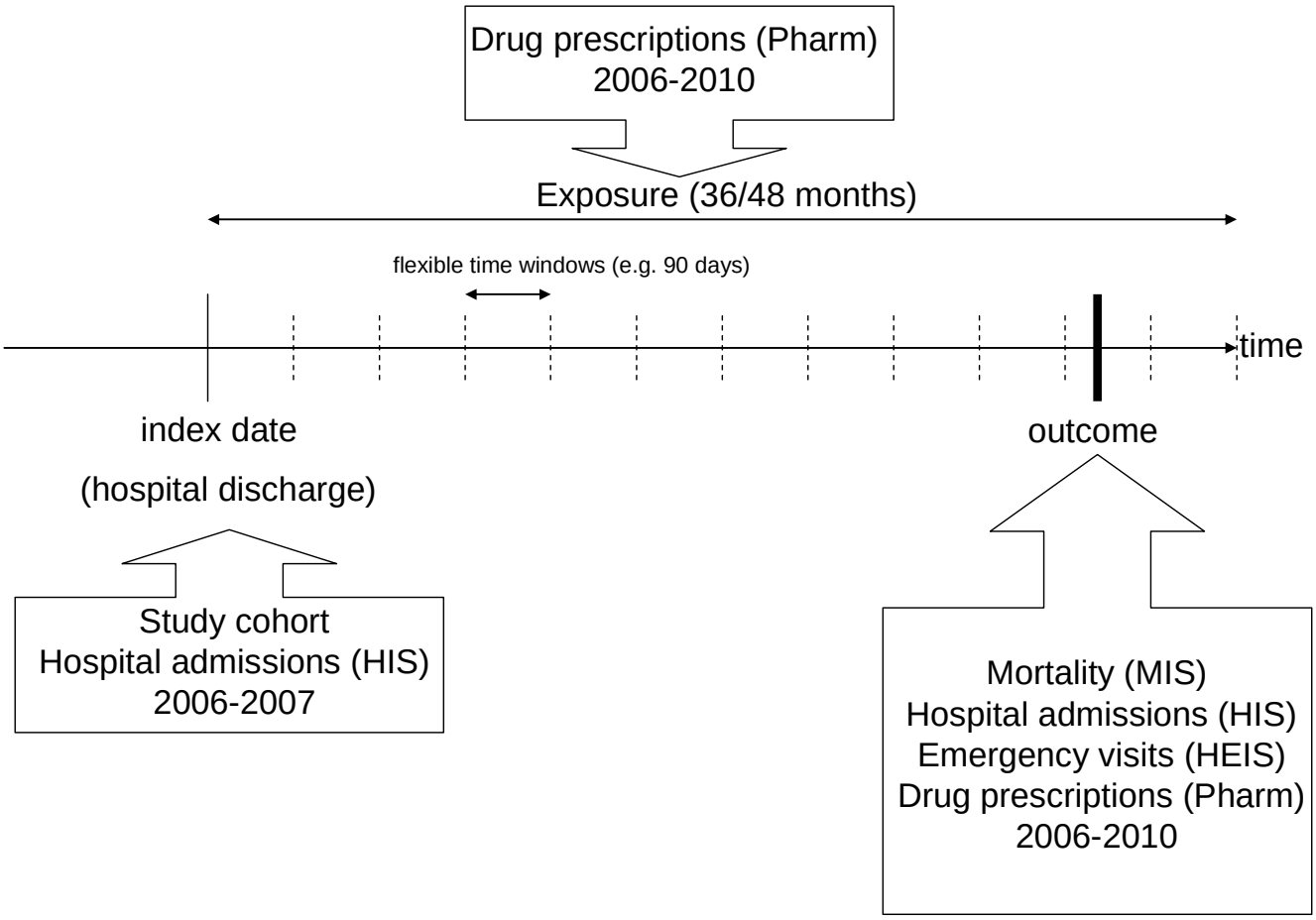
ANNEX SECTION

PART A - Study design: Figure 1 – overview of the study design



PART B – Data sources

1. The Mortality Information System (**MIS**), which includes information on demographic characteristics (name, age, gender, fiscal code, place and date of birth, residence, marital status, occupation), as well as date, place and cause of death, coded according to the International Classification of disease, Ninth Revision (ICD-9-CM codes).

