% of patient accrual, analysing the primary outcome and safety data. The safety data consists of observed adverse events and SAE. 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 significant evidence of benefit

8.5.1 Purpose of Interim Analyses

An interim analysis will be performed because of uncertainty about the safety of the PCT-guided treatment strategy. Subjects who will not receive antibiotic therapy in the presence of a bacterial infection (because of a false-low/negative PCT concentration) could deteriorate because of the withholding of antibiotic treatment. This could lead to adverse outcomes, such as longer duration of hospital stay, ICU admission or death.
Another reason for performing the interim analyses is the possibility of a significant evidence of benefit of the PCT-guided treatment strategy according antibiotic treatment. A significant reduction in treatment failure could also mean a significant reduction in ICU admission, need for non-invasive ventilation, readmission, re-exacerbation and death.

8.5.2 Planned Schedule of Interim Analyses

An interim analysis will be performed at 50% of patient accrual, analysing the primary outcome and safety data. The safety data consists of observed adverse events and SAE. A DSMB will assess this interim analysis.

8.5.3 Stopping Rules

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 significant evidence of benefit

8.5.4 Analysis Methods to Minimize Bias

The per protocol (PP) population is the main analysis population because of the non-inferiority design of the trial.

8.5.5 Adjustment of Confidence Intervals and p-values

An interim analysis will be performed after 50% of the participants needed has been accrued/included. The analysis will focus on the primary outcome and on safety. 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 [14]. The safety data consists of observed adverse events and SAE. 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.

8.5.6 Practical Measures to Minimize Bias

An interim analysis will be performed at 50% of patient accrual, analysing the primary outcome and safety data. The safety data consists of observed adverse events and SAE. The interim analysis will be performed by a Data Safety Monitoring Board (DSMB) comprised of dr. G.J. Braunstahl (pulmonologist Franciscus Gasthuis, Rotterdam) dr. M. van Westreenen (medical microbiologist

Erasmus Medical Center, Rotterdam) and prof. dr. ir. H. Boersma (professor of clinical epidemiology, Erasmus Medical Center). These three individuals will be the only persons with knowledge of the data at the interim analysis. The advice of the DSMB will only be sent to the principal investigator. 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.

8.6 Multiple Testing

Op dit moment niet van toepassing, mogelijk nog wanneer primair eindpunt zou veranderen.

9 Summary of Study Data

Table 1. Baseline characteristics

The baseline characteristics are given in the table below.

	Usual care (n = 308)	PCT-guided treatment (n = 308)
Age in years – mean±SD		
Male gender – no. (%)		
BMI – mean±SD		
Smoking status: - current – no. (%) - past – no. (%) - pack years (mean, range)		
FEV1 % predicted - mean±SD		
GOLD classification: - I – no. (%) - II – no. (%) - III – no. (%) - IV – no. (%)		
Exacerbation type: - type I – no. (%) - type II – no. (%) - type III – no. (%)		
Median duration of symptoms in days - mean±SD		
CRP in mg/L – median [IQR]		
WBC 10^9/L – mean±SD		
CAT score – median [IQR]		
EXACT- RS score – median [IQR]		

Primary outcome

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

- Binary outcome parameter: yes or no. Description: number and percentage.
- 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 of 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 an 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.

Table 2. Primary endpoint and secondary endpoints

	PCT-guided treatment (n = 315)	Usual care (n = 315)		p-value
Primary endpoint: **Overall treatment failure:** - Disease-related mortality - Endotracheal intubation - Vasopressors - Renal failure - Lung abcess/empyema - Pneumonia development - Hospital readmission	 **n (%)** n (%) n (%) n (%) n (%) n (%) n (%) n (%)	 **n (%)** n (%) n (%) n (%) n (%) n (%) n (%) n (%)	OR (95% CI)	
Secondary endpoints				
Incomplete resolution of the clinical signs and symptoms at day 30 after (scored using the modified Anthonisen criteria)	n (%)	n (%)	OR (95% CI)	

Change in QoL using the CAT: after 10 days after 30 days	 mean (SD)or median [IQR]	 mean (SD)or median [IQR]		
Start of antibiotic therapy after an initial opposite decision (after 48 hours)	n (%)	n (%)	OR (95% CI)	
Side effects (gastro-intestinal complaints, allergic reactions)	n (%)	n (%)	OR (95% CI)	
Cumulative antibiotic consumption	mean/median days (SD) or [IQR]	mean/median days (SD) or [IQR]		
Cumulative prednisolone consumption	mean/median days (SD) or [IQR]	mean/median days (SD) or [IQR]		
Length of hospitalization	mean/median days (SD) or [IQR]	mean/median days (SD) or [IQR]		
Time to complete resolution of symptoms (modified Anthonisen criteria)	mean/median days (SD) or [IQR]	mean/median days (SD) or [IQR]		
Re-exacerbation within 30 days	n (%)	n (%)	OR (95% CI)	
EXACT – Respiratory symptoms scale, change: after 10 days after 30 days	 mean (SD)or median [IQR]	 mean (SD)or median [IQR]		
Non-Invasive ventilation (>72h)	n (%)	n (%)	OR (95% CI)	

Only deviations from the general overview will be noted in the subsequent sub-sections within section 9.

9.1 Subject Disposition

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.
One of Castor®'s prime features is that it keeps an audit trail, i.e. provides documentary evidence of the sequence of activities by user that have affected at any time a specific operation, procedure, or event. Data entry will be done according to Standard Operating Procedures. Besides, study specific data entry guidelines will be provided to local datamanagers, promoting a uniform and standardized way of data entry and providing ways of working in case of exceptions (i.e. missings, unknowns etc). The local datamanagers will be trained in using the eCRF system Castor® prior to data entry start. All trainings will be documented conform GCP requirements.

If data are complete for day 10 and day 30 then we consider this as a completion of the study for this study subject. If data from day 10 and or day 30 are missing every attempt will be made to collect the primary endpoint. When these attempts fail to collect the primary endpoint, this will be scored as a loss-to-follow-up.

An overview of the time-dependent rates of recruitment is provided below. This is of course a prediction and in agreement with ZonMW, who provided the required budget for this trial, we made

a prediction for 4 years. We aim to include all 690 in these four years, and according to our estimations this should be realistic:

Year 1

Month	Center 1	Center 2	Center 3	Center 4	Center 5	Center 6	Center 7	Center 8	Total cumul.
	SFG	EMC	RUMC	OLVG	AZ	NWZ	Isala	GH	
Mar-21	4	1	1	3	4	4	4	3	24
Apr-21	5	1	1	4	5	5	5	3	53
May-21	5	1	1	4	5	5	5	3	82
Jun-21	4	1	1	3	4	4	4	2	105
Jul-21	4	1	1	3	4	4	4	2	141
Aug-21	2	1	1	2	2	2	2	2	155
Sep-21	2	1	1	2	2	2	2	1	168
Oct-21	1	0	0	1	1	1	1	1	174
Nov-21	1	0	0	2	1	1	1	1	181
Dec-21	2	1	1	2	2	2	2	2	195
Jan-22	4	1	1	3	4	4	4	2	218
Feb-22	4	1	1	3	4	4	4	2	241
Total/year	38	10	10	32	38	38	38	24	

Year 2

Month	Center 1	Center 2	Center 3	Center 4	Center 5	Center 6	Center 7	Center 8	Total cumul.
	SFG	EMC	RUMC	OLVG	AZ	NWZ	Isala	GH	
Mar-22	4	1	1	3	4	4	4	3	265
Apr-22	5	1	1	4	5	5	5	3	294
May-22	5	1	1	4	5	5	5	3	323
Jun-22	4	1	1	3	4	4	4	2	346
Jul-22	4	1	1	3	4	4	4	2	369
Aug-22	2	1	1	2	2	2	2	2	383
Sep-22	2	1	1	2	2	2	2	1	396
Oct-22	1	0	0	1	1	1	1	1	402
Nov-22	1	0	0	2	1	1	1	1	409
Dec-22	2	1	1	2	2	2	2	2	423
Jan-23	4	1	1	3	4	4	4	2	446
Feb-23	4	1	1	3	4	4	4	2	469
Total/year	38	10	10	32	38	38	38	24	

Year 3

Month	Center 1	Center 2	Center 3	Center 4	Center 5	Center 6	Center 7	Center 8	Total cumul.
	SFG	EMC	RUMC	OLVG	AZ	NWZ	Isala	GH	
dec-22	4	1	1	3	4	4	4	3	493
jan-23	5	1	1	4	5	5	5	3	522
feb-23	5	1	1	4	5	5	5	3	551
mrt-23	4	1	1	3	4	4	4	2	574
apr-23	4	1	1	3	4	4	4	2	597
mei-23	2	1	1	2	2	2	2	2	611
jun-23	2	1	1	2	2	2	2	1	624
jul-23	1	0	0	1	1	1	1	1	630
aug-23	1	0	0	2	1	1	1	1	637
sep-23	2	1	1	2	2	2	2	2	651
okt-23	4	1	1	3	4	4	4	2	674
nov-23	4	1	1	3	4	4	4	2	697
Total/year	38	10	10	32	38	38	38	24	

Year 4

Month	Center 1	Center 2	Center 3	Center 4	Center 5	Center 6	Center 7	Center 8	Total cumul.
	SFG	EMC	RUMC	OLVG	AZ	NWZ	Isala	GH	
dec-23	4	1	1	3	4	4	4	3	721
jan-24	5	1	1	4	5	5	5	3	750
feb-24	5	1	1	4	5	5	5	3	779
mrt-24	4	1	1	3	4	4	4	2	802
apr-24	4	1	1	3	4	4	4	2	825
mei-24	2	1	1	2	2	2	2	2	839
jun-24	2	1	1	2	2	2	2	1	852
jul-24	1	0	0	1	1	1	1	1	858
aug-24	1	0	0	2	1	1	1	1	865
sep-24	2	1	1	2	2	2	2	2	879
okt-24	4	1	1	3	4	4	4	2	902
nov-24	4	1	1	3	4	4	4	2	925
Total/year	38	10	10	32	38	38	38	24	

