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Quantitative Safety & Epidemiology

Non-Interventional Study Protocol

NVA237A2402T

Title	Multinational, multi-database cohort study to assess adverse cardiovascular and cerebrovascular outcomes and mortality in association with inhaled NVA237 in Europe
Protocol version identifier	v03 (clean)
Date of last version of protocol	19 December 2014
EU PAS register number	ENCEPP/SDPP/5035
Active substance	Glycopyrronium bromide (NVA237) (R03BB06)
Medicinal product	Seebri® Breezhaler® / Tovanor® Breezhaler® / Enurev® Breezhaler®
Product reference	NVA237
Procedure number	Seebri Breezhaler: EMEA/H/C/0002430 Tovanor Breezhaler: EMEA/H/C/0002690 Enurev Breezhaler: EMEA/H/C0002691
Marketing authorization holder(s)	Novartis Europharm Limited Wimblehurst Road Horsham West Sussex RH12 5AB United Kingdom

Joint PASS	No
Research questions and objectives	Use of inhaled anticholinergics has been associated with an increased risk of cardiovascular and cerebrovascular events. In the context of the NVA237 marketing application in Europe, the Committee for Medicinal Products for human use (CHMP) required the conduct of a post-authorisation safety study (PASS) to assess the association between the use of NVA237 and cardiovascular and cerebrovascular events. The objectives of this study are to assess the incidence rates and relative risks of 1) cardiovascular and cerebrovascular outcomes and 2) mortality among new users of NVA237 with COPD compared to new users of comparator drugs (long acting antimuscarinic antagonists [LAMAs] excluding NVA237) or long acting β2 agonists (LABAs).
Country (-ies) of study	UK, Denmark, Italy, The Netherlands, Spain
Author	[redacted], MD, PhD [redacted] The Netherlands Tel: [redacted]

QPPV or delegate	Signature	Date

Marketing authorization holder(s)

Marketing authorization holder(s)	Novartis Europharm Limited Wimblehurst Road Horsham West Sussex RH12 5AB United Kingdom
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2 List of abbreviations

ADM	Administrative
(A)MI	(Acute) Myocardial Infarction
ATC	Anatomical Therapeutic Chemical Classification
BNF	British National Formulary
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CV	Cardiovascular
EMA	European Medicines Agency
EMC	Erasmus Medical Center
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
FDC	Fixed-Dose Combination
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General Practitioner
GPP	Good Pharmacoepidemiology Practice
HF	Heart Failure
HR	Hazard Ratio
HSD	Health Search CSD Longitudinal Patient Database
ICD-9-CM	International Classification of Diseases, 9th rev., Clinical Modification
ICD-10-GM	International Classification of Diseases, 10th rev., German Modification
ICPC	International Classification of Primary Care
ICS	Inhaled Corticosteroid
IPCI	Integrated Primary Care Information Project

IR	Incidence Rate
IRR	Incidence Rate Ratio
HR	Hazard Ratio
LABA	Long Acting β2 Agonist
LAMA	Long Acting Muscarinic Antagonist
LTRA	Leukotriene Receptor Antagonist
MACE	Major Adverse Cardiac Event
MR	Medical Record
PS	Propensity Score
PAS	Post Authorization Safety
PASS	Post Authorization Safety Study
PDE	Phosphodiesterase
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
RCT	Randomized Controlled Trial
RRE	Remote Research Environment
SABA	Short Acting β2 Agonist
SAC	Scientific Advisory Committee
SAMA	Short Acting Muscarinic Antagonist
SD	Standard Deviation
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
TIA	Transient Ischemic Attack
THIN	The Health Improvement Network
UMLS	Unified Medical Language System
WHO	World Health Organization

3 Responsible parties

Table 3-1 Main responsible parties

Role	Person
Coordinating center	[redacted] [redacted] The Netherlands
Project leaders and principal investigators	[redacted], PharmD, PhD [redacted] [redacted] [redacted] [redacted] The Netherlands Tel: [redacted] e-mail: [redacted]
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MAH contact person	[redacted], MSc, PhD Novartis Pharma AG Quantitative Safety & Epidemiology – DS&E Novartis Campus CH-4002 Basel Switzerland [redacted]
Scientific Advisory Committee	Prof Dr [redacted], PhD [redacted] Canada e-mail: [redacted] Prof Dr [redacted], MD, PhD [redacted] Belgium e-mail: [redacted] Dr [redacted], PhD [redacted] USA e-mail: [redacted]

This protocol has been developed by the principal investigators and sub-investigators, in close collaboration with the MAH.