2. The Hospital Information System (**HIS**), which includes information on patients' characteristics (patient fiscal code, gender, date and place of birth, place of residence), admission and discharge dates, discharge diagnoses (up to 6) and procedure codes (up to 6 ICD-9-CM codes), ward(s) of stay, date(s) of in-hospital transfer, and a regional code corresponding to the admitting facility.

3. The Healthcare Emergency Information System (**HEIS**) collects all ED-visit records in the region and includes information on patients' characteristics, four categories of patient severity based on triage (red, yellow, green, white), main diseases, some clinical parameters, performed treatments, diagnoses at discharge (most of information is coded by ICD-9-CM codes).

4. The drug dispense registry (**Pharm**), which comprises individual records for each medical prescription dispensed in public and private pharmacies belonging to the territory of the local health authorities and referring to the resident population. The registry is limited to those drugs which are reimbursed by the health care system referring to outpatients. The drugs in study are all belonging to class A. Drugs are identified by the national drug register code, which refers to the international ATC classification and allows for the exact quantification of the dispensed drug. Individual patient data (patient fiscal code) and date of drug dispense are reported for every prescription.

PART C – Study population: Criteria for cohort selection and ICD-9-CM codes *(data source: HIS)*

Inclusion criteria:

Diagnosis	**ICD-D-CM codes**
Main diagnosis COPD	490 (bronchitis, not specified as acute or chronic) 491 (chronic bronchitis) 492 (emphysema) 494 (bronchiectasis) 496 (chronic airway obstruction, not elsewhere classified)
Main diagnosis of COPD-related causes AND secondary diagnosis of COPD	518.81- 518.84 (respiratory failure) OR 786.0 (dyspnoea and other respiratory distress) 786.2 (cough) OR 786.4 (abnormal sputum) AND 490 or 491 or 492 or 494 or 496 (COPD)

Exclusion criteria:

secondary diagnosis of major trauma (ICD-9-CM = 484-487)
major surgeries during the index event (surgical DRG excluding 482 and 483).

PART D – Exposure

Types of exposure

Main exposure is intake of drugs belonging to the following ATC groups:
R03AC Selective beta-2-adrenoreceptor agonists
R03AH Combinations of adrenergics*
R03AK Adrenergics and other drugs for obstructive airway diseases
R03BA Glucocorticoids (inhaled)
R03BB Anticholinergics

* at present not on market in Italy

Comparisons will be made between drug users and non users (=control group), as follows:
1. inhaled long-acting beta-2-agonists

Users: patients using (minimum prescription pattern to be defined) one of the following ATCs:
R03AC12 salmeterol
R02AC13 formoterol
R03AK03 fenoterol plus ipratropium bromide
R03AK04 salbutamol plus beclometason
R03AK04 salbutamol plus flunisolid
R03AK04 salbutamol plus ipratropium bromide
R03AK06 salmeterol plus fluticason
R03AK07 formoterol plus beclometason
R03AK07 formoterol plus budesonid

Stratified analysis will account for use of single or combined drugs.

Control group: patients treated with any drug not belonging to the R03AC or R03AK groups, including treatment with anticholinergics and/or inhaled corticosteroids, or not treated.

2. inhaled anticholinergics
Users: patients using (minimum prescription pattern to be defined) one of the following ATCs:
R03BB01 ipratropium bromide
R03BB02 oxitropium bromide
R03BB04 tiotropium bromide
R03AK03 fenoterol plus ipratropium bromide
R03AK04 salbutamol plus ipratropium bromide

Stratified analysis will account for use of single or combined drugs.

Control group: patients treated with any drug not belonging to the R03BB group, R03AK03 or R03AK04, including treatment with beta-2-agonsits and/or inhaled corticosteroids, or not treated.

