REG Study Protocol

Long Title:

Asthma-COPD Overlap: Comparability of Population Definitions Within & Between Global Databases – Developing Tools for Observational Research

Short Title:

ACO Population Definitions

Protocol developed by The Respiratory Effectiveness Group’s ACO Working Group
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**Date:** 20 July 2016; **Version:** 1.4
Recognising & Defining a “new” Clinical Reality: Asthma-COPD Overlap

Within routine care, some patients with chronic obstructive pulmonary disease (COPD) exhibit characteristics typically associated with asthma, such as high reversibility of airflow obstruction and fluctuating symptoms. Similarly, some patients with physician-diagnosed asthma (irrespective of their smoking history) go on to develop fixed airflow obstruction similar to that typically associated with COPD. In such instances (and others), it can be difficult for clinicians to establish a clear diagnosis of asthma or COPD and to decide on the optimum therapeutic management for the patient.

Randomised controlled trials (RCTs) of asthma therapies traditionally exclude patients with a history of smoking and, conversely, presence of comorbid asthma and/or reversibility tend to be standard exclusion criteria in trials for COPD. The result is the systematic exclusion of patients with a potentially mixed asthma-COPD phenotype from the RCT-based evidence.

In 2014, the Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) published their first joint statement on so-called asthma-COPD overlap syndrome (ACOS).\(^1\)\(^2\) The publication was the first time the hitherto “clinical reality” had been formally recognised in global guidelines that acknowledged the absence of these patients in their previous publications (i.e. of patients with asthma in GOLD guidance and of patients with COPD in prior GINA recommendations).

The 2014 GINA/GOLD ACOS statement details a list of asthma characteristics and a list of COPD characteristics, and arbitrarily proposes a diagnosis of ACOS when a patient’s disease characteristics is ticked three or more times in both lists (see APPENDIX I: GINA-GOLD joint statement on the diagnosis of acos).\(^3\) Other approaches are proposed by the Spanish,\(^4\) Czech\(^5\) and Finnish\(^6\) COPD guidelines, typically requiring fulfilment of a number of major and minor criteria for a COPD patient to be diagnosed with ACOS. The lack of a standard approach to defining ACOS that can be reliably implemented is an impediment to understanding the biology of ACOS (or of different ACOS subgroups) and to identifying optimum ACOS management approaches.

Prognostic & Therapeutic Relevance of ACOS

Large epidemiological studies, such as the COPDGene\(^7\) and EPI-SCAN\(^8\) have “defined” a patient with ACOS as one with clinical features of COPD (post-bronchodilator FEV\(_1\)/FVC<0.7) and a previous diagnosis of asthma before the age of 40 years. One important finding provided by these studies is that, compared with “traditional” COPD, ACOS appears to be associated with poorer quality of life, more frequent exacerbations and differential treatment response, although this finding has not been universally reported.\(^7\)\(^8\)

Therefore, identifying patients with ACOS could have important prognostic and therapeutic implications. If fixed airflow obstruction in a patient with asthma results from the longstanding progressive nature of their disease only, it may signal the presence of different disease mechanisms to those that might be implicated by the observation of fixed airflow obstruction in an patient with asthma who smoked. Thus, studies targeted at improving understanding of ACOS must stratify results by smoking status.

Optimum term of reference: ACOS vs ACO

It has recently been proposed that, while Asthma and COPD Overlap may correctly reflect the coexistence of features of both conditions in some patients that to call this clinical reality a “Syndrome” is potentially misleading. In medical terms, a “syndrome” refers to more than the co-existence of a set of signs and symptoms of concomitant conditions with/without known pathogeneses. As Barnes proposed, therefore, it may be more appropriate to refer to the apparent concomitant existence of asthma and COPD as Asthma-COPD Overlap rather than ACOS.\(^9\) Further research is required to
define the phenotypic or syndromic nature of the condition and to ascertain how best to identify and manage affected patients.

The term ACO (rather than ACOS) has been adopted hereafter in this protocol.

Unmet Needs in ACO Observational Research

As patients with comorbidities and/or mixed phenotypes are routinely excluded from traditional respiratory licensing trials—as they fail to meet the strict inclusion criteria required to ensure strong internal validity—observational studies drawing on population-level clinical or health administration data provide an important potential resource for initial ACO research.

To date, there is no gold standard (or even standard) definition of ACO for use in observational studies, and this lack of standardisation presents a barrier to research progress and improved understanding of the condition.

To address this unmet need, the Respiratory Effectiveness Group’s (REG’s) ACOS/ACO Working Group proposes to identify (and later characterise) a number of possible definitions of ACO—simple definitions to enable application across a range of databases—and to explore the implications of these different “starting points” for observational ACO studies in terms of ACO prevalence within and between global databases.

The proposed study will be an important first step towards characterising this little understood condition. Future phases of the work will go on to evaluate the clinical differences between the so-defined populations with a view to characterising different potential population definitions and providing a reference, and standard definitions and tools, to inform future ACO research.

STUDY AIMS

To inform standardised methods for future ACO observational research, the study aims to: test various smoking-related ACO population definitions (based on previous evidence), evaluating their respective prevalence and agreement (i) within and (ii) between a number of national and international research-quality databases.

Phased approach and follow-on work

Phase I: Prevalence & Agreement

This initial phase—the focus of this study—intends to compare prevalence and agreement rates for the different ACO definitions between different national and international databases. As such, simple ACO definitions will be used to ensure they can be operationalised across a number of databases.

As each database used will be specific to a patient population and (in most cases) to one country of origin, use of multiple databases affords a unique opportunity to examine the sensitivity of findings to how populations were included in different databases.

1 The first phase of the proposed work will focus on Western databases and smoking-related COPD. Later phases may extend to a wider range of databases and may also consider biomass-related COPD.
Asthma-COPD Overlap Syndrome: Definitions & Observational Research Tools

Phase II: Clinical Characterisation & Outcome Evaluations

Future phases of the REG ACO Working Group’s research programme will go on to characterize the different ACO populations from a clinical perspective (cross sectionally and historically) and to explore potential differential treatment outcomes associated with the different definitions.

It is expected to be considerable variation in characterization approaches in the follow-on clinical characterisation and outcome evaluation phases (owing to differences in available variables and the requirement to use a range of proxy measures in order to optimise approaches within each database). As such, this work will be treated as a separate second study phase (See APPENDIX II).