This study will be conducted according to the ENCePP Code of Conduct.

Novartis, as MAH of NVA237, will be responsible to register the protocol in the EU-PASS Register and will update the Register in case of amendments and will enter progress reports and the final study report in the Register.

4 Abstract

Title	Multinational, multi-database cohort study to assess adverse cardiovascular and cerebrovascular outcomes and mortality in association with inhaled NVA237 in Europe Study number: CNVA237A2402T
Version and Date	v03, 19 December 2014
Name and affiliation of main author	[redacted], MD, PhD, [redacted]
Rationale and background	NVA237 is a long-acting muscarinic antagonist (LAMA) which was approved in Europe in September 2012 as maintenance bronchodilator treatment to relieve symptoms of chronic obstructive pulmonary disease (COPD). In the context of the NVA237 marketing authorization application in 2012, the Committee for Medicinal Products for Human Use (CHMP) requested Novartis, the marketing authorisation holder of NVA237, to conduct a post-authorisation safety study (PASS) to examine cardio- and cerebrovascular safety concerns related to the use of NVA237.
Research question and objectives	To assess the risk of cardio- and cerebrovascular outcomes and of mortality in patients using NVA237 compared to patients using LAMA (excluding NVA237) or long acting β_2 agonists (LABAs).
Study design	Multinational, multi-database cohort study using information from five European electronic health care databases from the Netherlands, Italy, United Kingdom (UK), Denmark and Spain in new users of NVA237 vs. new users of two comparator drug classes. These comparators are 1) a cohort of new users of LABAs and 2) a cohort of new users of LAMA other than NVA237. For the analysis of each endpoint, these 3 treatment cohorts will be followed until the end of treatment, end of study, any of the cardiovascular and/or cerebrovascular endpoints, disenrollment from database or death, whichever comes first. The study will start upon the first launch of NVA237 in EU in the participating countries (November 2012). The end of the study is one year after inclusion of the 3000th patient in the new user cohort of NVA237. Based on the size of the databases and the expected market uptake of NVA237, the end of the study is estimated to be approximately 4.5 years after drug launch on 30/04/2017.
Population	All patients aged 40 years and above registered in the respective electronic health care databases (see below 'Data sources') with a minimum of 1 year of valid database history and a diagnosis of COPD who are newly (no use in the one year prior) treated with one of the single ingredient study drugs (NVA237, LAMA [excluding NVA237], LABA). The follow-up of each patient will start upon use of the respective study

	drugs and will end upon end of treatment, switch between or add-on of other study drugs, end of study, disenrollment from the database, death or the specific study endpoint of interest, whichever comes first.
Variables	The endpoints of interest are 1) *cardiovascular events* (major cardiovascular events, ischemic heart disease and cardiac arrhythmias), 2) *cerebrovascular endpoints* (stroke [ischemic stroke and cerebrovascular bleeding] and transient ischemic attack [TIA]) and 3) *overall mortality*. Demographic factors, lifestyle circumstances, concomitant drug use and underlying comorbidity will be assessed as confounding factors and effect modifiers.
Data sources	Data from five electronic health care databases from Europe will be used namely the Integrated Primary Care Information Project (IPCI) from the Netherlands, the Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP) from Spain, The Health Improvement Network (THIN) from the UK, the Health Search CSD Longitudinal Patient Database (HSD) from Italy, and the Aarhus University Prescription Database from Denmark. Assuming a COPD prevalence of 5%, the total number of COPD patients aggregated from all five databases will be around 400,000.
Study size	Based on sample size calculations and assuming in the worst case scenario that, for each new user of NVA237 there will be 4 new users of LAMA (excluding NVA237) or LABA, the new user cohort of NVA237 should include at least 2,079 patients to allow detecting an increased risk - if the risk is higher by at least a factor of two (incidence rate ratio, IRR=2) - of major cardiovascular events (myocardial infarction and stroke, and hospitalizations due to acute coronary syndrome and/or heart failure) (based on a baseline incidence of 10/1000 PY and a median treatment exposure of 180 days) with a power of 80% compared to the reference categories. The sample size estimation procedure followed here is different from the previous approach used in the agreed study synopsis and the initially submitted PASS protocol (dated 11 December 2012). Although the sample size estimated with the current approach (i.e. 2,079 patients) is considerably lower than the initially proposed 3,000 patients, we propose to include a sample size of 3,000 to be consistent with the previously agreed study synopsis and the initially submitted PASS protocol (dated 11 December 2012).
Data analysis	Both yearly progress reports and a final report will be prepared. For the yearly progress reports, the number of patients exposed and the crude incidence rate of the different outcomes of interest will be described for all 3 cohorts. The crude incidence rates will only be estimated if at least 1000 new NVA237 users have been enrolled. The final analysis will be conducted at the end of the study (upon validation of the endpoints) and will consist of a primary and secondary analysis. As primary analysis, the risk of overall mortality as well as the risk of the

