TITLE PAGE

Protocol Title: Investigation of the Clinical, Radiological and Biological factors associated with disease progression, phenotypes and endotypes of COPD in China

Protocol Number: 208630/02

Short Title: Investigation of COPD disease phenotypes and endotypes in China

Compound Number: GW685698+GW642444+GSK573719

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Regulatory Agency Identifying Number(s): Not applicable

Approval Date: 17-JUN-2021

SPONSOR SIGNATORY:

Protocol Title: Investigation of the Clinical, Radiological and Biological factors associated with disease progression, phenotypes and endotypes of COPD in China

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Chris Compton
Medical Affairs Lead, Respiratory Medical Franchise

Date

The signed page is a separate document.

Medical Monitor Name and Contact Information can be found in the Study Reference Manual

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol 208630/02

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:			
Professional Qualification		Position	
Investigator Address:			
Investigator Phone Number:			
CRU address			
CRU phone number			
Investigator Signature			Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	*17-JUN-2021*
Amendment 1	*19-JUN-2019*
Original Protocol	*18-OCT-2018*

Amendment 2- 17-JUN-2021

Overall Rationale for Amendment 2:

This protocol amendment was created to make some minor changes to the study design, add clarity to some sections of the protocol, and to correct typographical errors and inconsistencies. Protocol changes are described in the table below.

Section # and Name	Description of Change	Brief Rationale
Title page	Authors list removed	Updated based on template instructions
INVESTIGATOR PROTOCOL AGREEMENT PAGE	Added the investigator protocol agreement page	To meet GSK SOP requirement
Section 1. Synopsis	Updated information related to overall design and number of participants	Align the synopsis with the update of the study design in Section 5 of this protocol
Section 2. SCHEDULE of ACTIVITIES (SoA)	Added a clear definition of a month as 30 days and also adjusted the visit window from 28 days to 30 days for V2, V3 and V4	To ensure consistency in study operation
	Clarified that for the 4 clinic visits (V1-V4), all the participants should be clinically stable with no exacerbation or other acute medical event for at least 30 days prior to each scheduled visit	Ensure that the schedule visits intend to assess participants in stable state to avoid misunderstanding
	Edited the timeframe around the 2 exacerbation visits to “at least 21 days” instead of “at least 6 months”	To prevent this study from missing the exacerbations that occurred within 6 months of each other or at the start of study
	Added a statement for the sub-cohort that the planned clinic visits should be scheduled with an interval of at least 60 days after a completed exacerbation visit	To provide an appropriate time interval between an exacerbation visit and a scheduled visit for stable state
	Edited the visit window of Visit 1 to “+7 days” instead of “+3 days”	To ensure that all baseline procedures can be completed within a more reasonable window once there is any participant who is been required to undergo a nucleic acid test of COVID-19 before initiating the onsite screening procedures.

	Updated the footnote 6 to the procedure of lung HRCT scan to ensure "The CT scan for an exacerbation visit should only be performed if the last study CT scan performed was more than 14 days."	To clarify the minimal time interval between the CT scan for an exacerbation visit and a CT scan for a scheduled study visit
	Added a footnote to the procedure of blood draw and sputum respectively to ensure "No systemic corticosteroids or antibiotics used within 14 days before collecting the blood or sputum samples	To ensure obtain accurate sputum and EOS assessment data in COMPASS study. Any use of systemic corticosteroids or antibiotics within 14 days may affect their results
	Added a sputum sample point at V2 for those who do not have a qualified sputum cytology sample at baseline (footnote 11)	Provide another chance to ensure the collection of sputum cytology samples in this study
Section 3.1. Benefit/Risk Assessment	Updated the risk assessment related to ionising radiation and specified that participants <50 years of age will not be included in the sub-cohort, nor will females of child bearing potential	To make information clearer
Section 5.1. Overall Design	Added study sites in Xiamen and the rationale behind it	Xiamen, another coastal city of southeast China, is near Guangdong province. We added one site (maybe more if needed) in Xiamen based on feasibility to enhance the enrolment of this study
Section 5.2. Number of Participants	Removed the minimum requirement (15%) for the proportion of never smokers in each group of main cohort while retained the maximum requirement (30%), and updated Figure 2	To add the flexibility for Never-smoker subgroups based on the feasibility considerations
	Added flexibility for recruitment targets of GOLD I and GOLD II in main cohort	To ensure a wide and even distribution of airflow limitation across the patients recruited to this study

	Added flexibility for the target number of never smokers in each group of sub-cohort and updated figure 3 Added flexibility for recruitment approach of GOLD III never smokers in sub-cohort Adjusted the definition of Exacerbator. An exacerbation in the previous year is defined by the occurrence of an episode of increased cough (with or without phlegm), shortness of breath or chest symptoms (chest discomfort or tightness) which lasted 48 hours or more and interfered with the Participants usual activities. The requirement for treatment with antibiotic ± oral corticosteroid has been removed	To add the flexibility for Never-smoker subgroups based on the feasibility considerations To ensure that the target of enrolment of 50 patients with GOLD III was achieved as planned COMPASS is primarily designed to study patients with mild-moderate airways disease. Such patients have fewer treated exacerbations than those with more severe airflow limitation. This does not mean that they do not have exacerbations, it's equally possible that they may be less likely to report them. Studies with the EXACT diary have shown that there may be 2-5 more unreported exacerbations than those that are reported (Jones, 2014; Betsuyaku, 2018). Patients with unreported exacerbations appear to be less symptomatic when they are stable than those who do report them (Leidy, 2014). To ensure that we can identify and recruit patients whose exacerbations are not troublesome enough to make them seek treatment, we will use an exacerbation definition based on a definition used in two population surveys (BOLD and CANCOLD) that included mild subjects (Buist, 2007; Tan, 2014)
Section 6.1. Inclusion Criteria-COPD, Chronic Bronchitis and healthy participants	Changed the age limit for all main cohort participants from 50 years to 40 years	To involve in participants aged 40-50 to enable the recruitment of more early-stage COPD and keep consistent with other large COPD epidemiological studies

(common to all the group of participants)	Identified the additional criteria for each group in the sub-cohort to allow participants aged 50-80 years	Provide clear criteria for the sub-cohort to avoid misunderstanding
Section 6.1. Inclusion Criteria-COPD, Chronic Bronchitis	Reduced the pack-year limit for all ever smokers in the main cohort from 10 to 1	Allow the recruitment of ever smokers with 1-10 pack-year in the main cohort. Pack years smoking is very closely related to age. The typical patient with established moderate-severe COPD who is for example 65 years old will have smoked for 20 years more than a 45 year old.
Section 6.1. Inclusion Criteria-COPD participants	Edited "A baseline (post-bronchodilator) FEV1/FVC ratio <70%" to "A baseline (post-bronchodilator) FEV1/FVC ratio <0.70" Removed the requirement for the severity of historical exacerbation event (moderate or severe) in the additional criteria for sub-cohort	Use a fraction to 2 decimal places rather than a percentage of a whole number to make this inclusion criterion more precise and keep consistent with other COPD studies. This becomes especially important for patients with mild airflow limitation – who are an important subgroup in COMPASS Ensure consistency across the protocol
Section 6.1. Inclusion Criteria-Chronic Bronchitis and healthy participants	Edited "Baseline post-bronchodilator FEV1/FVC ratio >70%" to "Baseline post-bronchodilator FEV1/FVC ratio ≥0.70"	To involve in participants whose Baseline post-bronchodilator FEV1/FVC ratio is greater than or equal to 0.70
Section 6.2. Exclusion Criteria-COPD, Chronic Bronchitis and healthy participants (common to all the group of participants)	Specified that COVID-19 should be excluded in each group Removed "Mandarin" in the No. 13 exclusion criterion related to read and understand Chinese	Provide specified information To make it clear. There are lots of local languages in China. Mandarin is the most widely used official language. To allow the participants to participate in the study who can speak other local languages except Mandarin

Section 6.2. Exclusion Criteria-Chronic Bronchitis and healthy participants	Edited "FVC<80% Predicted" to "Post-bronchodilator FVC<80% Predicted normal"	According to GOLD and ATS/ERS criteria, clarify the requirement of post bronchodilator FVC <80% Predicted normal.
Section 6.4. Screen Failures	Added "Only in certain special cases, re-screening of participants will be allowed. Investigator will be asked to provide detailed information. Special cases will be discussed at the EST (Empowered Study Team) meeting. After permission from the medical monitor of this study is granted, the participants can only be re-screened once."	Re-screening was allowed for certain special cases to prevent missing early stage COPD participants, especially the GOLD 1 COPD participants
Section 9.1. Baseline data collection	Added the item of "Number of exacerbations in the previous 12 months and 24 months" Added more airway parameters for spirometry	Ensure consistency across the protocol To achieve a more comprehensive evaluation of small airway function – which is particularly important in mild and early disease
Section 9.2.3. Spirometry	Specified the same measurements as baseline spirometry Removed the requirement of "Spirometry will be performed after the completion of any PRO questionnaires"	Ensure consistency across the protocol To reduce the visit time of participants
Section 9.2.6. Patient Reported Outcome Measures	Added "All Patient reported outcome measures should be collected in a nice, quiet setting without distractions (e.g., television, cell phones)." Removed the original timing and order requirements for collecting the CAT, mMRC and SGRQ-C assessments. Only required to collect CAT at the beginning of the study visits (before any other procedures).	To ensure the data quality, the most important is to have a nice, quiet setting to do the assessments. To minimize the visit duration of the study participants. It's not necessary to require the CAT, mMRC and SGRQ-C assessments to be done in a fixed order at the beginning of the study visits.

Section 9.2.6.2. Evening Diary (sub-cohort only)	Removed the level 5 headings and presented headings in bullets. • Exacerbations of Chronic Pulmonary Disease Tool (EXACT) and Evaluating Respiratory Symptoms in COPD (E-RS: COPD) • Additional questions	Updated as per template requirements
Section 9.3. Exacerbation Visits (sub-cohort only)	Updated figure 4: removed X in second box and corrected spelling of units, as well as reflected use of EXACT score	To correct the typo
Section 10.2.8. Interim Analyses	Deleted the statement of "Scientific steering committee will oversee the interim analyses". Add the statement, The Scientific Steering Committee will have sight of, and approve, all requests for analyses that come from the Working Groups	Clarify the responsibilities of the Scientific Steering Committee
Section 11: References	Added references: Jones, 2014; Betsuvaku, 2018; Leidy, 2014; Buist 2007; Tan, 2014	To support the data
Section 12.3. Appendix 3: Contraceptive and Barrier Guidance	Added this guidance	Provided the information related to Woman of non-child bearing potential
Throughout	Corrected spelling errors, added abbreviations to abbreviation list, added punctuations wherever applicable	For consistency and clarity

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1. SYNOPSIS

Protocol Title: Investigation of the Clinical, Radiological and Biological factors associated with disease progression, phenotypes and endotypes of COPD in China

Short Title: Investigation of COPD disease phenotypes and endotypes in China

Rationale:

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of morbidity and mortality resulting in significant humanistic and economic burden to patients, healthcare system and society worldwide. COPD prevalence in China has been significantly increasing. A national screening survey, conducted in 2002-2004, reported that the overall prevalence of spirometry-defined COPD among people over 40-year-old was 8.2% in China. The recently published China Pulmonary Health study (2018) indicated the prevalence of COPD among Chinese over 40 years old had increased to 13.7%. A study in 2013 including 634 COPD patients from 83 tertiary hospitals in 17 provinces in China estimated the average cost of COPD per patient per year to be RMB 20,107.58. Further, COPD led to a large productivity loss of RMB 6,941.33 yuan/per person-year; the value of working time loss was RMB 613.86 yuan/per person-year. Although COPD management in China has been greatly improved over the past decades, many challenges persist. One of them is substantial under-diagnosis: up to 65% of people with airflow limitation pattern compatible with COPD were found not to have a clinical COPD diagnosis. Further, majority of COPD patients (64.7%) exhibit high symptom burden, defined as at least one respiratory symptom (cough, phlegm, wheezing, and breathlessness), despite treatment.

COPD prevalence and disease burden have been well studied in North America and Western Europe through large cohort studies. The ECLIPSE study recruited patients with moderate-severe airflow limitation from secondary care; COPDGene, COPDMAP and SPIROMICS largely recruited patients of a wide range of disease severity from a variety of healthcare settings. However, so far there have been no dedicated cohort studies conducted in China with a specific focus on high density phenotyping of COPD, including biomarkers and clinical features associated with disease activity, severity and progression in China. Existing large populational cohorts, like the China Kadoorie Biobank, inform on the extent of disease burden of airflow limitation; however, due to its general population-based nature, they provide only limited information on clinical and humanistic burden and therapeutic management of diagnosed COPD.

With an aging population and persistent air pollution in China, the humanistic and economic burden of COPD is expected to increase and will require more healthcare resources in the future. COPD has been identified as a key disease of focus under the China government's Thirteenth Five programme. Therefore, to inform clinical practice and aid public health resource allocation, it is important to advance knowledge and understanding of disease progression and clinical management of COPD, especially at early disease stages, in China.

