Investigation of the Clinical, Radiological and Biological Factors Associated with Disease Progression, Phenotypes and Endotypes of COPD in China (COMPASS): study design, protocol and rationale

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Shareable abstract (@ERSpublications)
COMPASS, a prospective, multicentre, observational study of Chinese patients with COPD, will characterise stable and exacerbation phenotypes/endotypes, treatment pathways and HRU, and investigate COPD progression biomarkers' relevance to these patients https://bit.ly/3dyIpf1

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Abstract

COPD is heterogeneous, and its presentation varies between countries. The major COPD cohort studies have only been performed in Western populations; the disease is not well characterised in other regions. The COMPASS (Investigation of the Clinical, Radiological and Biological Factors, Humanistic and Healthcare Utilisation Burden Associated with Disease Progression, Phenotypes and Endotypes of COPD in China; NCT04853225) is a prospective, 2.5-year-long, multi-centre, longitudinal, observational study with three aims: 1) to characterise stable and exacerbation phenotypes/endotypes in terms of clinical characteristics, blood and sputum biomarkers, lung microbiome and lung imaging; 2) to understand the relevance of markers of COPD disease progression identified in Western cohorts to Chinese patients; and 3) to characterise treatment pathways and healthcare resource utilisation. COMPASS will recruit 2000 participants, of which 1700 will be in Global Initiative for Chronic Obstructive Lung Disease (GOLD) Grades I–IV (n=700, 700, 200 and 100, respectively), 180 participants with chronic bronchitis without airflow limitation and 120 never-smoker healthy controls. Study visits will be at baseline, 6, 18 and 30 months and at exacerbation. Assessments include lung function, exacerbation frequency, health status, blood biomarkers and, in a sub-cohort of 400 patients, chest high-resolution computed tomography, additional blood and sputum biomarkers, airway micro-, viral- and myco-biome, and physical activity. COMPASS will establish a unique clinical and biological dataset in a well-characterised cohort of individuals with COPD in China, with a particular focus on milder patients. As the first study of its kind attempting to understand the disease in an Asian setting, it will provide valuable insights into regional and ethnic differences in COPD.

Introduction

COPD is one of the leading causes of morbidity and mortality resulting in significant humanistic and economic burden to patients, healthcare systems and societies worldwide. It is the third leading cause of death globally, and in 2019 there were 3.23 million deaths due to COPD [1]. COPD prevalence in China has been increasing significantly. A national screening survey, conducted from 2002 to 2004, reported that the overall prevalence of spirometry-defined COPD among people over 40 years old was 8.2% [2]. The recently published China Pulmonary Health Study (2018) suggested that the prevalence of COPD among Chinese over 40 years old had increased to 13.7% [3]. Although COPD management in China has greatly improved over the past decades, many challenges persist. One of them is a substantial under-diagnosis: in a 2007 study, up to 65% of people with airflow limitation pattern compatible with COPD did not have a clinical diagnosis of COPD [2]. Furthermore, most individuals diagnosed with COPD (64.7%) exhibited a significant symptom burden, defined as at least one respiratory symptom (cough, phlegm, wheezing and breathlessness), regardless of treatment [2]. Its health status impact, as judged by COPD Assessment Test (CAT) score, also appears to be higher in China than in the West. In one study of over 6000 patients across China, the mean score was 24, compared to under 20 commonly reported in Europe [4].

COPD is a heterogeneous and complex condition displaying a range of phenotypes and endotypes with distinct underlying mechanisms, different clinical outcomes, varying patterns of progression, prognostic characteristics and different responses to treatment. The heterogeneity reflects the fact that not all COPD components are present in all patients and the complexity is due to dynamic and nonlinear interactions between the components that are present [5]. This indicates the need for personalised management, for example using a treatable traits approach to assessment, classification and management of COPD [6, 7].

Three large observational studies – Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) [8], Genetic Epidemiology of COPD (COPDGene) Study [9], and Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS) [10] – were designed to address the complexity and heterogeneity of COPD, but they were all conducted in North America and Europe. A fourth study in individuals with obstructive lung disease (NOVELTY) is ongoing and includes patients in Asia. In contrast to the other three studies, it includes individuals with asthma as well as COPD, but does not have the same comprehensive range of in-depth assessment [11] (*e.g.* sputum biomarkers). The absence of studies in Asia is a limitation, not only locally within the region, but also globally in terms of understanding the full picture of the disease. For example, lung growth as measured by forced vital capacity (FVC) is related to a country's gross national income per capita [12], which is important with the increasing recognition that failure of full lung growth in childhood and early adulthood is a cause of COPD [13]. In addition, there may be substantial differences between countries in different continents in terms of respiratory symptoms and comorbid respiratory conditions [14], since significant racial differences have been reported between Korea and the USA in the pattern of extrapulmonary comorbidities [15]. Age-standardised disability-adjusted life years due to COPD vary quite widely between the USA and China and even within Europe [16]. Pollution is an important factor in COPD, and, setting aside the well-known effects of industrial pollution, levels of death due to indoor air pollution are much higher in China and Asia than in Europe and the USA [17]. Taken together with high levels of biomass fuel exposure for a significant part of the lives of currently middle-aged people before the relatively recent mass urbanisation that has taken place in China, these factors may result in a higher proportion of non-cigarette-smoking-related COPD.

COPD patients in China show significant differences when compared with Western patients. In the Asian cohort study [18] of the Tiotropium Safety and Performance In Respimat (TIOSPIR) trial [19], Zhong *et al.* [18] demonstrated that Asian COPD patients had significantly lower body mass index (BMI), had a higher proportion of males, less cardiovascular disease and fewer but more severe exacerbations than those in the West. With an ageing population, persistent air pollution and significant biomass fuel exposure 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, and its appropriate management is a healthcare priority in China. To inform clinical practice and aid public health resource allocation, it is important to gain a better understanding of disease progression and clinical management of COPD in China. In particular it is important to understand the characteristics of the disease earlier in the evolution of the disease and in patients with milder airflow limitation, because this is where disease-modifying strategies will have greatest long-term benefit.

The COMPASS study (GlaxoSmithKline study Number 208630, ClinicalTrials.gov identifier: NCT04853225) is a 2.5-year longitudinal study with the overall objective of expanding understanding of the pattern of COPD disease phenotypes/endotypes, clinical, humanistic, and healthcare utilisation burden,

disease progression and management of COPD in China, especially in patients with mild-to-moderate COPD. This article describes the purpose, design and objectives of this study.

Methods

Study objective

The key objectives of COMPASS are to: 1) characterise stable disease and exacerbation phenotypes/endotypes in China through assessment of clinical characteristics, blood biomarkers, lung microbiome and radiological features of COPD; 2) understand the relevance of predictors of COPD disease progression identified in Western cohorts to Chinese patients; 3) characterise treatment pathways and healthcare resource utilisation and costs in COPD; 4) explore the utility of integrated digital data collected from multiple sources in the assessment and management of COPD patients.

Study design

COMPASS is a prospective, longitudinal 2.5-year multi-centre, non-drug interventional, observational study being conducted at 41 centres in Guangdong and Fujian, China. It will enrol 2000 participants into three strata (never-smoker healthy participants, chronic bronchitis without airflow limitation and COPD current or former smokers or never-smokers) as shown in figure 1. A sub-cohort with 400 participants will be studied in greater detail (figure 1).

Study participants

Inclusion criteria are participants must be 40–80 years of age at baseline for the main cohort, have a smoking history of <1 pack-year (for never-smoking COPD participants, chronic bronchitis and healthy participants) or ⩾1 pack-year (smoking and ex-smoking COPD and chronic bronchitis) and meet lung function criteria as specified in table 1. Major exclusion criteria are respiratory disorders other than COPD (*e.g.* lung cancer, sarcoidosis, active tuberculosis, lung fibrosis, severe bronchiectasis, cystic fibrosis and alpha-1 antitrypsin deficiency). A current primary diagnosis of asthma is an exclusion criterion but individuals with a primary diagnosis of COPD but who also have had asthma can be included. Previous major lung surgery (*e.g.* lobectomy, lung reduction, lung transplant) is an exclusion criterion, as is a diagnosis of any cancer: current and within the last 5 years (patients in remission for ⩾5 years could be included). Table 1 contains the inclusion criteria. An exacerbation is defined as 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 h or more and interfered with the subject's usual activities. It is based on a definition used in the BOLD and CANCOLD surveys that also included mild patients [20, 21] To minimise the risk of ionising radiation as a consequence of repeated exposure to low-dose computed tomography scans of the chest, a minimum age of 50 years was selected for the sub-cohort. The study was approved by the ethics committee of each research centre and Human Genetic Resource Administration of China (HGRAC).

Baseline and follow-up assessments

There will be four on-site visits – baseline, 6 months, 18 months and 30 months – to collect concurrent medications, smoking status, spirometry, CAT score, healthcare resource utilisation/cost, *etc*. Participants will also receive trimonthly follow-up calls to assess CAT score, medication/treatment and exacerbation events. At baseline and 30 months biomarkers including the following will be collected: fibrinogen [22]/high-sensitivity C-reactive protein (hsCRP)/blood cell count and blood biomarkers (inclusive of serum sRAGE, CC16, HbA1c and IP-10; sub-cohort only). In the sub-cohort, sputum cytology, sputum microbiome and chest high-resolution computed tomography (HRCT) scan (at maximum inspiration and expiration) will be performed.

Outcome measurements

End-points measured in COMPASS include rate of decline in forced expiratory volume in 1 s (FEV_1), rate of moderate/severe exacerbations, change in health status scores over time, clinically important deterioration composite outcome, rate of decline in lung density change from baseline in airway diameter (quantified by HRCT; sub-cohort only), mortality and blood biomarker, *etc*. The key end-points are listed in figure 2.

Airway micro-, viral- and myco-biome

The airway microbial community (microbiome) is a complex mixture of organisms [23]. In COPD, airway microbial dysbiosis (change in microbiome diversity and composition) is associated with disease severity and exacerbations [24–26]. Such studies have almost exclusively assessed patients in North America and Europe. Although studies of airway microbiome are now being performed in Asia [15], there is very limited information on the composition of the airway microbiome and host–microbiome interactions in

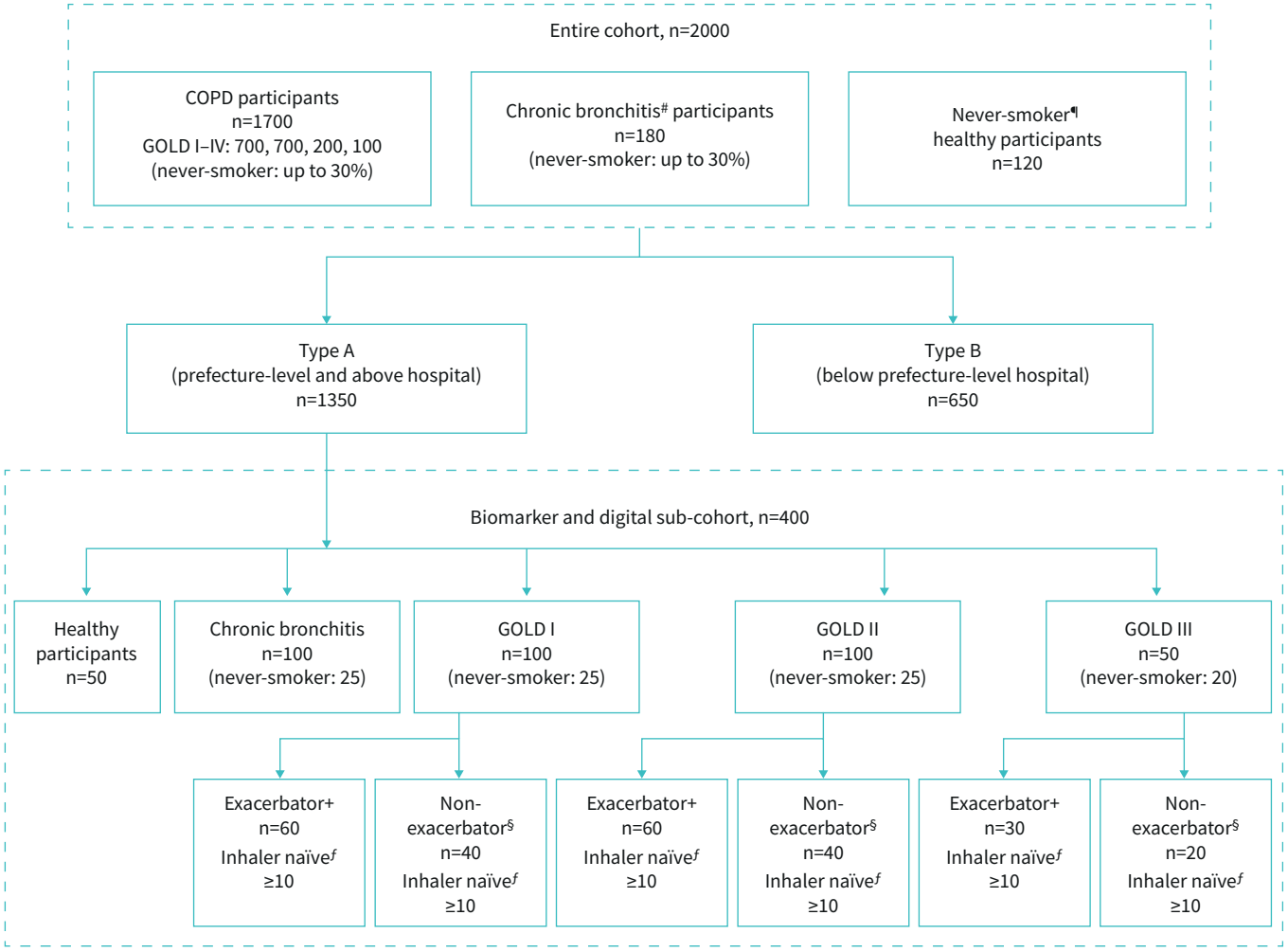

FIGURE 1 COMPASS enrolment strata. Type A hospitals include all hospitals at prefecture level or higher; Type B hospitals include all hospitals below the prefecture level, including community hospitals. #: chronic bronchitis defined by at least 3 months of cough and phlegm in a year in the past 2 years and normal spirometry. ¶: never-smokers are defined as a lifetime exposure of <1 pack-year. +: exacerbator is a patient who has one or more exacerbations in the 2 years before recruitment (see text). §: non-exacerbator is defined as a patient who has not had an exacerbation in the 2 years before entry into the study. f: inhaled maintenance treatment naïve patients are 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 β2-agonists. GOLD: Global Initiative for Chronic Obstructive Lung Disease.

Asian patients with chronic respiratory diseases. It is plausible that, given differences in genetics, environment and lifestyle, the airway microbiome in Asia may differ from that observed in Western cohorts. In the COMPASS digital and biomarker subgroup, in addition to in-depth clinical and biomarker profiling we will conduct a detailed analysis using induced or spontaneous sputum samples to analyse the bacterial, viral and fungal components of the airway microbiome. Sputum samples are more easily obtainable than bronchoalveolar lavage samples, and studies have shown that sputum has utility in assessing the abundance of microbiota and that sputum microbiome alterations correlate with clinical outcomes [27]. These sputum samples will be collected at baseline, at the last visit (Month 30 or early withdrawal visit) and following a visit for an exacerbation. This will be one of the largest studies of the airway microbiome to date.

Sample size considerations

This study is exploratory with no formal pre-specified hypotheses associated with the study objectives. Confidence intervals will accompany all effects estimates. Sample size justification is based on precision (half width of confidence interval) for the difference between the rates of decline in FEV_1 of Global Initiative for Chronic Obstructive Lung Disease (GOLD) 1 and GOLD 2 subjects over 2.5 years. Under the foregoing assumptions, with 95% confidence interval and a 25% drop out, ~700 subjects for each group

TABLE 1 Inclusion criteria

	COPD participants	Chronic bronchitis participants	Healthy participants
Inclusion criteria (all the following criteria apply)			
Aged 50–80 years inclusive	✓	✓	✓
Baseline (post-bronchodilator) FEV_1/FVC ratio	<70%	⩾70%	⩾70%
CAT score <10			✓
BMI <35 (for CT scanning reasons)	✓	✓	✓
Chronic mucus hypersecretion (⩾3 months of cough and phlegm in a year in the past 2 years)		✓	
No exacerbations for ⩾1 month prior to recruitment	✓	✓	
Ever-smoker (lifetime exposure of ⩾1 pack-year) or never-smoker (lifetime exposure of <1 pack-year) (for healthy participants, ever-smokers and passive smokers are not eligible)	✓	✓	✓
Additional criteria for sub-cohort of COPD participants			
150 COPD participants with ⩾1 moderate or severe exacerbation event within the past 2 years	✓	N/A	N/A
60 COPD participants without inhaler maintenance treatment history for ⩾12 months prior to the entry of the study	✓	N/A	N/A

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; CAT: COPD Assessment Test; BMI: body mass index.