POPULATION DEFINITIONS

Published / Reference Population Characteristics

The population definition criteria that will be used will reflect those in the current literature – highlighted as features of ACO within large epidemiological studies (e.g. COPDGene\(^6\) and EPI-SCAN\(^7\)) and in the Postma and Rabe New England Journal of Medicine Expert Review (see summary table below).\(^{10}\)

In these publications, the authors “defined” a patient with ACO as one with clinical features of COPD (post-bronchodilator FEV1/FVC<0.7) and a previous diagnosis of asthma before the age of 40 years.

Table 1. Description of four patients with obstructive airway disease by Postma and Rabe\(^{10}\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient with “Easy” Asthma</th>
<th>Patient with “Easy” COPD</th>
<th>Patient with ACOS Stemming from Asthma</th>
<th>Patient with ACOS Stemming from COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>21</td>
<td>65</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Atopy</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Current smoker</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Pack-years</td>
<td>0</td>
<td>95</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Recurrent</td>
<td>Chronic</td>
<td>Chronic with flares</td>
<td>Chronic with flares</td>
</tr>
<tr>
<td>Wheezing</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Reversible airway obstruction</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Bronchial hyperresponsiveness</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes or no</td>
</tr>
</tbody>
</table>

\(^{2}\) “Easy” asthma and “easy” COPD are the easily recognized extremes of asthma and COPD. The two patients with the asthma–COPD overlap syndrome (ACOS) have a similar age, and both have atopy. Despite not being a smoker, the patient with ACOS stemming from asthma has irreversible airway obstruction, which is accompanied by chronic dyspnea and flare-ups of wheezing and bronchial hyperresponsiveness. The patient with ACOS stemming from COPD has some reversibility of airway obstruction after bronchodilator use, chronic dyspnea, and flare-ups of wheezing, which may or may not be accompanied by hyperresponsiveness. In the two patients with ACOS, whether the syndrome stems from asthma or from COPD cannot be easily distinguished by their phenotype.

Population Definitions

This study will apply simplified versions of the Postma and Rabe description (above) and published guideline definitions (APPENDIX I) to enable initial identification across a range of databases. Twelve population definitions will be considered across 4 Parent Population Series (COPD, Asthma & COPD, Asthma, Reference: Series A–D, respectively).
Eligible patients will have non-missing data for all proposed ACO criteria, i.e. clinical diagnosis (see later definition), age, smoking history, airway obstruction and airway reversibility.

Within each complete Parent Series, four subpopulations will be examined; patie:

- **Subpopulation A, B, C, D**: will be the largest subpopulation, containing patients in each parent series who have valid diagnosis data (coded or inferred through encounter codes – see table below) and are aged >40 years.
- **Subpopulation A1, B1, C1, D1**: a subset of populations A–D that also has evidence of prior smoking exposure.
- **Subpopulation A2, B2, C2, D2**: a subset of populations A1–D1 that has evidence of persistent airflow obstruction (post BD fixed ratio FEV1/FVC<0.7).
- **Subpopulation A3, B3, C3, D3**: a subset of populations A2–D2 that has evidence of airway reversibility (post BD increase in FEV1 by ≥12% and ≥200mL)

The proposed definition of ACO within each patient population will be A3, B3, C3, D3, with a second (sensitivity) definition also proposed as A2, B2, C2, D2. The sensitivity definition reflects current uncertainty as to the relevance of reversibility as a characteristic of ACO.

Comparison of the prevalence obtained for the two proposed definitions will provide important information as to the yield of those databases for the purposes of future ACO research and (in subsequent analyses) enable exploration of the clinical implications of different definitions (in terms of treatment response, pathophysiology, etc.).

<table>
<thead>
<tr>
<th>Definition Criterion</th>
<th>A: COPD only</th>
<th>B: COPD &amp; ASTHMA</th>
<th>C: ASTHMA Only</th>
<th>D: Reference population</th>
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<td>Approach 1: Dx of COPD only at 2 different encounters over 2-yr observation period; no dx of asthma at any encounter over the 2-yr observation period</td>
<td>A</td>
<td>A1</td>
<td>A2</td>
<td>A3</td>
</tr>
<tr>
<td>Approach 2: Physician Dx of COPD within 5-years of the 2-yr observation period; no dx of asthma over the same period</td>
<td>k</td>
<td>k</td>
<td>k</td>
<td>k</td>
</tr>
<tr>
<td>Sensitivity analysis: repeat using a 10-year Dx window</td>
<td>k</td>
<td>k</td>
<td>k</td>
<td>k</td>
</tr>
</tbody>
</table>

| Age | >40 years | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Smoking* | Smoking history ever | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore |
| Obstruction | Post BD FEV1/FVC <70% | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore |
| Reversibility | post-BD increase in FEV1 by ≥12% and ≥200mL | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore | Ignore |

*Smoking criterion: history of past or current smoking based on physician diagnosis on a problem list or billing/administrative data source. The number of pack-years smoked was felt not to be feasible, as most clinical databases do not contain such information.

**Reversibility criterion: reversibility parameters (≥12% and ≥200mL increase in FEV1; post-bronchodilator) are in line with those proposed by the ERS/ATS Taskforce and GINA/GOLD ACOS definition documents. Secondary analyses may examine other definitions.
STUDY DESIGN & DATASET

Study Design

The study will draw on population-based high-quality research databases available to members of the REG ACOS/ACO Working Group.

**Database Inclusion Criteria**

**Source Data:** To be eligible for inclusion in the study, databases must be "population-based", requiring them to be largely representative of the broad, heterogeneous population treated within everyday routine care in their respective country of origin.

The following types of population-based studies may be eligible:

- Clinical databases (e.g. primary care databases)
- Administrative/billing-based (e.g. insurance claims records)

Clinical databases and claims databases may have incomplete clinical information (i.e. conferring risk of potential diagnostic misclassification), but they offer the advantage over selective RCT or cohort databases of examining populations that more closely mimic typical clinical practice.

All eligible databases must also meet the following inclusion criteria:

- Have at least two continuous years of “recent” (within the last 10 years: 2006-2015) clinical data
- Have produced at least one publication in a peer reviewed journal
- Include variables permitting:
  - Evaluation of patient age (i.e. patient age or date/year of birth)
  - Evidence of current or past smoking (e.g. smoking status, pack years, prescription of smoking cessation therapy/advice).

**Database Exclusion Criteria**

To maximise the external validity of the study findings and avoid biasing outcomes by working within pre-selected populations unrepresentative of the diversity of patients managed in routine clinical practice, the following will not be eligible for inclusion in the initial phase of this study:

- Clinical trials databases
- Case series of patients.