3. inhaled corticosteroids
Users: patients using (minimum prescription pattern to be defined) drugs belonging to the ATC:
R03BA inhaled Glucocorticoids
R03AK04 salbutamol plus beclometason
R03AK04 salbutamol plus flunisolid
R03AK06 salmeterol plus fluticason

R03AK07 formoterol plus beclometason
R03AK07 formoterol plus budesonid

Stratified analysis will account for use of single or combined drugs.

Control group: patients treated with any drug not belonging to the R03BA group, R03AK04 (salbutamol plus beclometason, salbutamol plus flunisolid), R03AK06, R03AK07 including treatment with beta-2-agonsits and/or anticholinergics, or not treated.

Exposure assessment

The following issues will be addressed in exposure assessment:

1. *Immortal time bias*: in order to give the same opportunity of exposure to both cases and non-cases, it is suggested to exclude all cases occurring on an initial accrual period, i.e. 90 days. In other words, even if observation starts from the discharge date for each subject, a time-window for "baseline" exposure attribution has to be defined, and all cases occurring in this window have to be excluded from the analysis.
2. *Sensitivity to time-window chosen*: different time-windows will be chosen and analyzed, in order to check sensitivity of results to different accrual periods.
3. *Time-dependent exposure*: as alternative to the previous approach, the study period will be divided in disjoint strata (e.g. 90 day-strata), and exposure will be defined for each stratum as present (e.g. at least 80% days covered) or absent (e.g. less than 80% days covered). Furthermore, the cut-off can be varied to check robustness of results on cut-off chosen. Once the exposure is attributed for each stratum, it can be treated as time-dependent and the following steps in the analysis can be performed:
    - effect of first stratum exposure on following outcomes (time-fixed approach);
    - effect of cumulative exposure on following outcomes (long-term exposure);
    - effect of last stratum exposure on following outcomes (short-term exposure);
    - checking of assumptions underlying use of time-dependent variables.
4. *Dose-response relationship*: within the previous step, exposure will be classified as high/low dose, according to average DDD, and dosage will be analysed as effect modifier of treatment-heath endpoint association (e.g. beclometason or equivalent: <= 500μg/day; 501-1000 μg/day ; > 1000 μg/day)(25).

PART E - Outcomes

a- Mortality (data source: MIS)

Endpoints	***ICD-9- codes***
All cause mortality	001-999
Respiratory mortality	460-519
Cardiovascular mortality	390-459

b- COPD exacerbations (data sources: HIS, HEIS)

Endpoints	***ICD-9-CM codes***
COPD exacerbation	Main diagnosis of 490 (bronchitis, not specified as acute or chronic) 491 (chronic bronchitis) 492 (emphysema) 494 (bronchiectasis) 496 (chronic airway obstruction, not elsewhere classified) OR Main diagnosis 518.81- 518.84 (respiratory failure) 786.0 (dyspnoea and other respiratory distress) 786.2 (cough) 786.4 (abnormal sputum) AND secondary diagnosis COPD (490 or 491 or 492 or 494 or 496)

Note: Prescriptions for an oral corticosteroid.with/without systemic antibiotic (H02AB Glucocorticoids oral, J01 antibacterials for systemic use) will be also used to identify acute COPD exacerbations (data source Pharm).

c- Cardiovascular events and other adverse events (data sources: HIS, HEIS, MIS)

Endpoints	***ICD-9-CM codes***
Angina	411, 413
Atrial fibrillation/flutter	427.3, 427.4
Acute myocardial infarction	410
Tachycardia (supraventricular and ventricular)	427.0, 427.1, 427.2
Heart failure	428
TIA/ Stroke	430-437

Pneumonia	480-487.0
Osteoporotic fractures	820, 821

PART F– Potential Confounders/effect modifiers

F.1 Proxy measures of COPD severity

Respiratory diagnoses considered to define potential proxy measures of COPD severity (see text) *(data source HIS – HEIS) and ICD-9-CM codes*

