Statistical Analysis Plan

Study ID: 213550

Official Title of Study: COPD disease burden, patient characteristics, maintenance treatment patterns and factors influencing treatment decisions in China Tier 2 and Tier 3 hospitals

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GlaxoSmithKline (China) Investment Co., Ltd

COPD disease burden, patient characteristics, maintenance treatment patterns and factors influencing treatment decisions in China Tier 2 and Tier 3 hospitals

213550

Statistical Analysis Plan

Version: 2.0

Date: 09 Mar 2023

Sponsor Approval Page

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Analysis Purpose (see page 7)

Version: 2.0

Project Statistician: PPD

Company Name: Hangzhou Tigermed Consulting Co., Ltd

Signature: PPD Date: PPD

Review Statistician: PPD

Company Name: Hangzhou Tigermed Consulting Co., Ltd

Signature: PPD Date: PPD

Review Programmer: PPD

Company Name: Hangzhou Tigermed Consulting Co., Ltd

Signature: PPD Date: PPD

Approved by Sponsor: PPD

Company Name: GSK(China) R&D Co., Ltd.

Signature: PPD Date: PPD

Modification History

Version	Version Date	Author	Description
1.0	12 Apr 2021	PPD	First Finalized
2.0	09 Mar 2023		The main changes from SAP V1.0 are summarized below: • The SAP V2.0 is based on the protocol V2.0 and CRF V2.0, and the SAP V1.0 is based on the protocol V1.0 and CRF V1.0 • The Tigermed's template of SAP has been updated, so the framework of the SAP has also been modified according to the template. • The following analyses were added, see section 6.7 for details (1) The change of treatment in individual treatments by each maintenance treatment (2) LAMA, LAMA/LABA, ICS/LABA step up situation (3) MITT, SITT step down situation (4) COPD prescription for maintenance therapy step up situation of different patients (5) Change of CAT score when treatment stepping up and stepping down • The analyses of maintenance treatment prescription MITT, SITT were added.

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Abbreviation

Abbreviation	Specification
AE	Adverse Event
CAT	COPD assessment test
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
DECAF Score	Dyspnoea, Eosinopenia, Consolidation, Acidaemia and atrial Fibrillation (DECAF) Score
FEV1	Forced expiratory volume in one minute
GSK	GlaxoSmithKline
ICS	Inhaled corticosteroid
IPAQ	International physical activity questionnaire
LABA	Long-acting beta agonists
LAMA	Long-acting muscarinic antagonist
MET	Metabolic equivalent
mMRC	Modified Medical Research Council
OR	Odds Ratio
PHQ9	The patient health questionnaire
PI	Principle Investigator
Q1	25% quantile
Q3	75% quantile
SAC	Statistical Analysis Complete
SAP	Statistical analysis plan
SD	standard deviation
SOP	Standard Operation Procedure
TBD	To be determined

1. Introduction

This statistical analysis plan is for the "COPD disease burden, patient characteristics, maintenance treatment patterns and factors influencing treatment decisions in China Tier 2 and Tier 3 hospitals " (protocol ID: 213550) of GlaxoSmithKline (China) Investment Co., Ltd.
This statistical analysis plan is based on protocol (English version 2.0, 26May2022) and Case Report Form (Chinese CRF, version 2.0, 15Jul2022).

2. Study Design

2.1. Study Objective

2.1.1. Primary Objective

To quantify the pattern of COPD maintenance treatment prescribing in different patient groups in Tier 2 and 3 hospitals in China.

For the primary analysis, the patients will be categorized into 3 cohorts:

- Cohort 1: Patients presenting with stable disease
- Cohort 2: Patients presenting with a moderate exacerbation not requiring hospitalization
- Cohort 3: Patients requiring hospitalisation for an exacerbation

2.1.2. Secondary Objectives

- To examine factors (including disease severity and socio-economic factors) that are associated with different patterns of COPD maintenance treatment
- To assess the disease burden of patients (using baseline data)
- To assess the proportion of patients whose prescribed maintenance treatment is stepped up (adding another maintenance treatment), stepped down (withdraw any of the maintenance medication but kept the maintenance treatment), switch (between LAMA/LABA and ICS/LABA), stopped (stop all maintenance treatment) or remains the same across the different study time points
- To assess the proportion of patients receiving each treatment class at 3 months

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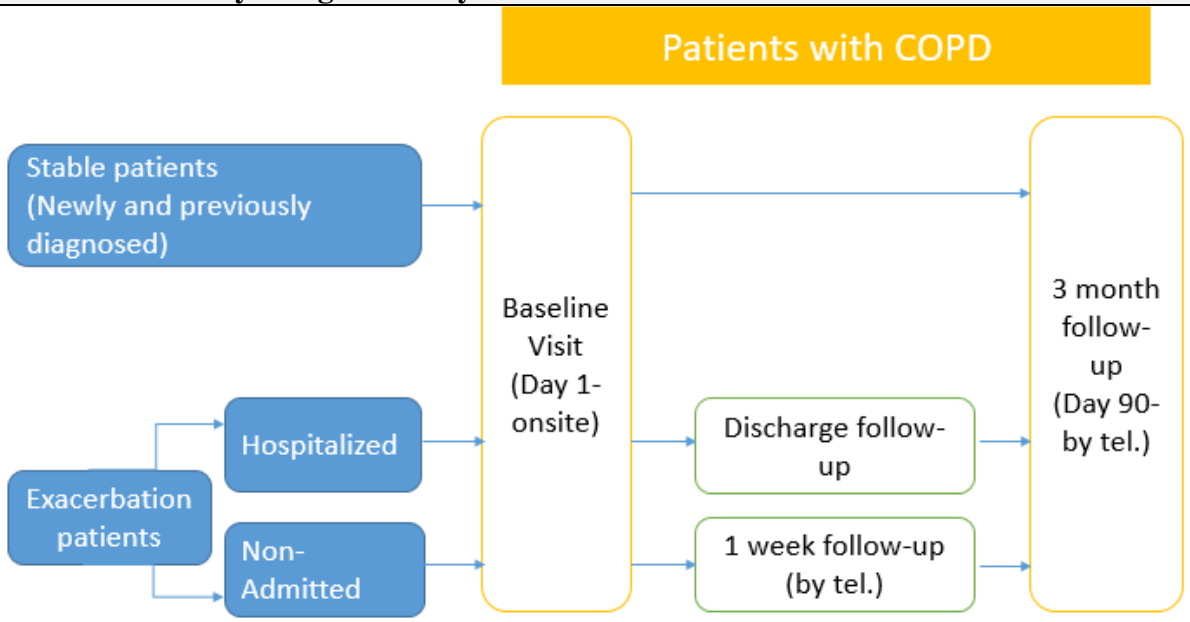
[redacted]