(GOLD 1 and GOLD 2) should be enrolled to maintain a precision (half width of confidence interval) of no more than 15 $mL \cdot year^{-1}$ for the difference between the rates of decline in FEV_1 of GOLD 1 to GOLD 2 subjects. Within each GOLD group and the chronic bronchitis group, a recruitment target of 15–30% of never-smokers has been set.

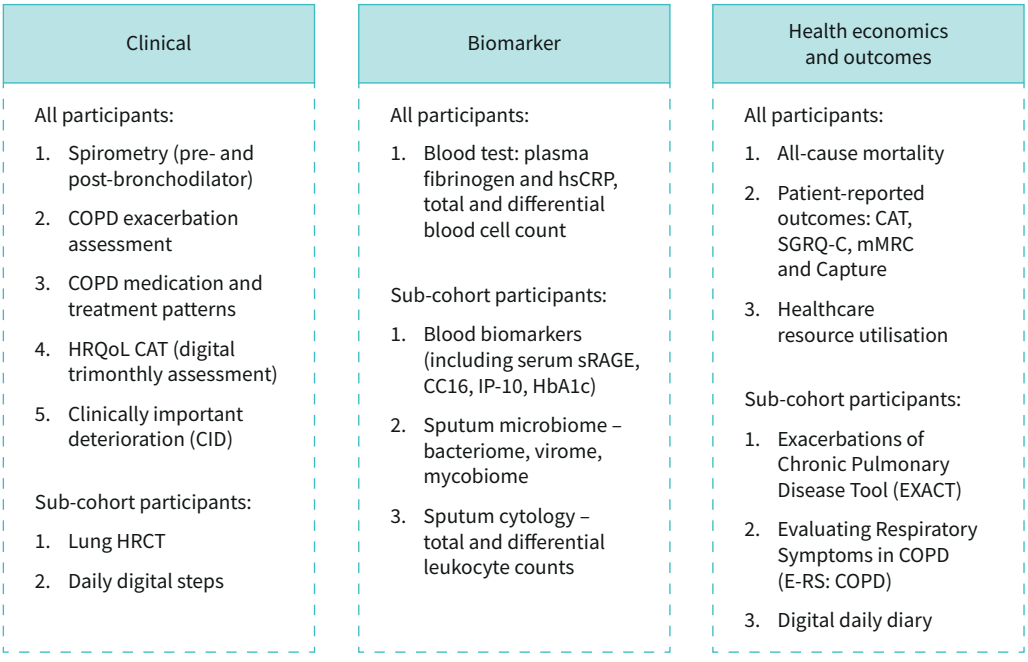

FIGURE 2 COMPASS Study end-points overview. HRQoL: health-related quality of life; CAT: COPD Assessment Test; HRCT: high-resolution computed tomography; hsCRP: high-sensitivity C-reactive protein; SGRQ-C: St George's Respiratory Questionnaire, COPD-specific version; mMRC: Modified Medical Research Council Dyspnoea Scale.

Study organisation

The COMPASS study is guided by a steering committee, consisting of academic senior investigators and representatives from the study sponsor (GlaxoSmithKline) (see figure 3). The recruiting sites are made up of a network of 25 Tier 3 university hospitals and 15 Tier 2 general hospitals. A number of Working Groups (WGs) will be established to cover different areas of research: *e.g.* imaging, microbiome, biomarker, spirometry, *etc*. Each will have a lead who may or may not come from the steering committee, and the membership will be comprised of senior and junior researchers. Overseas experts will be invited to join the WGs, as appropriate. Each WG will determine the scientific questions to be addressed in their area, specify the analyses to be done and write the papers. GlaxoSmithKline will provide operational and statistical support to the WGs. A hive structure is proposed in which the WGs also interact with each other to share insights and expertise.

Discussion

COMPASS has been designed to study the heterogeneity and complexity of COPD in China, building on disease understanding that has come from previous cohort studies in the West. It will support longitudinal analysis of a moderate sample size in terms of lung function and symptom progression measures which, together with a biomarker and digital subgroup, will provide in-depth data collected using HRCT, diary cards, activity monitors and biomarkers in blood and sputum. To ensure an adequate balance of different phenotypes, a key feature (and a significant recruitment challenge) is the establishment of specific recruitment targets for each clinical subgroup. The focus will be primarily on individuals with mild–moderate airflow limitation with specific targets for participants who may have different aetiologies and disease patterns; for example, never-smokers, individuals with mild airflow limitation but a history of exacerbations and treatment naïve individuals who had not been taking regular maintenance treatment before entry into the study.

COMPASS will allow us to test whether the phenotypes and endotypes seen in China follow patterns identified in Western cohorts. Whilst it is likely that no new types of COPD will be identified, their contribution may differ due to factors such as genetics, prior chest disease and environmental factors. The study will also focus recruitment on more defined populations than its predecessors, particularly patients with mild airflow limitation and never-smokers, so it may include unique features that will extend our understanding of COPD more generally. As aforementioned, COMPASS will recruit a high proportion of participants (70%) with milder COPD (GOLD 1–2) at baseline. These subjects will provide the

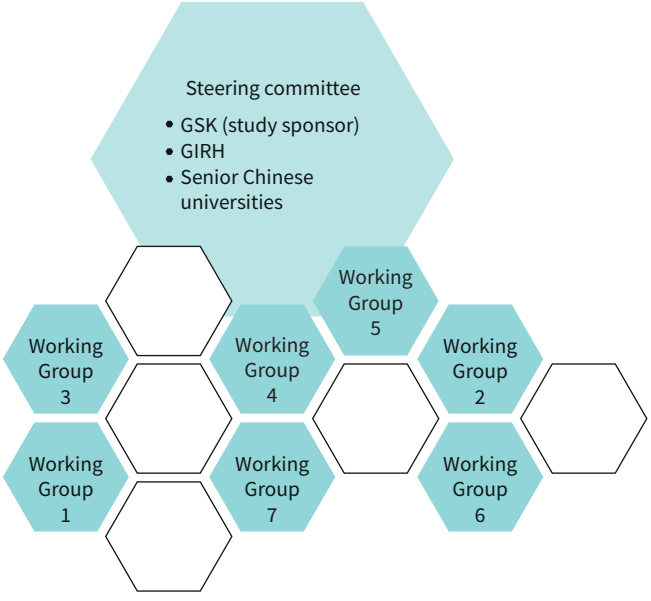

FIGURE 3 COMPASS Research network and the organisation of steering. The steering committee is made up of experts from GlaxoSmithKline (GSK), Guangzhou Institute of Respiratory Health (GIRH) and other senior Chinese universities. The Working Groups (WGs) will each have their own lead who will work closely with the steering committee. The number of WGs is illustrative. A hive structure is planned in which WGs will interact with each other as well as with the steering committee.

opportunity to investigate the lung function trajectories and disease progression patterns in mild–moderate COPD yielding insights and evidence for early intervention. Unlike the GOLD 3 and 4 COPD population, the GOLD 1 and 2 patients are a population that has not been well studied global wide due to the difficulties in identification and recruitment. More than 70% of patients with mild COPD have a low level of clinical symptoms which do not get the attention of the patients themselves or their doctors. Effective diagnosis in this population depends on the identification of risk factors and case-finding for spirometry, so few of them get detected and start intervention at a mild stage. However, lung function declines rapidly in these patients, and damage to the small airways is evident [28–30]. A previous study found that lung function of patients with GOLD Grade 2 declines more rapidly than patients with Grades 3 and 4, but few data are available for Grade 1 disease [31]. The recruitment to COMPASS is being carried out in a range of hospital types, not just university hospitals, because in China, patients are free to select their hospital and may triage themselves to higher grade hospitals if they have more symptoms. A further factor that should support COMPASS recruiting milder patients is that in recent years, with continuous investment and increasing attention from the Chinese government, the management of COPD in China is shifting from disease treatment to a focus on public health. This should create a good environment for the recruitment of COPD patients at an early stage in their disease, and it is a hope that COMPASS will help inform an early intervention strategy for COPD in China.

To understand the relationship between patients with mild airflow limitation and those with chronic bronchitis but normal spirometry, recruitment will include a target for people with chronic bronchitis including those who have been never-smokers. The subgroup of COPD participants who had not previously received maintenance treatment is primarily to allow comparison of their airway micro-, viral- and myco-biome with participants with similar degrees of airflow limitation who have received treatment such as long-acting bronchodilators and inhaled corticosteroids. This should also provide the opportunity to study changes of airway microbiota in participants who may have maintenance treatment initiated during the course of the study. From a clinical perspective, a particular feature of the protocol for the biomarker and digital subgroup is the investigations to be carried out during an acute exacerbation that will include HRCT, biomarker and airway microbiome analyses.

In addition to the clinical and scientific investigations, COMPASS will also investigate the feasibility of aggregating different types of digitally acquired data including electronic health records, electronic clinical outcome assessments and physical activity data through direct digital data capture and integration. In part, the purpose of this is to develop systems of collecting data that permit clinical trials of treatment efficacy and effectiveness in a setting that is closer to a real-world setting and minimise the influences and biases that can come from close or regular contact with healthcare professionals that is not reflected in routine care.

As with previous similar cohort studies (and where possible using similar methodology), COMPASS is designed to provide a cross-sectional comparison between well-defined groups of COPD patients and measure disease progression. It will also integrate these data with details of healthcare resource use, including treatment. The characterisation of defined phenotypes and endotypes (“treatable traits”) and their stability in mild–moderate patients over time will be important for the development of new treatments and the management of patients in the future. In that respect, a key feature of COMPASS is use of the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) diary to detect unreported exacerbations and determine their impact on the clinical status or accelerated disease progression.

The study is conducted mainly in the Guangdong province of China. A key reason for this was the availability of a diverse patient population to be recruited. Whilst confining the study primarily to Guangdong may appear to be a limitation since the findings may not represent the broader Chinese patient population, this is not a major concern. The total population of Guangdong was 104 million in the 2010 census (7.9% of the total population of China), of which 31 million were migrants from other areas of China who had spent at least 6 months of the previous year in Guangdong. Furthermore, this province has been growing fast in the past 15 years to become one of the biggest regions in China with a large population of younger people.

It is important to recognise that this study is not designed to determine the epidemiology of different COPD phenotypes in China. That is clear from the targeted recruitment strategy. Its purpose is to build on previous cohort studies to understand the patterns of disease and disease progression in patients in an Asian setting. Its importance is not limited to Asia, however, because understanding the heterogeneity and complexity of COPD in different environments and in patients with different backgrounds will lead to a greater understanding of the disease more generally and give greater insight into reasons why it is expressed differently in different patients.

In summary, COMPASS will establish a rich set of clinical and biological data on a relatively large cohort of well-characterised individuals with COPD in China of varying degrees of severity and different aetiologies, including patients who never smoked tobacco and may have COPD related to other factors such as environmental exposure to pollution including biomass smoke. The study will provide unique and detailed insight into personalised information about the pulmonary and extrapulmonary aspects of disease progression in Chinese patients, especially those with mild–moderate airflow limitation. It holds great promise to address the heterogeneity and complexity of multiple components in COPD.

The members of the COMPASS Steering Committee at the time of developing this manuscript are: Nanshan Zhong (The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China); Jinping Zheng (The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China); Rongchang Chen (First Affiliated Hospital of South University of Science and Technology of China, Shenzhen, China); Qianli Ma (The North Kuanren General Hospital, Chongqing, China); Yongchang Sun (Peking University Third Hospital, Beijing, China); Fuqiang Wen (West China Hospital of Sichuan University, Chengdu, China); Paul Jones (GlaxoSmithKline, Brentford, UK); Chris Compton (GlaxoSmithKline, Brentford, UK); Bruce E. Miller (GlaxoSmithKline, Collegeville, PA, USA); Julie Yates (GlaxoSmithKline, Research Triangle Park, NC, USA); Beulah Ji (GlaxoSmithKline, Research and Development, Shanghai, China); Jie Song (GlaxoSmithKline, Research and Development, Shanghai, China).

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This study is registered at www.clinicaltrials.gov with identifier number NCT04853225.

Data availability: Data will be made available when the study has completed through the Clinical Study Data Request website: ClinicalStudyDataRequest.com

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