Whilst COPD is a common disease across the world, its phenotypes and patterns of disease progression may differ geographically, impacting approaches to precision

medicine in China. Recent international studies showed substantial geographic variations in respiratory symptoms and other respiratory illnesses in COPD patients. The disease progression of COPD and clinical management in China is largely unknown. Recent studies in non-Asians have demonstrated that acute exacerbations of COPD (AECOPD) can be subdivided by type: infections (bacterial and/or viral), eosinophilic, and pauci-inflammatory and each subtype has been associated with increased levels of specific blood biomarkers. Moreover, recent data indicate that bacterial and eosinophilic exacerbations are likely to repeat within an individual, suggesting endotypic differences in Western frequent exacerbators. There is a need to compare and validate findings from cohorts conducted in predominantly Caucasian populations to guide clinical development of new COPD medicines in China.

With recent technology advances, Electronic Data Capture (EDC) has steadily increased in clinical research. Meanwhile, the Electronic Health Record (EHR) systems are becoming essential to routine clinical practice and has the potential to facilitate large-scale clinical research. Therefore, this study also aims to assess the feasibility of integrating EHR, electronic clinical outcome assessments (eCOA), biomarkers and physical activity data to support application of Digital Data Analytics (DDA) platform in China (e.g. direct digital data capture and integration).

Objectives and Endpoints:

Research Questions & Objectives	Endpoints
1. Evaluate whether the predictors of COPD disease progression identified in Western cohorts are applicable in China. • To evaluate disease progression in COPD and non-COPD participants over 2.5 years as assessed by lung function, exacerbation frequency, health status, lung high-resolution computed tomography (HRCT) scan, and changes in physical activity.	**Main cohort** Change from baseline in forced expiratory volume in 1 second (FEV_1) and rate of decline in FEV_1 Change from baseline in forced vital capacity (FVC) and rate of decline in FVC Rate of moderate/severe exacerbations* Change from baseline in COPD Assessment Test (CAT) score Assess CAPTURE to identify under diagnosed COPD patients in Chinese population Frequency of Clinically Important Deterioration (CID) and its components Death **Additional for sub-cohort** Change in Evaluating Respiratory Symptoms in COPD (E-RS: COPD) scores

Research Questions & Objectives	Endpoints
	Characterisation of EXAcerbation of COPD Tool (EXACT) events Change from baseline in airway thickness by lung HRCT Change in lung density by lung HRCT Change in physical activity measures (e.g. Daily steps, bouts of activity per day)
2. Characterise stable disease and exacerbation phenotypes in China through assessment of blood biomarkers, lung microbiome and radiological features of COPD	**Main cohort:** Plasma fibrinogen and high-sensitivity C-Reactive Protein (hsCRP) Differential blood cell count (e.g. eosinophils, neutrophils) and haemoglobin **Additional for sub-cohort** Blood biomarkers including but not limited to Serum interferon- γ -inducible protein -10 (IP-10), soluble Receptor for Advanced Glycation End Products (sRAGE), Club cell protein (CC16) and HbA1c Sputum microbiome as assessed by molecular methods Sputum total differential cell counts percentage[redacted]
3. Characterise treatment pathways and healthcare resource utilization and costs in COPD	Frequency of treatment with COPD medications; Treatment patterns at the time of study entry and during the study period Count of outpatient visits, emergency visits, hospitalizations (overall and COPD-specific) Direct medical costs associated with COPD medications and COPD disease management Insurance coverage and patient out-of-pocket payment

Research Questions & Objectives	Endpoints
4. Test the feasibility of integrating electronic health records, electronic clinical outcome assessments (eCOA) and physical activity data to support application of digital data analytics (DDA) platform in China studies (e.g. direct digital data capture and integration)	NA

*Moderate exacerbations are defined as COPD exacerbations that require either systemic corticosteroids (intramuscular (IM), intravenous, or oral) and/or antibiotics. Severe exacerbations are defined as COPD exacerbations requiring hospitalization (including intubation and admittance to an ICU) or result in death.

Overall Design:

This is a 2.5-year multi-center, prospective, longitudinal, non-drug interventional cohort study to investigate the pattern of COPD disease phenotypes, clinical, humanistic and healthcare utilization burden, disease progression, and management in China. Participants will be recruited from multiple hospitals (excluding tier 1) across Guangdong and Fujian province. In this study, hospitals at prefecture-level and above will be categorized as Type A hospitals; those below prefecture-level will be Type B hospitals. Site/hospital selection will consider pollution level and hospital type representativeness, as well as feasibility of applying digital data capture and hospital data integration.

A wide range of COPD patients across Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade I-IV will be included. Participants with chronic mucus hypersecretion who don't meet the criteria of COPD will be recruited in the chronic bronchitis group. Never smokers without COPD or chronic mucus hypersecretion or chronic respiratory symptoms and without other significant disease burden will be recruited in the healthy control group.

Baseline data will be recorded for all participants at Visit 1 and subjects will be followed up at 6 months and then every 12 months for a total of 2.5 years. Study visits will be conducted within ±30 days of the planned date. In addition to study visits, COPD and chronic bronchitis participants will be contacted by phone on a trimonthly basis within ± 7 days of the planned date to assess the CAT and collect information on exacerbations and COPD medications; healthy controls will be contacted by phone on trimonthly basis within ± 7 days of the planned date to assess the CAT only.

A subset of participants from selected Type A hospitals are planned to receive additional assessments including digital monitoring of daily steps; daily digital diary (EXACT/E-RS: COPD); monthly CAT; collection of blood for study defined biomarkers; lung HRCT scanning; sputum collection for molecular methods analysis. If moderate/severe exacerbations are reported by the participants or detected by investigators during the acute phase of event, this subset of participants will be invited to site hospital for an exacerbation visit (no more than twice throughout the study). Participants from this sub-cohort constitute the Biomarker and Digital sub-cohort.

In addition, daily air pollution index throughout the study in each participating city will be collected retrospectively from a local environmental monitoring centre.

This cohort study will not provide or recommend any treatment. Patients' diagnosis and treatment will be left to their physicians' judgement and routine practice. Data will be collected from various sources, including electronic case report forms (CRF), EHR from hospital databases, and other electronic sources, such as eCOA, and wearable devices.

Number of Participants:

A total of 2,000 participants are planned to be enrolled, consisting of 1,700 participants with COPD, 180 with chronic bronchitis but without COPD (i.e. without fixed airflow limitation), and 120 never smoker non-COPD healthy controls. COPD subjects will be further classified using the GOLD grades I – IV (i.e. mild, moderate, severe and very severe airflow limitation). To better understand the disease progression of early-stage COPD, i.e. GOLD I and II grades, targets will be set for COPD participants will be recruited in the following manner: GOLD I: 700, GOLD II: 700, GOLD III: 200, GOLD IV: 100. The purpose is to ensure a wide and even spread of the degree of airflow limitation across the study population. The number of participants recruited to each GOLD grade will be monitored and targets adjusted as necessary to ensure an even distribution. Among each GOLD grade and chronic bronchitis group, up to 30% of never smokers will be recruited in each group. All patient population sizes are approximate and allow ± 10% for feasibility.

All participants will be recruited from Type A and Type B hospitals in Guangdong and Fujian province. To represent the difference in patient profile and practice between different hospitals, the ratio of participants from Type A and Type B hospitals will be 2:1. Specifically, healthy control participants will be recruited from the physical examination department at site hospitals. For the healthy control group to be comparable with COPD participants, pre-set criteria on demographic profile (i.e. age, gender) will be specified in detail in the SRM based on previous studies or available real-world data. When appropriate, matching methods will also be used to adjust for differences in baseline factors (e.g. age, gender) in statistical analyses. Matching of the cohorts will be considered to address specific questions, e.g. biomarkers analysis. Methods to achieve balanced cohorts will be chosen based on a hypothesis and the extent of underlying differences between the cohorts and detailed in the main or ad-hoc RAP.

More assessments will be conducted among the 400 Biomarker & Digital sub-cohort participants who will be all recruited only from selected Type A hospitals. The sub-cohort will consist of 50 never smoker healthy control, 100 chronic bronchitis (N never smoker: up to 25), 100 GOLD I (N never smoker: up to 25), 100 GOLD II (N never smoker: up to 25) and 50 GOLD III participants (N never smoker: up to 20). All patient population sizes are approximate and subject to feasibility and the same considerations apply regarding breadth and evenness of spread of severity as apply to the main study cohort.

2. SCHEDULE OF ACTIVITIES (SOA)

Study participants will be followed up for 2.5 years and a total of 4 clinic visits (baseline, 6, 18, and 30 months) are scheduled for study assessments with a visit window of ±30 days (Table 1). Baseline data will be collected at Visit 1. In addition, COPD and chronic bronchitis participants will be contacted by phone on trimonthly basis within ± 7 days of the planned date to assess the CAT and to collect information on exacerbation rates and COPD medications; healthy controls will be contacted by phone on trimonthly basis within ± 7 days of the planned date to assess the CAT only. For the 4 clinic visits (V1-V4), all the participants should be clinically stable with no exacerbation or other acute medical event for at least 30 days prior to each scheduled visit.

A subset of participants will receive additional digital and biomarker assessments during the study. If moderate/severe exacerbations are reported by the participants or detected by the investigators during the acute phase of event, the participant will be invited to site hospital for an exacerbation visit. If multiple moderate/severe exacerbations are reported or detected, the participants will be contacted in consecutive manner for an exacerbation visit. The total number of the exacerbation visits should be no more than 2, with an interval of at least 21 days. Please note, for the sub-cohort, the planned clinic visits should be scheduled with an interval of at least 60 days after a completed exacerbation visit. When any participant in the sub-cohort is implemented an exacerbation visit, then his/her next planned clinic visit (V2-V4) should be scheduled at least 60 days after completing this exacerbation visit. In this case, the participant's clinic visit may be scheduled outside of the time window of ±30 days, which will not be considered as a Protocol Deviation (for more information please refer to the Protocol Deviation Management Plan [PDMP] for this study).

Table 1 Time and event table

Protocol Activity	Screen/Baseline	Study visit				
visit	**V1**	**V2**	**V3**	**V4**	**EW**	**Exacerbation visit (≤2)[1]**
Study month	**M0**	**M6**	**M18**	**M30**		
window	**+7 days**	**±30 days**	**±30 days**	**±30 days**		
Procedures						
Informed consent[2]	X	-	-	-	-	-
Demography	X	-	-	-	-	-
Medical history	X	-	-	-	-	-
Health and lifestyle information/Exposures	X	-	-	-	-	-

Protocol Activity		Screen/Baseline	Study visit				
Inclusion/Exclusion Criteria		X	-	-	-	-	-
COPD and Exacerbation History[3]		X	-	-	-	-	-
Concurrent medications		X	X	X	X	X	-
Smoking status		X	X	X	X	X	-
Spirometry[7]		X	X	X	X	X	X
Reversibility Testing		X	-	-	-	-	-
Patient reported Questionnaires	mMRC	X	-	-	-	-	
	SGRQ-C	X	-	-	-	-	
	CAPTURE	X		X			
	CAT (on-site visit)	X	X	X	X	-	X
	CAT (Phone Call)	Trimonthly Phone Call[4]					
Healthcare resource utilization and cost		-	X	X	X	X	X
Assessments							
COPD exacerbation assessment (on site visit)[5]		-	X	X	X	X	X
COPD exacerbation assessment (Phone Call)[5]		Trimonthly Phone Call[4]					
COPD medication and treatment (on site visit)[5]		X	X	X	X	X	X
COPD medication and treatment (Phone Call)[5]		Trimonthly Phone Call[4]					
Death		-	X				
Serious Adverse Event assessment[12]			X	X	X	X	X
Lab							
Blood Draw[13] for e.g. fibrinogen/hsCRP/Cell count		X	-	-	X	X	X
Sub-cohort only							
Lung HRCT scan[6]		X	-	-	X	X	X
Daily steps		X[8]	-	X[8]	-	-	-
Evening diary (EXACT plus additional questions)		X[9]	-	X[9]	-	-	-

Protocol Activity	Screen/Baseline	Study visit				
Monthly CAT	X[10]	-	X[10]	-	-	-
Blood biomarkers (inclusive of serum sRAGE, CC16, IP-10，HbA1c)	X	-	-	X	X	X
Sputum cytology[11]	X	-	-	X	X	X
Sputum microbiome[11]	X	-	-	X	X	X

CAT=COPD assessment test, COPD=Chronic Obstructive Pulmonary Disease, HRCT=High-resolution computed tomography, EW=Early Withdrawal, EXACT=EXAcerbation of COPD Tool; SGRQ-C=St.George's Respiratory Questionnaire for COPD. CAPTURE=COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk

1. Exacerbation visits only apply to subjects included in the Biomarker & Digital sub-cohort. Moderate exacerbations are defined as COPD exacerbations that require either systemic corticosteroids (intramuscular (IM), intravenous, or oral) and/or antibiotics. Severe exacerbations are defined as COPD exacerbations requiring hospitalization or result in death.
2. Informed consent must be conducted at the screen visit prior to performing any study procedures.
3. For COPD participants only;
4. When a trimonthly telephone interview overlaps a clinical visit, the COPD exacerbation assessment, COPD medication and treatment questionnaires will be completed at the clinic visit. A month is defined as 30 days in this study.
5. Data collection of COPD exacerbation assessment, COPD medication and treatment are not required for the healthy control participants.
6. CT scan should only be performed at withdrawal visit if the last study CT performed was more than a year ago. Inspiratory and expiratory HRCT scans are required at Visit 1 and Visit 4, while only inspiratory scan will be conducted on exacerbation visit. The CT scan for an exacerbation visit should only be performed if the last study CT scan performed was more than 14 days.
7. Pre-and post- bronchodilator values of spirometry test will be collected at each site visit.
8. Physical activity will be evaluated by daily steps as assessed by a wrist band dispensed at baseline. Participants are required to keep wearing the wrist band for 1 month from Visit 1 (baseline) and Visit 3
9. Daily digital EXACT measurement for 6 months from Visit 1 (baseline) and Visit 3
10. Monthly digital measurement from baseline for 6 months, and monthly digital measurement from V3 for 6 months
11. Sputum can be collected spontaneously or can be induced, as per investigator judgement. Sputum sampling should only be done if, in the opinion of the investigator, it is safe for the subject. No systemic corticosteroids or antibiotics used within 14 days before collecting the sputum sample. Participants who do not have a qualified sputum cytology sample at baseline will be requested to have a sputum cytology sample taken or re-sampled at V2 (Note: for COPD participants, they should be clinically stable and has no exacerbations for at least 30 days prior to sampling).
12. Only SAEs relating to the study procedures are collected.
13. No systemic corticosteroids or antibiotics used within 14 days before collecting the blood sample.