2.2. Overview of Study Design and Key Features

Overview of Study Design and Key Features



Overview of Study Design and Key Features	
Design Features	This is a 3-month, multi-center, prospective study in newly diagnosed and previously diagnosed patients with COPD presenting to clinics, either in a stable state, defined as no exacerbation for at least 1 month, or with acute exacerbation, in Tier 2 and 3 hospitals distributed across China.
Dosing	Since this is an observational study, the dosing will be collected as it is.
Time & Events	Refer to Appendix : Schedule of Activities
Treatment Assignment	The patients will be categorized into 3 cohorts: **Cohort 1:** Patients presenting with stable disease (newly and previously diagnosed) **Cohort 2:** Patients presenting with a moderate acute exacerbation not requiring hospitalization **Cohort 3:** Patients requiring hospitalization for an acute exacerbation
Interim Analysis	No interim analysis is planned.
Study Type and Control Type	There is no study type and control type.
Randomization and Blinding Design	Not applicable.

3. Estimand

Not applicable.

4. Sample Size Consideration

Sample Size Consideration

The primary objective of the study is to understand the prescription pattern of COPD maintenance treatment in Tier 2 and Tier 3 hospitals in China. Around 1500 patients with COPD will be enrolled which includes stable patients and patients with COPD exacerbations (moderate and severe). All enrolled patients will be included in the analysis. This sample size was chosen to ensure adequate patient representation and provide sufficient size for reliable analysis of different patient groups and key subgroups.

It is estimated that 750 patients each from tier 2 and tier 3 hospitals will be enrolled to provide adequate representation on healthcare status for COPD in China. The target number of patients in each tier of hospital and patient groups is shown in Table 1. After 500 patients have been recruited, the numbers will be reviewed to assess whether adequate number of participants have been enrolled for patient in stable state or with COPD exacerbations in each tier of hospital. At this point, recruitment policy might be changed to ensure an adequate distribution of patients. Thereafter, recruitment to different patient groups will be monitored monthly and further corrective action taken if needed.

Table 1: Patient recruitment strategy (estimated distribution ratio)

Patient Cohort	Tier 2 hospital (% of total patients)	Tier 3 hospital (% of total patients)
Stable	25%	25%
Moderate acute or Hospitalized exacerbation	25%	25%

The secondary objective of this study is to examine factors (include baseline disease severity and baseline socio-economic factors) that are associated with different patterns of maintenance treatment. In the secondary analysis, we attempt to find significant association between disease severity (GOLD Group: A&B vs. C&D) and triple therapy at baseline for COPD patients.

Based on a previous study[Brusselle, 2015][1], about 24% COPD patients in Group A&B were prescribed triple therapy at diagnosis and about 46% COPD patients in Group C&D were prescribed triple therapy at diagnosis. The proportion of patients in Group A&B accounted for 66% of the total. We will use logistic regression to test this association and the parameters mentioned will be used for power calculation.

With a two-sided 5% significance level and a sample size of 375 subjects of each patient group in each Tier of hospital, we will have a power bigger than 98% for demonstrating a statistically significant result for the association between disease severity (GOLD Group: A&B vs. C&D) and triple therapy at baseline for COPD patients.

5. Analysis Datasets

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility	• Study population
Enrolled	• All participants who passed screening (met eligibility criteria) and entered the study. • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study are excluded from the Enrolled population as they did not enter the study.	• Study population • Primary analysis • Secondary analysis CCI [redacted] • Safety analysis

6. Statistical Methods

6.1. General Statistical Consideration

Demographics and baseline characteristics data, primary data, secondary data, CCI [redacted] and safety data will be analyzed. CCI [redacted]

The final planned primary analyses will be performed after the completion of the following sequential steps:

- All participants have completed the study as defined in the protocol.
- All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.

6.1.1. Reporting Process

Software
• The SAS 9.4 version or above software will be used.
Analysis Datasets
• Analysis datasets will be created according to Tigermed's standards
Generation of RTF Files
• Both RTF and PDF files will be generated.

6.1.2. Reporting Standards

General
• Tigermed's template will be applied for reporting, unless otherwise stated.