Respiratory infections
480-487.0 (pneumonia)
510 (emphysema)
511 (pleurisy)
513 (abscess of lung and mediastinum)
011,012.0,012.1,012.2,012.8 (tuberculosis)

493 Asthma

Chronic respiratory disease other than COPD
495 (allergic alveolitis), 135 (sarcoidosis), 500-505 (pneumoconiosis), 508.1 (chronic and other pulmonary manifestations due to radiation), 515 (postinflammatory pulmonary fibrosis), 516 (other alveolar and parietoalveolar pneumonopathy), 517 (lung involvement in conditions classified elsewhere), 518.1 (interstitial emphysema), 518.2 (compensatory emphysema), 518.3 (pulmonary eosinophilia), 518.89 (other diseases of lung, not elsewhere classified), 519 (other diseases of respiratory system)

Concomitant exposure to other respiratory drugs for chronic management of COPD
Use of drugs (see ANNEX part D) during exposure period

R03CC Selective beta-2-adrenoreceptor agonists (oral)
R03DA Xanthines
H02AB Glucocorticoids (oral)
V03AN01 Oxygen

Exposure to respiratory drugs for chronic management of COPD in the previous 12 months
As a potential proxy measure of disease severity, the preceding 12 months exposure to all respiratory drugs for chronic maintenance will be examined:
R03AC Selective beta-2-adrenoreceptor agonists
R03AH Combinations of adrenergics*
R03AK Adrenergics and other drugs for obstructive airway diseases
R03BA Glucocorticoids (inhaled)
R03BB Anticholinergics
R03CC Selective beta-2-adrenoreceptor agonists (oral)
R03DA Xanthines
V03AN01 Oxygen

* at present not on market in Italy

History of acute exacerbations of COPD in the previous 12 months
For each patient the clinical history will be reconstructed through linkage with HIS and HEIS for the previous 24 months in order to screen for acute COPD exacerbations defined as either a hospital

admission/emergency visit for COPD or COPD related causes or a prescription for an oral corticosteroid with/without systemic antibiotic (H02AB Glucocorticoids oral, J01 Antibacterials for systemic use)

Diagnosis of chronic respiratory diseases other than COPD (index admission plus previous 2 year – period hospital admissions)
For each patient the clinical history will be retrieved through linkage with HIS and HEIS for the previous 2 years in order to screen for the following conditions, coded both in the index event or in the previous 2 year-period hospitalizations (any diagnosis):
-Hospital admissions/emergency visits for *Asthma*
-Hospital admissions/emergency visits for *Chronic Respiratory Disease other than COPD*

Diagnosis of pulmonary infections (index admission plus previous 2 year-period hospital admissions)
For each patient the clinical history will be retrieved through linkage with HIS and HEIS for the previous 24 months in order to screen for pulmonary infections, coded both in the index event or in the previous 2 year-period hospitalizations.

Diagnosis of respiratory failure in the index event
one of the followings ICD-9-CM codes 518.81- 518.84 (respiratory failure)

Diagnosis of acute pulmonary symptoms / conditions in the index event
one of the followings ICD-9-CM codes:
786.0 (dyspnoea and other respiratory distress)
512 (pneumothorax)
518.0 (pulmonary collapse)
415 (acute pulmonary heart disease)

F.2- Co-morbidity status *(data sources: HIS, HEIS)*

Chronic co-morbidity	**Codes for index admissions**	**Codes for previous 2-year admissions**
Diabetes	250.0 250.4-250.7, 250.9	250.0-250.9
Hypertension	401- 405	401-405
Ischemic heart disease	412	410- 414, 429.7
Heart failure / Pulmonary heart disease	428, 416.9	428, 416.9
Other chronic heart diseases	394-397.1, 424, 746.3-746.6, V42.2, V43.3, 393, 397.9, 398, 423 (excluding 423.0), 425, 745, V15.1, V42.2, V43.2, V45.0, V45.81 V45.82	429 (excluding 429.7) 093.2, 394-397.1, 424, 746.3-746.6, V42.2, V43.3, 393, 397.9, 398, 423, 391, 420, 421, 422, 425, 745, V15.1, V42.2, V43.2, V45.0, V45.81, V45.82 *procedures: 36.1, 36.0, 35, 37.0, 37.1, 37.3, 37.4, 37.5, 37.6, 37.9*
Arrythmia	426.0, 426.10, 426.12,	426.0, 426.10, 426.12,