Datasets

Through REG ACOS/ACO Working Group Discussion, the following databases have been selected for inclusion in the study; all five clinical databases containing physician data rather than health insurance claims data (see APPENDIX III for further dataset details):\(^2\)

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\(^2\) Repetition of the analysis within the Patient Centred Outcomes Research Network (PCORnet) database—a population-based electronic medical records database of approximately 100 million US patients—is proposed when PCORnet data becomes available for research purposes (date to be confirmed; anticipated late 2016).
Table 2. Summary of databases to be used in the study*

<table>
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<tr>
<th>Database</th>
<th>Country of Origin</th>
<th>Type of Sample</th>
<th>Maximum “starting populations” size (pre application of definitions criteria) in July 2015</th>
<th>Database citation (example)</th>
</tr>
</thead>
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* A cross-sectional market research database contributed to by >700 physicians who provide records (and associated disease-specific patient questionnaire data) on the next 10 patients who present with a “target” condition. Patient inclusion is therefore randomly selected from a set of pre-identified practices.11

Characteristics of participating databases will be reflected in the sensitivity analyses conducted for the between-database analysis and acknowledged in the final report.

**Patient Inclusion Criteria**

To be eligible for inclusion in the study, patients must have non-missing data for:
- Clinical diagnosis (see later for full definitions):
  - COPD only
  - Both Asthma and COPD
  - Asthma only
  - No current Asthma or COPD
- Age (≥40 years)
- Smoking history (ever smoker)
- Airway obstruction (post BD fixed ratio FEV1/FVC<0.7).
- Airway reversibility (post BD increase in FEV1 by ≥12% and ≥200mL)
**Patient Exclusion Criteria**

To maximise the external validity of the study findings, no additional exclusion criteria will be applied.

**Study Period**

The study period will include a 24-month continuous period from within the last 10-years (i.e. earliest period being 2006-2008; latest 2013-2015) to minimise potential temporal effects of changes in coding and clinical management.

Diagnostic Approach 2, will consider longer 5-year (primary) and 10-year (secondary) observation periods (see below).

**Diagnostic definitions: assigning patients to the appropriate parent series**

**Requirement for multiple coded events**

Few countries currently have a specific code for ACO owing to its relatively recent formal recognition as a clinical phenomenon. Identification of ACO and allocation of patients to the appropriate parent series (see population definitions above) will, therefore, typically require consideration of co-coding of asthma and COPD as a proxy for ACO.

**Approach 1 Rationale: use of healthcare encounter codes as a proxy for diagnosis**

Physician diagnosis data is not available in all databases used for respiratory research, particularly in administrative/billing databases. Suitable, clinically appropriate, proxies for diagnosis must therefore be defined in order to categories patients as having asthma, COPD, both or neither of these conditions, as appropriate.

In the case of administrative/billing databases, each encounter with healthcare/a healthcare practitioner is recorded and assigned a billing code to facilitate subsequent adminstration and payment. As such, the conditions coded at the time of a consultation indicate the condition that the patient was seen for and will be used for this study to infer the presence of a diagnosis – Approach 1.

A 24-month evaluation period (rather than a single year) is necessary because the reason for consultation/healthcare encounter is not always recorded in electronic medical records in some countries (including the country of origin of some of the databases proposed for inclusion in the study). Using consultation coding as a proxy for an active diagnosis could, therefore, exclude a large number of clinically relevant patients as a result of missing codes. However; asthma and COPD patients (across all countries contributing data to this parallel analysis) will have (at least) an annual asthma and COPD review that should be specifically recorded as such. Hence requiring evidence of a minimum of two coded events over a two-year period allows the inclusion of patients who have received one annual review in each of the two 12-month period.

**Parent Series Definitions: Approach 1 – encounter codes**

To avoid potential selection bias all patients included in the study must have at least two (relevantly-coded) consultations within the 24-month study period, not only patients in the Asthma and COPD parent series, i.e.:

**Series A. COPD Only**

Eligible patients within the COPD parent population must have: ≥2 coded encounters for COPD within the 24-month study period and no asthma code during the 24-month study period..

**Series B. Both Asthma and COPD**

Eligible patients within the Asthma & COPD parent population must have have one of the following:
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Series A. COPD only
Eligible patients within the COPD parent population must have: ≥2 COPD diagnostic codes within a 60-month (primary) and 120-month (secondary analysis) observation period and no recorded asthma or ACO diagnosis within the same time periods.

Series B. Both Asthma and COPD
Eligible patients within the Asthma & COPD parent population must have one of the following:
a) ≥2 coded ACO diagnostic codes within a 60-month (primary) and 120-month (secondary analysis) observation period;
b) ≥1 COPD diagnostic code and ≥1 asthma diagnostic code within a 60-month (primary) and 120-month (secondary analysis) observation period.

Series C. Asthma Only
Eligible patients within the asthma parent population must have: ≥2 coded encounters for asthma within the 24-month study period and no COPD code during the 24-month study period.

Series D. Reference Population (no current asthma or COPD)
Eligible patients within the control parent population must have:
a) ≥2 coded encounters not coded for asthma, ACO or COPD within the 24-month study period
b) 0 coded encounters coded for asthma, ACO or COPD within the 24-month study period

Figure 1.1 Approach 1: Illustration of parent population identification within the 24-month characterisation period using ≥2 encounter codes as a proxy for diagnosis (encounter dates are examples only)

Parent Series Definitions: Approach 2 – use of diagnostic codes as a proxy for active diagnosis in the evaluation period

In some healthcare systems diagnostic data does not accompany each healthcare encounter. In such cases, Approach 1 would not be feasible.

A second proxy for current diagnosis (Approach 2) will therefore use a physician diagnosis of asthma, COPD, Asthma, both (or ACO) or neither (e.g. ICD9, ICD10, Read or other codes) to infer active diagnosis during the 24-month cross-sectional evaluation period.

To reduce the potential for changes in coding practice to bias this approach, eligible patients will be limited to those with two or more diagnostic codes over a recent 60-month (5-year) primary evaluation period and (to assess the effect of different observation periods and temporal changes in coding practice) over a 120-month (10-year) secondary evaluation period.

In both cases (5-year and 10-year observation cohorts), the prevalence of ACO will be estimated among individuals with non-missing data for age, ever smoking, post-bronchodilator FEV1/FVC, and results of reversibility tests within a single 24-month period.
c) ≥1 ACO diagnostic code and ≥1 asthma diagnostic code within a 60-month (primary) and 120-month (secondary analysis) observation period;

d) ≥1 ACO diagnostic code and ≥1 COPD diagnostic code within a 60-month (primary) and 120-month (secondary analysis) observation period.

Series C. Asthma Only

Eligible patients within the asthma parent population must have: ≥2 asthma diagnostic codes within a 60-month (primary) and 120-month (secondary analysis) observation period and no recorded COPD or ACO diagnoses within the same time periods.