	different endpoints of interest among new users of NVA237 will be compared to the risk in the new users of LABA and LAMA (all LAMAs excluding NVA237) using Cox regression analysis. Each endpoint will be studied separately, so patients who experience more than one endpoint will be included in the analysis of each endpoint. Cox regression analyses will be conducted to estimate both crude and adjusted relative risks (expressed as hazard ratios [HRs] with 95% confidence intervals [95% CIs]), allowing for time-varying exposures. All analyses will at first be performed for each database separately. Effect estimates will be pooled across the databases, using a random effects meta-analytical approach. In addition, a pooled mega-analysis will be done by combining the data sources on a patient-level and adjusting for the database. As secondary analysis, subsequent episodes, with or without treatment, will be taken into account. Patients will be followed from start of first prescription of NVA237, LABA or LAMA (excluding NVA237) until the endpoint of interest, end of study, disenrollment from the database or death, whichever comes first. For this analysis, the HR of the events of interest will be estimated for NVA237 vs. no use of NVA237. This analysis will be repeated for LAMA vs. no use of LAMA and LABA vs. no use of LABA. In addition, a sensitivity analysis will be conducted only considering the first treatment episode during follow-up in patients naïve to both NVA237 and all of the comparator drugs. In addition, specific patient groups will be studied via stratified analysis on age, gender, underlying cardiovascular co-morbidity and COPD severity.
Milestones	Start of data collection: 01 November 2012 End of data collection: 30 April 2017 Interim report 1: December 2013 Interim report 2: November 2014 Interim report 3: November 2015 Interim report 4: November 2016 Registration in the EU PAS register: 25 October 2013 Final report of study results: November 2017

5 Amendments and updates

Major protocol updates are listed below in Table 5-1.

Table 5-1 Details of study protocol amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	29 May 2013	4 Abstract	Abstract was updated to reflect changes in the body of the protocol	Based on PRAC comments
2	29 May 2013	6 Milestones	End of data-collection: 30-Apr-2017 Final study report: maximum 5 years after launch of NVA237	Based on PRAC comments
3	29 May 2013	9.2.2 Study period	Removed “maximum of 5 years following the first launch” End of data collection added Added that the progress of identification of NVA237 within all databases will be monitored closely Launch dates updated	Based on PRAC comments
4	29 May 2013	9.2.3 In - and exclusion criteria	Missing age and gender has been added as exclusion criteria	Based on PRAC comments

Number	Date	Section of study protocol	Amendment or update	Reason
5	29 May 2013	9.3.1 Endpoints of interest and Annex 2 – Validation algorithm	Clarified how mortality data will be collected Clarification on validation of outcomes added (= blinded to exposure + free text validation algorithms added to protocol)	Based on PRAC comments
6	29 May 2013	9.3.5 Demography, life style factors and comorbidity	Atrial fibrillation and flutter have been added to the list of underlying comorbidity Further details on collection of hospitalization data have been added.	Based on PRAC comments
7	29 May 2013	9.4 Data sources	Details on the average follow-up time per patient (2.5 – 11 years) and completeness of data of the databases have been added.	Based on PRAC comments
8	29 May 2013	9.5 Study Size	A sample size justification, together with a range of sample sizes at different risk levels has been added	Based on PRAC comments
9	29 May 2013	9.6 Data management	The data management section in the protocol was expanded to include further details on the methods used for pooling of data	Based on PRAC comments

Number	Date	Section of study protocol	Amendment or update	Reason
10	29 May 2013	9.7 Data analysis	This section has been updated as following: clarification of analysis in case of 3-fold increase of IR of the different outcomes adding hospitalization for COPD exacerbation as confounder additional details and codes in relation to the propensity score have been added list of endpoints has been clearly defined further details on sensitivity analyses and stratified analyses have been added information on handling of missing data was updated	Based on PRAC comments
11	29 May 2013	Annex 3 – Event definitions	A definition of the codes used in the evaluation of major cardiovascular events (MACE) has been added	Based on PRAC comments

