Drug utilisation studies using data mapped to the OMOP Common Data Model: a proof of concept study assessing respiratory drug use in patients with asthma or COPD.

Document Status: Final Version 1.0

Date of final version of the study report: 02/07/2021

EU PAS register number: 41726

Principal Investigators		
Name	**Email address**	**Affiliation**
Katia Verhamme	k.verhamme@erasmusmc.nl	Department of Medical Informatics Erasmus University Medical Center, NL
Aniek Markus	a.markus@erasmusmc.nl	Department of Medical Informatics Erasmus University Medical Center, NL
Edward Burn	edward.burn@ndorms.ox.ac.uk	NDORMS, University of Oxford, Oxford, UK, 2) Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain
Anthony Sena	asena5@its.jnj.com	Janssen Research and Development, Titusville, NJ, USA
Peter Rijnbeek	p.rijnbeek@erasmusmc.nl	Department of Medical Informatics Erasmus University Medical Center, NL

Patrick Ryan	PRyan4@its.jnj.com	Janssen Research and Development, Titusville, NJ, USA, 2) Columbia University, New York, NY, USA
Daniel Prieto-Alhambra	daniel.prietoalhambra@ndorms.ox.ac.uk	NDORMS, University of Oxford, Oxford, UK, 2) GREMPAL Research Group, Idiap Jordi Gol and CIBERFes, Universitat Autonoma de Barcelona and Instituto de Salud Carlos III, Barcelona, Spain

Amendments and updates

Protocol amendment	**Date protocol amendment**	**Reason protocol amendement**

Table of contents

1. Background

1.1. Rationale

The use of healthcare data, generated through the delivery of normal clinical care is increasingly being proposed as a source of evidence to support not only drug development and regulatory decision-making but also to understand the physiology and pathogenesis of diseases.

Use of multiple electronic health care databases is important not only to increase sample size but also to investigate country specific differences, differences by type of databases (e.g. primary vs. secondary care) or to replicate findings. One of the challenges however are the differences between the databases with regard to the underlying structures and semantic mapping. A common data model could help harmonise healthcare data across multiple data sets and provide a mechanism to allow the conduct of multi-database, international studies. [1]

The European Health Data and Evidence Network (EHDEN) project (https://www.ehden.eu/) is an international project supported by the Innovative Medicines Initiative (IMI) aiming to standardize health care data to the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM) and to develop and implement tools to facilitate research on large electronic health care databases.

One of the objectives of the EHDEN project is to test existing methodologies but also to develop new methodologies and analytical tools to conduct (pharmaco)epidemiological research using electronic health care databases mapped to the OMOP CDM. To investigate the validity and functionality of this approach, we want to conduct a drug-utilisation study using EHR data. As proof of concept study we want to conduct a drug utilisation studies on respiratory drug use in patients with asthma and chronic obstructive pulmonary disease (COPD). This research is important and relevant as asthma and COPD are prevalent conditions, primarily treated in primary care.

1.2. Research objectives

By means of a drug utilisation study we want to investigate:

- The frequency of respiratory drug use in terms of prevalence and incidence of use
- Treatment pathways in particular treatment step-up and treatment step-down
- To investigate switching between respiratory drugs
- To investigate treatment adherence to respiratory drugs by means of the Medication Possession Ratio (MPR) and the Proportion Days Covered (PDC)

- To investigate the Controller to Total ratio as a measure of asthma or COPD control

These objectives - specifically related to respiratory drugs - will allow us to explore – in a broader perspective:

- Existing drug utilisation techniques and methodologies
- Gaps in current drug utilisation techniques/methodologies hampering the fast conduct of drug utilisation studies
- The development of key graphical assets facilitating the interpretation of drug utilisation data.

2. Methods

2.1. Study design

The study will be a retrospective cohort study based on routine-collected health care data which has been mapped to the OMOP CDM.

2.2. Data Sources

Routine-collected health care data which has been mapped to the OMOP CDM.

2.3. Study Period

The study period, when index events can be observed, will end at the latest on 31/12/2020 for all data sources. The start date for the study period will be from 01/01/2010 or from the start of the first available observation periods in the data source with sufficient data quality to address the study questions whichever comes last.

2.4. Study participants

Three mutually exclusive cohorts will be created, namely a cohort of patients with a COPD diagnosis only, a cohort of patients with an asthma diagnosis only and finally a third cohort will consist of patients with both disease codes for asthma and COPD the so called “Asthma & COPD overlap” (ACO). [2] We only include patients with at least 1 year of prior continuous observation and 3 year follow-up database time since diagnosis. Selection of these cohorts will be done by selecting the concept IDs related to asthma, COPD and ACO as described in Appendix 1. The index date will be the date of the first diagnosis of the respective conditions. Patient will contribute follow-up time in this cohort from the date on which a patient is diagnosed until they leave the practice, death, or the end of the study period, whichever occurs first. Furthermore, we have split up the asthma cohort according to age. This results in the following five study populations: asthma >=18, asthma >= 6 & < 18, asthma <= 5, COPD >= 40 and ACO >= 40 (see Appendix 1 for complete definitions).

2.5. Variables

2.5.1. Exposure of interest

A drug utilisation record of a respiratory drugs will be identified on the basis of the records in the drug exposure table in the CDM (for details see Appendix 2). The drug exposure table contains records about the utilisation of drugs, which depending on the data source, may be inferred from a range of concepts, such as prescriptions, pharmacy dispensations, or patient

recollection. Drug exposure in the CDM is standardised to RxNorm concepts. This has as advantage that the drug exposure contains details of ingredients, strength, and formulation (Clinical Drug Level), which is not directly available from the ATC code.

2.5.2. Creation of drug eras

From the individual drug exposures, drug eras will be created. A Drug Era is defined as a span of time when the person is assumed to be exposed to a respiratory drug class. A Drug Era is not the same as a Drug Exposure: Exposures are individual records corresponding to the source when the drug was delivered to the person, while successive periods of Drug Exposure are combined under certain rules to produce continuous Drug Eras.

2.5.3. Patient characteristics at index date

A diagnosis of asthma, COPD or ACO will be required for defining the study cohorts. These will be identified on the basis of records in the condition occurrence table in the CDM (see Appendix 1). This table includes records which indicate the presence of a medical condition, typically based on the presence of diagnosis codes.

The main covariates of interest are age, gender and year of index date. Disease specific covariates of interest include: anxiety, allergic rhinitis, atopic disorders, chronic rhinosinusitis, depressive disorder, diabetes mellitus, gastroesophageal reflux disease, heart failure, hypertensive disorder, ischemic heart disease, lower respiratory tract infections, nasal polyposis, obesity, cerebrovascular disease and Charlson Comorbidity Index. For definitions see Appendix 3.

2.6. Follow-up time

Follow-up will start from the day of the index date.

2.7. Analytic methods

2.7.1. Prevalence and Incidence or Respiratory Drug Use

Drug use will be assessed per respiratory class as a whole presented as prevalent and incident drug use. For prevalent drug use, the nominator consists of all patients with at least one day of exposure to the drug of interest in the calendar year. The denominator consists of all patients contributing at least one day of observation time in that calendar year.
For the incidence drug use calculation, the nominator consists of the number of incident users in the year. An incident user is defined as a patient with a record of exposure of the drug class of interest and no exposure within the previous 365 days. The denominator again consists of

all patients contributing at least one day of observation time in that calendar year. This implies that an individual can be defined as an incident user on multiple occasions during the study period. Also, if a person switches between respiratory drug classes, they may show up as new user of a certain ingredient but be a prevalent user of the class.
Drug use, both for prevalent and incident users, will be expressed as the number of users per 1,000 persons presented by calendar year, age category (10 years), and sex.