Series D. Reference Population (no current asthma or COPD)

Eligible patients within the control parent population must have: No diagnostic codes for asthma, COPD and/or ACO within a 60-month (primary) and 120-month (secondary) observation period.

OUTCOMES & ANALYSES

The primary outcomes of the study are the prevalence of proposed ACOS within each of the parent series (A: COPD only; B: both Asthma & COPD; C: Asthma only; D: Reference population) and the agreement between prevalence rates within databases and (when replicated across a number of databases) between different databases.

To facilitate this, the following will be evaluated – See Appendix IV. Flow diagrams for each parent population:

1. Total number of patients within each population series subpopulation:

   (a) Series A (COPD only parent population):
       (i) Number of patients in population A
       (ii) Number of patients in population A1
       (iii) Number of patients in population A2
       (iv) Number of patients in population A3

   (b) Series B (Asthma & COPD parent population):
       (i) Number of patients in population B
       (ii) Number of patients in population B1
       (iii) Number of patients in population B2
       (iv) Number of patients in population B3

   (c) Series C (Asthma only parent population):
       (i) Number of patients in population C
       (ii) Number of patients in population C1
       (iii) Number of patients in population C2
       (iv) Number of patients in population C3

   (d) Series D (Reference population – no current asthma or COPD):
       (i) Number of patients in population D
       (ii) Number of patients in population D1
       (iii) Number of patients in population D2
       (iv) Number of patients in population D3

2. Prevalence of “proposed ACO” within the parent populations, defined as:

   (a) A3/A x 100%; B3/B x 100%; C3/C x 100%; D3/D x 100%, and
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3. Within database (prevalence) agreement using different case definitions of ACO:

(a) Database I: A3/A x 100% vs B3/B x 100% vs C3/C x 100% vs D3/D x 100
(b) Database I (Sensitivity): A2/A x 100%; B2/B x 100%; C2/C x 100%; D2/D x 100%

4. Between database agreement using different case definitions of ACO:

(a) Proposed ACO:
   (i) A3/A x 100%: Database 1 vs Database 2 vs Database 3….
   (ii) B3/A x 100%: Database 1 vs Database 2 vs Database 3….
   (iii) C3/A x 100%: Database 1 vs Database 2 vs Database 3….
   (iv) D3/A x 100%: Database 1 vs Database 2 vs Database 3….

(b) Proposed ACO Sensitivity:
   (i) A2/A x 100%: Database 1 vs Database 2 vs Database 3….
   (ii) B2/B x 100%: Database 1 vs Database 2 vs Database 3….
   (iii) C2/C x 100%: Database 1 vs Database 2 vs Database 3….
   (iv) D2/D x 100%: Database 1 vs Database 2 vs Database 3….

ANALYSIS

General analysis approach

Evaluation of:

1. Outcome 1 (total number of patients) will require absolute count of patient numbers.
2. Outcome 2 (population prevalence) will require evaluation of the percent prevalence within different Parent Series.
3. Outcomes 3 & 4 (agreement within and between databases) will use the kappa statistic (k) or suitable alternatives (e.g., Chi-squared).12

Primary

The primary analyses will estimate the prevalence of ACO among individuals with non-missing data for age, ever smoking, post-bronchodilator FEV1/FVC, and results of reversibility tests within a single 24-month period – the latest period available for each database.

Secondary analysis

Additional secondary analyses we will estimate (and compare) the prevalence of ACO in patients with non-missing data for all 4 ACO criteria vs. those with missing data in one or more of the 4 ACO criteria.

LIMITATIONS OF STUDY DESIGN / ANALYSIS

As with all database studies, a number of limitations exist such as:

- How representative the database population is of the general population and of the general chronic airways diseases population
- Incomplete data for variables and misentry of participant data and the need to use proxy measures where explicit data are not available.
- Thresholds for some criteria (e.g., age at least 40 yrs; ever smoker; 200 mL and 12% reversibility) are arbitrary, but based on consensus and feasibility using electronic health records
  - Alternate definitions can be explored in subsequent analyses, using clinical sensible outcomes (e.g., treatment response) to establish appropriate criteria

Date: 20 July 2016; Version: 1.4
- Pack-years smoked rarely coded as discrete data in electronic medical records; reliability also unclear
- There is no means to capture second hand smoking exposure, biomass or occupational exposures

In terms of the specific approach used to identify patients with relevant diagnoses and characteristics, a number of approaches were considered (e.g. use of diagnostic codes rather than encounter codes as a proxy for diagnosis; cluster analysis rather than a priori definition of parent populations). Each approach had a number of advantages and trade offs, as is outlined in the cost/benefit (strengths/weaknesses) summary below.

Table 3. Summary of the relative benefits and trade offs of different evaluation approaches leading to the selection of Approach 1 as the primary method of patient series identification/definition for the study

<table>
<thead>
<tr>
<th>OPTION</th>
<th>STRENGTHS</th>
<th>WEAKNESSES</th>
</tr>
</thead>
</table>
| **Approach #1**: uses diagnosis codes recorded at encounters over a 24 month period (i.e. Asthma population series: ≥2 encounters for asthma in the evaluation period; COPD population series: ≥2 encounters for COPD; ACO population series: ≥2 encounters for ACO = diagnosis of ACO OR ≥1 encounter for asthma and ≥1 encounter for COPD in the 24-month evaluation period) | • Can be operationalized across a range of populations and countries  
• Feasible across different databases, i.e. maximum external validity  
• ≥2 encounters over 24-months (and ≥1 encounter per 12 month) reduces the potential pre-selection of patients with greater health problems than ≥2 encounters over 12-months | • Diagnosis codes may not be accurate  
• Need for diagnostic codes at point of consultation will limit population numbers (perhaps unnecessarily) and possibly induce selection bias where clinical data are being used as reason for consultation is not always coded  
• Cross-sectional analysis does not account for change in patient characteristics over time (potential project in phase II)  
• Does not include measures of airway inflammation (potential project in phase II) |
| **Approach #2**: relies on clinician diagnosis at any encounter within the last 5 years (primary analysis) or 10 years (secondary analysis) rather than disease codes over the past 24 months; could be diagnosis >>24 months ago. (i.e. Asthma population series: asthma diagnostic code ever; COPD population series: COPD diagnostic code ever; ACO population series: ACO diagnostic code ever and/or diagnostic code for asthma and COPD in the evaluation period) | • Draws on clinician diagnosis rather than coded reasons for consultation  
• Avoids potential pre-selecting a severe population by requiring patients to have multiple respiratory consultations in the evaluation period | • Diagnosis may not be accurate or current  
• May not be feasible in some databases (databases that do not include clinician diagnoses) |
| **Approach #3**: Selected patients who are ≥40y, have had a diagnostic (or administrative code) for asthma or COPD ever and characterize them (e.g. by comorbidities, inflammatory markers, duration of diagnosis, etc.) using, e.g., clustering techniques and/or other types of factorial techniques | • Avoids pre-defining / assuming anything about the nature of ACO patients and lets their features inform appropriate clinical “groupings” and future definitions | • Would result in substantial variation between databases as different databases may not have the same data to support cluster analyses, limiting the original intention to conduct a standard analysis across a range of database  
• Consensus on what variables to use does not currently exist (potential project in phase II) |
The study will undertake Approaches 1 & 2 in parallel, guided at a database level by the feasibility of both approaches and their clinical appropriateness given the nature of the data available. Only Approach 1 will be possible in some databases (claims databases); only Approach 2 in others, and only a minority of databases will be able to use both approaches. Together the two approaches provide complementary results.