Number	Date	Section of study protocol	Amendment or update	Reason
12	05 September 2013	7 Background	Results from more recent publications have been added and reference list has been updated accordingly (including Section 13)	More recent literature added
13	05 September 2013	9.2.3 In - and exclusion criteria	Clarified the plan for assessing the effect of non-cardiovascular life-threatening conditions on the final results	Based on PRAC comments (Sep-13)
14	05 September 2013	9.7 Data analysis	Clarified that 'full analysis' includes all details mentioned in section 9.7.2 Plan for stratified analysis in patients with or without non-cardiovascular life-threatening conditions was added	Based on PRAC comments (Sep-13)
15	05 September 2014	Not applicable	Transcription of the entire protocol into the Novartis protocol template for non-interventional PASS	To follow Novartis-internal guidelines

Number	Date	Section of study protocol	Amendment or update	Reason
16	05 September 2014	9.2.3 In - and exclusion criteria	Patients with COPD diagnosed (via disease codes) within 6 months after the first prescription of any of the exposure categories of interest will also be included within the study. Thus not only considering patients with COPD diagnosed prior to the first prescription of any of the exposure categories of interest	Based on comments from the Scientific Advisory Committee
17	05 September 2014	8.1 Main objective and 9.3.1 Endpoints of interest	Clarification that ventricular arrhythmia also includes AV block (this has been added to Annex 3 – event definition)	Based on comments from the Scientific Advisory Committee
18	05 September 2014	9.3.3 COPD and COPD severity	Manual validation has been clarified and use of spirometry has been limited to patients for whom date of spirometry and index date is less than 5 years	Based on comments from the Scientific Advisory Committee
19	05 September 2014	9.3.5 Demography, life style factors and comorbidity	Chronic kidney disease has been added to comorbidity	Based on comments from the Scientific Advisory Committee

Number	Date	Section of study protocol	Amendment or update	Reason
20	05 September 2014	9.7 Data analysis	A sensitivity analysis will be conducted only considering the first treatment episode during follow-up in patients who are naïve to both NVA237 and all of the comparator drugs.	Based on comments from the Scientific Advisory Committee
21	19 December 2014	8.1 Objective, 9.3.1 endpoints, 9.3.5 demography, 9.7 Data analysis, 9.7.1 Yearly analysis for study progress reports and yearly reports, Annex 3.1.5 and Annex 4.3	Cardiac arrhythmia as endpoint and as comorbidity has been clarified, based on the comments by PRAC	Based on PRAC comments/questions (Dec 2014)
22	19 December 2014	Annex 3.1.3	Definition of stroke has been updated	Alignment with Novartis' definition of stroke used for NVA237 and QVA149

6 Milestones

Table 6-1 Study milestones

Milestone	Planned date
Start of data collection	Upon launch of NVA237 (01 November 2012)
End of data collection	Approximately 4.5 years after drug launch on 30-Apr-2017 (estimated 1 year follow-up date of 3000th patient enrolled in the NVA237 cohort)
Study progress report(s)	Yearly progress reports – first report planned at 1 year after launch of NVA237
Interim report(s)	Yearly interim report – first report planned at 1 year after launch of NVA237
Registration in the EU PAS register	Following PRAC endorsement
Final report of study results	Maximum 5 years after launch of NVA237 (November 2017)

7 Rationale and background

Glycopyrronium bromide is a synthetic, quaternary ammonium, anticholinergic (antimuscarinic) agent that acts through competitive antagonism of acetylcholine at the muscarinic receptors. NVA237 is a dry powder formulation (44mcg delivered dose), developed as a once-daily inhalation treatment for patients with chronic obstructive pulmonary disease (COPD). COPD is characterized by a progressive decline in lung function which cannot be reversed by treatment. Bronchodilators are the mainstay of symptomatic management of COPD and include β_2 agonists, long-acting muscarinic antagonist (LAMAs), methylxanthines and phosphodiesterase (PDE)-4 inhibitors, used alone or in combination (Pauwels et al 2001). NVA237 is indicated as maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD.