2.7.2. Treatment pathways

This study will describe the treatment pathways (13) of patients diagnosed with asthma, COPD or ACO. The analysis will calculate the aggregate summary statistics for each diagnosis cohort (see Appendix 1) to determine the treatment pathway for each of the respiratory drugs in the study (see Appendix 2, a sensitivity analysis is performed for inhalers only).
For each of the cohorts, a sunburst diagram (14) is produced to describe the proportion of the respiratory drugs for each treatment sequence observed in the target population. The sunburst diagram will have a maximum of 5 levels and includes unique paths occurring at least 5 times. Drug eras starting after the index date of at least 5 days are included in the analysis (a sensitivity analysis is performed including drug eras up to 30 days before the index date and without a minimum number of days). Each respiratory drug exposure will be calculated using a gap of maximum 30 days between prescriptions/dispensings to combine exposures into a single continuous era of exposure. When different respiratory drug eras overlap for 30 days or longer, the analysis will combine these drug exposures into a single combination.
This analysis will provide information about the utilisation of all respiratory drugs as available in the contributing data source/s, allowing us to (i) summarise the most prevalent first-line therapies utilised, (ii) the proportion of individuals that discontinue treatment, switch treatments, or augment their therapy (see Appendix 4). Analyses will be performed separately for each data source.

2.7.3. Treatment adherence:

Adherence will be assessed using 2 measures of adherence namely the medication possession ratio (MPR) and the proportion days covered (PDC).
The MPR for each class of respiratory drugs will be calculated by dividing the total number of days' supply prescribed by the total days of follow-up, multiplied by 100, and expressed as a percentage:

$$MPR = (days\ of\ drug\ supply\ in\ period)/\ (last\ fill\ date - first\ fill\ date + last\ fill\ day's\ supply) \text{ x } 100$$

To calculate the MPR, the follow-up period is the interval between the first and last prescription of the drug of interest for that patient.

The proportion days covered is defined as the proportion of days in a fixed observation period where at least one of multiple medications is available.

$$PDC = (number\ of\ days\ in\ period\ covered)/\ (number\ of\ days\ in\ period)\ \text{x}\ 100$$

If for instance the follow-up period is 180 days and 30 of these days are covered by use of ICS and LABA as a combination of respiratory drugs, the PDC for ICS/LABA combination would be 30/180 thus 16%.

2.7.4. Asthma and COPD control:

The controller to total ratio (CTT), which is the number of controllers divided by the total number of medication, can be used as a proxy for asthma and COPD control.

$$\text{CTT}= (Units\ of\ controllers)/\ (Units\ of\ controllers + relievers)\ \text{x}\ 100$$

In patients with asthma, the controllers consist of ICS, ICS+LABA, LTRA, anti IgE, anti IL4 antagonist and anti IL5 antagonist or anti IL5 receptor blocker. Reliever therapy consists of SAMA, SABA or SAMA+SABA.

In patients with COPD, controller therapy includes LAMA, LABA, ICS, methylxanthines, and phosphodiesterase-4 enzyme inhibitors. Reliever medication includes SAMA, SABA or SAMA+SABA.

The CTR will be calculated in the 6 months, 12 months and 24 months following the index date (= date of the first diagnosis of the respective conditions).

Stanford et al. showed that a higher controller to total ratio is protective for exacerbations in COPD. [4] In patients with asthma, the same association has been described. [5]

2.7.5. PDD/DDD ratio, cumulative exposure and Cumulative annual dose

Dosing will be described by the median PDD (Prescribed Daily Dose)/DDD (Defined Daily Dose) ratio. The Cumulative exposure will be expressed by the cumulative duration, the cumulative dose (in mg and DDD) and cumulative annual dose (mg/PY).

To compare dosing between the different types of respiratory drugs, dosing will be expressed by the Prescribed Daily Dosage divided by the Defined Daily Dose (PDD/DDD Ratio). [6]. The PDD is the daily amount of a drug that is actually prescribed whereas the DDD is the maintenance dose per day for a drug product when used for its major indication in everyday practice. [7]

From the individual drug exposures, the cumulative exposure duration will be calculated which is the sum of the duration of the individual drug exposures (= drug eras) of an individual NOT taking into account gaps between exposures.
Next the cumulative dose will be calculated and will be expressed in three ways namely i) as the sum of the daily dose in mg (per individual respiratory drug), ii) as the sum of the number of DDDs over all drug exposures per respiratory drug class [8, 9] and iii) by the cumulative annual dose per respiratory drug class.

Descriptive statistics will be used to describe the characteristics of drug use and differences in prevalence and incidence rate will be tested my means of a Poisson Regression analysis (to check for the effect of age, sex and calendar time). Difference between continuous variables (for instance treatment adherence, controller to total ratio, …) will be tested by means of a non-parametrical test.

3. Study size

This study is a characterisation of all patient data captured in the data sets and meeting inclusion criteria for exposure to respiratory drugs. No hypothesis will be tested. Therefore, sample size calculation for the ability to reject the null hypothesis given an effect size will not be conducted.

4. Data Quality Checks

OHDSI and EHDEN have developed multiple quality control mechanisms for the Common Data Model. These are described in high detail in Chapter 15 of The Book of OHDSI (http://book.ohdsi.org/DataQuality.html). These quality control mechanisms are standard applied.
To assure the proper functionality of the software we will follow the best practices described in Chapter 17 of The Book of OHDSI (http://book.ohdsi.org/SoftwareValidity.html). This includes code review, the addition of unit tests where applicable, source code management, and full code documentation. The analytical pipeline of this study will be made available in opensource for full transparency and replicability.

5. Limitations of the research methods

First our study population consist of patients diagnosed with asthma, COPD or ACO based on the presence of disease codes. This is susceptible to selection/information bias in case of suboptimal coding or use of codes with less granularity.

Second, for this study we will use real world data from electronic health care records or claims data. There might exist differences between the databases with regard to availability of certain data (for instance information on dosing, duration of use, etc).

Third, if primary care databases are used, specialist prescribing (especially in patients with more severe respiratory conditions) will be lacking. This implies that use of certain respiratory drugs like monoclonal antibodies will be underrepresented.

6. Regulatory and ethical compliance

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology [10], the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct'.

7. Protection of human subjects

For this study, participants from various EU member states will process personal data from individuals which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All the databases used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to.

In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate non-identifiable aggregate summary results.

Prior to study initiation, the protocols will be reviewed by the Institutional Review Boards of the respective databases.

8. Management and reporting of adverse events/adverse reactions

According to the new guideline on good pharmacovigilance practice (EMA/873138/2011) there is no requirement for expedited reporting of adverse drug reactions from studies with secondary use of data (such as electronic health care databases).

9. Plans for disseminating and communicating study results

Dissemination activities to be undertaken will have mainly, although not exclusively, a scientific nature (articles, presentations at conferences, etc.).