Formats	
• For continuous data, min and max are rounded to the same decimal place as the original data; mean, median, Q1 and Q3 are rounded to one decimal place more than the original data; SD are rounded to two decimal places more than the original data. All above statistics will be rounded to no more than 4 decimal places. • For categorical data, percentage is rounded to 1 decimal place. If CI is needed, the lower and upper bounds will be rounded to 2 decimal places. • P value will be rounded to 4 decimal places. '<.0001' will be displayed when the P value is lesser than 0.0001 and '>.9999' will be displayed when the P value is greater than 0.9999.	
Unscheduled Visits	
• Unscheduled visits will not be included in summary tables and figures. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	number of non-missing subjects (n), number of missing patients (nmiss), mean, standard deviation (SD), median, 25% quantile (Q1), 75% quantile (Q3), minimum (min) and maximum (max)
Categorical Data	N, n, frequency, %
Statistical test whenever required	
Continuous Data	T test, ANOVA, Wilcoxon rank sum test or Wilcoxon signed-rank test
Categorical Data	Chi-square test, Fisher's exact test
Model Selection	
• Logistic regression The covariates with P-value less than 0.1 in univariate logistic regression and fixed variables (including Age, Gold grade, Baseline CAT score, Type of hospital and History of exacerbation) will be included in the multivariate logistic regression model.	
Significance of test	
• Statistical analysis will be performed under the bilateral significance level of 0.05 whenever required, unless otherwise specified.	

6.1.3. Baseline Definitions

The measurement at baseline visit will be defined as baseline, unless otherwise specified. If the patient is too ill, then baseline data will be collected before discharge. Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

Definition	Reporting Details
Change from Baseline	= Post-baseline Value – Baseline
% Change from Baseline	= 100 × [(Post-baseline Value – Baseline) / Baseline]

6.1.4. Multicenter Studies

It is estimated that 750 patients each from tier 2 and tier 3 hospitals will be enrolled to provide

adequate representation on healthcare status for COPD in China. All analyses of primary, secondary CCI [redacted] will be performed for Tier 2 and 3 hospitals separately.

6.1.5. Covariates and Other Strata

The list of covariates and other strata may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses. Additional covariates and other strata of clinical interest may also be considered.

Covariates	Details
Age	below 65 years old 65 years old and above
Gender	female male
Smoking history	Never smoking Used to smoke Current smoking
Any comorbidity	• Cardiovascular Disease (CVD defined as ischemic heart disease, heart failure, atrial fibrillation, hypertension): yes vs no • Diabetes: yes vs no • Hyperlipemia: yes vs no • Anxiety or Depression: yes vs no • Gastroesophageal reflux disease (GERD): yes vs no • Obstructive sleep apnea syndrome (OSAS): yes vs no • Concurrent asthma with COPD: yes vs no • Past history of tuberculosis: yes vs no
Baseline GOLD 2019 group	A B C D
Annual income (KRMB)	<30, 30-80, >80
Proportion of outpatient medical insurance (for COPD treatment) (%)	<33%, 33-66%, >66%
Place of residence	city vs outside city
Educational level	illiterate primary school junior mid-school high-school university
Gold grade（Classification of severity of airflow limitation in	I= Mild II=Moderate

Covariates	Details
CRF）	III=Severe IV=Very severe
mMRC	Grade 0, Grade 1, Grade 2, Grade 3, Grade 4
Baseline CAT score	≤10, 11-20, 21-30, 31-40. And it will be as continuous data in Logistic regression.
Type of hospital	Tier 2, Tier 3
History of exacerbation	None, Moderate exacerbation, Previous hospitalised exacerbation; And two level (none and exacerbation) will be used in Logistic regression.
Severity of exacerbation (only for exacerbation cohort)	Mild, Moderate, Severe

6.1.6. Examination of Subgroups

The list of subgroups may be used in descriptive summaries and statistical analyses. Additional subgroups of clinical interest may also be considered.

Subgroup	Categories
Disease status at baseline	stable exacerbation
Exacerbation status at baseline	moderate exacerbation, requiring hospitalization for an exacerbation
DECAF risk	Mild(0-1 score), moderate(2 score) and severe(3-6 score)
Treatment satisfaction	Satisfied with current treatment overall: yes vs no
Treatment confidence	More optimistic, very pessimistic and lost confidence, no strong feelings
Level of physical activities(IPAQ)	Low, moderate and high
Level of depression(PHQ9)	None-minimal(0-4 score), mild(5-9 score), moderate(10-14), moderately severe(15-19 score), severe(20-27 score)
Smoke	≥10 pack year vs < 10 pack year

6.1.7. Multiple Comparisons and Multiplicity

Analyses of endpoints will not be subject to any multiplicity adjustment.

6.2. Data Handling

6.2.1. Premature Withdrawal and Missing Data

- **Premature Withdrawals**

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as completion of all phases of the study. • Withdrawn subjects will not be replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

➢ **Handling of Missing Data and Outliers**

Element	Reporting Detail
Missing Data	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

➢ **Handling of Missing and Partial Dates**

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • The recorded partial date will be displayed in the listings
Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the CRF will not be imputed. • The recorded partial date will be displayed in listings.

6.2.2. Derivation and Transformation on Data

Baseline GOLD 2019 group
A: 0 or 1 exacerbation (not leading to hospital admission) and (CAT <10)
B: 0 or 1 exacerbation (not leading to hospital admission) and (CAT ≥ 10)