In 2008, concerns were raised on the cardiovascular and cerebrovascular safety of the first LAMA, Spiriva® Handihaler (tiotropium). These concerns were based on 1) a report to the US Food and Drug Administration (FDA), issued by the marketing authorization holder (MAH) of tiotropium, on pooled data from 29 placebo-controlled trials showing an increased risk of stroke in patients treated with tiotropium, and 2) a meta-analysis and a case-control study reporting an increased risk of mortality and/or cardiovascular events in patients who received inhaled anticholinergics (ipratropium or tiotropium) (Lee et al 2008, Sing, Loke and Furberg 2008, Michele, Pinheiro and Iyasu 2010). In their initial report to the FDA, the manufacturer also reported an increased risk of mortality with tiotropium Respimat® SMI device based on data from three one-year placebo controlled trials. In January 2010, the FDA warning on the use of inhaled tiotropium was overruled based on data from the UPLIFT study, an updated meta-analysis (including the UPLIFT study), and the FDA stated that the available data no longer supported an association between the use of inhaled tiotropium Handihaler® and an increased risk of stroke, heart attack or death from cardiovascular causes (Michele, Pinheiro and Iyasu 2010). However, the evidence on the safety of tiotropium remains conflicting and new concerns were raised based on two meta-analyses of randomized controlled trials (RCTs), showing an increased risk of mortality of inhaled tiotropium Respimat® compared to placebo and a new user cohort study reporting an increased risk of cardiovascular endpoints (stroke, angina and myocardial infarction) in patients treated with tiotropium Handihaler® vs. LABA (Singh et al 2011, Dong et al 2012, Jara et al 2012, Verhamme et al 2012). In addition, a database cohort study from the Netherlands showed that use of tiotropium Respimat® was associated with an almost 30% increase of mortality compared with tiotropium Handihaler®. The increased risk was mainly observed for cardiovascular and cerebrovascular deaths and in patients with underlying cardiovascular disease (Verhamme et al 2013). It is unclear though whether this association is causal or due to residual confounding (e.g. by COPD severity). Furthermore, a recent randomized, double blind, parallel-group trial showed that tiotropium Respimat® had a safety profile and exacerbation efficacy similar to that of tiotropium Handihaler® (Wise et al 2013).

In the context of the NVA237 marketing authorization application, the Committee for Medicinal Products for Human Use (CHMP) recently recommended conditions for marketing authorization and product information. In the day 180 list of outstanding issues, CHMP stated *'Considering the potential risk of adverse cardiovascular (CV) outcomes related to the mechanism of action of anticholinergic quaternary ammonium compounds and the recent concerns on cardiovascular safety of same class products, adverse CV outcomes should be followed closely in the post-marketing setting. Consequently, the Applicant should include a PASS in the RMP to monitor these outcomes post-marketing'. Further, CHMP proposed a 'Post-Authorisation Safety (PAS) Cohort Study of Inhaled NVA237 and the Risk of Selected Cardiovascular Endpoints'.*

8 Research question and objectives

With this non-interventional post-authorization safety study (PASS) we want to assess the risk of cardiovascular and cerebrovascular endpoints, and mortality in COPD patients using NVA237 compared to COPD patients using LAMA (excluding NVA237) or LABA.

8.1 Main objective

To assess the incidence rates and hazard ratios of cardiovascular and cerebrovascular outcomes, and of mortality among new users of inhaled NVA237 with COPD compared to new users of LAMA (non-NVA237) or new users of LABA in patients with COPD.

The outcomes of interest include:

- Major cardiovascular events (MACE) including myocardial infarction and stroke, and hospitalizations due to acute coronary syndrome and/or heart failure
- Ischemic heart disease including myocardial infarction and angina pectoris
- Cardiac arrhythmias (atrial fibrillation/flutter, atrioventricular (AV) block, premature depolarization, sick sinus, supraventricular tachycardia and ventricular arrhythmia including ventricular tachycardia, ventricular fibrillation and Torsade de Pointes/Long QT syndrome)
- Cerebrovascular disorders (ischemic and hemorrhagic stroke and transient ischemic attack
- Mortality

9 Research methods

9.1 Study design

A multinational, multi-database cohort study will be conducted using five electronic health care databases from various European countries, namely the Netherlands, Italy, the United Kingdom (UK), Denmark, and Spain (for details on the databases, see Section 9.4 'Data sources').

From these databases, a new user cohort of NVA237 for the treatment of COPD, will be defined as well as two comparator cohorts, namely a new user cohort of LABAs and a new user cohort of LAMAs (excluding inhaled NVA237). For the primary analysis, these cohorts will be followed from start of the first prescription of NVA237, LABA or LAMA (excluding NVA237) until the end of treatment (switching or add-on therapy), end of study, any of the endpoints of interest (cardiovascular or cerebrovascular), disenrollment from the database or death whichever comes first.