10. References

1. Gini, R., et al., *Data Extraction and Management in Networks of Observational Health Care Databases for Scientific Research: A Comparison of EU-ADR, OMOP, Mini-Sentinel and MATRICE Strategies.* EGEMS (Wash DC), 2016. **4**(1): p. 1189.
2. Cosio, B.G., D. Dacal, and L. Perez de Llano, *Asthma-COPD overlap: identification and optimal treatment.* Ther Adv Respir Dis, 2018. **12**: p. 1753466618805662.
3. GOLD, *Pocket guide to COPD diagnosis, management and prevention.* 2017.
4. Stanford, R.H., et al., *Validation of a New Risk Measure for Chronic Obstructive Pulmonary Disease Exacerbation Using Health Insurance Claims Data.* Ann Am Thorac Soc, 2016. **13**(7): p. 1067-75.
5. Schatz, M., et al., *The controller-to-total asthma medication ratio is associated with patient-centered as well as utilization outcomes.* Chest, 2006. **130**(1): p. 43-50.
6. Grimmsmann, T. and W. Himmel, *Discrepancies between prescribed and defined daily doses: a matter of patients or drug classes?* Eur J Clin Pharmacol, 2011. **67**(8): p. 847-54.
7. WHO. *Guidelines for ATC classification and DDD assignment 2013*. 2012; Available from: http://www.whocc.no/filearchive/publications/1_2013guidelines.pdf.
8. Brozek, W., et al., *Higher dose but not low dose proton pump inhibitors are associated with increased risk of subsequent hip fractures after first hip fracture: A nationwide observational cohort study.* Bone Rep, 2019. **10**: p. 100204.
9. Coupland, C.A.C., et al., *Anticholinergic Drug Exposure and the Risk of Dementia: A Nested Case-Control Study.* JAMA Intern Med, 2019.
10. *Guidelines for good pharmacoepidemiology practice (GPP).* Pharmacoepidemiol Drug Saf, 2016. **25**(1): p. 2-10.

11. Appendix: Supplementary documents

11.1. Appendix 1 – Study Participants

1) Cohort definition: Asthma >=18
Initial Event Cohort:
People with continuous observation of 365 days before and 1,095 days after event may enter the cohort when observing any of the following:
- Condition occurrence of Asthma* for the first time in the person's history.

Inclusion Criteria:
- Age >= 18 years.
- No condition occurrences of COPD** in their history or during follow-up time.
- Index date starting after December 31, 2009 and ending before December 31, 2020.

Cohort Exit: the person exits the cohort at the end of continuous observation.

2) Cohort definition: Asthma >= 6 & < 18
Initial Event Cohort:
People with continuous observation of 365 days before and 1,095 days after event may enter the cohort when observing any of the following:
- Condition occurrence of Asthma* for the first time in the person's history.

Inclusion Criteria:
- 6 <= Age < 18 years.
- Index date starting after December 31, 2009 and ending before December 31, 2020.

Cohort Exit: the person exits the cohort at the end of continuous observation.

3) Cohort definition: Asthma <= 5
Initial Event Cohort:
People with continuous observation of 365 days before and 1,095 days after event may enter the cohort when observing any of the following:
- Condition occurrence of Asthma* for the first time in the person's history.

Inclusion Criteria:
- Age <= 5 years.
- Index date starting after December 31, 2009 and ending before December 31, 2020.

Cohort Exit: the person exits the cohort at the end of continuous observation.

4) Cohort definition: COPD >= 40
Initial Event Cohort:
People with continuous observation of 365 days before and 1,095 days after event may enter the cohort when observing any of the following:
- Condition occurrence of COPD** for the first time in the person's history.

Inclusion Criteria:
- Age >= 40 years.
- No condition occurrences of Asthma* in their history or during follow-up time.
- Index date starting after December 31, 2009 and ending before December 31, 2020.

Cohort Exit: the person exits the cohort at the end of continuous observation.

5) Cohort definition: ACO >= 40

Initial Event Cohort:

People with continuous observation of 365 days before and 1,095 days after event may enter the cohort when observing any of the following:
- Condition occurrence of COPD** for the first time in the person's history
    - with at least one condition occurrence of Asthma* all days before and 0 days after index start date.
- Condition occurrence of Asthma* for the first time in the person's history
    - with at least one condition occurrence of COPD** all days before and 0 days after index start date.

Inclusion Criteria:
- Age >= 40 years.
- Index date starting after December 31, 2009 and ending before December 31, 2020.

Cohort Exit: the person exits the cohort at the end of continuous observation.

* Asthma is defined by the following concept set:

Concept ID	Name	Class	Domain ID	Vocabulary
252658	Intrinsic asthma without status asthmaticus	Clinical Finding	Condition	SNOMED
256448	Chronic asthmatic bronchitis	Clinical Finding	Condition	SNOMED
257581	Exacerbation of asthma	Clinical Finding	Condition	SNOMED
312950	IgE-mediated allergic asthma	Clinical Finding	Condition	SNOMED
313236	Cough variant asthma	Clinical Finding	Condition	SNOMED
317009	Asthma	Clinical Finding	Condition	SNOMED
443801	Exercise-induced asthma	Clinical Finding	Condition	SNOMED
761844	Inhaled steroid-dependent asthma	Clinical Finding	Condition	SNOMED
764677	Persistent asthma	Clinical Finding	Condition	SNOMED
764949	Persistent asthma, well controlled	Clinical Finding	Condition	SNOMED
4015819	Asthma disturbs sleep weekly	Clinical Finding	Condition	SNOMED
4015947	Asthma causing night waking	Clinical Finding	Condition	SNOMED
4017025	Asthma disturbing sleep	Clinical Finding	Condition	SNOMED
4017026	Asthma not limiting activities	Clinical Finding	Condition	SNOMED
4017182	Asthma disturbs sleep frequently	Clinical Finding	Condition	SNOMED
4017183	Asthma not disturbing sleep	Clinical Finding	Condition	SNOMED
4017184	Asthma never disturbs sleep	Clinical Finding	Condition	SNOMED
4017293	Asthma never restricts exercise	Clinical Finding	Condition	SNOMED
4022592	Millers' asthma	Clinical Finding	Condition	SNOMED
4051466	Childhood asthma	Clinical Finding	Condition	SNOMED
4075237	Brittle asthma	Clinical Finding	Condition	SNOMED
4110051	Mixed asthma	Clinical Finding	Condition	SNOMED