C: ≥2 exacerbations or 1 exacerbation leading to hospital admission and (or CAT <10) D: ≥2 exacerbations or 1 exacerbation leading to hospital admission and (CAT ≥ 10)
Level of physical activities(IPAQ)
See Appendix 3 for details.
Level of depression(PHQ9)
See Appendix 4 for details.
Body Mass Index (BMI)
• Calculated as Weight (kg) / [Height $(m)^2$]，rounded to 1 decimal place. BMI<18.5 underweight, 18.5≤ BMI<24 normal, 28>BMI≥24 overweight, BMI≥28 obesity
Days from enrolled date to completion or prematurely withdrew of the study
• Calculated as completion or early termination date – enrolled date + 1
Duration of COPD (months)
• (Calculated as enrolled date –COPD diagnosis date+1) ÷30.4375 days, round to 2 decimal places. If only the day of COPD diagnosis date is missing: Duration of COPD (months) = (the year of enrolled date – the year of COPD diagnosis date）×12+ (the month of enrolled date – the month of COPD diagnosis date). If the day and month of COPD diagnosis date are missing: Duration of COPD (months) = (the year of enrolled date – the year of COPD diagnosis date) ×12. If COPD diagnosis date is completely missing: duration of COPD is not calculated.
Annual income(KRMB)
• (Q6 + Q7)/1000, rounded to 3 decimal place. Patient survey and questionnaire: Q6: In the past 12 months, the total income of your family（you and your spouse）was ____ RMB？ Q7: In the past 12 months，the total economic support you have received from your children or others was ____RMB？
Proportion of outpatient medical insurance (for total medical treatment) (%)
(total cost of medical treatment(Q8) -actual total cost(Q8))/ total cost of medical treatment (Q8) × 100，rounded to 1 decimal place. Patient survey and questionnaire: Q8: In the past 12 months，the total cost of your medical treatment was____RMB？After reimbursement from insurance (if any)，the actual total cost was ____RMB？
Proportion of outpatient medical insurance (for COPD treatment) (%)
(total cost of medical treatment(Q9) -actual total cost(Q9))/ total cost of medical treatment (Q9) × 100，rounded to 1 decimal place. Patient survey and questionnaire:

Q9: In the past 12 months，the total cost of your COPD treatment was____RMB？After reimbursement from insurance (if any)，the actual total cost was____RMB？

6.3. Subject Disposition

The study population analyses will be based on the enrolled population, unless otherwise specified.

Study population analyses include analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, COPD exacerbation history, co-morbid diseases and concomitant medications. The summary will be displayed by different cohorts and "Total".

6.3.1. Subject's Disposition

The number of subjects included in screening population, those included in enrollment and reasons for screening failure will be summarized.

The number and percentage of subjects who completed the study as well as subjects who withdrew prematurely from the study will be summarized by completion status and reason for withdrawal. A listing of the subjects who withdrew from the study prematurely will be provided.

The subject's disposition analyses will be performed for Tier 2 and 3 hospitals separately.

6.3.2. Protocol Deviation

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarized. A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

All protocol deviations will be listed.

6.4. Demographics and Baseline Characteristics

The summary will be displayed by different cohorts and "Overall", and will also be performed for Tier 2 and 3 hospitals separately.

6.4.1. Demographic characteristics

Demographic characteristics listed below will be summarized either with descriptive statistics for continuous variables or with frequencies and percentages for categorical variables.

- Continuous variables: Height, Weight, Age, BMI
- Categorical Variables: Age(below 65 years old vs. 65 years old and above), Body mass index (BMI, BMI<18.5 underweight, 18.5≤ BMI<24 normal, 28>BMI≥24 overweight, BMI≥28 obesity), Gender

6.4.2. Baseline socio-economic characteristics

- Continuous variables: annual income, total cost of medical treatment, total cost of COPD treatment, out-of-pocket health expenditure, out-of-pocket COPD expenditure, proportion of outpatient medical insurance.
- Categorical Variables: education，living area，marriage condition ,with whom usually live, national basic medical insurance, commercial insurance.

6.4.3. Substance Use

- Continuous variables: the number of pack years for former smoker and current smoker.
- Categorical Variables: smoking status, the number of pack years for former smoker and current smoker (≥10 pack year vs < 10 pack year).

6.4.4. Disease severity characteristics

- Continuous variables: DECAF score, CAT score, FVC, FEV1, FEV1%pred, FEV1/FVC.
- Categorical Variables: DECAF score (mild, moderate and severe), CAT score (≤10, 11-20, 21-30, 31-40), mMRC score (Grade 0, Grade 1, Grade 2, Grade 3 and Grade 4), Baseline GOLD 2019 group (A, B, C and D), GOLD grade (I, II, III and IV).

Variables with multiple visit should be described by visits and calculated the change from baseline.

6.4.5. Questionnaire

- Continuous variables: IPAQ, PHQ9 score, GSE score.
- Categorical variables: IPAQ, PHQ9 score.

Variables with multiple visit should described by visits and calculated change from baseline.

6.4.6. COPD exacerbation history

- Duration of COPD (months), exacerbated in the past 12 months to the present(yes vs no), total frequency of exacerbations in previous 12 month， frequency of hospitalization due to exacerbation in previous 12 month.

6.4.7. Co-morbid diseases

Co-morbid diseases: Cardiovascular Disease (CVD defined as ischemic heart disease, heart failure, atrial fibrillation, hypertension), Diabetes, Hyperlipemia, Anxiety, Depression, Gastroesophageal reflux disease (GERD), obstructive sleep apnea syndrome (OSAS), concurrent asthma with COPD, past history of tuberculosis.

Number and percentage of patients who had each co-morbid diseases will be summarized using descriptive statistics. All disease name will also be summarized by System Organ Class (SOC) and preferred term (PT) that will be coded using the latest version of MedDRA. If a patient has more than one record in a relevant category, the patient will be counted only once for the category. The summary will be sorted in decreasing order of occurrence rate of SOC firstly and then sorted in decreasing order of occurrence rate of PT.

Detailed information of co-morbid diseases will be listed by patient.

6.5. Treatment Compliance and Concomitant Medication

6.5.1. Treatment Compliance

See section 6.7 for more details about the change of COPD prescription for maintenance.

6.5.2. Concomitant Medications

The CRF texts for concomitant medications will be coded using the WHO Drug Dictionary. A by-subject listing of concomitant medications using generic term will be provided.

6.6. Primary Analysis

6.6.1. Primary Analysis

- **Endpoint / Variables**

The COPD prescription for maintenance therapy at each visit.