Agreement evaluations between databases will consider agreement across all contributing databases but will also be stratified by approach used.

**DATA DISSEMINATION PLANS**

REG is committed to registering all research that it conducts (e.g. in the ENCePP or clinicaltrials.gov registries) and to publishing all study findings in order to ensure: (i) transparency of its activities and (ii) so that REG-funded research can be used to inform the research and lay community.

At least one abstract from the study will be submitted to a key international respiratory congress (e.g. the European Respiratory Society, American Thoracic Society or similar) and at least one manuscript will be developed and submitted to a peer review respiratory journal to disseminate the primary elements of the planned analysis.

**ETHICS**

Ethics approvals will be sought, where necessary and as appropriate for each participating dataset. The working group lead contact for each database will be responsible for advising and securing the relevant ethical approvals (where necessary) for use of their respective database.

In the UK, for example, the Optimum Patient Care Research Database (OPCRD) has been approved by the Trent Multi Centre Research Ethics Committee for clinical research use subject to individual study protocols applying for use of the database be submitted to the independent Anonymised Data Ethics Protocols and Transparency (ADEPT) Committee for approval, based on their clinical relevance and research merit. As such, use of the OPCRD for this study will be requested by submission of this protocol to the ADEPT Committee prior to data extraction.

**STUDY TEAM**

**Study / Co-Working Group Leads**

**Jerry Krishnan:** Population Health Sciences Program, University of Illinois Hospital and Health Sciences System, Chicago, IL, USA, and Department of Medicine, University of Illinois at Chicago, Chicago, IL, USA.

**Nicolas Roche:** Pneumologie et soins intensifs respiratoires, groupe hospitalier Cochin - site Val-de-Grâce, Assistance publique-Hôpitaux de Paris, 75014 Boulogne, France; EA2511, Université Paris Descartes, 75006 Paris, France

**Database Leads**

**Optimum Patient Care Research Database:**

- **David Price:** Primary Care Respiratory Medicine, University of Aberdeen, Aberdeen, UK; Owner of Optimum Patient Care Ltd and REG Chairman
- **Victoria Carter:** General Manager of Optimum Patient Care Ltd; Cambridge, UK
Asthma-COPD Overlap Syndrome: Definitions & Observational Research Tools

Dutch Asthma/COPD Service database:
- Janwillem Kocks: Department of General Practice, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

SIDIAP Database:
- Marc Miravitlles: Pneumology Department, University Hospital Vall d’Hebron, CIBER de Enfermedades Respiratorias (CIBERES), Barcelona, Spain

Adelphi Respiratory Database:
- Mark Small: Project Director, Adelphi Real World, Stockport, UK
- James Bailey: Project Manager, Adelphi Real World, Stockport, UK

MAJOrca Real-world Investigation in COPD and Asthma database (MAJORICA):
- Miguel Román: Primary Care Majorca Department, Son Pisà Primary Health Centre, C/ Vicenç Joan Perello Ribes, 65, Palma de Mallorca, Baleares, Spain
- Job van Boven: Unit of PharmacoEpidemiology & PharmacoEconomics, Department of Pharmacy, University of Groningen, Groningen, The Netherlands

REG Research Leads
- Alison Chisholm: REG Chief Scientific Officer, Cambridge, UK
- Anjan Nibber: REG Researcher, Cambridge, UK

Additional REG ACOS Working Group Members
Involved in protocol development and potential results interpretation and dissemination:
- Alan Kaplan: Family Physician Airways Group of Canada, Warwick, Canada
- Akki Niimi: Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan
- Caroline Gouder: Department of Medicine, Mater Dei Hospital, Msida, Malta
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- Eric Bateman: Division of Pulmonology, Department of Medicine, University of Cape Town, Cape Town, South Africa
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- Leif Bjermer: Department of Respiratory Medicine and Allergology, University Hospital, Lund, Sweden
- Ronald Dandurand: Montreal Chest Institute & Meakins-Christie Laboratories, McGill University, Montreal, QC, Canada
Richard Costello: Department of Respiratory Medicine, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland

TIMELINE

An indicative timeline for international roll out of the study will be developed in collaboration with the ACOS Working Group members during their July update call and with individual database leads throughout July 2016.

BUDGET

A budget for international roll out of the study will be developed in collaboration with individual database leads within the ACOS Working Group following the planned working group webex (July 2016).

REFERENCES

1. Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? Thorax 2009; 64: 728-735.
APPENDIX I: GINA-GOLD JOINT STATEMENT ON THE DIAGNOSIS OF ACOS

GOLD-GINA Approach

A summary of the typical characteristics of asthma, COPD and ACOS identified by the authors of the joint GOLD/GINA statement on ACOS are detailed in the table below (showing the similarities and differences in history and investigations). Given the extent of overlap between features of asthma and COPD (Table 2a), the approach proposed focuses on the features that are most helpful in distinguishing asthma and COPD (Table 2b). The following instructions are provided:

a. Assemble the features that favor a diagnosis of asthma or of COPD

From a careful history that considers age, symptoms (in particular onset and progression, variability, seasonality or periodicity and persistence), past history, social and occupational risk factors including smoking history, previous diagnoses and treatment and response to treatment, the features favoring the diagnostic profile of asthma or of COPD can be assembled. The check boxes in Table 2b can be used to identify the features that are most consistent with asthma and/or COPD. Note that not all of the features of asthma and COPD are listed, but only those that most easily distinguish between asthma and COPD.

b. Compare the number of features in favor of a diagnosis of asthma or a diagnosis of COPD