Concept ID	Name	Class	Domain ID	Vocabulary
4119298	Late onset asthma	Clinical Finding	Condition	SNOMED
4120261	Sulfite-induced asthma	Clinical Finding	Condition	SNOMED
4123253	Hay fever with asthma	Clinical Finding	Condition	SNOMED
4125022	Acute asthma	Clinical Finding	Condition	SNOMED
4138760	Exacerbation of intermittent asthma	Clinical Finding	Condition	SNOMED
4141978	Intermittent asthma	Clinical Finding	Condition	SNOMED
4142738	Moderate persistent asthma	Clinical Finding	Condition	SNOMED
4143474	Bakers' asthma	Clinical Finding	Condition	SNOMED
4143828	Mild persistent asthma	Clinical Finding	Condition	SNOMED
4145356	Severe persistent asthma	Clinical Finding	Condition	SNOMED
4145497	Intrinsic asthma	Clinical Finding	Condition	SNOMED
4146581	Mild intermittent asthma	Clinical Finding	Condition	SNOMED
4152292	Asthma causes night symptoms 1 to 2 times per month	Clinical Finding	Condition	SNOMED
4152418	Asthma never causes daytime symptoms	Clinical Finding	Condition	SNOMED
4152420	Asthma treatment compliance unsatisfactory	Clinical Finding	Condition	SNOMED
4152911	Asthma causes daytime symptoms most days	Clinical Finding	Condition	SNOMED
4152913	Severe asthma	Clinical Finding	Condition	SNOMED
4155468	Mild asthma	Clinical Finding	Condition	SNOMED
4155469	Moderate asthma	Clinical Finding	Condition	SNOMED
4155470	Occasional asthma	Clinical Finding	Condition	SNOMED
4155473	Asthma treatment compliance satisfactory	Clinical Finding	Condition	SNOMED
4156136	Asthma causes daytime symptoms 1 to 2 times per month	Clinical Finding	Condition	SNOMED
4161595	Asthma daytime symptoms	Clinical Finding	Condition	SNOMED
4191479	Allergic asthma	Clinical Finding	Condition	SNOMED
4191827	Asthma night-time symptoms	Clinical Finding	Condition	SNOMED
4194289	Asthma - currently active	Clinical Finding	Condition	SNOMED
4206340	Asthma without status asthmaticus	Clinical Finding	Condition	SNOMED
4211530	Wood asthma	Clinical Finding	Condition	SNOMED
4212099	Occupational asthma	Clinical Finding	Condition	SNOMED
4217558	Detergent asthma	Clinical Finding	Condition	SNOMED
4225553	Cheese-makers' asthma	Clinical Finding	Condition	SNOMED
4225554	Isocyanate induced asthma	Clinical Finding	Condition	SNOMED
4232595	Platinum asthma	Clinical Finding	Condition	SNOMED
4245676	Chemical-induced asthma	Clinical Finding	Condition	SNOMED
4271333	Extrinsic asthma without status asthmaticus	Clinical Finding	Condition	SNOMED
4279553	Eosinophilic asthma	Clinical Finding	Condition	SNOMED
4301938	Tea-makers' asthma	Clinical Finding	Condition	SNOMED
4309833	Non-IgE mediated allergic asthma	Clinical Finding	Condition	SNOMED
4312524	Substance induced asthma	Clinical Finding	Condition	SNOMED
35609846	Life threatening acute exacerbation of extrinsic asthma	Clinical Finding	Condition	SNOMED
35609847	Life threatening acute exacerbation of non-allergic asthma	Clinical Finding	Condition	SNOMED
36674599	Asthma never causes night symptoms	Clinical Finding	Condition	SNOMED
36684328	Acute severe exacerbation of allergic asthma	Clinical Finding	Condition	SNOMED
36684335	Exacerbation of allergic asthma due to infection	Clinical Finding	Condition	SNOMED

Concept ID	Name	Class	Domain ID	Vocabulary
37108580	Severe controlled persistent asthma	Clinical Finding	Condition	SNOMED
37108581	Severe uncontrolled persistent asthma	Clinical Finding	Condition	SNOMED
37109103	Oral steroid-dependent asthma	Clinical Finding	Condition	SNOMED
37116845	Acute severe refractory exacerbation of asthma	Clinical Finding	Condition	SNOMED
40481763	Acute exacerbation of chronic asthmatic bronchitis	Clinical Finding	Condition	SNOMED
40483397	Seasonal asthma	Clinical Finding	Condition	SNOMED
42535716	Asthma in pregnancy	Clinical Finding	Condition	SNOMED
42536207	Life threatening acute exacerbation of asthma	Clinical Finding	Condition	SNOMED
42536208	Moderate acute exacerbation of asthma	Clinical Finding	Condition	SNOMED
42536649	Uncomplicated non-allergic asthma	Clinical Finding	Condition	SNOMED
42538744	Exacerbation of allergic asthma	Clinical Finding	Condition	SNOMED
42539549	Uncomplicated allergic asthma	Clinical Finding	Condition	SNOMED
43530693	Acute exacerbation of chronic obstructive airways disease with asthma	Clinical Finding	Condition	SNOMED
43530745	Asthma with irreversible airway obstruction	Clinical Finding	Condition	SNOMED
44805087	Asthma causes night time symptoms 1 to 2 times per week	Clinical Finding	Condition	SNOMED
44805089	Asthma causes symptoms most nights	Clinical Finding	Condition	SNOMED
44810117	Chronic asthma with fixed airflow obstruction	Clinical Finding	Condition	SNOMED
45766727	Allergic asthma due to Dermatophagoides pteronyssinus	Clinical Finding	Condition	SNOMED
45766728	Allergic asthma due to Dermatophagoides farinae	Clinical Finding	Condition	SNOMED
45768910	Uncomplicated asthma	Clinical Finding	Condition	SNOMED
45768911	Exacerbation of mild persistent asthma	Clinical Finding	Condition	SNOMED
45768912	Exacerbation of severe persistent asthma	Clinical Finding	Condition	SNOMED
45768963	Uncomplicated mild persistent asthma	Clinical Finding	Condition	SNOMED
45768964	Uncomplicated moderate persistent asthma	Clinical Finding	Condition	SNOMED
45768965	Uncomplicated severe persistent asthma	Clinical Finding	Condition	SNOMED
45769350	Acute severe exacerbation of severe persistent asthma	Clinical Finding	Condition	SNOMED
45769351	Acute severe exacerbation of moderate persistent asthma	Clinical Finding	Condition	SNOMED
45769352	Acute severe exacerbation of mild persistent asthma	Clinical Finding	Condition	SNOMED
45769438	Acute severe exacerbation of asthma	Clinical Finding	Condition	SNOMED
45769441	Acute exacerbation of allergic asthma	Clinical Finding	Condition	SNOMED
45769442	Acute severe exacerbation of allergic asthma	Clinical Finding	Condition	SNOMED
45769443	Acute severe exacerbation of intrinsic asthma	Clinical Finding	Condition	SNOMED
45771045	Acute exacerbation of asthma	Clinical Finding	Condition	SNOMED
45772937	Exacerbation of moderate persistent asthma	Clinical Finding	Condition	SNOMED
45773005	Acute exacerbation of intrinsic asthma	Clinical Finding	Condition	SNOMED
46269767	Acute severe exacerbation of asthma co-occurrent with allergic rhinitis	Clinical Finding	Condition	SNOMED
46269770	Severe persistent allergic asthma	Clinical Finding	Condition	SNOMED
46269771	Acute severe exacerbation of severe persistent asthma co-occurrent with allergic rhinitis	Clinical Finding	Condition	SNOMED