	426.13, 426.7, 426.9, 427 (excluding 427.1, 427.2, 427.5), 785.0, V45.0, V53.3	426.13, 426.7, 426.9, 427, 785.0, 996.01, 996.04, V45.0, V53.3
Cerebrovascular diseases	433, 437, 438	430-438
Peripheral vascular diseases	440-448 (excluding 441.1, 441.3, 441.5, 441.6, 444), 557.1, 093.0	440-448, 557, 093.0
Obesity – Dyslipidemia	278.0, 272	278.0, 272
Liver disease	456.0- 456.2 571-572 (excluding 571.1, 572.0- 572.2), 573.0, V42.7	456.0-456.2 570-573 V42.7
Chronic digestive disease (excluding liver)	577.1-577.9, 555, 556	0.70, 577.0-577.9, 555, 556
Chronic Renal Diseases	582-583, 585-588, V42.0, V45.1, V56 *procedures 38.95, 39.95, 54.98*	582-588, V42.0, V45.1, V56 *procedures 38.95, 39.95, 54.98, 55.6*
Neurological and muscle disease	334.1, 342, 343, 344, 331, 332, 332.1, 333.4, 333.5, 334-335, 336.2, 340, 341, 345, 348.1, 348.3, 784.3, 356, 358, 359	334.1, 342, 343, 344, 331, 332, 333.4, 333.5, 334-335, 336.2, 340, 341, 345, 348.1, 348.3, 784.3, 356-359
Anemia and coagulation disorders	280, 281, 285.9 286, 287.1, 287.3-287.5	280, 281, 285.9 286, 287.1, 287.3-287.5
Thyroid Disease	240-241, 243-245 (excluding 245.0 e 245.1), 246	240-246
Depression	300.4, 301.12, 309.0, 309.1, 311	300.4, 301.12, 309.0, 309.1, 311
Psychiatric Disease	293.8, 295-298, 299.1 290.0-290.4, 294.1, 331.0	293.8, 295-298, 299.1 290.0-290.4, 294.1, 331.0
Cancer	140.0–208.9, V10	140.0–208.9, V10

Note: The prescribing patterns of medications other than respiratory will be also examined to obtain an integrated definition of comorbidity status (data source: Pharm).

Drug groups considered for co-morbidities:

A10 Drugs used in diabetes
B01 Antithrombothic agents
C Cardiovascular system, with special focus on:
C02 Antihypertensives
C07 Beta blocking agents
C08 Calcium channel blockers
C09 Agents acting on the renin-angiotensin system
C10 Lipid modifying agents
M05BA Bisphosphonates
M05BB Bisphosphonates, combinations

PART H – Statistical analysis

H.1 Preliminary analysis: ATC groups for drug intake pattern description

R03 DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES
R03A ADRENERGICS, INHALANTS
R03AC Selective beta-2-adrenoreceptor agonists
R03AH Combinations of adrenergics*
R03AK Adrenergics and other drugs for obstructive airway diseases
R03B OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS
R03BA Glucocorticoids (inhaled)
R03BB Anticholinergics
R03CC Selective beta-2-adrenoreceptor agonists (oral)
R03DA Xanthines
H02AB Glucocorticoids (oral)
V03AN01 Oxygen
J01 Antibacterials for systemic use

* at present not on market in Italy

Information will be gathered also regarding less specific treatments, i.e. cough and cold preparations (R05), antihistamines for systemic use (R06), other respiratory system products (R07) and antibacterials for systemic use (J01).

PART L - Timing

Figure 2: Flow chart of the timing of the study