3. BACKGROUND AND STUDY RATIONALE

COPD is a leading cause of morbidity and mortality resulting in significant humanistic and economic burden to patients, healthcare system and society worldwide. COPD prevalence in China has been significantly increasing. A national screening survey, conducted in 2002-2004, reported that the overall prevalence of spirometry-defined COPD among people over 40-year-old was 8.2% in China [Zhong, 2007].The recently published China Pulmonary Health study (2018) indicated the prevalence of COPD among Chinese over 40 years old had increased to 13.7% [Wang. 2018]. A study in 2013 including 634 COPD patients from 83 tertiary hospitals in 17 provinces in China estimated the average cost of COPD per patient per year to be RMB 20,107.58. Further, COPD led to a large productivity loss of RMB 6,941.33 yuan/per person-year; the value of working time loss was RMB 613.86 yuan/per person-year [Li, 2015]. Although COPD management in China has been greatly improved over the past decades, many challenges persist. One of them is substantial under-diagnosis: up to 65% of people with airflow limitation pattern compatible with COPD were found not to have a clinical COPD diagnosis [Zhong, 2007]. Further, majority of COPD patients (64.7%) exhibit high symptom burden, defined as at least one respiratory symptom (cough, phlegm, wheezing, and breathlessness), despite treatment [Zhong, 2007].

COPD prevalence and disease burden have been well studied in North America and Western Europe through large cohort studies. The ECLIPSE study recruited patients with moderate-severe airflow limitation from secondary care [Vestbo, 2008; Vestbo, 2014; Faner, 2014]; COPDGene [Regan, 2010], COPDMAP [Wang, 2017] and SPIROMICS [Couper, 2014] largely recruited patients of a wide range of disease severity from a variety of healthcare settings. However, so far there have been no dedicated cohort studies conducted in China with a specific focus on high density phenotyping of COPD, including biomarkers and clinical features associated with disease activity, severity and progression in China. Existing large populational cohorts, like the China Kadoorie Biobank, inform on the extent of disease burden of airflow limitation; however, due to its general population-based nature, they provide only limited information on clinical and humanistic burden and therapeutic management of diagnosed COPD [Kurmi, 2014].

With an aging population and persistent air pollution in China, the humanistic and economic burden of COPD is expected to increase and will require more healthcare resources in the future. COPD has been identified as a key disease of focus under the government's Thirteenth Five programme. Therefore, to inform clinical practice and aid public health resource allocation, it is important to advance knowledge and understanding of disease progression and clinical management of COPD, especially at early disease stages, in China.

Whilst COPD is a common disease across the world, its phenotypes and patterns of disease progression may differ geographically, impacting approaches to precision medicine in China. Recent international studies showed substantial geographic variations in respiratory symptoms and other respiratory illnesses in COPD patients [Kim, 2017; Landis, 2014]. The disease progression of COPD and clinical management in China is largely unknown. Recent studies in non-Asians have demonstrated that acute exacerbations of COPD (AECOPD) can be subdivided by type: infections (bacterial

and/or viral), eosinophilic, and pauci-inflammatory and each subtype has been associated with increased levels of specific blood biomarkers [Wilkinson, 2017; Wang, 2016; Wang, 2017; Dickson, 2014; Gomez, 2016]. Moreover, recent data indicate that bacterial and eosinophilic exacerbations are likely to repeat within an individual, suggesting endotypic differences in Western frequent exacerbators [Mayhew, 2018]. There is a need to compare and validate findings from cohorts conducted in predominantly Caucasian populations to guide clinical development of new COPD medicines in China.

With recent technology advances, Electronic Data Capture (EDC) has steadily increased in clinical research. Meanwhile, the Electronic Health Record (EHR) systems are becoming essential to routine clinical practice and has the potential to facilitate large-scale clinical research. Therefore, this study also aims to assess the feasibility of integrating EHR, electronic clinical outcome assessments (eCOA), biomarkers and physical activity data to support application of Digital Data Analytics (DDA) platform in China (e.g. direct digital data capture and integration).

3.1. Benefit/Risk Assessment

This cohort study will not provide or recommend any treatment; thus, detailed information on investigational product (IP) is not applicable. The participants' diagnosis and treatment will be left to their physicians' judgement and routine practice.

Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP)		
No investigational product (IP) will be investigated in this study; thus, detailed information on IP is not applicable	**Not applicable**	**Not applicable**
Study Procedures		
Potential risk for injury with phlebotomy	Risks with phlebotomy include bruising, bleeding, infection, and nerve damage.	• Procedures to be performed by trained personnel (i.e., study nurse)
Potential risk for sputum induction	Risks associated with sputum induction include worsened expiratory airflow limitation and oxygen desaturation	• Sputum induction to be conducted in sub-cohort participants only. • Procedures to be performed by trained personnel (i.e., study nurse). • A standardized sputum induction protocol to be applied which have minimal deleterious effects on lung function and oxygen saturation and safety checks during the procedure.
Subjects exposed to ionising radiation as a consequence of participation in this study.	The ionising radiation exposure comes from repeated low dose CT scans of the chest. Participants with COPD will be subject to a maximum of 6 scans, resulting in an effective dose of ionising radiation in the range 10-16mSv. This is equivalent	The study has been designed to keep the radiation dose as low as reasonably practicable (ALARP) whilst obtaining images of sufficient quality to meet the objectives. Participants <50 years of age will not be included in the sub-cohort, nor will females of child bearing potential. Healthy control participants will be

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	to approximately 4.5-7 times the average yearly exposure (2.3 mSv) from natural background radiation in China. The additional risk of developing a fatal malignancy as a result of a 16mSv exposure has been estimated as approximately 1 in 1250 for an adult in normal health. The reduced life expectancy of the patient population to be studied will result in a lower risk for these individuals. Healthy control participants will be subject to a maximum of 4 scans, resulting in an effective dose of ionising radiation in the range 8-12mSv. This is equivalent to approximately 3.5-5.5 times the average yearly exposure (2.3 mSv) from natural background radiation in China. The additional risk of developing a fatal malignancy as a result of a 12mSv exposure has been estimated as approximately 1 in 1650 for an adult in normal health. The guidance set out by the International Commission on Radiological Protection in ICRP 62 is generally followed when considering	subject to fewer CT scans than participants with COPD. Each CT scan will be optimised, using Automatic Exposure Control, to obtain sufficient image quality whilst using the least possible radiation, hence the ranges of possible dose estimates. The highest exposures will be required only in larger participants with a BMI >30.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	radiation exposure for research purposes. These radiation doses fall between Risk Categories IIb (intermediate risk) and IIIa (moderate risk) and are justified by the expected scientific impact of the study which is expected to provide information that will have a beneficial impact on the management of COPD in the target population.	
Wrist band	Allergy to wrist strap, belt clip, belt strap or device case (if device is put on upside down). Worn on broken skin	If participants allergy to the rubber wrist strap or have broken skin around wrist, please do not included them in the sub-cohort.

Benefit Assessment

Evidence on disease progression, e.g.; decline in lung function, exacerbation types and rates and worsening of physical activity, will allow healthcare professionals in China to target innovative medicines to the right patients.

In this study, participants will be monitored regularly throughout the 2.5-year follow-up. This will help their physicians to have a better overview of their disease status, phenotype and hence provide holistic disease management reflecting underlying disease severity, its progression and the participant's health status.

Overall Benefit: Risk Conclusion

This observational cohort study will provide an opportunity to the participants and their physicians to have a comprehensive overview of their disease and to inform individualized therapy. There is no investigational drug. Considering the measures taken to minimize risk to participants in this study, the potential risk from the study procedures is minimal and overall can be justified by the anticipated benefits.

4. OBJECTIVES AND ENDPOINTS

Research Questions & Objectives	Endpoints
Evaluate whether the predictors of COPD disease progression identified in Western cohorts are applicable in China. • To evaluate disease progression in COPD and non-COPD participants over 2.5 years as assessed by lung function, exacerbation frequency, health status, lung HRCT scan, and changes in physical activity.	**Main cohort** Change from baseline in forced expiratory volume in 1 second (FEV_1) and rate of decline in FEV_1 Change from baseline forced vital capacity (FVC) and rate of decline in FVC Rate of moderate/severe exacerbations* Change from baseline in COPD Assessment Test (CAT) score Assess CAPTURE to identify under diagnosed COPD patients in Chinese population Frequency of Clinically Important Deterioration (CID) and its components Death **Additional for sub-cohort** Change in Evaluating Respiratory Symptoms in COPD (E-RS: COPD) scores Characterization of EXAcerbation of COPD Tool (EXACT) events Change from baseline in airway thickness by lung HRCT Change in lung density by lung HRCT Change in physical activity measures (e.g. Daily steps, bouts of activity per day)
Characterise stable disease and exacerbation phenotypes in China through assessment of blood biomarkers, lung microbiome and radiological features of COPD	**Main cohort:** Plasma fibrinogen, Serum high-sensitivity C-Reactive Protein (hsCRP) Differential blood cell count (including eosinophils, neutrophils) and hemoglobin **Additional for sub-cohort** Blood biomarkers including but not limited to Serum interferon- γ -inducible protein -10 (IP-10), soluble Receptor for

Research Questions & Objectives	Endpoints
	Advanced Glycation End Products (sRAGE), Club cell protein (CC16)) and HbA1c Sputum microbiome as assessed by molecular methods Sputum total differential cell counts and percentage CCI [redacted]
Characterise treatment pathways and healthcare resource utilization and costs in COPD	Frequency of treatment with COPD medication and Treatment patterns at the time of study entry and during the study period Count of outpatient visits, emergency visits, hospitalizations (overall and COPD-specific, separately) Direct medical costs associated with COPD medications and COPD disease management Insurance coverage and patient out-of-pocket payment
Test the feasibility of integrating electronic health records, electronic clinical outcome assessments (eCOA) and physical activity data to support application of digital data analytics (DDA) platform in China studies (e.g. direct digital data capture and integration)	NA

*Moderate exacerbations are defined as COPD exacerbations that require either systemic corticosteroids (intramuscular (IM), intravenous, or oral) and/or antibiotics. Severe exacerbations are defined as COPD exacerbations requiring hospitalization (including intubation and admittance to an ICU) or result in death.

5. STUDY DESIGN

5.1. Overall Design

This is a 2.5-year multi-center, prospective, longitudinal, non-drug interventional cohort study to investigate the clinical, radiological and biological factors associated with disease progression in COPD in Guangdong and Fujian, China. Guangdong, a coastal province of southeast China, is the most populous province in China with 109 million people in 2015. The residents in Guangdong are Chinese in ethnicity with a mix of urban

and rural population which is representative of the general Chinese population. Guangdong has a similar healthcare system across the province that will enable data integration. Xiamen, a coastal city in Fujian province (Fujian is another province of southeast China), is near Guangdong province. We added one site (maybe more if needed) in Xiamen based on feasibility to enhance the enrolment of this study due to the advantages of Xiamen on population screening of COPD.

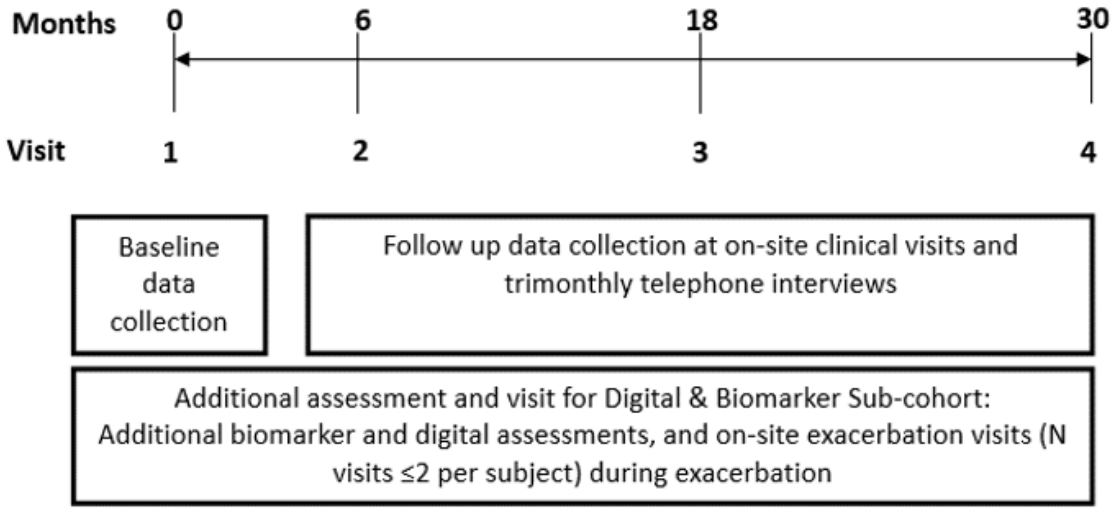
This cohort study will not provide or recommend any treatment. During the study period, patients' diagnosis and treatment will be left to their physicians' judgement and routine practice.

A total of approximately 2,000 subjects will be recruited from multiple hospitals (excluding tier 1) across Guangdong & Fujian province. In this study, hospitals will be categorized by administrative regions: those at prefecture-level and above will be categorized as Type A hospitals; those below prefecture-level will be categorized as Type B hospitals. Site/hospital selection will consider the representativeness of pollution level and hospital type, as well as the feasibility of being part of an integrated electronic system with linked hospital databases and various data sources.

A wide range of COPD patients across GOLD grades I-IV and chronic bronchitis patients will be included. Never smokers with no significant diseases will be recruited as healthy control group.

Baseline data will be recorded for all subjects at Visit 1 and subjects will be followed up at 6 months and then every 12 months for a total of 2.5 years (Figure 1). Study visits will be conducted within ±30 days of the planned date. In addition to study visits, COPD and chronic bronchitis participants will be contacted by phone on trimonthly basis within ± 7 days of the planned date to assess the CAT and to collect information on exacerbation rates and COPD medications; healthy controls will be contacted by phone on trimonthly basis within ± 7 days of the planned date to assess the CAT.

Figure 1 Study schema



A subset of participants from selected Type A hospitals are planned to receive additional assessments including digital monitoring of daily steps; completion of an evening electronic diary (including EXACT/ E-RS: COPD); the monthly CAT; collection of blood for study defined biomarkers; lung HRCT scanning; sputum collection for microbiome and cytology analysis. If moderate/severe exacerbations are reported by the participants or detected by investigators during the acute phase of the event, this subset of participants will be invited to the site hospital for an exacerbation visit (no more than twice with an interval of at least 21 days throughout the study). Participants from this sub-cohort constitute the Biomarker and Digital sub-cohort.

In addition, daily air pollution index throughout the study in each participating city will be collected retrospectively from a local environmental monitoring center.

5.2. Number of Participants

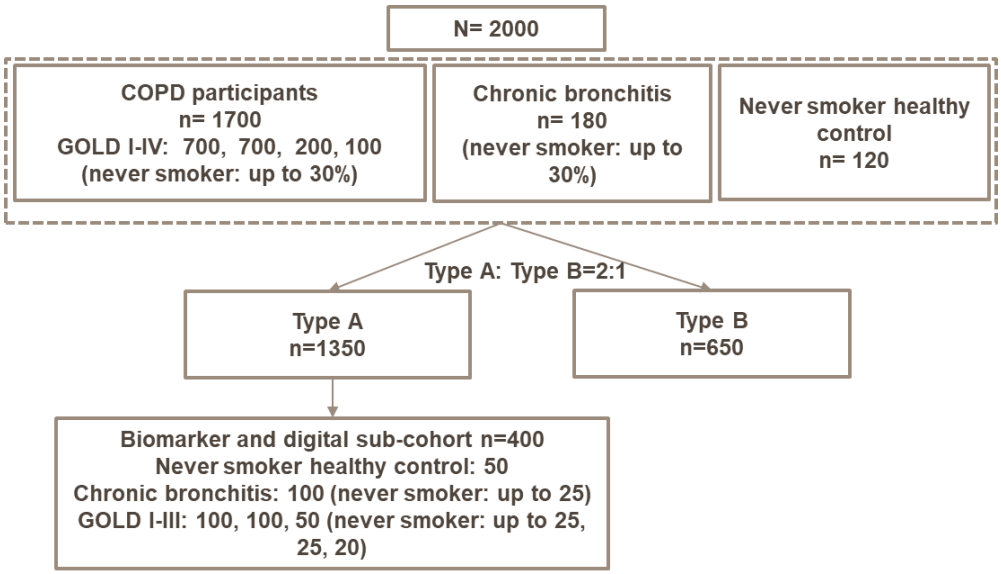
A total of approximate 2,000 participants are planned to be enrolled, consisting of 1,700 participants with COPD, 180 with chronic bronchitis but without fixed airflow limitation, and 120 never smoker healthy control. Specifically, COPD subjects will be classified using the GOLD grades I – IV (i.e. mild, moderate, severe and very severe). To better understand the disease progression of early stage COPD, i.e. GOLD I and II grades, COPD participants will be recruited in the following manner: GOLD I: 700, GOLD II: 700, GOLD III: 200, GOLD IV: 100 (Figure 2). Among each GOLD category and chronic bronchitis group, up to 30% of never smokers will be recruited in each group.

We set the target number for each grade group (GOLD I- IV) based on the study operational perspective, to ensure a wide and even distribution of airflow limitation across the participants recruited to this study. During recruitment, we will closely monitor the enrolment progress and post-bronchodilator FEV1 distribution, especially the GOLD I and GOLD II groups. If necessary, the recruitment targets for GOLD I and GOLD II in the main cohort may be adjusted to achieve an even distribution of participants between

mild and severe. This may include combining targets for specific GOLD grades to ensure that total recruitment numbers are achieved.

All participants will be recruited from Type A and Type B hospitals in Guangdong province. To represent the difference in patient profile and practice between different hospitals, the ratio of participants from Type A and Type B hospitals will be 2:1. Specifically, healthy control participants will be recruited from the physical examination department at site hospitals. For the healthy control group to be comparable with COPD participants, pre-set criteria on demographic profile (i.e. age, gender) will be specified in detail in SRM based on previous studies or available real-world data. During the recruitment, we will closely monitor the demographic profile (i.e. age, gender) of enrolled participants of both groups and adjust the demographic distribution of the healthy controls. When feasible, matching methods will be used to adjust for differences in baseline factors (e.g. age, gender, smoking status) in statistical analyses. Various matching approaches (e.g. pair-wise matching) will be considered depending on specific questions to be addressed, e.g. biomarkers analysis, and the extent of underlying differences between the cohorts. Details will be specified in the main or ad-hoc RAP.

Figure 2 Study Population Schematic

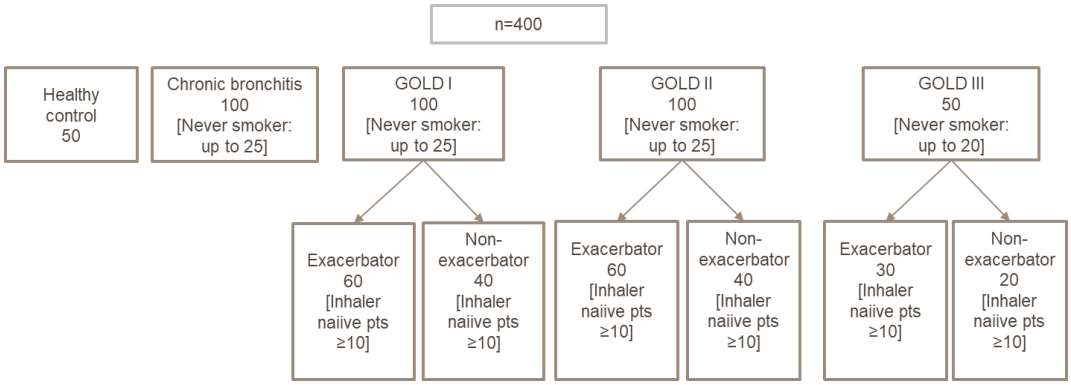


More assessments will be conducted among the 400 Biomarker & Digital sub-cohort participants who will be recruited from selected Type A hospitals. The sub-cohort consists of 50 never smoker healthy control, 100 chronic bronchitis (N never smoker: up to 25), 100 GOLD I (N never smoker: up to 25), 100 GOLD II (N never smoker: up to 25) and 50 GOLD III participants (N never smoker: up to 20) (Figure 2). Given the GOLD III never smokers are rare [Wang. 2018], based on feasibility, when necessary, a recruitment approach of combining Ever smoker and Never smoker will be implemented to ensure that the target of enrolment of 50 patients with GOLD III is achieved as planned. During the recruitment, the enrolment progress will be closely monitored.

In GOLD I-III grades, certain number of COPD participants with previous exacerbation history (i.e. exacerbators) will be recruited (target number of subjects are as follows -

GOLD I: 60 exacerbators, GOLD II: 60 exacerbators, GOLD III: 30 exacerbators). Further, a proportion of those who are maintenance inhaler treatment naïve will be recruited, aiming for: 10 participants who are maintenance inhaler treatment naive will be recruited among exacerbators and non-exacerbators in each GOLD I, II, III groups respectively (Figure 3). All patient population sizes are approximate and allow ± 10% for feasibility.

Figure 3 Sub-cohort Population Schematic



For subjects included in COPD groups, Non-exacerbator is defined as a patient who has not had an exacerbation (see definition of exacerbation below) in the 2 years before entry into the study; Exacerbator is a patient who has 1 or more exacerbations in the 2 years before recruitment. In this study, an exacerbation is defined by the occurrence of an episode of increased cough (with or without phlegm), shortness of breath or chest symptoms (chest discomfort or tightness) which lasted 48 hours or more and interfered with the participant's usual activities (with or without treatment).

Inhaled maintenance treatment naïve patients will be defined as not being treated in at least prior 12 months with any long-acting inhaled medications inclusive of inhaled corticosteroids, long-acting antimuscarinic or long-acting beta2-agonists.

To minimize selection bias, study investigators are encouraged to follow their routine clinical practice and consecutively recruit all eligible patients at their practice. The investigator will maintain a screening log to collect details (e.g. age, sex, smoking status, presence of chronic mucus hypersecretion (CMH) and maintenance inhaler treatment) of all participants screened, to confirm eligibility, and to record reasons for study exclusion, as applicable. Recruitment process will be closely monitored to ensure the proper number of participants within each subgroup. A patient informed consent will be obtained from all participants to allow their past, current and follow-up period information to be collected and used. Sub-cohort participants are required to provide a separate consent for additional assessments.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit (Visit 4).

The end of the study is defined as the date of the last visit of the last participant in the study.

5.4. Scientific Rationale for Study Design

To reflect the real-world management and patient outcomes of COPD in China, a non-drug interventional study design was chosen. Patient diagnosis and treatment will be left to their physicians' judgement and routine practice. This study will not provide or recommend any treatment. By capturing the prospective and longitudinal patient-level data in a real-world clinical setting, the study will fulfil the needs to understand the phenotypes and their disease progression, and current disease management more comprehensively and in depth. Study results will inform clinical practice and may improve patient outcomes.

This study will use COPD and non-COPD cohorts to provide cross-sectional and longitudinal data on multiple clinical, radiological and biological evaluations. Study participants will mostly represent mild to moderate airflow limitation grades of COPD and symptomatic non-COPD (i.e. chronic bronchitis) populations, whose disease progression is not well understood in China.

Air pollution and increased biomass exposure are likely to be key contributors to the development of COPD in China. Previous nation-wide studies showed a large proportion of COPD patients (20-40%) in China are never smokers. Kurmi et al. reported that 5.4% of never smokers had airflow obstruction (AFO) among Kadoorie cohort [Kurmi, 2014]. The prevalence of COPD was estimated to be 5.2% among never smokers in Zhong et al [Zhong, 2007].This suggested that factors other than smoking (e.g. biomass, occupational exposure, and air pollution) may also play an important role in COPD progression. However, there is a lack of data on phenotypes and disease progression in never smokers with COPD. Differing from the Western cohorts in which participants were required to have at least 10-pack year smoking history, never smokers with diagnoses of COPD or chronic bronchitis (with respiratory symptoms who don't meet the spirometric criteria of COPD) are also recruited. In addition, air pollution data will be collected retrospectively to explore the association between air pollution and COPD natural history.

Healthy subjects who are never smokers and without a diagnosis of respiratory condition and other significant diseases will also be recruited to this study as controls, e.g. providing data on baseline natural lung function decline and lung structural damage in a general population.

This study will also set up a Biomarker and Digital sub-cohort aiming to identify early disease and rapid progression and associated endotypes among Chinese COPD patients through enhanced repeated collection and analysis of biological samples and chest computer tomography. COPD is characterised by abnormal spirometric results, with a focus on FEV_1. Decline in FEV_1 is currently the gold standard for assessment of COPD progression. However, disease burden and worsening are also inextricably linked with disease activity represented by symptom load and exacerbations of COPD. This study

will aim to evaluate multifactorial framework of disease severity in Chinese population similar to work by Agusti and colleagues [Agusti, 2016].