Concept ID	Name	Class	Domain ID	Vocabulary
46269772	Severe persistent allergic asthma controlled	Clinical Finding	Condition	SNOMED
46269773	Severe persistent asthma controlled co-occurrent with allergic rhinitis	Clinical Finding	Condition	SNOMED
46269774	Severe persistent allergic asthma uncontrolled	Clinical Finding	Condition	SNOMED
46269775	Severe persistent asthma uncontrolled co-occurrent with allergic rhinitis	Clinical Finding	Condition	SNOMED
46269776	Mild persistent allergic asthma	Clinical Finding	Condition	SNOMED
46269777	Acute severe exacerbation of mild persistent allergic asthma co-occurrent with allergic rhinitis	Clinical Finding	Condition	SNOMED
46269778	Mild persistent asthma controlled	Clinical Finding	Condition	SNOMED
46269779	Mild persistent asthma controlled co-occurrent with allergic rhinitis	Clinical Finding	Condition	SNOMED
46269780	Mild persistent allergic asthma uncontrolled	Clinical Finding	Condition	SNOMED
46269781	Mild persistent asthma uncontrolled	Clinical Finding	Condition	SNOMED
46269782	Mild persistent asthma uncontrolled co-occurrent with allergic rhinitis	Clinical Finding	Condition	SNOMED
46269783	Moderate persistent asthma controlled	Clinical Finding	Condition	SNOMED
46269784	Moderate persistent allergic asthma	Clinical Finding	Condition	SNOMED
46269785	Acute severe exacerbation of moderate persistent asthma co-occurrent with allergic rhinitis	Clinical Finding	Condition	SNOMED
46269786	Moderate persistent allergic asthma controlled	Clinical Finding	Condition	SNOMED
46269787	Moderate persistent controlled asthma co-occurrent with allergic rhinitis	Clinical Finding	Condition	SNOMED
46269788	Moderate persistent allergic asthma uncontrolled	Clinical Finding	Condition	SNOMED
46269789	Moderate persistent asthma uncontrolled co-occurrent with allergic rhinitis	Clinical Finding	Condition	SNOMED
46269790	Moderate persistent asthma uncontrolled	Clinical Finding	Condition	SNOMED
46269802	Chronic obstructive asthma co-occurrent with acute exacerbation of asthma	Clinical Finding	Condition	SNOMED
46270028	Severe persistent asthma co-occurrent with allergic rhinitis	Clinical Finding	Condition	SNOMED
46270029	Mild persistent asthma co-occurrent with allergic rhinitis	Clinical Finding	Condition	SNOMED
46270030	Intermittent asthma co-occurrent with allergic rhinitis	Clinical Finding	Condition	SNOMED
46270082	Acute exacerbation of mild persistent asthma	Clinical Finding	Condition	SNOMED
46270322	Intermittent asthma uncontrolled	Clinical Finding	Condition	SNOMED
46270573	Intermittent asthma well controlled	Clinical Finding	Condition	SNOMED
46273452	Acute exacerbation of asthma co-occurrent with allergic rhinitis	Clinical Finding	Condition	SNOMED
46273454	Moderate persistent asthma co-occurrent with allergic rhinitis	Clinical Finding	Condition	SNOMED
46273462	Acute severe exacerbation of moderate persistent allergic asthma	Clinical Finding	Condition	SNOMED
46273487	Acute exacerbation of moderate persistent asthma	Clinical Finding	Condition	SNOMED
46273635	Steroid dependent asthma	Clinical Finding	Condition	SNOMED
46274059	Acute severe exacerbation of severe persistent allergic asthma	Clinical Finding	Condition	SNOMED
46274060	Mild persistent allergic asthma controlled	Clinical Finding	Condition	SNOMED
46274124	Acute severe exacerbation of mild persistent allergic asthma	Clinical Finding	Condition	SNOMED
46287068	At risk of severe asthma exacerbation	Clinical Finding	Condition	SNOMED

Concept ID	Name	Class	Domain ID	Vocabulary
4057952	Meat-wrappers' asthma	Clinical Finding	Condition	SNOMED
4080516	Printers' asthma	Clinical Finding	Condition	SNOMED
4119300	Colophony asthma	Clinical Finding	Condition	SNOMED
46274062	Asthma-chronic obstructive pulmonary disease overlap syndrome	Clinical Finding	Condition	SNOMED

** COPD is defined by the following concept set:

Concept ID	Name	Class	Domain ID	Vocabulary
255573	Chronic obstructive lung disease	Clinical Finding	Condition	SNOMED
256448	Chronic asthmatic bronchitis	Clinical Finding	Condition	SNOMED
257004	Acute exacerbation of chronic obstructive airways disease	Clinical Finding	Condition	SNOMED
36685451	GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2017 group A	Clinical Finding	Condition	SNOMED
36685452	GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2017 group B	Clinical Finding	Condition	SNOMED
36685453	GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2017 group C	Clinical Finding	Condition	SNOMED
36685454	GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2017 group D	Clinical Finding	Condition	SNOMED
36685455	GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2017 spirometric grade 1	Clinical Finding	Condition	SNOMED
36685456	GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2017 spirometric grade 2	Clinical Finding	Condition	SNOMED
36685457	GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2017 spirometric grade 3	Clinical Finding	Condition	SNOMED
36685458	GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2017 spirometric grade 4	Clinical Finding	Condition	SNOMED
4046986	End stage chronic obstructive airways disease	Clinical Finding	Condition	SNOMED
4110056	Chronic obstructive pulmonary disease with acute lower respiratory infection	Clinical Finding	Condition	SNOMED
4115044	Acute infective exacerbation of chronic obstructive airways disease	Clinical Finding	Condition	SNOMED
4193588	Moderate chronic obstructive pulmonary disease	Clinical Finding	Condition	SNOMED
4196712	Mild chronic obstructive pulmonary disease	Clinical Finding	Condition	SNOMED
4209097	Severe chronic obstructive pulmonary disease	Clinical Finding	Condition	SNOMED
43530693	Acute exacerbation of chronic obstructive airways disease with asthma	Clinical Finding	Condition	SNOMED
44782563	Pulmonary hypertension due to chronic obstructive pulmonary disease	Clinical Finding	Condition	SNOMED
44788819	Mult COPD emerg hosp admission	Clinical Finding	Condition	SNOMED
44791725	Very severe chronic obstructive pulmonary disease	Clinical Finding	Condition	SNOMED
44807895	Acute non-infective exacerbation of chronic obstructive pulmonary disease	Clinical Finding	Condition	SNOMED
46269701	Chronic obstructive lung disease co-occurrent with acute bronchitis	Clinical Finding	Condition	SNOMED
46274062	Asthma-chronic obstructive pulmonary disease overlap syndrome	Clinical Finding	Condition	SNOMED

11.2. Appendix 2 – Respiratory Drugs

Patients prescribed either ICS, SABA, LABA, SAMA, LAMA, leukotriene modifier (LTRA), xanthines, systemic glucocorticosteroids, systemic B2 agonists, anti IgE, anti IL4 and anti IL5(R) treatment will be identified from the databases by an automated search on the respective RxNorm concepts of the prescription records/dispensing records in the respective databases.

The concept set for each drug class is build up according to the following steps:

1. Find all descendants of the selected concept ids
2. Filter out concept ids based on dose form (keep missing dose forms)
3. Filter out combinations (drugs with multiple ingredients) + manual removal of irrelevant concepts

In addition, we consider the following fixed combination classes: LABA-ICS, LABA-LAMA, LABA-LAMA-ICS, SABA-SAMA. These are identified by records containing multiple ingredients from the respective classes.

Drug class	ATC code	Ingredient	Concept ID	DDD	Included dose forms
ICS	R03BA01	beclomethasone	1115572	800 mcg	Inhalant, Inhalation Powder, Inhalation Solution, Inhalation Spray, Inhalation Suspension, Metered Dose Inhaler, Dry Powder Inhaler, Gas for Inhalation
	R03BA02	budesonide	939259	800 mcg	
	R03BA03	flunisolide	1196514	1000 mcg	
	R03BA05	fluticasone	1149380	600 mcg	
	R03BA07	mometasone	905233	400 mcg	
	R03BA08	ciclesonide	902938	160 mcg	
	R03BA04	betamethasone	920458	Not defined	
	R03BA06	triamcinolone	903963	Not defined	
	R03BA09	fluticasone furoate	Not available (falls under fluticasone)	Not defined	
SABA	R03AC02	salbutamol/albuterol	1154343	800 mcg	Inhalant, Inhalation Powder, Inhalation
	R03AC03	terbutaline	1236744	2000 mcg	