From Table-2b, count the number of checked boxes in each column. Having several (three or more) of the features listed for either asthma or for COPD, in the absence of those for the alternative diagnosis, provides a strong likelihood of a correct diagnosis. However, the absence of any of these features has less predictive value, and does not rule out the diagnosis of either disease. For example, a history of allergies increases the probability that respiratory symptoms are due to asthma, but is not essential for the diagnosis of asthma since non-allergic asthma is a well-recognized asthma phenotype; and atopy is common in the general population including in patients who develop COPD in later years. When a patient has similar numbers of features of both asthma and COPD, the diagnosis of ACOS should be considered.

c. Consider the level of certainty around the diagnosis of asthma or COPD, or whether there are features of both suggesting Asthma-COPD Overlap Syndrome

In the absence of pathognomonic features, clinicians recognize that diagnoses are made on the weight of evidence, provided there are no features that clearly make the diagnosis untenable. Clinicians are able to provide an estimate of their level of certainty and factor it into their decision to treat. Doing so consciously may assist in the selection of treatment and, where there is significant doubt, it may direct therapy towards the safest option - namely, treatment for the condition that should not be missed and left untreated.
Asthma-COPD Overlap Syndrome: Definitions & Observational Research Tools

## Spanish Guideline (GesEPOC) Approach

The Spanish Guidelines propose four phenotypes are:

1. **(A) infrequent exacerbators with either chronic bronchitis or emphysema**
2. **(B) overlap COPD-asthma**
3. **(C) frequent exacerbators with emphysema predominant**
4. **(D) frequent exacerbators with chronic bronchitis predominant**

### Table 2a. Usual features of asthma, COPD and ACOS

<table>
<thead>
<tr>
<th>Feature</th>
<th>Asthma</th>
<th>COPD</th>
<th>ACOS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of onset</strong></td>
<td>Usually childhood onset but can commence at any age</td>
<td>Usually &gt; 40 years of age</td>
<td>Usually age &gt;40 years, but may have had symptoms in childhood or early adulthood</td>
</tr>
<tr>
<td><strong>Pattern of respiratory symptoms</strong></td>
<td>Symptoms may vary over time (day to day, or over longer periods), often limiting activity. Often triggered by exercise, emotions including laughter, dust or exposure to allergens</td>
<td>Chronic usually continuous symptoms, particularly during exercise, with ‘better’ and ‘worse’ days</td>
<td>Respiratory symptoms including exacerbational dyspnea are persistent but variability may be prominent</td>
</tr>
<tr>
<td><strong>Lung function</strong></td>
<td>Current and/or historical variable airflow limitation, i.e. BOD reversibility, AHR</td>
<td>FEV1 may be impaired by therapy, but post-BID FEV1/FVC &lt; 0.7 persists</td>
<td>Airflow limitation not fully reversible, but often with current or historical variability</td>
</tr>
<tr>
<td><strong>Lung function between symptoms</strong></td>
<td>May be normal between symptoms</td>
<td>Persistent airflow limitation</td>
<td>Persistent airflow limitation</td>
</tr>
<tr>
<td><strong>Past history or family history</strong></td>
<td>Many patients have allergies and a personal history of asthma in childhood, and/or family history of asthma</td>
<td>History of exposure to noxious particles and gases (mainly tobacco smoke and biomass fuels)</td>
<td>Frequently a history of doctor-diagnosed asthma (current or previous), allergies and a family history of asthma, and a history of noxious exposures</td>
</tr>
<tr>
<td><strong>Time course</strong></td>
<td>Often improves spontaneously or with treatment, but may result in fixed airflow limitation</td>
<td>Generally, slowly progressive over years despite treatment</td>
<td>Symptoms are partly but significantly reduced by treatment. Progression is usual and treatment needs are high</td>
</tr>
<tr>
<td><strong>Chest X-ray</strong></td>
<td>Usually normal</td>
<td>Severe hyperinflation &amp; other changes of COPD</td>
<td>Similar to COPD</td>
</tr>
<tr>
<td><strong>Exacerbations</strong></td>
<td>Exacerbations occur, but the risk of exacerbations can be considerably reduced by treatment</td>
<td>Exacerbations can be reduced by treatment. If present, comorbidities contribute to impairment</td>
<td>Exacerbations may be more common than in COPD but are reduced by treatment. Comorbidities can contribute to impairment</td>
</tr>
<tr>
<td><strong>Typical airway inflammation</strong></td>
<td>Eosinophils and/or neutrophils</td>
<td>Neutrophils in spumum, lymphocytes in airways, may have systemic inflammation</td>
<td>Eosinophils and/or neutrophils in spumum.</td>
</tr>
</tbody>
</table>

### Table 2b. Features that favor asthma or COPD

<table>
<thead>
<tr>
<th>Feature</th>
<th>Favors Asthma</th>
<th>Favors COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Onset before age 20 years</td>
<td>Onset after age 40 years</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Symptoms worse during the night or early morning</td>
<td>Symptoms triggered by exercise, emotions including laughter, dust or exposure to allergens</td>
</tr>
<tr>
<td><strong>Airflow limitation</strong></td>
<td>Record of variable airflow limitation (spirometry, peak flow)</td>
<td>Record of persistent airflow limitation (post-bronchodilator FEV1/FVC &lt; 0.7)</td>
</tr>
</tbody>
</table>

*Syndromic diagnosis of airways disease: how to use Table 2b*

Shaded columns list features that, when present, best distinguish between asthma and COPD. For a patient, count the number of check boxes in each column. If three or more boxes are checked for either asthma or COPD, that diagnosis is suggested. If there are similar numbers of check boxes in each column, the diagnosis of ACOS should be considered. See Step 2 for more details.

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Date: 20 July 2016; Version: 1.4
The overlap COPD-asthma phenotype is characterised by incompletely reversible obstruction of airflow accompanied by symptoms or signals of increased reversibility of the obstruction. Epidemiological studies of COPD incidence show that young patients with asthma who smoke and develop airflow obstruction that is not fully reversible (i.e. COPD) have a disease with different characteristics from those with no history of asthma. In the first case, allergic rhinitis, bronchial hyperresponsiveness, and the presence of wheezing as well as higher plasma concentrations of IgE are significantly more frequent, indicating that this is an overlap phenotype between asthma and COPD. Also, asthma by itself is a risk factor for the development of chronic airflow obstruction, particularly if undertreated, and in advanced stages may be indistinguishable from smokers’ COPD. The prevalence of this mixed phenotype is unknown, but there are different estimates of its importance in the context of COPD. COPDGene estimated it was 13% of their sample. Soriano et al. estimated that approximately 23% of COPD patients aged 50–59 years could have a mixed phenotype, increasing to 52% of those with COPD aged 70–79 years. The relevance of this phenotype, already described in the Canadian and Japanese guidelines, is its enhanced response to inhaled corticosteroids, which must be prescribed together with long-acting bronchodilators irrespective of the severity of the airflow obstruction. Recently, a group of experts have proposed a series of criteria for the diagnosis of the overlap phenotype of asthma and COPD.