- **Summary Measure**

The number and percentage of patients who receive any maintenance treatment prescription at each visit will be summarized.

The number and percentage of patients who receive different pattern of the maintenance treatment prescription at each visit. The categories will be binary, e.g. treatment class used: Yes/No.

The above analyses will also be performed for Tier 2 and 3 hospitals separately.

- **Population of Interest**

The primary analyses will be based on the enrolled population.

- **Statistical Analyses / Methods**

The number and percentage of patients who receive the maintenance treatment prescription 1/2/3 at each visit will be summarized. Moreover, for those who receive the maintenance treatment prescription, the number and percentage of patients will be summarized for each of the following pattern of maintenance treatment prescription:

- Long-Acting Muscarinic Antagonist [LAMA]
- Long-Acting Beta-Agonist [LABA]
- Dual bronchodilator [LABA/LAMA]
- Inhaled corticosteroid [ICS]/ Long-Acting Beta-Agonist [LABA]
- Triple therapy [ICS/LABA/LAMA, SITT]

- MITT
- Theophylline
- MITT or SITT
- N-acetyl cysteine/carbocysteine

The maintenance treatment prescription: including LAMA, LABA, LABA/LAMA, ICS/LABA, SITT, MITT, Theophylline, MITT or SITT, N-acetyl cysteine/carbocysteine.

The inhaler maintenance treatment prescription: including LAMA, LABA, LABA/LAMA, ICS/LABA, SITT, MITT, Theophylline.

The oral maintenance treatment prescription: including Theophylline, N-acetyl cysteine/carbocysteine.

If the patient received both LAMA and ICS/LABA at the same visit, the patient's pattern of maintenance treatment prescription was MITT, and the treatment pattern could not be identified as either LAMA or ICS/LABA.

The results for patients with stable disease and patients with exacerbation at baseline will be analyzed separately for the following visits: baseline visit, 1-week follow up (for moderate exacerbations) and discharge follow-up (for hospitalized exacerbations).

The results for patients with stable disease and patients with exacerbation will be pooled together for analysis for 3-month follow-up visit. The percentage will be compared between stable and exacerbating patients by maintenance treatment.

Statistical Methodology Specification

Endpoint / Variables
• The COPD prescription for maintenance therapy at each visit
Model Specification
• Chi-square test or Fisher's exact test • Bonferroni-corrected P value will be calculated when the P value of Chi-square test or Fisher's exact test is less than 0.05.
Model Checking & Diagnostics
• N/A
Model Results Presentation
• The number and percentage of patients who receive any maintenance treatment prescription will be reported. • The number and percentage of patients who receive different pattern of the maintenance treatment prescription will be reported separately. • The P value will be reported.

Subgroup Analyses
• N/A
Sensitivity Analyses
• N/A
Supportive Analyses
• N/A

6.6.2. Sensitivity Analysis

None.

6.7. Secondary Analysis

6.7.1. Secondary Endpoints

- The COPD prescription for each maintenance therapy at baseline.
- The disease burden of the patients, including mMRC score, CAT score at baseline, number of exacerbations in previous 1 year
- The change of COPD prescription for maintenance therapy.
- Each COPD treatment used at 3 months.

6.7.2. Summary Measure

- **The COPD prescription for each maintenance therapy at baseline:**
  - Descriptive analysis of categorized covariates (see 6.1.5 Covariates and Other Strata) will be summarized.
  - Adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) of each covariates based on univariate logistic regression (see 6.7.4. Model Specification).
  - The number and percentage of patients in each pattern of maintenance treatment will be summarized by the covariates used in the multivariate logistic regression.
  - Separate analyses will be performed for stable and exacerbating patients
- **The disease burden of the patients**
  - Number and percentage in different mMRC score intervals, CAT score intervals, Baseline GOLD 2019 group, Gold grade, numbers of historic exacerbation according to the usage of different historic treatments.
    - mMRC score intervals are defined as : Grade0, Grade1, Grade2, Grade3, Grade4
    - CAT categories are defined as: ≤10, 11-20, 21-30, 31-40.
    - Baseline GOLD 2019 group is defined as: A, B, C, D.
    - Gold grade is defined as: I, II, III, IV.
  - Mean and standard deviation of mMRC score, CAT score, number of historic exacerbations according to the usage of different historic treatments.
  - The above analyses will also be performed for Tier 2 and 3 hospitals separately.
- **The change of COPD prescription for maintenance**

The number and percentage of participants in each category across the different study time points.

The categories are defined as:

Categories	Definition
Stepped up	Adding another maintenance treatment: The latter visit increased by any one or more of LAMA, LABA, or ICS treatments compared to the previous visit.
Stepped down	Withdraw any of the maintenance medication but kept the maintenance treatment: The latter visit reduced by any one or more of LAMA, LABA, or ICS treatments compared to the previous visit.
Stopped	Stopped all LAMA, LABA and ICS treatments.
Switched	Between LAMA and LABA; Between LAMA/LABA and ICS/LABA.
Remained	The LAMA, LABA and ICS combinations in the prescription in the latter visit are the same as the combinations in the previous visit; No LAMA, LABA and ICS in the prescription in the latter visit and previous visit.

The time points are coupled as:

Population	Time points	Summary Measure
Stable patients	3 months vs baseline	-Descriptive analysis of categorized covariates (see 6.1.5 Covariates and Other Strata) will be summarized. -Adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) of each covariates based on univariate multinomial logistic regression (see 6.7.4. Model Specification). -The number and percentage of patients in the change of COPD prescription for maintenance therapy will be summarized by the covariates used in the multivariate multinomial logistic regression.
Exacerbation patients	3 months vs pre baseline	Descriptive analysis of the change of COPD prescription for maintenance therapy.
	1-week/ discharge follow-up vs pre baseline	-Descriptive analysis of categorized covariates (see 6.1.5 Covariates and Other Strata) will be summarized. -Adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) of each covariates based on univariate logistic regression (see 6.7.4. Model Specification). -The number and percentage of patients in the change of COPD prescription for maintenance therapy will be summarized by the covariates used in the multivariate logistic regression.
	3 months vs 1-week/ discharge follow-up	

The above analyses will also be performed for Tier 2 and 3 hospitals separately.

In addition, the following content will also be summarized:
(1) The change of treatment in individual treatments by each maintenance treatment

The number and percentage of patients who stopped or started a maintenance treatment prescription at the time points (including 1-week follow-up/discharge follow-up compare to baseline, 3 months follow up compare to baseline, 3 months follow up compare to 1-week follow-up/discharge follow-up) will be calculated.
The above analyses will also be performed for Tier 2 and 3 hospitals separately.

(2) LAMA, LAMA/LABA, ICS/LABA step up situation

The number and percentage of patients who stepped up or not stepped up to any treatment at the time points (including 1-week follow-up/discharge follow-up compare to pre baseline, 3 months follow up compare to baseline (stable patients) or pre baseline (exacerbating patients), 3 months follow up compare to 1-week follow-up/discharge follow-up) will be calculated.
The definition of step up to any treatment for patients with LAMA: LAMA at baseline switched to MITT, SITT, LAMA/LABA or ICS/LABA.
The definition of step up to any treatment for patients with LAMA/LABA: LAMA/LABA at baseline switched to MITT or SITT.
The definition of step up to any treatment for patients with ICS/LABA: ICS/LABA at baseline switched to MITT or SITT.

Comparison will be considered in two directions. For each specific treatment (LAMA, LAMA/LABA, ICS/LABA), the overall significant test will be conducted to detect the difference of stepping up to MITT and SITT (and LAMA/LABA, ICS/LABA when the treatment at baseline is LAMA; Chi-square test or Fisher's exact test will be used and Bonferroni-corrected P value will be calculated when the P value of Chi-square test or Fisher's exact test is less than 0.05). Additionally, when the stepping up situations is MITT, significant test will be conducted to detect the difference of different baseline treatments. Chi-square test or Fisher's exact test will be used and Bonferroni-corrected P value will be calculated when the P value of Chi-square test or Fisher's exact test is less than 0.05; similarly, for SITT. Chi-square test or Fisher's exact test will be used.

(3) MITT, SITT step down situation
The number and percentage of patients who stepped down or not stepped down to any treatment, stopped all treatment or not stopped all treatment at the time points (including 1-week follow-up/discharge follow-up compare to pre baseline, 3 months follow up compare to baseline (stable patients) or pre baseline (exacerbating patients), 3 months follow up compare to 1-week follow-up/discharge follow-up) will be calculated.
The definition of step up to any treatment for patients with MITT: MITT at baseline/pre baseline/1-week follow-up/discharge follow-up switched to LAMA, LABA, LAMA/LABA or ICS/LABA.
The definition of step up to any treatment for patients with SITT: SITT at baseline/pre baseline/1-week follow-up/discharge follow-up switched to LAMA, LABA, LAMA/LABA or ICS/LABA.

Comparison will be considered in two directions. For each specific treatment (MITT and SITT), the difference of stepping down to LAMA, LABA, LAMA/LABA and ICS/LABA will be compared. Chi-square test or Fisher's exact test will be used and Bonferroni-corrected P value will be calculated when the P value of Chi-square test or Fisher's exact test is less than 0.05.

Additionally, when the stepping down situations is LAMA, significant test will be conducted to detect the difference of different baseline treatments; similarly, for LABA, LAMA/LABA, ICS/LABA. Chi-square test or Fisher's exact test will be used.

(4) COPD prescription for maintenance therapy step up situation of different patients

The number and percentage of patients who stepped up or not stepped up to any treatment, stepped down or not stepped down to any treatment at the time points (including 1-week follow-up/discharge follow-up compare to pre baseline, 3 months follow up compare to baseline (stable patients) or pre baseline (exacerbating patients), 3 months follow up compare to 1-week follow-up/discharge follow-up) will be calculated and compared by the following covariates: Age (below 65 years old, 65 years old and above), Gender (female, male), Smoking status (Used to smoke, Current smoking, Never smoking), Cardiovascular Disease (yes, no), Concurrent asthma with COPD (yes, no), Past history of tuberculosis (yes, no), Annual income (KRMB) (<30, 30-80, >80), Gold grade (I, II, III, IV), Baseline CAT score (≤10, 11-20, 21-30, 31-40), Type of hospital (Tier 2, Tier 3), History of exacerbation (None, Moderate, Previous hospitalized).

Chi-square test or Fisher's exact test will be used and Bonferroni-corrected P value will be calculated when the P value of Chi-square test or Fisher's exact test is less than 0.05.

(5) Change of CAT score when treatment stepping up and stepping down
CAT score will be described by visits (baseline and 3 months follow up) and calculated the change from baseline. These analyses will be summarized by the treatment stepping up and stepping down situation.

- **Each COPD treatment used at 3 months**
  - Number and percentage of patients who actually use each maintenance treatment at 3 months will be summarized
  - The above analyses will also be performed for Tier 2 and 3 hospitals separately.

6.7.3. Population of Interest

The secondary analyses will be based on the enrolled population.

6.7.4. Statistical Analyses / Methods

One of the secondary objectives of this study is to examine factors (include baseline disease severity and baseline socio-economic factors) that are associated with different patterns of maintenance treatment at baseline. Separate analyses will be performed for stable and exacerbating patients, since it is possible that the factors that influence a physician's choice of treatment may differ between the two conditions. Multivariate logistic regression will be used to identify influence factor for having a certain maintenance treatment versus none.

Separate analyses of disease burden will be performed for stable and exacerbating patients.

Statistical Methodology Specification

Endpoint / Variables
• COPD prescription for each maintenance therapy at baseline
Model Specification

Univariate / Multivariate logistic regression with binary endpoint.

- Dependent variable: each pattern of the following maintenance treatment at baseline. The categories will be binary, e.g. treatment class used: Yes/No.
  - Long-Acting Muscarinic Antagonist [LAMA]
  - Long-Acting Beta-Agonist [LABA]
  - Dual bronchodilator
  - Inhaled corticosteroid [ICS]/ Long-Acting Beta-Agonist [LABA]
  - Triple therapy
  - Theophylline
  - N-acetyl cysteine/carbocysteine
  - MITT
  - MITT or SITT
- Independent variables: variables defined in 6.1.5 Covariates

Model Checking & Diagnostics

- Collinearity diagnostics
- The covariates with P-value less than 0.1 in univariate logistic regression and fixed variables (including Age, Gold grade, Baseline CAT score, Type of hospital and History of exacerbation) will be included in the multivariate logistic regression model.

Model Results Presentation

- Adjusted odds ratios (ORs) with 95% confidence intervals (95% CIs) and P-value for each covariates.

Subgroup Analyses

- Separate analysis for stable and exacerbating patients will be provided.

Sensitivity Analyses

- N/A

Supportive Analyses

- N/A

Endpoint / Variables

- The change of COPD prescription for maintenance

Model Specification

Univariate / Multivariate (Multinomial) logistic regression

- Dependent variable:

Stable patients: No change (Remained), Stepped up, Stepped down/Stopped.
Exacerbating patients: Stepped up (Yes/No)
Exacerbating patients:Stepped down/Stopped (Yes/No)

• Independent variables: variables defined in 6.1.5 Covariates
Model Checking & Diagnostics
• Collinearity diagnostics • The covariates with P-value less than 0.1 in univariate (multinomial) logistic regression and fixed variables (including Age, Gold grade, Baseline CAT score, Type of hospital and History of exacerbation) will be included in the multivariate (multinomial) logistic regression model.
Model Results Presentation
• Adjusted odds ratios (ORs) with 95% confidence intervals (95% CIs) and P-value for each covariates.
Subgroup Analyses
• Separate analysis for stable and exacerbating patients will be provided.
Sensitivity Analyses
• N/A
Supportive Analyses
• N/A

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[redacted]

6.9. Safety Analysis

The safety analyses will be based on the enrolled population, unless otherwise specified.

6.9.1. Exposure

Not applicable.

6.9.2. Adverse Events

Adverse Events will be coded by the latest version of MedDRA.

Overall AEs, ADRs, SAEs, AEs leading to drug withdrawal and AEs leading to withdrew from study will be summarized by number of occurrences, number of patients and incidence.

The number of occurrences, number of patients and incidence will be summarized for AEs by SOC, PT and severity using coded terms. If multiple AEs in the same category have occurred in the same patient when summarizing the number of patients, it will be counted as 1 patient when calculating the incidence of this category of AEs. When summarizing the number of patients by severity, if multiple AEs in the same category have occurred in the same patient, the event with the worst severity will be patient to analysis. When summarizing the number of occurrences, all the AEs will be accounted for without any pretreatment.

Detailed information of the different categories of AEs will be listed by patient.

6.9.3. Laboratory Test Results

None.

6.9.4. 12 lead electrocardiogram

None.

6.9.5. Other Safety Results

- Physical examination

Physical examination will be summarized using descriptive statistics.

6.10. Subgroup Analysis

No other subgroup analysis.

6.11. Supplementary Analysis

None.

7. Multiplicity

None.

8. Interim Analyses

None.

9. Change from the Analysis Plan in Protocol

<table>
<tr><th>Section in SAP</th><th>Original descriptions in protocol</th><th>Current descriptions in SAP</th></tr>
<tr><td>Section 6.7.2</td><td>stepped up (adding another maintenance treatment), stepped down (withdraw any of the maintenance medication but kept the maintenance treatment), switch (between LAMA+LABA and ICS/LABA), stopped (stop all maintenance treatment) or remains the same across the different study time points</td><td>• The definition of change of COPD prescription for maintenance was described in detail:
<table>
<tr><th>Categories</th><th>Definition</th></tr>
<tr><td>Stepped up</td><td>Adding another maintenance treatment: The latter visit increased by any one or more of LAMA, LABA, or ICS treatments compared to the previous visit.</td></tr>
<tr><td>Stepped down</td><td>Withdraw any of the maintenance medication but kept the maintenance treatment: The latter visit reduced by any one or more of LAMA, LABA, or ICS treatments compared to the previous visit.</td></tr>
<tr><td>Stopped</td><td>Stopped all LAMA, LABA and ICS treatments.</td></tr>
<tr><td>Switched</td><td>Between LAMA and LABA;
Between LAMA/LABA and ICS/LABA.</td></tr>
<tr><td>Remained</td><td>The LAMA, LABA and ICS combinations in the prescription in the latter visit are the same as the combinations in the previous visit;
No LAMA, LABA and ICS in the prescription in the latter visit and previous visit.</td></tr>
</table></td></tr>
</table>

10. Reference

[1] Brusselle , G, Price D, Gruffydd-Jones K, Miravittles M, Kleiner DL, Stewart R, et al. The inevitable drift to triple therapy in COPD: an analysis of prescribing pathways in the UK. International Journal of COPD. 2015; 10: 2207-2217.

11. TFL Shell and Dataset Specification

11.1. TFL Shell

The data display shells are contained in separate documents which are available on request.