	R03AC04	fenoterol	19053979	600 mcg	Solution, Inhalation Spray, Inhalation Suspension, Metered Dose Inhaler, Dry Powder Inhaler, Gas for Inhalation
	R03AC05	rimiterol	19063387	1600 mcg	
	R03AC06	hexoprenaline	19068969	1500 mcg	
	R03AC07	isoetharine	1181809	Not defined	
	R03AC08	pirbuterol	1125449	1200 mcg	
	R03AC09	trimetoquinol hydrochloride hydrate	35198052	Not defined	
	R03AC10	carbuterol	40798689	Not defined	
	R03AC15	reproterol	19035396	Not defined	
	R03AC16	procaterol	19028950	60 mcg	
	R03AC17	bitolterol	1138050	Not defined	
LABA	R03AC11	tulobuterol	19043191	1600 mcg	Inhalant, Inhalation Powder, Inhalation Solution, Inhalation Spray, Inhalation Suspension, Metered Dose Inhaler, Dry Powder Inhaler, Gas for Inhalation
	R03AC12	salmeterol	1137529	100 mcg	
	R03AC13	formoterol	1196677	24 mcg	
	R03AC14	clenbuterol	19097824	Not defined	
	R03AC18	indacaterol	40240664	150 mcg	
	R03AC19	olodaterol	45775116	5 mcg	
	Not available	vilanterol	43532539	Not defined	
SAMA	R03BB01	ipratropium	1112921	120 mcg	Inhalant, Inhalation Powder, Inhalation Solution, Inhalation Spray, Inhalation Suspension, Metered Dose Inhaler, Dry Powder Inhaler, Gas for Inhalation
	R03BB02	oxitropium	19018882	600 mcg for inhalation aerosol, 4000 mcg for inhalation solution	
LAMA	R03BB04	tiotropium	1106776	10 mcg (DPI) 5 mcg (soft mist inhaler)	Inhalant, Inhalation Powder, Inhalation Solution, Inhalation Spray, Inhalation
	R03BB05	aclidinium	42873639	644 mcg	
	R03BB06	glycopyrronium	45775571	44 mcg	

	R03BB07	umeclidinium	44785907	55 mcg	Suspension, Metered Dose Inhaler, Dry Powder Inhaler, Gas for Inhalation
LTRA	R03DC01	zafirlukast	1111706	40 mg	Buccal Tablet, Delayed Release Oral Tablet, Disintegrating Oral Tablet, Chewable Tablet, Delayed Release Oral Capsule, Extended Release Oral Tablet, Extended Release Suspension, Oral Capsule, Oral Gel, Oral Granules, Oral Lozenge, Oral Ointment, Oral Paste, Oral Powder, Oral Solution, Oral Suspension, Effervescent Oral Tablet, Extended Release Oral Capsule, Powder for Oral Suspension, Sublingual Tablet, Tablet for Oral Suspension, Oral Tablet, Pack
	R03DC02	pranlukast hydrate	43009065	Not defined	
	R03DC03	montelukast	1154161	10 mg	
	R03DC04	ibudilast	43009091	Not defined	
Xanthines	R03DA01	diprophylline/dyphylline	1140088	1 g	Buccal Tablet, Delayed Release Oral Tablet, Disintegrating Oral Tablet, Chewable Tablet, Delayed Release Oral Capsule, Extended Release Oral Tablet, Extended Release Suspension, Oral Capsule, Oral Gel, Oral
	R03DA02	choline theophyllinate	1195334	600 mg	
	R03DA03	proxyphylline	19029547	1.2 g	
	R03DA04	theophylline	1237049	400 mg	
	R03DA05	aminophylline	1105775	600 mg	
	R03DA06	etamiphyllin	40798802	Not defined	
	R03DA07	theobromine	19137056	Not defined	
	R03DA08	bamifylline	19018518	Not defined	

	R03DA09	acefylline piperazine	40798596	Not defined	Granules, Oral Lozenge, Oral Ointment, Oral Paste, Oral Powder, Oral Solution, Oral Suspension, Effervescent Oral Tablet, Extended Release Oral Capsule, Powder for Oral Suspension, Sublingual Tablet, Tablet for Oral Suspension, Oral Tablet, Pack
	R03DA10	bufylline	Not available	Not defined	
	R03DA11	doxofylline	43009019	800 mg	
Systemic glucocorticosteroids	H02AB01	betamethasone	920458	1.5 mg	Injectable Solution, Injectable Suspension, Auto-Injector, Intravenous Solution, Prefilled Syringe, Injection, Intramuscular Solution, Buccal Tablet, Delayed Release Oral Tablet, Disintegrating Oral Tablet, Chewable Tablet, Delayed Release Oral Capsule, Extended Release Oral Tablet, Extended Release Suspension, Oral Capsule, Oral Gel, Oral Granules, Oral Lozenge, Oral Ointment, Oral Paste, Oral Powder, Oral Solution, Oral Suspension, Effervescent Oral Tablet, Extended Release Oral Capsule,
	H02AB02	dexamethasone	1518254	1.5 mg	
	H02AB03	fluocortolone	19055344	10 mg	
	H02AB04	methylprednisolone	1506270	7.5 mg	
	H02AB05	paramethasone	19027186	4 mg	
	H02AB06	prednisolone	1550557	10 mg	
	H02AB07	prednisone	1551099	10 mg	
	H02AB08	triamcinolone	903963	7.5 mg	
	H02AB09	hydrocortisone	975125	30 mg	
	H02AB10	cortisone	1507705	37.5 mg	
	H02AB11	prednylidene	19011127	12 mg	
	H02AB12	rimexolone	977421	Not defined	
	H02AB13	deflazacort	19086888	15 mg	
	H02AB14	cloprednol	19050907	Not defined	
	H02AB15	meprednisone	19009116	Not defined	
	H02AB17	cortivazol	19061907	Not defined	
	H02AB90	flumetasone	19055156	Not defined	

					Powder for Oral Suspension, Sublingual Tablet, Tablet for Oral Suspension, Oral Tablet, Pack
Systemic B2 agonist	R03CC02	albuterol	1154343	12 mg	Injectable Solution, Injectable Suspension, Auto-Injector, Intravenous Solution, Prefilled Syringe, Injection, Intramuscular Solution, Buccal Tablet, Delayed Release Oral Tablet, Disintegrating Oral Tablet, Chewable Tablet, Delayed Release Oral Capsule, Extended Release Oral Tablet, Extended Release Suspension, Oral Capsule, Oral Gel, Oral Granules, Oral Lozenge, Oral Ointment, Oral Paste, Oral Powder, Oral Solution, Oral Suspension, Effervescent Oral Tablet, Extended Release Oral Capsule, Powder for Oral Suspension, Sublingual Tablet, Tablet for Oral Suspension, Oral Tablet, Pack
	R03CC03	terbutaline	1236744	15 mg	
	R03CC04	fenoterol	19053979	10 mg	
	R03CC05	hexoprenaline	19068969	1.5 mg	
	R03CC06	isoetharine	1181809	40 mg	
	R03CC07	pirbuterol	1125449	30 mg	
	R03CC08	procaterol	19028950	0.1 mg	
	R03CC09	trimetoquinol hydrochloride hydrate	35198052	9 mg	
	R03CC10	carbuterol	40798689	6 mg	
	R03CC11	tulobuterol	19043191	4 mg	
	R03CC12	bambuterol	19034275	20 mg	
	R03CC13	clenbuterol	19097824	40 mcg	
	R03CC14	reproterol	19035396	Not defined	
Anti IgE	R03DX05	omalizumab	1110942	16 mg	Injectable Solution, Injectable Suspension,