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram

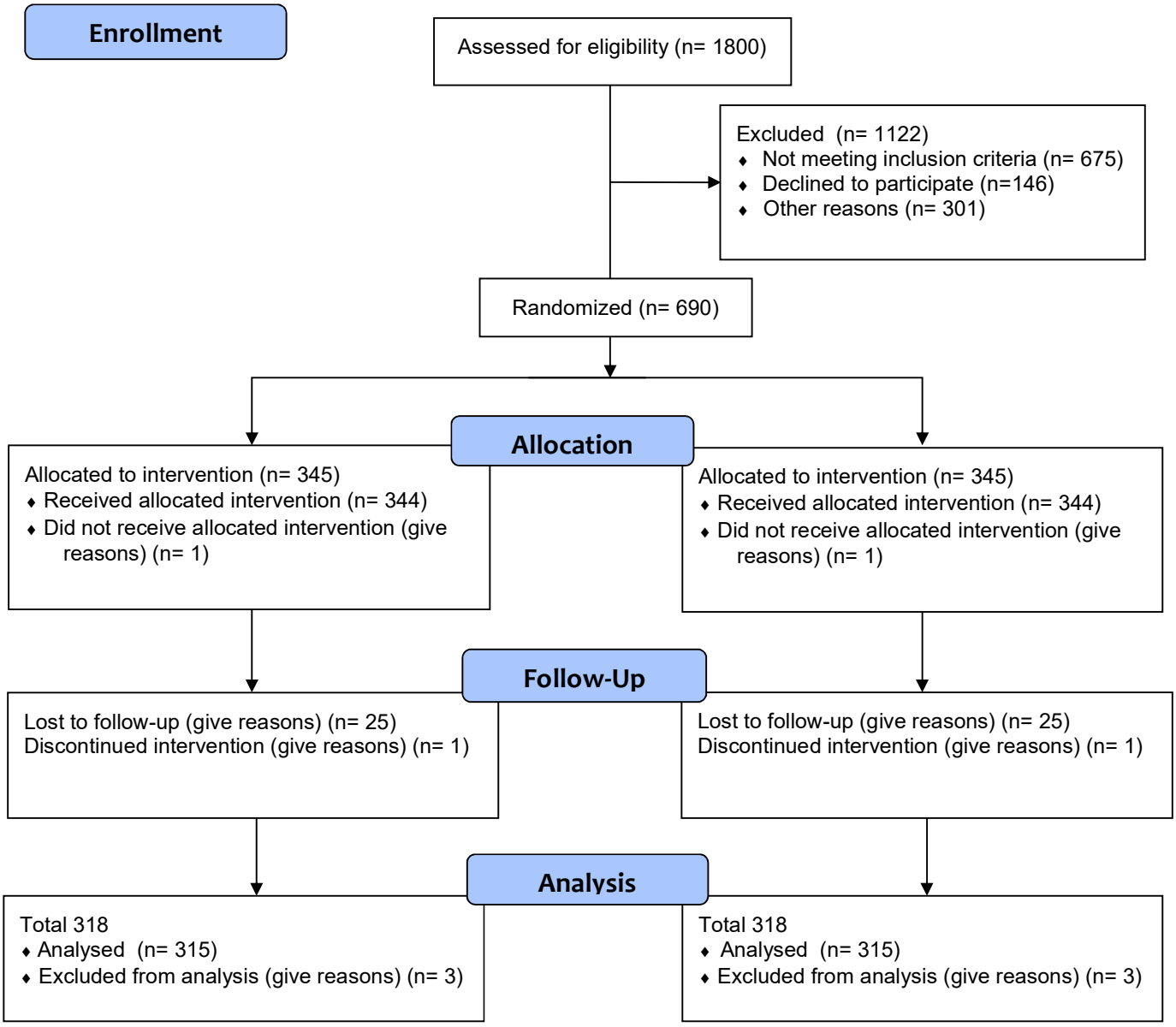

Figure 1. Consort flow diagram

9.2 Derived variables

The primary endpoint consists of several variables: disease-related mortality, endotracheal intubation, vasopressors, renal failure, lung abcess/empyema, pneumonia development and hospital readmission.
The key secondary endpoint is derived from the scores of the diary card with the modified Anthonisen criteria* the patient will fill in on baseline, day 3, day 5, day 10 and day 30. This endpoint will be scored by an independent physician. If there is incomplete resolution of symptoms, this will result in treatment failure. The symptoms are scored as categorical variables and include shortness of breath (slightly or much worse or 'as baseline condition prior to exacerbation'), sputum production (slightly or much more or 'as baseline condition prior to exacerbation'), sputum discoloration (slightly or strongly increased or 'as baseline condition prior to exacerbation') and minor symptoms as coughing, sore throat, fever, wheezing or a blocked or running nose.
When one of these symptoms has not been resolved on day 30 this should result in scoring this as treatment failure.

*Example of the diary card with the modified Anthonisen criteria we used to derive our own diary card in Dutch. This original diary card was designed by Jaap Trappenburg et al. and used in a trial that was published in 2011 [15](Thorax 2011;66:977e984):

After evening diner

Compared with previous weeks ...	DAY 1 __/__/ 2009	DAY 1 __/__/ 2009	DAY 1 __/__/ 2009
I am more short of breath than normal	◻ No ◻ Yes, slightly increased ◻ Yes, clearly increased	◻ No ◻ Yes, slightly increased ◻ Yes, clearly increased	◻ No ◻ Yes, slightly increased ◻ Yes, clearly increased
I produce more sputum than normal	◻ No ◻ Yes, slightly increased ◻ Yes, clearly increased	◻ No ◻ Yes, slightly increased ◻ Yes, clearly increased	◻ No ◻ Yes, slightly increased ◻ Yes, clearly increased
My sputum is more green / yellow / brown than normal	◻ No ◻ Yes, slightly increased ◻ Yes, clearly increased	◻ No ◻ Yes, slightly increased ◻ Yes, clearly increased	◻ No ◻ Yes, slightly increased ◻ Yes, clearly increased
I have more complaints of:	◻ Coughing ◻ Sore throat ◻ Wheezing ◻ Running nose / blocked nose ◻ Fever (more than 38° C	◻ Coughing ◻ Sore throat ◻ Wheezing ◻ Running nose / blocked nose ◻ Fever (more than 38° C)	◻ Coughing ◻ Sore throat ◻ Wheezing ◻ Running nose / blocked nose ◻ Fever (more than 38° C)

Figure 2. Anthonisen diary card

9.3 Protocol Deviations

When a physician decides to prescribe antibiotic therapy even though the patient has a low serum concentration of procalcitonin (≤0.25ug/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 quick recovery and gets discharged from the hospital without antibiotic therapy and then has a relapse. We do not expect this to happen more 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).

9.4 Demographic and Baseline Variables

The summary statistics will be produced in accordance with section 9.

9.5 Concurrent Illnesses and Medical Conditions

The summary statistics will be produced in accordance with section 9.

10 Efficacy Analyses

- Summary statistics that will be produced for continuous and categorical data:
    - 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 scored 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 an 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.

- Analysis populations that will be used and identification of the primary population.
    - We will analyze the population with a per-protocol analysis and an intention-to-treat analysis. The primary population will be the per-protocol population.

- A statement of the clinical objective rephrased in precise statistical terms (null and alternative hypotheses):
    - Null hypothesis: PCT-guided treatment regarding antibiotic use is inferior to usual care in patients with an acute exacerbation of COPD
    - Alternative hypothesis: PCT-guided treatment regarding antibiotic use is non-inferior to usual care in patients with an acute exacerbation of COPD

- The nature of the hypothesis is confirmatory

10.1 Primary Efficacy Analysis

The summary statistics will be produced in accordance with section 9.
The non-inferiority of the treatment will be decided based on the 95% confidence interval of the OR from the logistic mixed model for the treatment arm versus the usual care arm.

10.2 Secondary Efficacy Analyses

10.2.1 Secondary Analyses of Primary Efficacy Endpoint

Our primary analysis population will be the per-protocol population because of the non-inferiority design. The secondary analysis population will be the intention-to-treat analysis.

10.2.2 Analyses of Secondary Endpoints

- 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.
    - Dichotomous variable (yes/no)
    - Description: Number and percentage
    - Test: logistic mixed-effects model

- Change in quality of life using the COPD assessment test
    - Measurements are continuous and paired (multiple (3) measurements in all patients (day 1, 10 and 30))
    - Description:
        - Normal distribution: mean score±SD
        - Skewed distribution: median (IQR)
    - Test:
        - mixed effects model with random effects for center and patient to account for the extra hierarchical level in the data. In case of violations of the normality assumptions, transformations of the dependent variable will be applied or the bootstrapping procedure will be used to obtain robust confidence intervals.
    - MCID = a decrease of 2 points after treatment is considered a minimal clinically important difference. When the difference in improvement of the CAT is < 2 points, then this will be considered a clinically non-significant difference[16,17].

- EXACT – Respiratory symptoms scale
    - Measurements are continuous and paired (multiple (3) measurements in all patients (day 1, 10 and 30))
    - Description:
        - Normal distribution: mean score±SD
        - Skewed distribution: median (IQR)
    - Test:
        - mixed effects model with random effects for center and patient to account for the extra hierarchical level in the data. In case of violations of the normality assumptions, transformations of the dependent variable will be applied or the bootstrapping will be used to obtain robust confidence intervals.
    - MCID: symptomatic improvement is defined by a decrease of the RS-total score of at least 2 points. When the difference in improvement of the EXACT is < 2 points, then this will be considered a clinically non-significant difference[18].

- Time to complete resolution of symptoms in days according to daily symptom diaries evaluating the modified Anthonisen criteria
    - Continuous variable, unpaired
    - Description:
        - Normal distribution: mean score±SD
        - Skewed distribution: median (IQR)
    - Test: mixed-effects model

- Decision to start antibiotic treatment after an initial opposite decision (after 48 hours)
    - Dichotomous variable (yes/no)
    - Description: Number and percentage
    - Test: logistic mixed-effects model.

- Non-Invasive ventilation after 72 hours of admission
    - Dichotomous variable (yes/no)
    - Description: Number and percentage
    - Test: logistic mixed-effects model.
- Length of hospitalization in days
    - Continuous variable, unpaired
    - Description:
        - Normal distribution: mean score±SD
        - Skewed distribution: median (IQR)
    - Test: mixed-effects model

- Re-exacerbation within 30 days
    - Dichotomous variable (yes/no)
    - Description: Number and percentage
    - Test: logistic mixed-effects model.

- Side effects (gastro-intestinal complaints, allergic reactions)
    - Nominal/dichotomous variable (yes/no), unpaired
    - Description: Number and percentage
    - Test: logistic mixed-effects model.

- Cumulative antibiotic consumption in days
    - Continuous variable, unpaired
    - Description:
        - Normal distribution: mean score±SD
        - Skewed distribution: median (IQR)
    - Test: mixed-effects model

- Cumulative prednisolone consumption in days
    - Continuous variable, unpaired
    - Description:
        - Normal distribution: mean score±SD
        - Skewed distribution: median (IQR)
    - Test: mixed-effects model

11 Safety Analyses

All (serious) adverse events reported spontaneously by the subject or observed by the investigator or his staff from the moment of informed consent until the end of the 30 days of follow-up will be recorded. Suspected unexpected serious adverse reactions will also be recorded.

We will list the following (serious) adverse reactions:

- Mortality
    - With a description of the frequencies and percentage in both groups
    - Analysis will be done using Chi square's test or Fisher's exact test, depending on the number of deaths.
- (Serious) adverse reactions
    - With a description of the frequencies and percentage in both groups
    - Analysis will be done using Chi square's test or Fisher's exact test, depending on the number of reactions/events.

Serious adverse events will be summarized as in the table below:

Table 3. Summary of all (serious) adverse events

Outcome measure	Usual care			PCT-guided treatment			(adjusted) odds ratio or relative risk	95% confidence interval	
	n	freq.	%	n	freq.	%		lower limit	upper limit
Mortality									
Adverse effects from antibiotics - Allergic reaction - Diarrhea - Clostridium difficile infection									
Readmission, overall									
Readmission, with AECOPD									
Pneumonia									
ICU-admission									

When calculating the incidence of adverse events, or any sub-classification thereof by treatment, time period, severity, etc., each subject will only be counted once and any repetitions will be ignored; the denominator will be the total population size.

Per ClinicalTrial.gov reporting requirements, three tables summarizing adverse events are required:

- All-Cause Mortality: A table of all anticipated and unanticipated deaths due to any cause, with number and frequency of such events in each arm/group of the clinical study.

Table 4. All-Cause Mortality

Outcome measure	Usual care			PCT-guided treatment			(adjusted) odds ratio or relative risk	95% confidence interval	
	n	freq.	%	n	freq.	%		lower limit	upper limit
All-cause mortality									

- Serious Adverse Events:

Table 5. Serious Adverse Events

Type of SAE	Usual care			PCT-guided treatment			(adjusted) odds ratio or relative risk	95% confidence interval	
	n	freq.	%	n	freq.	%		lower limit	upper limit
Respiratory system: - Pneumonia - Respiratory failure/need for NIV									
Cardiovascular system: - myocardial infarction - acute heart failure									
Gastro-intestinal system - severe diarrhea									

- Other (Not Including Serious) Adverse Events: A table of anticipated and unanticipated events (not included in the serious adverse event table) that exceed a frequency threshold (for example, 5 %) within any arm of the clinical study, grouped by organ system, with number and frequency of such events in each arm/group of the clinical study.

Table 6. Other (Not Including Serious) Adverse Events

Outcome measure	Usual care			PCT-guided treatment			(adjusted) odds ratio or relative risk	95% confidence interval	
	n	freq.	%	n	freq.	%		lower limit	upper limit
Respiratory system - Need for more intensive use of nebulizer									
Cardiovascular system - Hypertension									
Gastrointestinal system									

- Diarrhea - constipation									

11.1 Extent of Exposure

The summary statistics will be produced in accordance with section 9.

11.2 Adverse Events

The summary statistics will be produced in accordance with section 9."

When calculating the incidence of adverse events, or any sub-classification thereof by treatment, time period, severity, etc., each subject will only be counted once and any repetitions of adverse events will be ignored; the denominator will be the total population size.

Adverse events reported from informed consent until the end of the 30 day follow-up will be reported and analyzed in accordance with section 9.
We will report the AEs that are of interest. The most important AEs are the ones related to the antibiotic treatment, because we expect a difference in the incidence between the usual care group and the PCT-guided treatment group. These AEs include:

- Gastro-intestinal symptoms caused by the antibiotic treatmen:
    - Mainly diarrhea
    - Clostridium difficile infection
- Allergic reactions to antibiotic treatment

Other AEs of interest are re-admission (all-cause), re-admission (for AECOPD), ICU admission, need for Non-invasive ventilation, death.

11.3 Deaths, Serious Adverse Events and other Significant Adverse Events

We will report deaths and serious adverse events separate from adverse events. Serious adverse events and other significant adverse events will be reported by organ-system if appropriate.

11.4 Pregnancies (As applicable)

Pregnancy is one of the exclusion criteria of our trial. We do not expect any pregnancies after inclusion, but when there is a suspicion this will be tested. The included population is above 40 years of age which makes a pregnancy less likely to happen during our trial period.

11.5 Clinical Laboratory Evaluations

The summary statistics will be produced in accordance with section 9.
We do not expect difficulties in differences between centers in normal ranges of the most important laboratory evaluations. The PCT concentration has a fixed cut-off, determined by the initiators of the trial. CRP concentration will be reported with a mean value with standard deviations, the normal ranges do not interfere with the type of reporting of this value.

11.6 Prior and Concurrent Medications (As applicable)

Not applicable

11.7 Other Safety Measures

Vital signs will be reported at baseline, these include blood pressure, respiratory frequency, oxygen saturation, heart frequency and body temperature. The summary statistics will be produced in accordance with section 9.

12 Pharmacokinetics (As Applicable)

Not applicable

13 Other Analyses

A cost-effectiveness analysis will be performed led by prof. dr. MPMH Rutten - van Mölken.
The statistics used for this analysis are reported globally below.

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 [19]. 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) [20]. 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 [21]. 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 [22].
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 [23]. 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 [24,25].

14 Reporting Conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

15 Quality Assurance of Statistical Programming (As Applicable)

The following study-specific documents will be used:

- Study protocol, current version 8, date 19-03-21 (amendment pending version 9, 09-09-21)
- Labmanual, current version 1.0, date 09-03-21
- Informed consent form, current version 1.3, date 26-08-21 (amendment pending version 9, 09-09-21)
- SAE and SUSAR form, current version 1.0, date 28-01-2020

SPSS and R will be used as statistical software. SPSS (version xx.xx), R version (xx.xx). The operating system used will be Windows 10.
The data will be stored in ….
To be able to replicate the analyses performed with SPSS and R the syntax will be accompanied by comments to explain the analyses.

16 References

1. Mathers C, Fat DM, Boerma T. The Global Burden of Disease: 2004 Update. World Health Organization, Geneva. 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. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease GOLD executive summary. Am. J. Respir. Crit. Care Med. 2013. p. 347–65.

5. 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.
6. 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.
7. 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.
8. Schuetz P, Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database Syst. Rev. John Wiley and Sons Ltd; 2017.
9. Miravitlles 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.
10. 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
11. 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.
12. 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.
13. Huang DT, Yealy DM, Filbin MR, Brown AM, Chang C-CH, Doi Y, et al. Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection. N Engl J Med [Internet]. 2018;379:236–49. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1802670
14. Gogtay N, Thatte U. Principle of Interim Analysis. J Assoc Physicians Inda. 2017;65:78–83.
15. Trappenburg JCA, Monninkhof EM, Bourbeau J, Troosters T, Schrijvers AJP, Verheij TJM, et al. Effect of an action plan with ongoing support by a case manager on exacerbation-related outcome in patients with COPD: A multicentre randomised controlled trial. Thorax. BMJ Publishing Group; 2011;66:977–84.
16. 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.
17. 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.
18. 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.
19. Zorginstituut Nederland. Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg. 2015 Nov.
20. Bouwmans C, De Jong K, Timman R, Zijlstra-Vlasveld M, Van Der Feltz-Cornelis C, Tan 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.
21. 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.
22. Koopmanschap MA, Rutten FFH, Martin Van Ineveld B, Van Roijen L. The friction cost method for measuring indirect costs of disease. J. Health Econ. 1995.

23. Hoogendoorn M, Oppe M, Boland MRS, Goossens LMA, Stolk EA, Rutten–van Mölken MPMH. Exploring the Impact of Adding a Respiratory Dimension to the EQ-5D-5L. Med Decis Mak. SAGE Publications Inc.; 2019;39:393–404.
24. 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.
25. ZonMW. Budget Impact Analyses in de praktijk. Leidraad Budget Impact analyse [Internet]. 2020 Feb. Available from: www.facebook.com/zonmwNL

17 Listing of Tables, Listings and Figures

Tables:

- Table 1.:
    - Title: Baseline characteristics
    - 3 columns, at least twelve rows
    - Per-protocol population will be given, since this is the primary analysis population
    - Mean will be reported with one decimal, just as the standard deviation and range
    - Median will be reported with one decimal
    - Frequencies will be reported in rounded numbers
    - Percentages will be reported after the frequency as (%) with one decimal
    - Interquartile range will be reported after the median as [IQR] with one decimal

- Table 2:
    - Title: Primary endpoint and secondary endpoints
    - 5 columns, 14 rows
    - Per-protocol population will be given, since this is the primary analysis population
    - Frequencies will be reported in rounded numbers
    - Percentages will be reported after the frequency as (%) with one decimal
    - Interquartile range will be reported after the median as [IQR] with one decimal
    - Adjusted odds ratio/RR/RD will be reported with 2 decimals
    - 95% C.I. will be reported with 2 decimals
    - P-value will be reported with 3 decimals
    - Mean/median value of the CAT and EXACT will be reported with one decimal, just as the standard deviation or the interquartile range[IQR]

- Table 3:
    - Title: Summary of (serious) adverse events
    - 5 main columns, 10 minor columns, number of rows is not known at this point
    - Frequencies will be reported as rounded numbers
    - Percentages will be reported after the frequency as (%) with one decimal
    - The adjusted OR/RR will be reported with 2 decimals
    - 95% C.I. will be reported with 2 decimals

- Table 4.
    - Title: All-Cause Mortality
    - 5 main columns, 10 minor columns, 2 rows
    - Frequencies will be reported as rounded numbers
    - Percentages will be reported after the frequency as (%) with one decimal
    - The adjusted OR/RR will be reported with 2 decimals

- 95% C.I. will be reported with 2 decimals

- Table 5:
  - Title: Serious Adverse Events
  - 5 main columns, 10 minor columns, number of rows is unknown at this moment
  - Frequencies will be reported as rounded numbers
  - Percentages will be reported after the frequency as (%) with one decimal
  - The adjusted OR/RR will be reported with 2 decimals
  - 95% C.I. will be reported with 2 decimals

- Table 6:
  - Title: Other (Not Including Serious) Adverse Events
  - 5 main columns, 10 minor columns, number of rows is unknown at this moment
  - Frequencies will be reported as rounded numbers
  - Percentages will be reported after the frequency as (%) with one decimal
  - The adjusted OR/RR will be reported with 2 decimals
  - 95% C.I. will be reported with 2 decimals

Figures:

- Figure 1: Consort Flow Diagram
  - According to the rules of the Consort Flow Diagram
    - Frequencies will be reported as rounded numbers

- Figure 2: Picture of Anthonisen Diary Card
  - Will not be included in the trial manuscript