11.2. Dataset Specification

Analysis datasets will be created according to the analysis dataset specification. Refer to attached document of the SAP.

12. Other Appendix

12.1. Appendix 1: Schedule of Activities

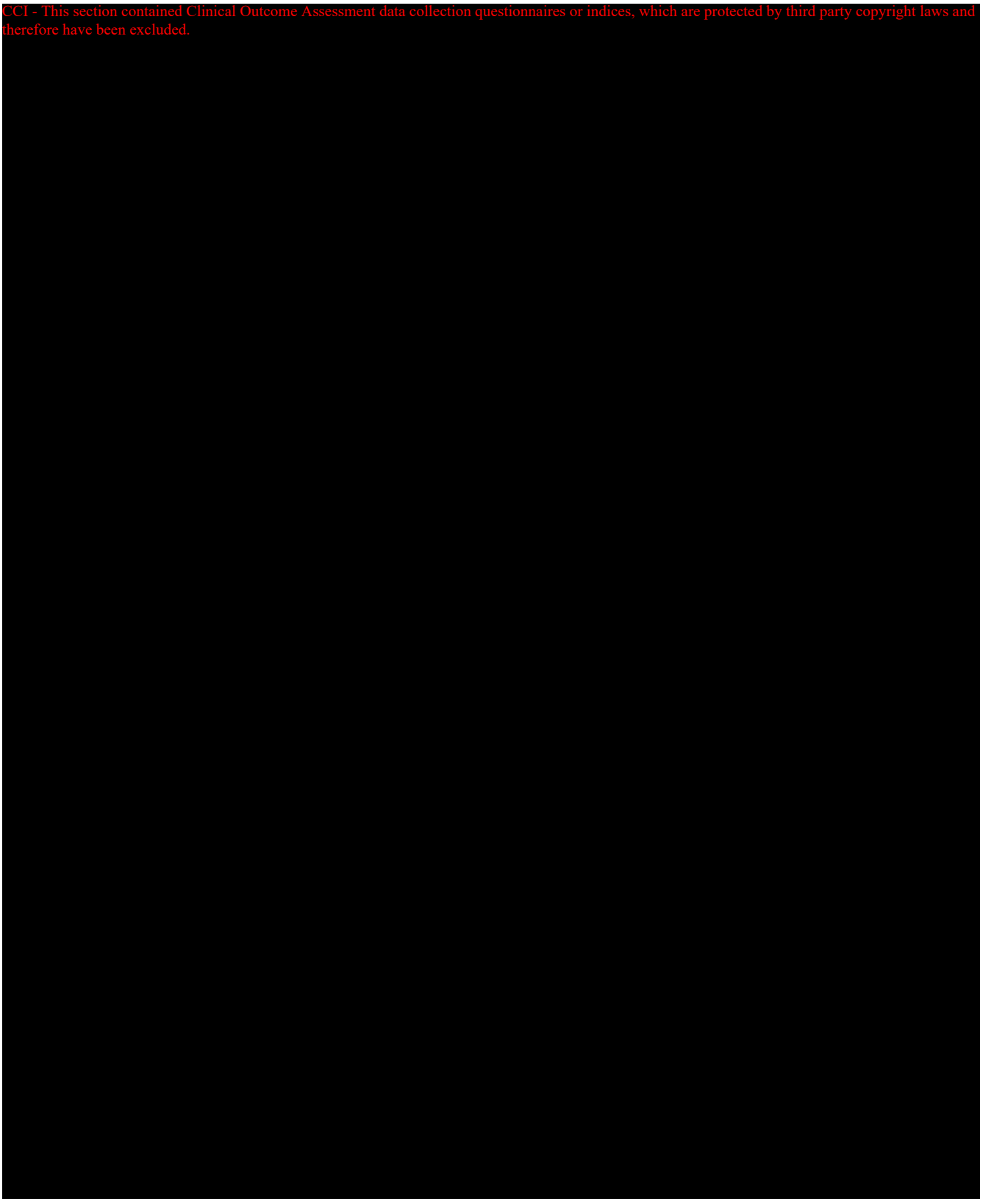
Procedure	Baseline Visit	Discharge follow-up for admitted patients	1-week follow up for non-admitted patients Day 8+3 (Telephone)	3 months follow up ±7 (Telephone)	Notes
Informed consent	X				
Inclusion and exclusion criteria	X				
Demography	X				
Full physical examination including height and weight	X				
Co-morbidities	X				
COPD diagnosed history	X				
COPD exacerbation history in prior 12 month	X				
Current COPD disease condition (stable or acute)	X				
Smoking history	X				
COPD prescription	X	X[a]	X	X	a. COPD prescription when discharge
Current COPD medication	X[a]		X	X	a. within past 1 month before baseline visit
Prescription date, physician and hospital of current COPD medication				X[a]	a. will be collected from medical records or patients' recall
Spirometry	X	X[a]			

DECAF score assessment (admitted patients)	X[a]				a. can be assessed during hospitalization period
Physician's survey	X				
Patient's survey and questionnaire	X			X	
CAT	X	X	X	X	
mMRC Dyspnea Scale	X				
Socio-economic	X				
Insurance details	X				
Inhaler availability	X				
Discharge time		X			
COPD Clinic revisit times and reason			X[a]	X[a]	a. If patient visits to clinic
Frequency of COPD exacerbation between baseline visit and 3 months follow up				X	
Concomitant medication review	X	X	X	X	
AE review		----------X----------			*AE data will not be collected directly. A physician can document the adverse event or concern reported by the patients.
SAE review		----------X----------			*SAE data will not be collected directly. A physician can document the event or concern reported by the patients.

12.2. Appendix 2: Flow chart of patient disposition

Flow chart of patient disposition will be contained in separate document which are available on request.

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



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