					Auto-Injector, Intravenous Solution, Prefilled Syringe, Injection, Intramuscular Solution
Anti IL4R	D11AH05	dupilumab	1593467	21.4 mg	Injectable Solution, Injectable Suspension, Auto-Injector, Intravenous Solution, Prefilled Syringe, Injection, Intramuscular Solution
Anti IL5(R)	R03DX08	reslizumab	35603983	7.1 mg	Injectable Solution, Injectable Suspension, Auto-Injector, Intravenous Solution, Prefilled Syringe, Injection, Intramuscular Solution
	R03DX09	mepolizumab	35606631	3.6 mg	
	R03DX10	benralizumab	792993	0.54 mg	
PDE4	R03DX07	roflumilast	40236897	500 mcg	Buccal Tablet, Delayed Release Oral Tablet, Disintegrating Oral Tablet, Chewable Tablet, Delayed Release Oral Capsule, Extended Release Oral Tablet, Extended Release Suspension, Oral Capsule, Oral Gel, Oral Granules, Oral Lozenge, Oral Ointment, Oral Paste, Oral Powder, Oral Solution, Oral Suspension, Effervescent Oral Tablet, Extended Release Oral Capsule, Powder for Oral Suspension, Sublingual

					Tablet, Tablet for Oral Suspension, Oral Tablet, Pack

*= DDD for combinations equals the DDD of the individual ingredients

11.3. Appendix 3 – Definition patient characteristics

Name	Concept IDs (any time prior through 0 days relative to index)
Gender (Male)	-
Age (in years)	-
Charlson comorbidity index score	-
Atopic disorders	133834
Gastroesophageal reflux disease	318800,765110,4046097,4076267,4144111,4159148,4159156, 36687117,36712768,36712969,36713492,36713493,42535063
Diabetes mellitus	201820
Obesity	433736
Chronic rhinosinusitis (allergic fungal sinusitis, chronic rhinitis, chronic sinusitis)	132932,134661,134668,139841,257012,259848,761761,761762, 765276,4048184,4048185,4051475,4051486,4051487,4051488, 4110027,4110489,4110490,4112365,4112367,4112497,4112498, 4112529,4145495,4173466,4179673,4181738,4230641,4247588, 4288156,4316066,4316067,4322228
Allergic rhinitis	257007
Nasal polyposis	42537251
Anxiety	441542
Depressive disorder	440383
Inflammatory disorder of lower respiratory tract (previous year) (labeled in protocol as Lower Respiratory Tract Infection (LRTI))	4028876
Hypertensive disorder	316866
Heartfailure	316139
Ischemic heart disease (angina pectoris and/or myocardial infarction)	4185932
Cerebrovascular disease (stroke and/or TIA)	381591
Smoking	- Smoking status (40766362): current (4034855) or past (4132507) - Current smoker (40766945), ex-smoker (4310250), tobacco user (40058233) - Tobacco dependence syndrome (437264)

Details of Concept IDs can be found on https://athena.ohdsi.org/

11.4. Appendix 4 – Definition augment/switch treatments

We label switches between treatments with two definitions:

1. A narrow definition following guideline recommendations. This results in a clean definition, but leads to undefined switches due to heterogeneity of observational data.

Definition following GINA guidelines - Asthma:

SABA	SABA+SAMA	step up
SABA	ICS+SABA	step up
SABA	ICS	step up
SABA	LTRA	step up
SAMA	SABA+SAMA	step up
SAMA	ICS+SABA	step up
SAMA	ICS	step up
SAMA	LTRA	step up
ICS	ICS+LABA	step up
ICS	ICS+LAMA	step up
ICS	ICS+LTRA	step up
ICS+LABA	ICS+LABA+LAMA	step up
ICS+LABA	ICS+LABA+Systemic glucocorticoids (therapy)	step up
ICS+LABA	Anti IgE+ICS+LABA	step up
ICS+LABA	Anti IL5(R)+ICS+LABA	step up
ICS+LABA	Anti IL4R+ICS+LABA	step up
ICS+LTRA	ICS+LABA+LAMA	step up
ICS+LTRA	ICS+LABA+LAMA	step up
ICS+LTRA	ICS+LABA+Systemic glucocorticoids (therapy)	step up
ICS+LTRA	Anti IgE+ICS+LABA	step up
ICS+LTRA	Anti IL5(R)+ICS+LABA	step up
ICS+LTRA	Anti IL4R+ICS+LABA	step up
SABA	SAMA	switching
SAMA	SABA	switching
ICS	LTRA	switching
LTRA	ICS	switching
ICS+LABA	ICS+LTRA	switching
ICS+LTRA	ICS+LABA	switching
ICS+LABA	ICS+LAMA	switching
ICS+LAMA	ICS+LABA	switching
ICS+LABA+LAMA	ICS+LABA+Systemic glucocorticoids (therapy)	switching
ICS+LABA+LAMA	Anti IgE+ICS+LABA	switching

ICS+LABA+LAMA	Anti IL5(R)+ICS+LABA	switching
ICS+LABA+LAMA	Anti IL4R+ICS+LABA	switching
ICS+LABA+Systemic glucocorticoids (therapy)	ICS+LABA+LAMA	switching
ICS+LABA+Systemic glucocorticoids (therapy)	Anti IgE+ICS+LABA	switching
ICS+LABA+Systemic glucocorticoids (therapy)	Anti IL5(R)+ICS+LABA	switching
ICS+LABA+Systemic glucocorticoids (therapy)	Anti IL4R+ICS+LABA	switching
Anti IgE+ICS+LABA	ICS+LABA+Systemic glucocorticoids (therapy)	switching
Anti IgE+ICS+LABA	Anti IL5(R)+ICS+LABA	switching
Anti IgE+ICS+LABA	Anti IL4R+ICS+LABA	switching
Anti IL5(R)+ICS+LABA	ICS+LABA+LAMA	switching
Anti IL5(R)+ICS+LABA	Anti IgE+ICS+LABA	switching
Anti IL5(R)+ICS+LABA	Anti IL4R+ICS+LABA	switching
Anti IL4R+ICS+LABA	ICS+LABA+Systemic glucocorticoids (therapy)	switching
Anti IL4R+ICS+LABA	ICS+LABA+LAMA	switching
Anti IL4R+ICS+LABA	Anti IgE+ICS+LABA	switching
Anti IL4R+ICS+LABA	Anti IL5(R)+ICS+LABA	switching
SABA+SAMA	SABA	step down
ICS+SABA	SABA	step down
ICS	SABA	step down
LTRA	SABA	step down
SABA+SAMA	SAMA	step down
ICS+SABA	SAMA	step down
ICS	SAMA	step down
LTRA	SAMA	step down
ICS+LABA	ICS	step down
ICS+LAMA	ICS	step down
ICS+LTRA	ICS	step down
ICS+LABA+LAMA	ICS+LABA	step down
ICS+LABA+Systemic glucocorticoids (therapy)	ICS+LABA	step down
Anti IgE+ICS+LABA	ICS+LABA	step down
Anti IL5(R)+ICS+LABA	ICS+LABA	step down
Anti IL4R+ICS+LABA	ICS+LABA	step down
ICS+LABA+LAMA	ICS+LTRA	step down
ICS+LABA+LAMA	ICS+LTRA	step down
ICS+LABA+Systemic glucocorticoids (therapy)	ICS+LTRA	step down
Anti IgE+ICS+LABA	ICS+LTRA	step down
Anti IL5(R)+ICS+LABA	ICS+LTRA	step down

Anti IL4R+ICS+LABA	ICS+LTRA	step down

Definition following GOLD guidelines - COPD:

SABA	SABA+SAMA	step up
SABA	LABA	step up
SABA	LAMA	step up
SABA	Xanthines	step up
SAMA	SABA+SAMA	step up
SAMA	LABA	step up
SAMA	LAMA	step up
SAMA	Xanthines	step up
LABA	LABA+LAMA	step up
LABA	ICS+LABA	step up
LABA	ICS+LAMA	step up
LAMA	LABA+LAMA	step up
LAMA	ICS+LABA	step up
LAMA	ICS+LAMA	step up
Xanthines	LABA+LAMA	step up
Xanthines	ICS+LABA	step up
Xanthines	ICS+LAMA	step up
LABA+LAMA	ICS+LABA+LAMA	step up
ICS+LABA	ICS+LABA+LAMA	step up
ICS+LABA	ICS+LABA+PDE4	step up
ICS+LAMA	ICS+LABA+LAMA	step up
SABA	SAMA	switching
SAMA	SABA	switching
LABA	LAMA	switching
LABA	Xanthines	switching
LAMA	LABA	switching
LAMA	Xanthines	switching
Xanthines	LABA	switching
Xanthines	LAMA	switching
LABA+LAMA	ICS+LABA	switching
LABA+LAMA	ICS+LAMA	switching
ICS+LABA	LABA+LAMA	switching
ICS+LABA	ICS+LAMA	switching
ICS+LAMA	LABA+LAMA	switching
ICS+LAMA	ICS+LABA	switching
ICS+LABA+LAMA	ICS+LABA+PDE4	switching
ICS+LABA+PDE4	ICS+LABA+LAMA	switching
SABA+SAMA	SABA	step down

LABA	SABA	step down
LAMA	SABA	step down
Xanthines	SABA	step down
SABA+SAMA	SAMA	step down
LABA	SAMA	step down
LAMA	SAMA	step down
Xanthines	SAMA	step down
LABA+LAMA	LABA	step down
ICS+LABA	LABA	step down
ICS+LAMA	LABA	step down
LABA+LAMA	LAMA	step down
ICS+LABA	LAMA	step down
ICS+LAMA	LAMA	step down
LABA+LAMA	Xanthines	step down
ICS+LABA	Xanthines	step down
ICS+LAMA	Xanthines	step down
ICS+LABA+LAMA	LABA+LAMA	step down
ICS+LABA+LAMA	ICS+LABA	step down
ICS+LABA+PDE4	ICS+LABA	step down
ICS+LABA+LAMA	ICS+LAMA	step down

2. Broad definition categorizing all possible switches by defining drug class levels and subsequent patient treatment levels (sum of drug class levels received by a patient).

Labels:

- Step up
- Step down
- Switching
- Start/end of acute exacerbation
- Off label use*
    - Not conform (off label AND counterindication)**
- Stopped

Drug class levels:

	For asthma	**For COPD**	**For ACO**
Level 0 (relievers)	SABA SAMA Systemic B2 agonist	SABA SAMA Systemic B2 agonist	SABA SAMA Systemic B2 agonist
Level 1	ICS LTRA PDE4* Xanthines	 LABA LAMA Xanthines	ICS LTRA PDE4 Xanthines
Level 2	LABA**	ICS	LABA

	LAMA**	LTRA* PDE4	LAMA
Level 3	Systemic glucocorticosteroids (therapy) Biologic: Anti IgE Anti IL4R Anti IL5(R)	Systemic glucocorticosteroids (therapy) Biologic: Anti IgE* Anti IL4R* Anti IL5(R)*	Systemic glucocorticosteroids (therapy) Biologic: Anti IgE Anti IL4R Anti IL5(R)

Patient treatment levels:

Sum of drug class levels received determines patient treatment level (capped at level 4), for examples see table below:

	For asthma
Level 0	SABA, SAMA, SABA + SAMA
Level 1	ICS, LTRA, ICS+SABA,
Level 2	ICS+LTRA
Level 3	ICS+LABA, ICS+LAMA, Systemic glucocorticoids
Level 4	LABA + LAMA, ICS+LABA+LTRA, ICS+LAMA+LTRA, ICS+Systemic glucocorticosteroids, LTRA+ Systemic glucocorticosteroids
Level 5	ICS+LABA+LAMA
Level 6+	ICS+LABA+LAMA+LTRA (6), ICS+LABA+LAMA+Systemic glucocorticosteroids (8), ICS+LABA+LAMA+Biologic (8) …

Rules to give labels (order of coding -> later rules 'overrule' the earlier):

- To higher patient treatment level = step up
- To lower patient treatment level = step down
- To same patient treatment level = switching

- To 'Systemic glucocorticoids (acute)' = start of exacerbation
- From 'Systemic glucocorticoids (acute)' = end of exacerbation

- To PDE4 for asthma = off label
- To LTRA, Anti IgE, Anti IL4R, Anti IL5 for COPD = off label

- To LABA (without ICS), LAMA (without ICS) for asthma = not conform

- To "End" = stopped

11.5. Appendix 5 – ENCePP checklist for study protocols

Study title: Drug utilisation studies using data mapped to the OMOP Common Data Model: a proof of concept study assessing respiratory drug use in patients with asthma or COPD

EU PAS Register® number: 41726 **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	2. Methods
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☐	☐	☒	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	Page 2 – Research objectives
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	2.1. Study design
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	2.2. Data sources
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	2.7. Analytic methods
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	2.4. Study participants
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	2. Methods
	4.2.2 Age and sex	☒	☐	☐	
	4.2.3 Country of origin	☒	☐	☐	
	4.2.4 Disease/indication	☒	☐	☐	
	4.2.5 Duration of follow-up	☒	☐	☐	
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	2.4. Study population

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	2.5. Variables
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	2.5. Variables
5.3	Is exposure categorised according to time windows?	☒	☐	☐	2.5.2. Drug eras
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	2.7.5. PDD/ DDD ratio, cumulative exposure and Cumulative annual dose
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☐	☐	☒	
6.2	Does the protocol describe how the outcomes are defined and measured?	☐	☐	☒	
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	5. Limitations of research – limitations of research
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	5. Limitations of research – limitations of research
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	5. Limitations of research – limitations of research

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				2.2. Data sources
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	2.2. Data sources
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☐	☐	☒	
9.1.3 Covariates and other characteristics?	☒	☐	☐	2.2. Data sources
9.2 Does the protocol describe the information available from the data source(s) on:				2.2. Data sources
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	2.5.1. Exposure of interest
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	2.5.3. Patient characteristics
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	2.5.1. Exposure of interest
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☒	☐	☐	2.5.3. Patient characteristics
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	2.7. Analytic methods
10.2 Is study size and/or statistical precision estimated?	☒	☐	☒	3. Study size
10.3 Are descriptive analyses included?	☒	☐	☐	2.7. Analytic methods
10.4 Are stratified analyses included?	☒	☐	☐	2.7. Analytic methods
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	2.7.2. Treatment pathway

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.4. Data quality check
11.2 Are methods of quality assurance described?	☒	☐	☐	8.4. Data quality check

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	8.4. Data quality check

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	5. Limitations
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☒	☐	

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	6. Regulatory and ethical compliance
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	6. Regulatory and ethical compliance
13.3 Have data protection requirements been described?	☒	☐	☐	7. Protection of human subjects

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	Page 2 – Amendment to the study protocol

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	9. Plans for dissemination and communicating of study results
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	9. Plans for dissemination and communicating of study results

Comments:

Name of the main author of the protocol: Katia Verhamme

Date: 30th/June/2021

Signature: