EXAcerbations of COPD and their OutcomeS on CardioVascular diseases (EXACOS-CV) Programme: protocol of multicountry observational cohort studies

Clementine Nordon, Kirsty Rhodes, Jennifer K Quint, Claus F Vogelmeier, Sami O Simons, Nathaniel M Hawkins, Jonathan Marshall, Mario Ouwens, Edeltraut Garbe, Hana Müllerová

ABSTRACT

Introduction In patients with chronic obstructive pulmonary disease (COPD), the risk of certain cardiovascular (CV) events is increased by threefold to fivefold in the year following acute exacerbation of COPD (AECOPD), compared with a non-exacerbation period. While the effect of severe AECOPD is well established, the relationship of moderate exacerbation or prior exacerbation to elevated risk of CV events is less clear. We will conduct cohort studies in multiple countries to further characterise the association between AECOPD and CV events.

Methods and analysis Retrospective longitudinal cohort studies will be conducted within routinely collected electronic healthcare records or claims databases. The study cohorts will include patients meeting inclusion criteria for COPD between 1 January 2014 and 31 December 2018. Moderate exacerbation is defined as an outpatient visit and/or medication dispensation/prescription for exacerbation; severe exacerbation is defined as hospitalisation for COPD. The primary outcomes of interest are the time to (1) first hospitalisation for a CV event (including acute coronary syndrome, heart failure, arrhythmias or cerebral ischaemia) since cohort entry or (2) death. Time-dependent Cox proportional hazards models will compare the hazard of a CV event between exposed periods following exacerbation (split into these periods: 1–7, 8–14, 15–30, 31–180 and 181–365 days) and the unexposed reference time period, adjusted on time-fixed and time-varying confounders.

Ethics and dissemination Studies have been approved in Canada, Japan, the Netherlands, Spain and the UK, where an institutional review board is mandated. For each study, the results will be published in peer-reviewed journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Retrospective longitudinal cohort studies will be run in Germany, Spain, Italy, the Netherlands, the UK, Japan and Canada allowing us to explore the consistency and differences of results across different healthcare systems, database types and patient populations.

⇒ The inclusion of large population-based cohorts of patients, through the use of electronic medical records and claims databases, will minimise selection bias and allow sufficient statistical power to explore different categories of cardiovascular (CV) events separately.

⇒ Misdiagnoses of respiratory events with CV events are likely in the first days following exacerbation owing to similar clinical presentations, and results will be interpreted with cautiousness.

⇒ Although time-fixed and time-dependent confounders will be taken into account through modelling, unmeasured confounding is inevitable in observational research, particularly when secondary data are used.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a prevalent condition affecting approximately 10% of the adult population globally and is a leading cause of premature death. The disease is characterised by persistent respiratory symptoms and airflow limitation owing to airway and/or alveolar abnormalities. The most common symptoms of COPD include dyspnoea, cough and sputum production; wheezing, chest tightness and chest congestion are less common. The disease may also involve acute worsening of symptoms, referred to as COPD exacerbation. COPD is associated with a twofold to threefold increased risk of having cardiovascular disease (CVD), independent of age, sex, smoking history or other confounders, and CVD contributes significantly to the burden of disease in people living with COPD. Hence, the importance of identifying and...
monitoring cardiopulmonary risk factors or CVD in patients with COPD is increasingly emphasised.9 10
In addition to the strong interplay of COPD and CVD, an association between COPD exacerbation and cardiovascular (CV) events is described in the literature.11–13 Specifically, the risk of experiencing an acute CV event is increased by threefold to fivefold in the first 12 months following severe (hospitalised) exacerbation of COPD, compared with during the non-exacerbation periods.11 13–17 In a recent systematic review and meta-analysis, the rate ratio of myocardial infarction in the first 3 months after moderate or severe exacerbation of COPD (compared with periods without exacerbation) was 2.4 (95% CI 1.4 to 4.2), and that of ischaemic and/or haemorrhagic stroke was 1.7 (95% CI 1.2 to 2.4).18 Several hypotheses have been suggested regarding the nature of

<table>
<thead>
<tr>
<th>Country</th>
<th>Database</th>
<th>Population and data used for the study</th>
</tr>
</thead>
</table>
| Canada  | Claims database: the Alberta Health and Alberta Precision Laboratories44 built from the Alberta Health chronic disease cohort that identified patients with COPD between 1 April 1985 and 31 March 2021 | ▶ Population covered: ≈4.3 million residents of Alberta province eligible for the Alberta Health Care Insurance Plan  
▶ Data sources: population registry; practitioner claims; National Ambulatory Care Reporting System; pharmaceutical information; inpatient hospitalisation—discharge abstract database; vital statistics |
| Spain   | Claims database: the BIGPAC database45 | ▶ Population covered: ≈1.9 million individuals who benefit from the public national healthcare system, and followed up in various primary care centres and hospitals of seven autonomous communities across Spain  
▶ Data sources: outpatient visits (primary and specialist care); hospital and emergency department data; outpatient and inpatient pharmacy dispensation; date of death (registered by the GP) |
| Italy   | Claims database: Fondazione Ricerca e Salute46 47 | ▶ Population covered: ≈5 million residents of different local health units and regions in Italy  
▶ Data sources: outpatient specialist visit; hospital data; drug dispensation: all drugs reimbursed by the national healthcare service and supplied by both local and hospital pharmacies; disease waiver claims for some chronic diseases and death status (cause available when occurring in the hospital) |
| Germany | Claims database: WIG26 using data from the German statutory health insurance system | ▶ Population covered: ≈4.5 million individuals from all parts of Germany and insured in one of the different sickness funds within the statutory health insurance system  
▶ Data sources: demographics; outpatient care visits (reported for each quarter of a year); pharmacy data; hospital data (emergency department: not available); death status (cause available when occurring in the hospital) |
| The Netherlands | The PHARMO Database Network-validated algorithms48 in the Netherlands, a population-based network of electronic healthcare databases, combine data from primary and secondary healthcare settings | ▶ Population covered: ≈7 million individuals out of 17 million inhabitants of the Netherlands  
▶ Data sources: GP database; outpatient pharmacy database; hospital database—hospital admissions; date of death |
| The UK  | Electronic healthcare records: CPRD Aurum linked with HES and National Statistics | ▶ Population covered: ≈13 million individuals in England  
▶ Data sources: GP database (Aurum); HES (hospital data, disease codes, dates and procedures); death statistics |
| Japan   | Claims database: Medical Data Vision49 | ▶ Population covered: individuals taken care of in ≈22% of the 1727 ‘Diagnosis Procedure Combination’ hospitals in Japan (ie, hospitals that agreed to be reimbursed by the government based on detailed healthcare utilisation—and thus able to provide such information)  
▶ Data sources: outpatient visits provided in the hospital; hospitalisation (emergency department: not available); pharmacy dispensations; death status: available when occurring in the hospital |

COPD, chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; EXACOS-CV, EXAcerbations of COPD and their OutcomeS on CardioVascular diseases; GP, general practitioner; HES, Hospital Episode Statistics.
the association between COPD exacerbation and a subsequent CV or cerebrovascular event (hereinafter referred to as CV events). The progressive inflammation and vessel wall abnormalities involved in COPD may lead to oxidative stress, arterial stiffness, ventilation-perfusion mismatch and chronic hypoxaemia. In turn, an acute worsening of airway and alveolar disease leading to hyperinflation with additional hypoxaemia and increased cardiac stress may increase the risk of plaque rupture or of decompensated heart failure (HF).

Despite extensive research on the interplay between CVD and COPD, important questions are still to be addressed. First, there is conflicting evidence on whether or not exacerbation managed in the outpatient setting (usually called moderate exacerbation) is also associated with an increased risk of CV events in the short term. Portegies et al suggested the absence of such an association, whereas Rothnie et al and Reilev et al suggested that moderate exacerbation is associated with an increased risk of ischaemic stroke and myocardial infarction. Second, the impact of the cumulative number of previous exacerbations on the strength of association has only been explored in a single study that was limited to the 12 months preceding the CV event, which is a relatively short period of time, considering that COPD is a chronic, progressive and incurable disease. The authors suggest that the greater the number of exacerbations, the weaker the association. This finding is counterintuitive because the cumulative number of exacerbations over time is known to be associated with lung function decline and poorer lung function is associated with a higher risk of CV events. Thus, it can be hypothesised that the risk of experiencing a CV event increases with increasing number of COPD exacerbations. Finally, the risk of a wide range of CV events, such as HF decompensation and new-onset atrial fibrillation (AF) following exacerbation of COPD, has not been thoroughly explored. These elements are important from a clinical standpoint and could help physicians to identify more precisely patients at risk of CV events and the periods of particular risk of CV events, and in turn potentially improve quality of care and patient management.

To bridge these gaps, we have designed a series of retrospective longitudinal cohort studies that will be conducted across multiple countries to evaluate the temporal association between exacerbation of COPD and acute CV events requiring hospitalisation (hereinafter referred to as severe CV events). Performing studies in multiple countries will allow us to explore the consistency and differences in results across healthcare systems, database types and patient populations.

The specific objectives of this study programme are (1) to determine the associations between periods following exacerbation of COPD and the occurrence of severe CV events, including death, compared with periods without exacerbation; (2) to determine these associations for moderate and severe exacerbation separately; and (3) to characterise these associations after first, second or third exacerbation of COPD in a subset of patients with an incident diagnosis of COPD.

**METHODS AND ANALYSIS**

**Study design**

The EXAcerbations of COPD and their OutcomeS on CardioVascular diseases (EXACOS-CV) Programme encompasses a group of longitudinal retrospective observational cohort studies that will analyse electronic healthcare records or claims databases. Study locations will include Canada, Spain, Italy, Germany, the Netherlands, the UK and Japan. Additional studies will be conducted in the USA, France and China; however, the current manuscript will not describe these three studies, since their methodologies will be different, driven by the nature of data that can be accessed.

The applicable, country-specific databases of routinely collected electronic healthcare records or insurance claims to be used are described in table 1. The selection period, eligibility criteria and definition of exposure and outcomes will be as comparable as possible across all countries to the extent that information is available. The study design and periods are detailed in figure 1.
Table 2  Definitions of COPD in the EXACOS-CV studies

<table>
<thead>
<tr>
<th>Country</th>
<th>Identification of patients with COPD</th>
</tr>
</thead>
</table>
| Canada²⁷ | ► Diagnosis of COPD between 1 April 2014 and 31 March 2019, approximated by a medical encounter for COPD (ICD-9 codes 491, 492 and 496); ≥1 in the inpatient setting or ≥2 in the outpatient setting; the date of the first medical encounter for COPD is the CED  
  ► Age ≥40 years upon CED |
| Spain | ► Diagnosis of COPD between 1 January 2014 and 31 December 2018, approximated by a medical encounter for COPD (ICD-10 codes J44, J44.0, J44.1, J44.8 and J44.9); ≥1 in the inpatient setting or ≥2 in the outpatient setting, or, in case only 1 outpatient visit for COPD is identified, the presence of a spirometry measurement recorded in the 3 years prior or following the outpatient visit, the earliest code being the CED  
  ► Age ≥40 years upon CED |
| Italy²⁸ | ► Diagnosis of COPD between 1 January 2015 and 31 December 2018, approximated by (1) criterion A: ≥1 hospitalisation for COPD (ICD-9 codes 491.x, 492.x or 496 in a primary or secondary discharge code); (2) and/or, if not available, criterion B: a disease waiver claim for COPD; (3) and/or, if not available, criterion C: ≥4 packs of COPD-related drugs dispensed in the same 12-month period; CED is when the first criterion above is met  
  ► Age ≥45 years upon CED |
| Germany²⁹ | ► Diagnosis of COPD between 1 January 2014 and 31 December 2018 approximated by ≥2 outpatient ICD-10-GM diagnoses for COPD (as primary codes) in two different quarters of a year and/or ≥1 inpatient ICD-10-GM diagnosis for COPD (primary or secondary codes) within the selection period; the date of the first medical encounter for COPD is the CED  
  ► Age ≥40 years upon CED |
| The Netherlands³⁰ | ► Diagnosis of COPD between 1 January 2014 and 31 December 2018, approximated by an outpatient visit to the GP with a code for COPD (or free text)  
  ► And (1) a GP-reported GOLD classification, or (2) a spirometry measurement, regardless of result recorded in 3 years prior, or following the date of the first identified diagnosis of COPD (CED)  
  ► Age ≥40 years upon CED |
| The UK³¹ | ► Diagnosis of COPD using validated codes (SNOMED-CT codes)  
  ► Aged ≥40 years old at (the first) COPD diagnosis  
  ► Current or ex-smoker |
| Japan | ► Diagnosis of COPD between 1 January 2015 and 31 December 2018, approximated by ≥2 outpatient codes for COPD (ICD-10 codes J41–44 in any position) or ≥1 inpatient discharge code for COPD (in any position) identified; the earliest code will define the CED  
  ► Age ≥40 years upon CED |

CED, cohort entry date; COPD, chronic obstructive pulmonary disease; EXACOS-CV, EXAcerbations of COPD and their OutcomeS on CardioVascular diseases; GOLD, Global Initiative for Chronic Obstructive Pulmonary Disease; GP, general practitioner; ICD, International Statistical Classification of Diseases; SNOMED-CT, Systematized Nomenclature of Medicine—Clinical Terms.

Study population

In general, the study cohorts will include adult patients with COPD (using frequently used algorithm²⁶–²⁸ unless another algorithm has been validated for the specific database used³⁹) who meet the following inclusion criteria: (1) at least two outpatient diagnosis codes for COPD (International Statistical Classification of Diseases, ICD)-10 code J44) or at least one inpatient diagnosis code for COPD identified between 1 January 2014 and 31 December 2018 (selection period); the first date of COPD diagnosis identified during the selection period will define the cohort entry date (CED); (2) age ≥40 years upon CED. In addition, patients were to have continuous data availability in the 24 months preceding the CED. Specific details on COPD definition are provided in table 2. Patients with a record of alpha-1 antitrypsin deficiency (ICD-10 E88.0) will be excluded. In turn, patients will be considered as newly diagnosed with COPD, as opposed to prevalent, if no diagnosis code for COPD is identified during the 24-month baseline period.

Patients with at least 1 day of follow-up after CED will be included and will be followed from CED until the first of (1) a first severe CV event since CED, including death (first of any type, and first of each CV category), or (2) 31 December 2019 (administrative censoring), or (3) loss to follow-up in the database (eg, owing to change of health insurance or leaving the medical practice). The follow-up period stopped prior to the start of the pandemic because of modifications in patient behaviours and the patterns of diagnosis and management of patients with COPD incurred by COVID-19.³¹

Regarding sample size, previous publications suggest the possibility of identifying approximately 71 000 patients with COPD in Canada,³² 45 000 in Spain,³³ 200 000 in Italy,³⁴ 250 000 in Germany,³⁵ 3600 in the Netherlands³⁶ and 340 000 in the UK.³⁷

Definition of exposure

The exposure of interest is acute exacerbation of COPD. Definitions of moderate and severe exacerbation in each country are provided in online supplemental table 1. Moderate exacerbation of COPD will be generally defined as (a) an outpatient visit to a physician for a reason related to COPD with (b) a prescription (approximated by a dispensation) of systemic corticosteroids.
within the 5 days following the visit and for duration of <15 days. Alternatives to this definition are listed in online supplemental table 1. The start date (day 1) of moderate exacerbation of COPD is defined as the date of the outpatient visit or, in the absence of this information, the date of systemic corticosteroid dispensation.

Severe exacerbation of COPD will be defined as hospitalisation of at least one night or a visit to the emergency department with a primary or secondary discharge code for (acute exacerbation of) COPD or lower respiratory tract infection (online supplemental table 1). The start date (day 1) of severe exacerbation according to primary discharge code will be the date of inpatient admission. Two exacerbations of COPD occurring within a 14-day period will be considered as the same event, and the highest severity level will determine the overall severity.

**Exposure periods**

The exposure period during which a patient will contribute data on the risk of a severe CV event will be the 365-day period starting on day 1 of COPD exacerbation. This exposure period would last less than 365 days in the case of a CV event, another exacerbation or censoring. The time prior to exacerbation of COPD and time beyond the end of a 365-day exposure period will be considered an unexposed period and will form the common reference period. All exacerbations of COPD that occur after the CED will be measured, thus allowing patients to contribute data for several exposure periods. Several possible sequences of exposed and unexposed periods in relation to patients are illustrated in figure 2.

Based on previous studies, it is anticipated that the risk of a severe CV event will not be constant over the 365-day exposure period, and the highest risk is expected to occur within the first 30 days. The post-exacerbation exposure period will be a priori segmented into five mutually exclusive time frames: 1–7 days, 8–14 days, 15–30 days, 31–180 days and 181–365 days. For the study in the UK, an alternative data-driven approach will be used, to identify time points at which the risk of a CV event changes following exacerbation. This approach may identify differences across CV outcomes, in terms of periods of time with greater rate of change.

**Outcome**

The outcome of interest will be the time to the first non-fatal severe CV event or death (all-cause, and then CVD or COPD related). Non-fatal severe CV events will comprise four categories: acute coronary syndrome (myocardial infarction and unstable angina), HF decompensation (including acute pulmonary oedema), cerebral ischaemia (ischaemic stroke and transient ischaemic attack) and new or acute arrhythmias (AF and other arrhythmias, including resuscitated cardiac arrest). Non-fatal severe CV events will be defined as hospitalisation with a primary or secondary discharge code related to the non-fatal severe CV event(s) of interest (online supplemental table 1). Death will also be an outcome of interest and, when possible, will be categorised as CVD related, COPD related or related to another reason. The first severe CV event will be categorised as (1) a CV event of any category (including non-fatal events and death) and then (2) a CV event of each category, separately (e.g., the first acute coronary syndrome, the first HF decompensation).

The date of a severe CV event will be determined using the same methodology as that for severe exacerbation (i.e., depending on whether the CV event is identified through a primary or a secondary discharge code). For severe CV events occurring during a hospital stay, the date of the event will be determined using healthcare resource use in the hospital, for
example, transfer to a stroke unit, a brain CT scan for stroke or revascularisation for acute myocardial infarction.

**Other measures**

Potential confounders in the association between exacerbation of COPD and a severe CV event were determined based on the literature and confirmed based on discussions with subject matter experts (table 3).

**Descriptive approach**

The analyses will follow a predetermined global statistical analysis plan, whereby country-specific modifications will be made according to the data source at hand. To that end, the methodology will be broadly aligned across the seven countries to lend robustness and credibility to the results. Missing data will be reported in terms of percentages. The overall included patient cohort will be described via a Consolidated Standards of Reporting Trials flow diagram. General characteristics and potential baseline confounders will be described overall and separately for patients who ever or never had exacerbation of COPD during the study period, as well as for patients without any or at least one severe CV event during the study period. The same descriptive analyses will be conducted in the subgroup of patients who are

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Potential confounders in the association between exacerbation of COPD and a severe CV event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potential confounders</strong></td>
<td><strong>Period of measurement</strong></td>
</tr>
<tr>
<td>Age at cohort entry</td>
<td>Baseline</td>
</tr>
<tr>
<td>Sex</td>
<td>Baseline</td>
</tr>
<tr>
<td>Urban area</td>
<td>Baseline</td>
</tr>
<tr>
<td>Year of cohort entry</td>
<td>Baseline</td>
</tr>
<tr>
<td>Number of GP visits in the 12 months preceding cohort entry</td>
<td>Time updated annually</td>
</tr>
<tr>
<td>Number of exacerbations since baseline period</td>
<td>Time updated upon occurrence of exacerbation</td>
</tr>
<tr>
<td>Newly diagnosed COPD (vs prevalent)</td>
<td>Baseline</td>
</tr>
<tr>
<td>Season when AECOPD occurs (winter vs not)</td>
<td>Time updated upon occurrence of exacerbation</td>
</tr>
</tbody>
</table>

**Comorbidities (ICD-10 codes)**

- Smoking history (F17)
- Alcohol use disorder (F10)
- Obesity (E66)
- Diabetes mellitus type 2 (E11)
- Any disorders of lipoprotein metabolism and other dyslipidaemias, including any of the E78 codes (eg, hyperlipidaemia (E78), hypercholesterolaemia (E78.0) and dyslipidaemia (E78.6, E78.1))
- Ischaemic heart diseases (I20–I25)
- Hypertensive diseases (I11–I15)
- Heart failure (I50)
- Pulmonary oedema (J81)
- Pulmonary hypertension (I27.0, I27.2)
- Venous thromboembolism (I26, I80, I82, O08.2, O22.3, O87.1, O88.2)
- Cerebrovascular disease (I60–I69)
- Arrhythmia (I46, I48, I49)
- Current asthma (J45/J46)
- Chronic kidney disease and renal failure (N17–N19, I12.0, I13.1, I13.2)
- Any severe mental illness, defined as recurrent and persistent depressive disorders (F33 and F34) and/or bipolar disorder (F30–31) and/or schizophrenia (F20–29)
- Anxiety disorder (F40–48)

**Medication (ATC codes)**

- Any use of cardiac agent (B01, C01–03, C07–09)
- Any use of metabolic agent (C10 and A10)
- Any use of COPD medication (R03: LABA, LAMA, ICS, SABA, SAMA, theophylline and roflumilast)
- AECOPD, acute exacerbation of chronic obstructive pulmonary disease; ATC, Anatomical Therapeutic Chemical; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; GP, general practitioner; ICD, International Statistical Classification of Diseases; ICS, inhaled corticosteroids; LABA, long-acting beta 2-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting beta 2-agonist; SAMA, short-acting muscarinic antagonist.
newly diagnosed with COPD. Details of follow-up will be reported, including summaries of total exposed and unexposed time. The number and percentage of patients with at least one severe CV event will be described, with severe CV events being described individually, by main category and overall. Kaplan-Meier curves will visually summarise the cumulative incidence of a first CV event of any type and for each category.

Modelling approach
A time-to-event approach will be used, with the first severe CV event (including death) being the event of interest. Because the hazard of a CV event is expected to change over the 365 days following day 1 of exacerbation, time-dependent Cox proportional hazards models will be used, \(^{31}\) with binary indicators of each exposed time frame, as time-varying covariates. Although COPD is a progressive disease, and the risk of CV events may increase overtime outside exacerbation periods, we decided to pool the unexposed periods, so as to simplify modelling and interpretation of results. However, if descriptive results reveal differences in crude incidence rates of a CV event between the time period prior to first exacerbation and the time period post-365 days following exacerbation, the reference unexposed time period may be revised prior to modelling, to include only time prior to first exacerbation.

Time-dependent Cox models will compare the hazard of a first CV event between exposed subtime periods and the overall unexposed time period and will be fitted with and without adjustment for baseline and time-varying confounders. The target of inference will be the association between each exposed subtime period (vs the unexposed time period) and the outcome of time to first severe acute CV event. For the first objective, analyses will be carried out for (1) time to first severe CV event of any category as the dependent variable and (2) for any type and for each category.

DISCUSSION
To our knowledge, this programme of observational studies will be the first to explore the association between exacerbation of COPD and a wide range of CV outcomes in routine clinical practice. \(^{43}\) The inclusion of newly diagnosed patients, followed up prospectively since the incept disease diagnosis, will provide an insight into patients’ trajectory. Additionally, the evaluation of associations between exacerbation and CV events following the first, second and third exacerbation of COPD will provide important information on the impact of COPD progression on the strength of the relationship between COPD and CVD.

Conducting the studies in countries with different healthcare systems will also provide an insight into how patterns of care, comorbidities and patient characteristics may differ while also checking the consistency of our results across countries.

Several limitations apply. Having multiple databases with heterogeneous nature brings variability into the point estimate of associations evaluated. Namely, the precision and completeness of real-life diagnosis and recording may vary between data sources. To minimise

**Ethics and dissemination**
For all countries, except Germany and Italy, submission to an institutional review board (IRB) and approval are necessary prior to data use. In Germany and Italy, as per local regulation, the use of anonymised, secondary data does not require ethical approval. The studies have already been approved in Canada (HREBA.CHC-22-0006, 3 March 2022), Japan (MINS-REC-220211, 7 April 2022), the Netherlands (kenmerk AC/nWMO/22.013, 22 April 2022), Spain (Ethics Committee of Consorci Sanitari de Terrassa, protocol code AZ-EXA-2022-06, 13 June 2022) and the UK (approval obtained for the EXACOS-UK Study). \(^{35}\) East Midlands, Derby, REC reference number 05/MRE04/87). The general framework is as follows: data repository or data providers (eg, Clinical Practice Research Datalink) will provide data to the data analysis team under an ad hoc agreement. Data extraction will start after IRB agreement is confirmed. All data will be transferred to the data analysis team after de-identification.

For each individual country-based study, the results will lead to at least one publication in peer-reviewed journals and an abstract submission to a conference. No meta-analysis of results is planned at this stage. Given the limited number of studies, it is not sure that statistical power and precision of a random-effects meta-analysis would be improved.

**Patient and public involvement**
Although no patient was involved in the development of the protocol, clinicians (pulmonologists and cardiologists) have been involved to take account of the clinical practice perspective and maximise the relevance of this research to patients.

the risk of measurement error, we have selected databases extensively used in medical research and applied published validated algorithms and code lists where feasible. Although CV events are the outcomes of interest, CV-related death will not be used. Instead, all-cause death will be measured. Secondary databases do not allow for a precise measure of the cause of death and adjudication of the cause of death based on proxy variables is quite challenging.

This study should inform clinical practice on the timing of interventions to reduce the risk of subsequent severe CV events among patients with COPD. In addition to targeting the right patients at the right time with short-term strategies to reduce the risk of excess severe CV events, long-term preventive strategies that can reduce the risk of exacerbation of COPD should be considered. We hypothesise that reducing the risk of exacerbation, or even preventing the first exacerbation, would reduce the overarching cardiopulmonary risk of patients, improving their quality of life and their chances of longer-term survival. Hence, preventive strategies that would reduce this cardiopulmonary risk may greatly improve the survival and quality of life of patients with COPD.

We encourage decision-making by health system administrators, clinicians and patients to consider the need for multidisciplinary management of CV risk before, during and following COPD exacerbation.

Author affiliations
1Medical and Payer Evidence, BioPharmaceuticals Medical, AstraZeneca, Cambridge, UK
2Respiratory Epidemiology, National Heart and Lung Institute, Imperial College London, London, UK
3Department of Medicine, Pulmonary and Critical Care Medicine, German Center for Lung Research (DZL), Philipps University of Marburg, Marburg, Germany
4Department of Respiratory Medicine, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre, Maastricht, The Netherlands
5Department of Medicine, University of British Columbia, Centre for Cardiovascular Innovation, Vancouver, British Columbia, Canada
6Clinical Epidemiology Group, Leibniz Institute for Prevention Research and Epidemiology—BIPS, Bremen, Germany

Acknowledgements The authors acknowledge Nairinder Bhatia for his help in the protocol development.

Contributors CN and KR contributed to the development of the core protocol and statistical analysis plan, and their adaptation in each country, and drafted the manuscript. JKQ, CFV, SOS and NMH contributed to the adaptation of the protocol and statistical analysis plan in each country; they also contributed to drafting the manuscript and reviewed the last version. JM, MO, EG and HM contributed to the development of the core protocol and statistical analysis plan; they also contributed to drafting the manuscript and reviewed its last version.

Funding This work is supported by AstraZeneca, the sponsor of the study, and is conducted by external public or private research teams.

Competing interests CN, KR, JM, MO and HM are employees of AstraZeneca and own stock and/or stock options in the company. JKQ has received grants from MRC, HDR UK, GSK, Bayer, BI, asthma+lung, Chiesi and AstraZeneca; and personal fees for advisory board participation or speaking fees from GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, Boehringer Ingelheim, CSL Behring, Chiesi, GlaxoSmithKline, Grifols, Insmed, Menarini, Novartis, Nuvaira and MedUpdate. SOS has received grants from Boehringer Ingelheim, AstraZeneca and GlaxoSmithKline, consulting fees from GlaxoSmithKline, honoraria for educational events from AstraZeneca and Chiesi, and honoraria for participation on advisory board from Boehringer Ingelheim and Chiesi, all paid to his institution. NMH has acted as speaker for and received consulting fees from AstraZeneca, Novartis and Servier. EG has been chairwoman of a department at the Leibniz Institute that occasionally performed studies for pharmaceutical industries. The pharmaceutical companies included Byk-Gulden, Nycomed, Bayer, Colgene, GlaxoSmithKline, Mundipharma, Novartis, Sanofi-Aventis, Sanofi Pasteur MSD and STADA. EG has been a consultant to Bayer-Schering, Nycomed, GlaxoSmithKline, Schwabe, Teva, Novartis and AstraZeneca.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Clementine Nordon http://orcid.org/0000-0001-9441-9723
Jennifer K Quint http://orcid.org/0000-0003-0149-4869
Sam T Simons http://orcid.org/0000-0002-4296-5076
Hana Müllerová http://orcid.org/0000-0002-0949-0101

REFERENCES