**Czech Pneumological and Phthisiological Society Guideline Approach**

Summary of elementary COPD phenotypes in the Czech Guidelines, including overlap COPD/Asthma:

<table>
<thead>
<tr>
<th>COPD phenotypes</th>
<th>Basic features of COPD phenotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchitic phenotype</td>
<td>The presence of productive cough (≥ 3 months/year in two or more consecutive years)</td>
</tr>
<tr>
<td>Emphysematic phenotype</td>
<td>Lifetime absence of productive cough and clinical signs of pulmonary emphysema*</td>
</tr>
<tr>
<td>Overlap COPD + asthma</td>
<td>Major criteria:</td>
</tr>
<tr>
<td></td>
<td>(a) strong BDT positivity (FEV₁ &gt; 15% and &gt; 400 mL),</td>
</tr>
<tr>
<td></td>
<td>(b) BCT positivity,</td>
</tr>
<tr>
<td></td>
<td>(c) FENO ≥ 45-50 ppb and/or ↑ eo (sputum) &gt; 3%,</td>
</tr>
<tr>
<td></td>
<td>(d) history of asthma</td>
</tr>
<tr>
<td></td>
<td>Minor criteria:</td>
</tr>
<tr>
<td></td>
<td>(a) mild BDT positivity (FEV₁ &gt; 12% and &gt; 200 mL),</td>
</tr>
<tr>
<td></td>
<td>(b) ↑ total IgE, (c) history of atopy</td>
</tr>
<tr>
<td></td>
<td>- and definite COPD diagnosis</td>
</tr>
<tr>
<td>Overlap COPD + bronchiectasis</td>
<td>Accented, almost daily, purulent sputum expectoration, younger age, lower or no smoking burden,</td>
</tr>
<tr>
<td></td>
<td>history of prolonged/recurrent respiratory infections, hemoptysis, HRCT confirmation of bronchiectasis</td>
</tr>
<tr>
<td></td>
<td>- and definite COPD diagnosis</td>
</tr>
<tr>
<td>Frequent-exacerbation phenotype</td>
<td>Presence of frequent exacerbations (≥ 2/year) treated with ABT and/or corticosteroids</td>
</tr>
<tr>
<td>Pulmonary cachexia phenotype</td>
<td>BMI &lt; 21 kg/m² - no other cause (FFMI &lt; 16 kg/m² in males or &lt; 15 kg/m² in females)</td>
</tr>
</tbody>
</table>

* It is useful (not necessary) to verify this by function assessment (TLCO, KCO < LLN, RV > ULN) for non-A patients and by chest HRCT if targeted therapy of emphysematous phenotype is planned
** COPD + asthma phenotype is confirmed by the presence of 2 major criteria or 1 major plus 2 minor criteria
*** FFMI can be measured by densitometry, antropometry or bioelectrical impedance analysis
Finnish Guideline Approach

The principles of diagnostics and phenotype-specific therapy of chronic obstructive pulmonary disease (COPD).6
APPENDIX II: PHASE II CLINICAL CHARACTERISATION

Once Phase I (as described in this protocol) is complete, a Phase II study to characterize the populations—their clinical characteristics and implications on treatment outcomes—is intended. Some approaches to characterization are provided below; these may be expanded further depending on the results of Phase I.

1. **Presence of atopy, defined as ≥1 of the following:**
   - (a) Physician diagnosis of eczema
   - (b) Physician diagnosis of allergic rhinitis
   - (c) Eosinophilia (cut off >200/μl; REG COPD blood eosinophilia study used ≥450μl)³
   - (d) Positive skin prick test
   - (e) Positive to ≥1 allergen

2. **Smoking history:**
   - (a) Pack years, where available
   - (b) Duration of smoking, defined as:
     - (i) For ex-smokers: years between first current smoking/active smoking code and non-smoker or smoking cessation code
     - (ii) For current smokers: years between first current smoking record and year of study/cross-sectional analysis

3. **Historical “onset” of disease:**
   - (a) Duration of asthma, defined as years between first recorded asthma diagnosis/encounter and year of study/cross-sectional analysis
   - (b) Duration of COPD, defined as years between first recorded COPD diagnosis/encounter and year of study/cross-sectional analysis
   - (c) Time between first recorded asthma diagnosis/encounter and first COPD diagnosis/encounter

4. **COPD severity:** in terms of GOLD status (where evaluable)⁴

5. **Comorbidities:**
   - (a) Cardiovascular disease
   - (b) Other chronic respiratory conditions
   - (c) Diabetes
   - (d) Gastroesophageal reflux disease (GERD)
   - (e) Charleson Comorbidity Index
   - (f) Lung Cancer

6. **Respiratory treatment**
   Current management (i.e. during the phase 1 24-month cross-sectional analysis period), records (prescriptions for/claims data) for the following, and combinations of the following, will be examined: SABA, SAMA, LABA, LAMA, ICS, theophylline, LTRA, Roflumilast, chronic azithromycin.

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³ Kenneth D, McClatchey. *Clinical Laboratory Medicine*. Lippincott Williams & Wilkins, 2002

7. Exacerbations:

Functional consequences of different definitions, (i) proportion of patients and (ii) annualised rate of respiratory-related exacerbations over the phase 1 24-month evaluation period, where a respiratory-related event is defined as any of the following:

(a) Physician diagnosis of asthma exacerbation;
(b) Physician diagnosis COPD exacerbation;
(c) Accident & Emergency / Emergency Room attendance with a lower respiratory code
(d) Hospital admission with a lower respiratory code
(e) A course of prednisolone
(f) A course of systemic antibiotics coded for a lower respiratory tract infection
## APPENDIX III: DATABASE CHARACTERISTICS

### Appendix II

Descriptive summary of the databases potentially available to the REG ACOS Working Group (through direct working group member contacts) in terms of: the type of data they hold, the country of origin, latest 12-month period for which data are available, number of the population definitions evaluable in them and approximate starting population for the “active” and control population series.