The selected 2.5-year follow up is required as a minimum period to achieve sufficient precision on the rate of decline in key study measures balanced against any perceived burden this study may impose on participants which could result in early withdrawal from the study.

The clinical, radiological and biological factors identified to be associated with disease progression in Western cohorts will be investigated to test the hypotheses whether these predictors are applicable in China and characterise the exacerbator phenotype in China. Healthcare resource utilization and costs in COPD will be assessed to evaluate the economic impact of COPD for the different groups of COPD patients in Guangdong province. The following table lists all study endpoints and summarizes the rationale of including them.

Study Outcomes	Rationale
• Change from baseline and rate of decline in FEV1 and FVC	• Change in FEV_1 is currently the gold standard for assessment of COPD progression.

• Rate of moderate/severe exacerbations
  ○ Healthcare resource utilization definition
  ○ EXACT events (sub-cohort only)
	• Exacerbations are important events influencing disease severity, disease progression, health-related quality of life, and mortality and are also contributing significantly to healthcare resource utilization. The characterisation of exacerbation frequency, type and duration could be of significant importance to clinical practice and medical resource allocation. Acute exacerbations of COPD (AECOPD) will be collected using:
	  ○ Healthcare resource utilization definition where moderate events are classified as managed by antibiotics (ATB) and/or systemic (intramuscular (IM), intravenous, or oral corticosteroid (OCS)) and severe as hospital admission or resulting in death [EMA, 2010].
	  ○ In a sub-cohort, EXACT, a daily diary evaluating symptoms of exacerbations will be employed to collect EXACT events [Leidy, 2013].

• Clinically Important Deterioration (CID) composite outcome	CID is a new composite outcome (developed by GSK; Singh, 2016; Naya, 2018) for the risk prediction of long-term adverse outcomes of COPD. In this study, the CID will be derived from three key clinical assessments, which are 1) moderate/severe exacerbations, 2) worsening of FEV_1, and 3) worsening of health status using the CAT questionnaire.

• Change from baseline in CAT score
• Change in E-RS: COPD score (sub-cohort only)
	• COPD-related health status including respiratory symptom level is a predictor of long-term adverse outcomes of COPD.
	  ○ The CAT questionnaire will capture the well-being and health-related quality of life of COPD patients and also will be used to calculate CID [Jones, 2009].
	  ○ E-RS: COPD (a subset of the EXACT assessment) will be used to capture the impact of COPD symptoms in a sub-cohort [Leidy, 2014].

Study Outcomes	Rationale
• Assess CAPTURE to identify under diagnosed COPD patients in Chinese population	• To assess the sensitivity and specificity of the CAPTURE questionnaire as a case finding tool in obstructive lung disease
CCI [redacted]	
• Daily Activity as measured by number of steps (sub-cohort only).	• This will be measured by using digital mobility device worn by participants.
• Mortality	Vital status will be collected
• Plasma fibrinogen • high-sensitivity C-reactive protein (hsCRP)	• Airway inflammation is a key component of the pathogenesis of COPD. The inflammation can be characterised by various differential cell profiles in induced sputum and the blood. The systemic component of COPD may be reflected by raised mean values of blood fibrinogen, CRP. CRP and fibrinogen are associated with GOLD stage of disease and are elevated during exacerbations. Elevated levels of CRP and fibrinogen have also been associated with increased risk for hospitalization and death from this disease. CRP shows significant variability in COPD while fibrinogen is much more stable. Because of its stability, association with COPD-related outcomes (exacerbation, hospitalization and death) and sensitivity to intervention, fibrinogen was assumed to be a very promising biomarker. Fibrinogen has been qualified as a biomarker for patient population stratification for clinical trials [Miller, 2016].

Study Outcomes	Rationale
• Total and Differential blood cell counts including eosinophils, neutrophils and hemoglobin	• Blood eosinophil measurements is a surrogate biomarker for sputum eosinophils both in stable COPD patients and during exacerbations. Eosinophilic inflammation is a distinctive phenotype of AECOPD. Further, it provides a measure of the probability of benefit from inhaled corticosteroids.
• Other blood biomarkers inclusive of sRAGE, CC16, IP-10(sub-cohort only), HbA1c	• sRAGE is a marker for emphysema and its progression • CC16 is a potential marker for lung function decline • IP-10 is a biomarker of Human Rhinovirus Infection at Exacerbation of COPD • HbA1c is a biomarker used in the diagnosis and progression of diabetes, it often reflects the average level of blood sugar over the past 2 to 3 months.
• Sputum microbiome (sub-cohort only)	• Changes in lung microbiome are associated with COPD disease severity: airflow limitation (and CAT) • Lung microbiome differs between exacerbation subtypes
• Sputum cytology (sub-cohort only)	• Sputum total differential cell counts and percentage in stable COPD patients predicted the clinical response to systemic corticosteroids
Frequency of treatment with COPD medication and Treatment patterns at the time of study entry and during the study period Count of outpatient visits, emergency visits, hospitalizations, (overall and COPD-specific, separately) Direct medical costs associated with COPD medications and COPD disease management Insurance coverage and patient out-of-pocket payment	• Quantifying the medical costs aids COPD clinical management and public health resource allocation decision-making. • Hospital Information Systems (HIS) will be tested for feasibility to provide granular information

5.5. Dose Justification

Not applicable.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Participants will be eligible for inclusion in the main cohort only if all inclusion criteria apply and none of the exclusion criteria apply.

Eligible participants in the main cohort from selected Type A hospitals, consented with willingness to use electronic devices for daily patient-reported outcomes collection (e.g. logpads), attend more frequent visits and receive additional assessments will be recruited to the Biomarker and Digital sub-cohort.

It is planned to enrol approximately 1,700 COPD subjects in the study, approximately 180 controls with chronic bronchitis, and approximately 120 never smoker healthy controls.

COPD subjects will fall into the GOLD categories I - IV. It is intended to recruit the COPD subjects in the following manner: 700 GOLD I, 700 GOLD II, 200 GOLD III and 100 GOLD IV.

All patient population sizes are approximate and subject to feasibility.

6.1. Inclusion Criteria

COPD Participants

A COPD subject will be eligible for inclusion in this study only if all the following criteria apply:

1. Male or female participants, aged 40-80 years inclusive.

A female is eligible to enter and participate in the study if she is of non-child bearing potential.

2. A baseline (post-bronchodilator) FEV1/FVC ratio <0.70
3. Clinically stable and has no exacerbations for at least 1 month prior to recruitment. All courses of oral corticosteroids or antibiotics must be completed at least 2 weeks before study start.
4. Ever smoker (with a lifetime exposure of $\geq$1 pack-year) or never smoker (with a lifetime exposure of <1 pack-year)
5. A signed and dated written informed consent is obtained prior to participation
6. Additional criteria for sub-cohort COPD participants to be recruited:
    - Only include participants aged 50-80 years (inclusive)
    - BMI<35 kg/m^2

- Only include ever smoker with a lifetime exposure of ≥10 pack-year or never smoker with a lifetime exposure of <1 pack-year
- About 150 COPD participants with a history of at least 1 exacerbation event(s) within the past 2 years at the entry of the study
- About 60 COPD participants without inhaler maintenance treatment history for at least 12 months prior to the entry of the study (including inhaled corticosteroids, inhaled long-acting antimuscarinics, and inhaled long-acting beta2-agonists).

Chronic Bronchitis Participants

A chronic bronchitis participant will be eligible for inclusion in this study only if all of the following criteria apply:

1. Male or female participants, aged 40-80 years inclusive, who are free from significant disease as determined by history, physical examination and screening investigations.

   A female is eligible to enter and participate in the study if she is of non-child bearing potential.
2. Baseline post-bronchodilator FEV1/FVC ratio ⩾0.70.
3. Chronic bronchitis is defined as at least 3 months of cough and phlegm in a year in the past 2 years.

   The definition of chronic bronchitis is used for recruiting subjects to Chronic Bronchitis group. This would be identified by asking two questions such as: "How many MONTHS in the past 12 months have you had bronchitis or chronic coughing with phlegm or sputum from the chest?" AND "For how many years have you had bronchitis or chronic coughing with phlegm or sputum from the chest?" with at least 3 months in past year and for at least past 2 years representing a minimum qualifying criteria.
4. Clinically stable and has no exacerbations for at least 1 month prior to recruitment.
5. Ever smoker (with a lifetime exposure of ≥1 pack-year) or never smoker (with a lifetime exposure of <1 pack-year)
6. A signed and dated written informed consent is obtained prior to participation.
7. Additional criteria for sub-cohort Chronic Bronchitis participants to be recruited:
   - Only include participants aged 50-80 years (inclusive)
   - BMI <35 kg/m^2
   - Only include ever smoker with a lifetime exposure of ≥10 pack-year or never smoker with a lifetime exposure of <1 pack-year

Healthy Participants

1. Male or female participants, aged 40-80 years inclusive, who are free from significant disease as determined by history, physical examination and screening investigations.

   A female is eligible to enter and participate in the study if she is of non-child bearing potential.
2. Baseline post-bronchodilator FEV_1/FVC ratio $\geqslant$0.70
3. A CAT score <10
4. Never smoker with a lifetime exposure of <1 pack-year. Passive smoker is not eligible
5. A signed and dated written informed consent is obtained prior to participation.
6. Additional criteria for sub-cohort Healthy participants to be recruited:
   - Only include participants aged 50-80 years (inclusive)
   - BMI <35 kg/m^2

6.2. Exclusion Criteria

COPD Participants

A COPD participant will not be eligible for inclusion in this study if any of the following criteria applied:

1. In the opinion of the investigator, there was a current primary diagnosis of asthma (patients with a primary diagnosis of COPD but who also had asthma could be included).
2. Known respiratory disorders, or disorders identified at screening/visit 1(including identification on the first CT scan), other than COPD (e.g. COVID-19, lung cancer, sarcoidosis, active tuberculosis, lung fibrosis, cystic fibrosis) that may significantly impact clinical assessments according to investigator judgement
3. Having undergone lung surgery (e.g. lung reduction, lung transplant)
4. Known history of significant inflammatory disease, other than COPD (e.g. rheumatoid arthritis and Lupus)
5. Serious, uncontrolled disease (including serious psychological disorders) likely to interfere with the study or impact on subject safety
6. Diagnosis of cancer: included current and within the last 5 years (patients in remission for ≥ 5 years could be included).
7. Participants who were concurrently participating in any clinical studies where investigational drugs were tested within 4 weeks prior to Visit 1 (baseline), or who were scheduled to start any during the study period or enrolled in a study where there is significant radiation exposure (e.g. CT scans).

8. Unable or unwilling to use required digital devices, e.g. wrist band, digital diary (sub-cohort only)
9. Have, in the opinion of the investigator, evidence of alcohol or drug abuse
10. Have received a blood transfusion in the 4 weeks prior to study start
11. Is on long term oral corticosteroids (long term is considered use for more than 3 consecutive months)
12. Unable to walk
13. Unable to read and understand Chinese

Chronic Bronchitis Participants

A chronic bronchitis participant will not be eligible for inclusion in this study if any of the following criteria applied:

1. Known respiratory disorders, or disorders identified at screening/visit 1(including identification on the first CT scan), (e.g.: COVID-19, COPD, current asthma, lung cancer, sarcoidosis, active tuberculosis, lung fibrosis, cystic fibrosis) that may significantly impact clinical assessments according to investigator judgement
2. Post-bronchodilator FVC<80% Predicted normal
3. Having undergone lung surgery (e.g. lung reduction, lung transplant)
4. Known history of significant inflammatory disease, other than COPD (e.g. rheumatoid arthritis and Lupus)
5. Serious, uncontrolled disease (including serious psychological disorders) likely to interfere with the study or impact on subject safety
6. Diagnosis of cancer – included current and within the last 5 years (patients in remission for ≥ 5 years could be included).
7. Participants who were concurrently participating in any clinical studies where investigational drugs were tested within 4 weeks prior to Visit 1 (baseline), or who were scheduled to start any during the study period, or enrolled in a study where there is significant radiation exposure (e.g. CT scans).
8. Unable or unwilling to use required digital devices, e.g. wrist band, digital diary (sub-cohort only)
9. Have, in the opinion of the investigator, evidence of alcohol or drug abuse
10. Have received a blood transfusion in the 4 weeks prior to study start
11. Is on long term oral corticosteroids (long term is considered use for more than 3 consecutive months)
12. Unable to walk
13. Unable to read and understand Chinese

Healthy Participants

A healthy participant will not be eligible for inclusion in this study if any of the following criteria applied:

1. Known respiratory disorders or disorders identified at screening/visit 1(including identification on the first CT scan) (e.g. COVID-19, COPD, current asthma, lung cancer, sarcoidosis, active tuberculosis, lung fibrosis, cystic fibrosis) that may significantly impact clinical assessments according to investigator judgement
2. Post-bronchodilator FVC<80% Predicted normal
3. Having undergone lung surgery (e.g. lung reduction, lung transplant)
4. Known history of significant inflammatory disease, other than COPD (e.g. rheumatoid arthritis and Lupus)
5. Serious, uncontrolled disease (including serious psychological disorders) likely to interfere with the study or impact on subject safety
6. Diagnosis of cancer – included current and within the last 5 years (patients in remission for ≥ 5 years could be included).
7. Participants who were concurrently participating in any clinical studies where investigational drugs were tested within 4 weeks prior to Visit 1 (baseline), or who were scheduled to start any during the study period, or enrolled in a study where there is significant radiation exposure (e.g. CT scans).
8. Unable or unwilling to use required digital devices, e.g. wrist band, digital diary (sub-cohort only)
9. Have, in the opinion of the investigator, evidence of alcohol or drug abuse
10. Have received a blood transfusion in the 4 weeks prior to study start
11. Is on long term oral corticosteroids (long term is considered use for more than 3 consecutive months)
12. Unable to walk
13. Unable to read and understand Chinese

6.3. Lifestyle Restrictions

No lifestyle restrictions are required.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants. Minimal information includes demography, screen failure details, eligibility criteria.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. Only in certain special cases, re-screening of participants will be

allowed. Investigator will be asked to provide detailed information. Special cases will be discussed at the EST (empowered study team) meeting. After permission from the medical monitor of this study is granted, the participants can only be re-screened once.

7. TREATMENTS

This cohort study will not provide or recommend any treatment. Patients' diagnosis and treatment will be left to their physicians' judgement and routine practice. This section is not applicable.

7.1. Treatments Administered

Not applicable.

7.2. Dose Modification

Not applicable

7.3. Method of Treatment Assignment

Not applicable

7.4. Blinding

Not applicable

7.5. Preparation/Handling/Storage/Accountability

Not applicable

7.6. Treatment Compliance

Not applicable

7.7. Concomitant Therapy

Not applicable

7.8. Treatment after the End of the Study

Not applicable

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Not applicable. This cohort study will not provide or recommend any treatment. Patients' diagnosis and treatment will be left to their physicians' judgement and routine practice.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.
- A subject will be considered withdrawn from the study if he/she joins any clinical studies where investigational drugs are tested.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws consent for disclosure, the site may use any publicly information to determine vital status at the end of the study and this information would be included in the final analyses.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she is unreachable and fails to come back for both Visit 3 and 4.

9. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in schedule of activities (Table 1)

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue the study.

Site staff will make every effort to work with participants to collect all study assessments.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, spirometry) and obtained before signing of informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.

9.1. Baseline data collection

A specifically designed baseline survey will be used to collect the following information at baseline from all participants, including:

Informed consent

Inclusion/exclusion criteria assessment

Socio-demographics

- Age
- Race/ethnicity
- Gender
- Education
- Economic status
- Occupation
- Insurance information (basic, commercial)

Health and lifestyle information

- Height, weight, body mass index (BMI)
- Blood pressure, heart rate
- Smoking status: Never smokers are defined as those with a lifetime exposure of <1 package/year in their life (excluding passive smoker). Ever smokers (current or former) are defined as those with a lifetime exposure of ≥10 package/year. Former smokers are those who have stopped smoking for at least 6 months. Current smokers are those who are currently smoking. Passive smokers are

defined as those with the presence of smokers living in the same household, or co-workers smoking nearby while indoors

- Smoking history including Pack-years of smoking: Number of pack years = (number of cigarettes per day / 20) x number of years smoked, e.g., 10 pack-years means 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years)
- Biomass exposure: refer to the biomass exposure questionnaire
- Occupational exposures: Whether had the participant worked in occupations known or suspected to be associated with the risk of COPD ≥6 months， e.g. organic/inorganic dust, irritant gases, fumes, or vapors chef，traffic police Toxic and harmful jobs（eg.in pollution factory or chemical work, etc)

COPD Medical history (for COPD participants only)

- Disease duration
- Treatment history (e.g. the time of initiating maintenance treatment, current treatment)
- Number of exacerbations in the previous 12 months and 24 months
- Number of moderate and severe exacerbations in the previous 12 months and 24 months and their management with oral corticosteroids and/or antibiotics and/or hospitalization
- Family history of COPD or other respiratory diseases

Lower respiratory infections including chest colds (for chronic bronchitis patients only)

Medical history (including previous asthma history)

Current co-morbid conditions and childhood respiratory disease

Concomitant medications: Respiratory medications, antibiotics, oral steroids, anti-diabetic， anti-hypertension gastroesophageal reflux disease (GERD) therapy, cardiovascular disease therapy and whether taking traditional Chinese medicines

Patient reported outcomes: CAT, SGRQ-C and mMRC, CAPTURE

Spirometry (pre- and post-bronchodilator)

- FEV_1
- Forced vital capacity (FVC) & Percent Predicted FVC and FEV_1/FVC ratio & Percent Predicted FEV1/FVC
- Forced expiratory volume in 6 seconds (FEV6)
- Forced expiratory flow between 25% and 75% of vital capacity (FEF 25-75) & Percent Predicted FEF 25-75, Forced Expiratory Flow 25% (FEF25), Forced Expiratory Flow 50% (FEF50) and Forced Expiratory Flow 75% (FEF75)
- Peak Expiratory Flow (PEF) & Percent Predicted PEF, time to Peak Expiratory Flow (tPEF) and Maximal Mid-Expiratory Flow (MMEF)
- Forced Expiratory Time (FET) and Volume back extrapolation (VEXT)

- FEV_1 percent of predicted and reversibility test
  - Reversibility will be assessed at Visit 1 (baseline) by measurement of FEV_1 before and 10 to 30 minutes after administration of a short-acting bronchodilator (e.g. 400μg β_2-agonist or up to 160μg anticholinergic). Prior to testing, the patients should not have taken inhaled short-acting bronchodilators in the previous six hours, long-acting bronchodilator in the previous 12 hours or sustained-release theophylline in the previous 24 hours.
  - Reversibility will be calculated as follows: % Reversibility = $\frac{\text{Highest post-bronchodilator } FEV_1 - \text{Highest pre-bronchodilator } FEV_1}{\text{Highest pre-bronchodilator } FEV_1} \times 100$

Collection of blood samples for protocol defined analysis (plasma fibrinogen and hsCRP, total and differential blood cell count)

In addition, the following assessments will be conducted among the Biomarker & Digital sub-cohort participants only:

Blood biomarkers (including serum sRAGE, CC16, IP-10，HbA1c)

Sputum sample collection for protocol defined analyses (microbiome through molecular methods, cytology)

Lung HRCT

Issue and training in use of electronic diary: EXACT questionnaire (start after clinic visit at baseline)

Digital steps (start after clinic visit at baseline)

9.2. Follow up data collection

9.2.1. COPD medications and treatments and concomitant medications

COPD medications and treatments will be derived from medical records in site hospitals' Hospital Information System (HIS) complemented by site interview at each clinic visit including exacerbation visits and trimonthly telephone interviews including those not captured in HIS (e.g. purchased in pharmacies, prescribed by HCPs outside the research site hospitals). Pictures of COPD medication will be provided to assist patient recall during telephone interviews and clinic interviews.

Concomitant medications collected in this study will include: respiratory medications, antibiotics, oral steroids, gastroesophageal reflux disease (GERD) therapy, cardiovascular disease therapy and whether taking traditional Chinese medicines.

9.2.2. Smoking status

Smoking status will be reassessed at each scheduled clinic visit evaluated by participants' self-report (e.g. never smoker, current smoker, former smoker).

9.2.3. Spirometry

Spirometry (same measurements as baseline spirometry, refer to Section 9.1) will be performed in triplicate at time points listed in the SoA Table 1. Spirometry assessments should be performed in accordance with ATS/ERS guidelines as outlined in the SRM. Predicted values will be based upon the spirometric reference values for Chinese [Jian, 2017].

9.2.4. COPD exacerbations

COPD subjects will be asked for a history of AECOPD using components of moderate/severe exacerbation definition at each clinic visit including exacerbation visits. Additionally, COPD subjects will be contacted by phone every 3 months by the study staff and asked about their exacerbation details for the previous 3 months. Study staff will check Hospital Information System (HIS) during the interview to confirm the event of exacerbation wherever possible.

9.2.5. Clinically important deterioration (CID) components

Clinically important deterioration (CID) is a new composite outcome (developed by GSK) for the prediction of future risk of long-term adverse outcomes. In this study, the CID will be derived from three key clinical assessments, which are 1) count of moderate/severe exacerbations, 2) worsening of FEV_1, and 3) change in the CAT score measured over 6 months. CID was defined as: decrease of ≥100 mL in post-bronchodilator FEV_1, or increase of ≥2 units in the CAT, or an occurrence of a moderate/severe exacerbation.

9.2.6. Patient Reported Outcome Measures

All Patient reported outcome measures should be collected in a nice, quiet setting without distractions (e.g., television, cell phones).

The COPD Assessment Test (CAT) will be collected at the beginning of study visits where applicable, before any other procedure.

The modified Medical Research Council (mMRC) Dyspnea Scale and St. George's Respiratory Questionnaire for COPD (SGRQ-C) will be administered at baseline.

The EXAcerbation of COPD Tool (EXACT) will be administered each evening among sub-cohort participants using an electronic diary.

COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk (CAPTURE) will be administered at baseline and Visit3.

9.2.6.1. COPD Assessment Test (CAT)

The COPD Assessment Test (CAT) is a validated, short and simple patient completed questionnaire which has been developed for use in routine clinical practice to measure the health status of patients with COPD [Jones, 2009; Jones, 2012]. The CAT is an 8-item questionnaire suitable for completion by all patients diagnosed with COPD. When

completing the questionnaire, participants rate their experience on a 6-point scale, ranging from 0 (no impairment) to 5 (maximum impairment) with a scoring range of 0-40. Higher scores indicate greater disease impact [Jones, 2009, CAT website].

For all participants, CAT will be completed at baseline, each follow up clinic visit, and tri-monthly phone interviews. Interviewer-administered approach (face-to-face or over the phone) will be used.

Additionally, for monitoring purpose, monthly CAT will be interviewer-administered over phone call in the sub-cohort for 6 months after baseline visit and 6 months after Visit 3.CAT will also be assessed in the sub-cohort at exacerbation visits.

9.2.6.2. Evening Diary (sub-cohort only)

Participants in the sub-cohort will complete an eDiary each evening consisting of the 14 item EXACT and additional questions as described below. Participants will be trained to use the eDiary at baseline visit and will complete the diary each evening in line with SOA.

- ***Exacerbations of Chronic Pulmonary Disease Tool (EXACT) and Evaluating Respiratory Symptoms in COPD (E-RS: COPD)***

The Exacerbation of Chronic Pulmonary Disease Tool-Patient Reported Outcomes (EXACT) is a 14-item participant reported outcome instrument designed to capture information on the occurrence, frequency, severity, and duration of symptoms suggestive of an exacerbation of disease in participants with COPD. EXACT captures information on the severity of the respiratory and systemic manifestations of a COPD exacerbation as reported by the participant [Leidy, 2013].

The Evaluating Respiratory Symptoms in COPD (E-RS: COPD) consists of 11 items from the 14-item EXACT instrument. The E-RS: COPD is intended to capture information related to the respiratory symptoms of COPD, i.e. breathlessness, cough, sputum production, chest congestion, and chest tightness. The E-RS: COPD has a scoring range of 0-40, with higher scores indicating more severe symptoms [Leidy, 2014]. Three subscales of the E-RS: COPD are used to describe different symptoms: breathlessness, cough and sputum, and chest symptoms.

The EXACT questionnaire will be completed each day at bedtime in the daily digital diary during the pre-defined study period. EXACT events will be identified from the 14 EXACT questions. Changes in overall symptoms and in the subscales of breathlessness, cough and sputum, and chest symptoms will be measured using the E-RS: COPD subset of EXACT.

- ***Additional questions***

In addition to the collection of EXACT, participants will also complete 5 additional daily diary questions to provide the information on other symptoms suggestive of an exacerbation: sputum purulence (color), wheezing, sore throat, colds (nasal discharge and/or nasal congestion) and fever without other cause.

The additional symptoms questions, combined with EXACT responses to questions on dyspnea, cough and sputum quantity will be assessed in stream and used to trigger prompts to both site and patients about symptom changes that may be indicative of an exacerbation.

9.2.6.3. Other PRO assessments

Chronic mucus hypersecretion (CMH) is defined as: At least 3 months of cough & phlegm in past year. This will be identified by asking a question as "How many months in the past 12 months have you had bronchitis or chronic coughing with phlegm or sputum from the chest?" Meanwhile, SGRQ-C and the CAT will be used for identification of CMH in this study. This would be identified by cough and phlegm related questions in SGRQ-C or CAT (details to be specified in the RAP).

The SGRQ-C is a disease-specific questionnaire designed to measure the impact of respiratory disease and its treatment on a COPD patient's HRQL [Meguro, 2007]. The SGRQ-C is a recent adaptation of the SGRQ instrument and the resulting SGRQ-C scores is transformed into the one equivalent to the original instrument.

The CATPURE is a short, five-item questionnaire that can be easily completed by patients and are used to identify individuals who may have undiagnosed, clinically significant COPD.

9.2.7. Computed tomography (CT) (sub-cohort only)

CCI [redacted]

Inspiratory and expiratory HRCT scans are required at Visit 1(baseline) and Visit 4 (the end of study), while only inspiratory scan will be conducted on exacerbation visit.

HRCT on the study participants may reveal the presence of previously undiagnosed malignant or other suspicious lesions (nodules). A local radiologist will review the HRCT scans solely for this purpose and notify the PI of any such observations. The radiologist should notify the PI of any observations within a week of the HRCT. The PI will then notify the subject's own doctor, who will be responsible for referral to further medical care. The follow up care will be in line with local hospital or clinic procedures for dealing with nodules.

9.2.8. Digital physical activity (sub-cohort only)

Daily digital steps will be collected in sub-cohort only. Participants are required to keep wearing the wrist band for 1 month from visit 1 and 3 as outlined in the time and event table.

9.2.9. Biomarker(s)

9.2.9.1. Blood biomarkers

Blood samples will be taken at Visit 1 and throughout the study as defined in the Time and Events Table. (Table 1*)*

- Plasma fibrinogen, hsCRP, total/differential blood cell count measurements and haemoglobin will be conducted at central lab for all participants
- Additional protein analysis will be conducted at central lab for the sub-cohort using validated assays. Analytes chosen will include serum sRAGE, CC16 and IP-10，HbA1c.

The blood biomarker assessments will be conducted according to the study reference manual.

9.2.9.2. Sputum microbiome and sputum cytology (sub-cohort only)

Sputum samples for microbiome and sputum cytology will be collected in sub-cohort only as defined in the Time and Events Table (Table 1). Sputum can be collected spontaneously or can be induced, as per investigator judgement, induced sputum is preferred. Sputum sampling should only be done if, in the opinion of the investigator, it is safe for the subject. The sputum microbiome and sputum cytology assessments will be conducted according to the sputum assessment procedure (Refer to study reference manual).

Additional analyses may include the measurement of viruses and fungi.

9.2.10. Healthcare Resource Utilization and Cost

To reflect the routine medical care, the information on COPD-related healthcare resource utilization and cost occurred within site hospitals will be captured on the study questionnaire form where possible using the HIS (based on site feasibility). Information collected include:

- Unscheduled COPD outpatient visits and emergency visits
  - Number of visits, date of visit, diagnosis of visit, cost
- COPD hospitalization (including intensive care)
  - Number of hospitalization, date and length of stay, diagnosis of visit, cost
- Prescribed COPD medications
  - Medication name, date of prescription, dosage, administration, cost, whether the prescription is picked up at hospital, etc.
- Other COPD treatment, e.g. oxygen therapy, nebulizers
  - Treatment name, date, cost, etc
- Lab tests, image tests, surgeries, and other tests and procedures (e.g., spirometry, Chest X-Ray, CT)
  - Test or procedure, date of operation, cost, etc.

- Healthcare cost if feasible, e.g. general service usage, consultation fee
  - Item, date of charge
- Insurance coverage and patient out-of-pocket payment if feasible

In addition, healthcare resource utilization could occur in other places outside of the site hospitals including: (1) hospitals other than the site hospital where the subject is recruited; (2) retail pharmacy stores; (3) subjects' home. Healthcare resource utilized and associated costs will be collected using standard questionnaires at trimonthly subjects' phone interviews. Information collected include COPD-related diagnosis and treatment in the above sources:

- Outpatient visit, emergency visit, and hospitalization
  - Date, reason, length of stay (for hospitalization)
- Prescribed medications
- Over-the-counter (OTC) medications
- Other therapies, e.g. oxygen therapy, nebulizers
- Associated costs if feasible
- Lab tests, image tests, surgeries, and other tests and procedures (e.g., spirometry, Chest X-Ray, CT)

Given the high co-morbidities among COPD patients, non-COPD healthcare resource utilization will also be captured by extracting data from the HIS/EMR complimented by tri-monthly patient interviews. Information collected include:

- Non-COPD outpatient visits and emergency visits
  - Number of visits, date of visit, diagnosis of visit
- Non-COPD hospitalization (including intensive care)
  - Number of hospitalization, date and length of stay, diagnosis of visit

9.2.11. Mortality

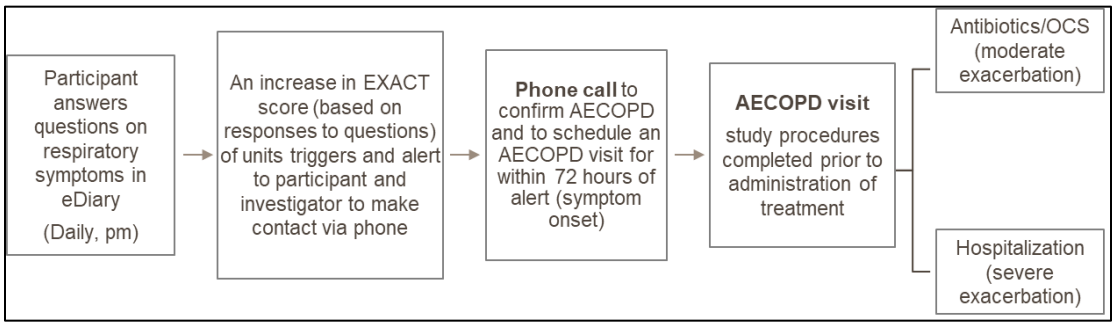
Details of any patient deaths, including date of death, will be recorded in the CRF. Information will be obtained from the telephone interview and from medical records in HIS. Cause of death will be recorded if available. Data from publicly available source will be used if participant is not contactable at the end of the study.

9.3. Exacerbation Visits (sub-cohort only)

Exacerbation visits only apply to subjects included in the Biomarker & Digital sub-cohort. Exacerbations that occur during the study will be detected through several pathways of reporting, including: direct contact with the study site or using a process of screening questions triggering a site alert and follow-up consultation, at which the investigator will determine whether the worsening of symptoms identified by evening diary meets the definition of a moderate/severe exacerbation and if it does then an exacerbation visit is scheduled. This triggering process is described in Section 9.2.6.2. Visit will be scheduled to occur within 72 hours of the alert (symptom onset) (Figure 4).

At the exacerbation Visit, the following study procedures will be completed: (1) PROs: e.g. the CAT, (2) blood sampling, (3) spirometry, (4) sputum sampling including induced sputum if required, (5) chest imaging, (6) healthcare resource utilization and cost including COPD medication and treatment. The sputum samples must be collected before the subjects receive antibiotics and/or systematic corticosteroids.

Figure 4 Exacerbation Detection Through Evening Diary Questions



After completion of study procedures at the AECOPD Visit, the investigator will administer treatment for the exacerbation. Follow-up phone call(s) will be made by the investigator to the participant at least every 2 weeks until the AECOPD has resolved. No more than 2 AECOPD experienced during the study will be evaluated. If a participant experiences another exacerbation while on study, then they are to contact their regular physician for treatment.

9.4. Adverse Events

No study drug will be given in this study, only study procedure related serious adverse events (SAE) will be recorded. All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Table 1).

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an SAE, provided in this protocol. During the study when there is a safety evaluation, the investigator or site staff will be responsible for detecting, documenting and reporting SAEs.

Adverse Events (AE) will not be captured in the study. It is possible that participants could spontaneously describe potential adverse events that occurred during the course of study visits. As part of the site orientation process, study team members will be trained in the recognition of potentially-reportable adverse events. If an AE (serious or non-serious) or complaint with any specifically named GSK product is reported spontaneously by a subject during the course of the study, the site staff will complete the AE reporting form and transmit the report to the GSK China within 24 hours of being made aware of the AE.

AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed

medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

- Results in death,
- Is life-threatening,
- Requires hospitalization or prolongation of existing hospitalization,
- Results in disability/incapacity,
- Is a congenital anomaly/birth defect?
- Other: medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Possible drug-induced liver injury

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

See study Pharmacovigilance Plan (sPVP) for details. sPVP will include the following elements to ensure a comprehensive approach to safety event collection and reporting:

Supplier pharmacovigilance training

Investigator and site staff pharmacovigilance training

Safety-specific roles

SAEs collection and reporting processes

SAEs collection forms

Frequency of data review

Reporting process and timelines

Interim reports

Study-specific PVP monitoring process

9.5. Treatment of Overdose

This cohort study will not provide or recommend any treatment. Patients' diagnosis and treatment will be left to their physicians' judgement and routine practice. Thus, this section is not applicable.

9.6. Safety Assessments

This cohort study will not provide or recommend any treatment. No safety assessment is scheduled.

9.7. Pharmacokinetics

PK parameters are not evaluated in this study.

9.8. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.9. Genetics

Genetics are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

10.1.1. Hypotheses

This study is mainly descriptive with no formal inference associated with the study objectives. Confidence intervals will accompany all effect estimates.

10.1.2. Study Design Considerations

This is a longitudinal study in subjects with COPD and controls. The follow-up period is 2.5 years with scheduled clinic visits at study entry, 6 months, 18 months, and 30 months.

10.1.3. Sample size Considerations

Sample size was decided based on practical consideration; however, some justification of GOLD I and II Grades and for sample size for all COPD patients is provided below.

There is no formal inference planned, meaning no powered hypothesis test for overall study will be performed. Sample size justification is based on precision of effect estimates for rate of decline in FEV_1 over 2.5 years.

A review of data from Study HZC113782 FEV_1 was collected at 3-month intervals on moderate COPD subjects suggests that a within subject standard deviation (model based residual error estimate) as 155 mL, and a standard error of the rate of decline in FEV1 as 2.5 mL/year from placebo group. Those variability estimates were increased to 50% higher as 233 mL and 3.8 mL/year, respectively, for the following sample size calculation; this is mainly based on the consideration that a more heterogeneous study population and non-drug interventional cohort nature by design will yield higher variability comparing to those observed in a randomized clinical trial.

To make simple calculation, it is assumed within subject's standard deviation and standard error of the rate of decline in control groups (Chronic Bronchitis, Healthy Control) are the same as the assumption for COPD subjects.

To detect a difference of Δ units between the mean rate of decline in two groups, Schlesselman [Schlesselman, 1973] proposed the following formula to calculate N,

$$N = \left[2(Z_{\alpha/2} + Z_{\beta})^2\{\hat{\sigma}_{\beta}^2 + 12(P-1)\hat{\sigma}^2/[D^2P(P+1)]\}\right]/\Delta^2$$

where $\hat{\sigma}_{\beta}^2$ is an estimate of the variance associated with the rate of decline in FEV_1, $\hat{\sigma}^2$ is an estimate of the variation about the regression line within a person, D is the duration of the study, P is the number of measurements collected during the study, $Z_{\alpha/2}$ is the upper $(1-\alpha/2)$ critical value for the standard normal distribution, and Z_{β} is the upper $(1-\beta)$ critical value for the standard normal distribution. It can be adapted to determine N for a

$100(1-\alpha)\%$ two-sided confidence interval for the difference between the rates of decline in FEV_1 of two groups that has precision Δ as

$$N_1 = Z^2_{\alpha/2}\hat{\sigma}^2_p(r+1)/(r\Delta^2)$$

where $\hat{\sigma}^2_p = \hat{\sigma}^2_\beta + 12(P-1)\hat{\sigma}^2/[D^2P(P+1)]$, $r = N_2/N_1$, and N_1 and N_2 are the sample sizes associated with each of the two groups.

In this study, it is planned to collect P=4 measurements of FEV_1 over D=2.5 years. One of interest is an estimate of the rate of decline in FEV_1 between subjects GOLD I and II.

Under the above assumptions with 95% confidence and a 25% drop out, the following table gives sample sizes necessary to attain the levels of precision of Gold I vs. Gold II comparison.

Table 2 Sample size for Gold I vs. Gold II under given precision

Interested comparison	Precision* (ml/yr)	Subgroup	Completers	Total sample size including 25% drop out
Gold I vs. Gold II $r = 1:1$	15	Gold I	525	700
		Gold II	525	700

*: half width of a 95% confidence interval

Based on the total completed $N = 1275$ COPD subjects, a 95% two-sided confidence interval for the rate of decline in FEV_1 of all COPD subjects will have a total width of

$$W = 2 \times Z_{\alpha/2} \times \hat{\sigma}_p/\sqrt{N} = 2 \times 1.96 \times 125.1/\sqrt{1275} = 13.7\ ml/year$$

where $\hat{\sigma}_p = \sqrt{\hat{\sigma}^2_\beta + 12(P-1)\hat{\sigma}^2/[D^2P(P+1)]} = 125.1$

10.1.4. Sample Size Sensitivity

The width of any confidence interval will be wider than expected, if the true standard deviation of an endpoint is larger than assumed. For example, if the within subject standard deviation of the rate of decline in FEV_1 is 250ml/year, then the 95% confidence interval for COPD subjects overall rate of decline in FEV_1 will have width 14.7ml/year. Conversely, actual standard deviations that are smaller than assumed will result in narrower confidence intervals.

10.1.5. Sample Size Re-estimation

Sample size maybe re-estimated during the conduct of study.

10.2. Key Elements of Analysis Plan

The high-level analytic approaches and methods are described for each objective. Further details and exploratory analyses will be described in the Reporting and Analysis Plan (RAP).

10.2.1. Populations for Analyses

For purposes of analysis, the following populations will be defined:

Population	Description
Full population	The Full Population will consist of all subjects who are enrolled in the study and attend Visit 1.
Sub-cohort population	Subjects who are enrolled in the Biomarker & Digital sub-cohort and who provided a least one additional sub-cohort assessment.
Completer Population	The Completer Population will consist of all subjects in the Full Population who complete all scheduled clinic visits over 2.5 years.

Other sub-populations may be defined based on disease severity, co-morbidities, age, gender, or subject phenotypes. This will be detailed in RAP.

10.2.2. Descriptive Analyses

Each endpoint collected during the study that represents a continuous measure will be summarized with descriptive statistics with mean, median, min, max and SD at each clinic visit as actual values and as change from baseline (Visit 1), if appropriate. Endpoints that are discrete in nature will be summarized as frequencies and percentages at each clinic visit. Counts (e.g. exacerbations of COPD) will be expressed as event rates per person-year.

mMRC dyspnea score will be summarized using descriptive statistics for the Full population. Wilcoxon-rank sum test will be used to analyse mMRC dyspnea score among different type of subjects, if data permit.

SGRQ-C score will be transformed into SGRQ score and summarized using descriptive statistics.

10.2.3. Disease Progression Analyses

Disease progression in clinical, radiological and biological measurements will be described based on longitudinal data.

10.2.3.1. Main Cohort

- Change from baseline and Rate of decline in FEV_1 in millilitres (mL):

  Descriptive statistics of FEV_1 and change from baseline FEV_1 will be reported for baseline and all subsequent visits. The raw mean change from baseline at each visit will be presented graphically.

  Rates of decline in FEV_1 will be estimated for each type of COPD subjects, overall COPD subjects, chronic bronchitis group and healthy control group.

  In order to obtain rate of decline in FEV_1, particular from a mixed effects model, a random coefficients model, will be used. FEV_1 after baseline will be fitted as the response variable with the proposed selection of predictors including type of subjects (i.e. GOLD I-IV, chronic bronchitis, healthy control), age, gender, smoking status, baseline FEV_1, count of COPD exacerbations, site, time on study and type of subjects by time interaction. Participants and time on study will be random effects. Further details will be included in RAP.

  Rates of decline in other endpoints may also be estimated in a similar fashion, if warranted.

- Rate of moderate/severe exacerbations:

  Exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation. The exacerbation frequency, type and duration will be summarized using descriptive statistics for Full population.

  A generalized linear model assuming the negative binomial distribution will be used to analyze the exacerbations rate among different type of subjects. Additional methods including time to event analysis will be considered as appropriate.

- Change from baseline in CAT score:

  CAT score and change from baseline value will be summarized using descriptive statistics for the Full population.

  If appropriate, Mixed Models Repeated Measures (MMRM) model will be used to analyze CAT score among different type of subjects.

- Clinically important deterioration (CID) components:

  CID will be summarized for Full population using descriptive statistics.

  If data permit, generalized linear mixed model will be used to analyze CID among different type of subjects and time to CID will be assessed using time to event models.

10.2.3.2. Sub-cohort

General summary/analysis information for each sub-cohort endpoints are listed as below. More details will be included in RAP.

- EXACT events: the analysis will summarize N of events, their onset, duration and severity. EXACT events will be derived according to the EXACT manual [Leidy, 2013] with any alternative considerations detailed in the RAP.

- E-RS: COPD total and domain scores: each 4-week interval summary/analysis will be done. If data permit, mean weekly scores will be considered for the analysis; this assumption will be tested prior starting data analysis. Relationships between mean E-RS scores and other study variables will be evaluated using a range of analysis of variance and analysis of covariance. Changes from baseline in Total and domain scores at pre-defined time points will be analysed using a mixed model for repeated measures, adjusted for baseline E-RS scores and other key variables.
- CCI [redacted]
- Daily Activity: summary/analysis with appropriate statistics will be done based on the data extracted from wrist band.

10.2.4. Phenotypic Analyses

The data available at Visit 1 will assist in determination of participant phenotypes in disease manifestation. Phenotypes associated with progression of disease will be based on longitudinal data. Phenotype identification will also refer to the findings of previous Western cohorts. Complete details will be included in the RAP.

10.2.5. Treatment Pattern and Healthcare Resource Utilization/Cost

For COPD-related treatment, the following endpoints will be described using frequency and percentage:

- Each type of treatment for COPD patients
- Initiation of maintenance treatment
- Switches to another maintenance treatment
- Addition of other maintenance treatment
- Stepping up to triple therapy
- Discontinuation of treatment

COPD-related and non-COPD healthcare resource utilization and cost will be described with appropriate descriptive statistics:

- Total medical cost, pharmacy cost, and other costs
- Number of outpatient visit and cost
- Number of emergency visit and cost
- Number of hospitalization, length of stay, and cost
- Treatment of exacerbation and cost

10.2.6. Safety Analyses

Length of Time in Study

Length of time in study will be calculated as the number of days from enrollment to study completion or study discontinuation (i.e., the span of time between Visit 1 and final visit: Final visit date – Visit 1 date + 1). This will be summarized as a discrete variable based on ranges of days. The number of subjects that attend each visit will also be tabulated.

Adverse Event Assessments

Study procedure-related SAEs will be summarized using descriptive statistics. SAEs will be assigned preferred terms and categorized into body systems according to the MedDRA classification of the World Health Organisation terminology.

10.2.7. Other Analyses

CCI

[redacted]

10.2.8. Interim Analyses

Interim analyses will be conducted at various points during the conduct of the study. At the end of Visit 1, data from subjects in the Full Population will be used to address questions associated with subject phenotypes, characterisation of disease severity, and inter-individual variability of each endpoint. At the end of visit 2, 3 and 4, available clinical, radiological, biomarker, PRO, and health economics endpoints will be assessed based on the appropriate population. Scientific Steering Committee will have sight of, and approve, all requests for analyses that come from the Working Groups.

Summaries of the interim analyses will be described in RAP.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

ACT	Asthma Control Test
AE	Adverse Event
AECOPD	Acute exacerbations of COPD
CAT	COPD Assessment Test
CC16	Club cell protein
CID	Clinically Important Deterioration
CMH	Chronic Mucus Hypersecretion
COPD	Chronic Obstructive Pulmonary Disease
COVID	Coronavirus disease
CRF	Case Report Form
CRP	C-Reactive Protein
CSR	Clinical Study Report
CT	Computed Tomography
CAPTURE	COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk
DDA	Digital Data Analytics
eCOA	electronic Clinical Outcome Assessment
EDC	Electronic Data Collection
EHR	Electronic Health Record
ePRO	Electronic Patient-reported Outcomes
E-RS: COPD	Evaluating Respiratory Symptoms in COPD (subset of EXACT)
EST	Empowered Study Team
EXACT	EXAcerbation of COPD Tool
FEF	Forced Expiratory Flow
FET	Forced Expiratory Time
FEV1	Forced Expiratory Volume in one second
FEV6	Forced Expiratory Volume in six second
FRC	Functional residual capacity
FSH	Follicle stimulating hormone
FVC	Forced Vital Capacity
GERD	Gastroesophageal Reflux Disease
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GIRH	Guangzhou Institute of Respiratory Health
HbA1c	Glycated haemoglobin A1c
HIS	Hospital Information System
hsCRP	High-sensitivity C-Reactive Protein
HRCT	High-resolution computed tomography
HRT	Hormonal replacement therapy
HRQoL	Health-related Quality of Life
ICF	Informed Consent Form

IP	Investigational Product
MMEF	Maximal Mid-Expiratory Flow
mMRC	modified Medical Research Council dyspnea scale
PRO	Patient reported outcome
SAE	Serious Adverse Events
SGRQ-C	St. George's Respiratory Questionnaire for COPD
sRAGE	soluble Receptor for Advanced Glycation End Products
sPVP	study-specific Pharmacovigilance Plan
SoA	Schedule of Activity
TLC	Total Lung Capacity
tPEF	time to Peak Expiratory Flow
OTC	Over-the-counter
VEXT	Volume back extrapolation

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
CAT

Trademarks not owned by the GlaxoSmithKline group of companies
MedDRA

12.2. Appendix 2: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- Data from eCRF, ePROs and mobile devices will be encrypted and automatically transmitted to vendor's server for integration. HIS data will be de-identified and be encrypted and transferred via secured portal for data integration.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

Data Quality Assurance

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor and the third-party vendors are responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing monitoring activities to ensure that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Digital data collection from electronic CRF, electronic medical records in hospital databases, ePROs, and wearable device along with CT and biomarker data are the key sources for data analysis. The study database will be housed on a third-party vendor's secure network. Datasets from various sources will be delivered in CDISC ODM standards for integration.
- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines

Inadequate recruitment of participants by the Investigator

12.3. Appendix 3: Contraceptive and Barrier Guidance

12.3.1. Definitions:

Definitions
Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered to be Woman of Childbearing Potential

1. Premenarchal
2. Premenopausal female with ONE of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Females on HRT and whose menopausal status is in doubt will be excluded unless they agree to discontinue HRT to confirm their postmenopausal status

12.4. Appendix 4: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1 19-JUN-2019

Section # and Name	Description of Change	Brief Rationale
Title page	Authorship has been changed: added external SC members, Yongchang Sun,Fuqiang Wen and Qianli Ma. Removed people who have left GSK,including Lihong Zhuang,Na Guo,Wela Huang and Hana Mullerova.	According to ICMJE criteria, people who left do not meet the authorship criteria for this version of amendment.
Section 6.1. Inclusion Criteria-COPD Participants	Edited “A baseline (post-bronchodilator) FEV1/FVC ratio ≤70% ” to “A baseline (post-bronchodilator) FEV1/FVC ratio ＜ 70%”	Should be consist with GOLD.
Section 6.1. Inclusion Criteria-COPD Participants/Chronic Bronchitis Participants Section 9.1. Baseline data collection	Redefined smoking status as “Ever smoker (with a lifetime exposure of ≥10 pack-year or never smoker (with a lifetime exposure of <1 pack-year”	The original protocol defined smoking status as 100 cigarettes which are not as commonly used in clinical practice and treatment guideline.
Section 6.1. Inclusion Criteria-COPD Participants, CMH participants and healthy participants	Added “BMI＜35” on additional criteria for sub-cohort COPD participants,CMH participants and healthy participants	To ensure patient’s safety in doing CT scan, and also to obtain sufficient image quality whilst using the least possible radiation, hence the ranges of possible dose estimates. The highest exposures will be required only in larger participants with a BMI >30. Therefore, only patients with BMI ＜35 will be included.

Section # and Name	Description of Change	Brief Rationale
Section 1 Synopsis Section 2 SOA Section 4.Objectives and Endpoints Section 5.4. Scientific Rationale for study design Section 9.1. Baseline and data collection Section 9.2.6 Patient Reported Outcome Measures Section 9.2.6.3 Other PRO assessments	Added CAPTURE questionnaire	To assess the utility of the CAPTURE questionnaire as a case finding tool in obstructive lung disease
Section 9.1. Baseline data collection	Added “Biomass questionnaire” and removed the “Biomass definition and detailed information including ventilation in the kitchen ”	Combined biomass related information to make it clear for better understanding of the relationship between Biomass in Guangdong region and COPD development,

Section # and Name	Description of Change	Brief Rationale
Section 1. Synopsis; Section 2. Schedule of Activities Section 4. Objectives and Endpoints Section 5.4. Scientific Rationale for Study Design Section 9.1. Baseline data collection Section 9.2.9.1. Blood Biomarkers Section 12.1. Appendix1	Added HbA1c test and its rationale for sub cohort as an endpoint.	In order to explore the relationship between glycaemic control and AECOPD/mortality/Hospitalization, etc
Section 1. Synopsis; Section 4. Objectives and Endpoints Section 5.4. Scientific Rationale Section 9.2.7. Computed tomography (CT) (sub-cohort only) Section 10.2.3.2. Sub-cohort	CCI [redacted]	Lung HRCT endpoints have been changed to a general description so that all the analyses for this objective could be conducted.
Section 2. Schedule of activities (SOA)	Added +3 days window for baseline visit	It may be hard for patients to complete all examination in one day and according to study as there will be
Section 3.1. Benefit/Risk assessment	Potential risk for HRCT scans has been refined to exposure to ionising radiation as a consequence of participation	Justified the current dose of ionising radiation which will do no harm to participants whose BMI is ＜35.

Section # and Name	Description of Change	Brief Rationale
Section 3.1. Benefit/Risk assessment	Added Potential risk for wrist band	Include the description of wrist band.
Section 9.2.9.2 Sputum microbiome and sputum cytology (sub-cohort only)	Added Additional analyses may measurement of viruses and fungi	To explore on how respiratory microbiota can influence the efficacy of common therapies for chronic respiratory disease in Chinese population.
Section 9.2.3. Spirometry	Removed central read procedure by GIRH. Updated equation and procedure.	To perform the lung function in a standardized way in order to ensure the data quality.
Section 1 Synopsis Section 5.2. Number of participants	Edited "All patient population sizes are approximate and allow subject to feasibility" to "All patient population sizes are approximate and allow ± 10% for feasibility"	Since the sample size in this study is justified by feasibility, no formal hypotheses will be tested. Therefore, allowing a range ± 10% will not have impact about the analysis.
Throughout	Minor editorial and document formatting revisions	