<table>
<thead>
<tr>
<th>Description of Information Requested</th>
<th>Type of Sample</th>
<th>Country</th>
<th>Source of data – Clinical Data (EMR) or Administrative Billing Data</th>
<th>Number of population definitions evaluatable</th>
<th>Number of unique patients with ID (ACOS, COPD, both of ACOS and COPD) in the latest 12-month period</th>
<th>Number of unique patients with ID (ACOS, COPD, both of ACOS and COPD) in the most recent year</th>
<th>Number of unique patients with ID (ACOS, COPD, both of ACOS and COPD) not cached for analysis, ACOS or COPD in the most recent year</th>
<th>Number of unique patients with ID (ACOS, COPD, both of ACOS and COPD) not cached for analysis, other than ACOS and COPD in the most recent year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutch ASHMA / COPD Index</td>
<td>Dutch Index</td>
<td>The Netherlands</td>
<td>Electronic Medical Records</td>
<td>12 of 12</td>
<td>Jan 2013 - Dec 2014</td>
<td>Author: 18644 COPD 5141 ACOS 2871</td>
<td>ACOS: 4436 COPD: 2711</td>
<td>Database contains data from 1 encounter or visit</td>
</tr>
<tr>
<td>Adapted Respiratory Disease Specific Prognostic</td>
<td>Consonerance sample of community patients seeking physician (both primary and specialist care settings)</td>
<td>France, Germany, Italy, Spain, UK, USA, Japan, China, Canada</td>
<td>Electronic Medical Records</td>
<td>12 of 12</td>
<td>Dec 2014 - Nov 2015</td>
<td>Author: 18644 COPD: 5171 ACOS: 4436</td>
<td>Database contains data from 1 encounter or visit</td>
<td>Author: 18644 COPD: 5171 ACOS: 4436</td>
</tr>
<tr>
<td>Optimum Patient Care Researcher’s Database</td>
<td>UK</td>
<td>United Kingdom</td>
<td>Electronic Medical Records</td>
<td>12 of 12</td>
<td>March 31, 2011 – April 1, 2012</td>
<td>Author: 18644 COPD: 15549 ACOS: 12364</td>
<td>ACOS: 15549 COPD: 12364</td>
<td>Database contains data from 1 encounter or visit</td>
</tr>
<tr>
<td>SIDAP</td>
<td>Sweden</td>
<td>Sweden</td>
<td>Electronic Medical Records</td>
<td>12 of 12</td>
<td>Jan 2013 – Dec 2013</td>
<td>Author: 18644 COPD: 17441 ACOS: 18161</td>
<td>ACOS: 17441 COPD: 18161</td>
<td>Database contains data from 1 encounter or visit</td>
</tr>
<tr>
<td>MajorDatas</td>
<td>Germany</td>
<td>Germany</td>
<td>Electronic Health Records</td>
<td>12 of 12</td>
<td>Jan 1, 2014 – Dec 31, 2014</td>
<td>Based on ICD code: COPD: 27174 ACOS: 3718</td>
<td>Based on ICD code: COPD: 27174 ACOS: 3718</td>
<td>Database contains data from 1 encounter or visit</td>
</tr>
<tr>
<td>POCHET Common Data Model</td>
<td>Population-based (pairs with at least one household member for every age group)</td>
<td>USA</td>
<td>Electronic Health Records</td>
<td>12 of 12</td>
<td>Jan 1, 2014 – Dec 31, 2014</td>
<td>All patients: 72,002,030碣brush injuries</td>
<td>All patients: 46,301,508碣brush injuries</td>
<td>Database contains data from 1 encounter or visit</td>
</tr>
<tr>
<td>HealthCore</td>
<td>Medicare claims data and beneficiaries; also includes individuals and families with Medicare Advantage and Medicare Part D coverage; includes Medicare enrollees with all Medicare Part D coverage</td>
<td>USA</td>
<td>Administrative/Billing Data</td>
<td>12 of 12</td>
<td>May 1, 2014 – May 1, 2015</td>
<td>Author: 18644 COPD: 64651 ACOS: 62980</td>
<td>Author: 18644 COPD: 64651 ACOS: 62980</td>
<td>Database contains data from 1 encounter or visit</td>
</tr>
<tr>
<td>MarketScan</td>
<td>Medicare Supplemental, and Medigap policies; 150 million members 18644</td>
<td>USA</td>
<td>Administrative/Billing Data</td>
<td>12 of 12</td>
<td>May 1, 2015 – May 1, 2016</td>
<td>Author: 18644 COPD: 13,532 ACOS: 11,867</td>
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APPENDIX IV. FLOW DIAGRAMS FOR EACH PARENT POPULATION

**POPULATION A**

Clinical diagnosis of COPD

\[ N = \]

Aged ≥ 40 years

\[ N = \] Subgroup A

Evidence of smoking

\[ N = \] Subgroup A1

Airflow obstruction (Post BD FEV₁ per cent predicted or FEV₁/FVC < 0.7)

\[ N = \] Subgroup A2

Airflow reversibility (≥12% and ≥200 mL increase in post-bronchodilator FEV₁)

\[ N = \] Subgroup A3

**Population Prevalence**

<table>
<thead>
<tr>
<th></th>
<th>A2/A x 100</th>
<th>%</th>
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<tbody>
<tr>
<td></td>
<td>A3/A x 100</td>
<td>%</td>
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</tbody>
</table>

**POPULATION B**

Clinical diagnosis of Asthma & COPD

\[ N = \]

Aged ≥ 40 years

\[ N = \] Subgroup B

Evidence of smoking

\[ N = \] Subgroup B1

Airflow obstruction (Post BD FEV₁ per cent predicted or FEV₁/FVC < 0.7)

\[ N = \] Subgroup B2

Airflow reversibility (≥12% and ≥200 mL increase in post-bronchodilator FEV₁)

\[ N = \] Subgroup B3

**Population Prevalence (%)**

<table>
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<th>B2/B x 100</th>
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<tr>
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<td>B3/B x 100</td>
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</table>
Asthma-COPD Overlap Syndrome: Definitions & Observational Research Tools

**POPULATION C**

- **n=** (Patient is <40 years)
- **n=** (No evidence of smoking – current or ex)
- **n=** (No airflow obstruction)
- **n=** (No airflow reversibility)

Clinical diagnosis of Asthma

Aged ≥ 40 years

Evidence of smoking

Airflow obstruction

Airflow reversibility

Subgroup C

Subgroup C1

Subgroup C2

Subgroup C3

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<td>C3/C x 100</td>
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</table>

**POPULATION D**

- **n=** (Patient is <40 years)
- **n=** (No evidence of smoking – current or ex)
- **n=** (No airflow obstruction)
- **n=** (No airflow reversibility)

Reference Population

Aged ≥ 40 years

Evidence of smoking

Airflow obstruction

Airflow reversibility

Subgroup D

Subgroup D1

Subgroup D2

Subgroup D3

<table>
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<th>Population Prevalence</th>
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