In a secondary analysis, the complete study follow-up of the patient will be taken into account. This implies that patients will be followed from the first prescription of NVA237, LABA or LAMA (excluding NVA237) until the endpoint of interest, end of study, disenrollment from the database or death, whichever comes first. For this analysis, the hazard ratio (HR) of the events of interest will be estimated for NVA237 vs. no use of NVA237. This analysis will be repeated for LAMA vs. no use of LAMA and LABA vs. no use of LABA (for more details, see 'Sensitivity analyses' in Section 9.7.2).

As each endpoint will be studied separately, patients who experience more than one endpoint during study follow-up will be included in the analysis of each endpoint respectively. E.g. follow-up for the endpoint of cardiac arrhythmia ends when a patient is newly diagnosed with atrial fibrillation – if that same patient later develops stroke, this patient would still be enrolled in the stroke analysis as well as in the analysis for MACE endpoints.

9.2 Setting

9.2.1 Study population and study cohorts

Data from five European electronic health care databases will be used, namely the 'Integrated Primary Care Information Project' (IPCI) from the Netherlands, the 'Health Search Database' (HSD) from Italy, 'The Health Improvement Network' (THIN) from the UK, the 'Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària' (SIDIAP) from Spain and the 'Aarhus University Prescription Database' from Denmark. For more detailed information on the individual databases, see Section 9.4 'Data sources'.

From these databases, we will first select a population of patients, 40 years of age or older with at least 1 year of valid database history and a recorded diagnosis of COPD (for the definition of COPD, see Annex 6). For all patients an eligibility date will first be defined, which is the latest of the following dates: reaching 40 years of age, having one year of data in the database or having fulfilled the criteria for a diagnosis of COPD. Diagnoses of COPD may be searched in the entire prior history of a patient.

We have chosen for an age restriction (≥ 40 years) to minimize the risk of misclassification of COPD. The differential diagnosis between chronic asthma and COPD is difficult to make but

COPD is mainly diagnosed in patients older than 40 years whereas asthma is a chronic respiratory condition of the young (GOLD 2014). Especially as LABAs, frequently used for the symptomatic treatment of asthma, are one class of comparator drugs, it is important to overcome the risk of misclassification of COPD diagnosis. If not, there is the potential of comparing the safety profile of LAMAs in patients with COPD versus the safety profile of LABAs in patients with asthma.

Within this COPD cohort, three study cohorts will be defined, namely patients who are newly (i.e. no use in the one year prior) prescribed/dispensed:

1. NVA237
2. All single ingredient LABA (thus, no fixed combinations of LABA/inhaled corticosteroid (ICS), free combinations of LABA + ICS are acceptable)
3. All single ingredient LAMA (excluding NVA237) (thus, no fixed combinations of LAMA+LABA are acceptable)

Because of the size of the databases and the fact that the comparator groups are well established treatments in COPD, we assume in the worst case scenario a 1:4 ratio of NVA237 vs. LAMA, (excluding NVA237), or vs. LABA. All identified new users will be used, thus, the ratio of NVA237 vs. the comparator group might be higher than 1:4.

New single ingredient LABA or LAMAs coming onto the market during the course of the study will also be captured. The list of drugs as mentioned in Annex 5 might thus be updated during the course of the study.

Patients can enter in different cohorts if the criteria apply. Patients cannot re-enter a second time in the same cohort.

9.2.2 Study period

The study will cover patient's data from the first launch of NVA237 in one of the European countries of interest (i.e. November 2012 [Denmark, UK]) up to one year after inclusion of the 3000th patient in the new user cohort of NVA237. The end of the study is one year after inclusion of the 3000th patient in the new user cohort of NVA237. Based on the size of the databases and the expected market uptake of NVA237, the end of the study is estimated to be approximately 4.5 years after drug launch, i.e. approximately April 2017 (estimated 1 year follow-up date of 3000th patient enrolled in the NVA237 cohort). During the study, the progress of identification of NVA237 within all databases will be monitored closely.

Launch dates of NVA237 in the five countries are specified in Table 9-1.

Table 9-1 Launch dates for NVA237 in the five participating countries

Country	Launch date
Denmark	November 2012
Italy	April 2013
Netherlands	February 2013
Spain	April 2013
United Kingdom	November 2012

9.2.3 In- and exclusion criteria

Inclusion criteria

All patients fulfilling the criteria for a COPD diagnosis, 40 years or older, with at least 1 year of database history, and a first time prescription/dispensing for NVA237, a LAMA other than NVA237, or a LABA after 01 November 2012 will be included in the study.

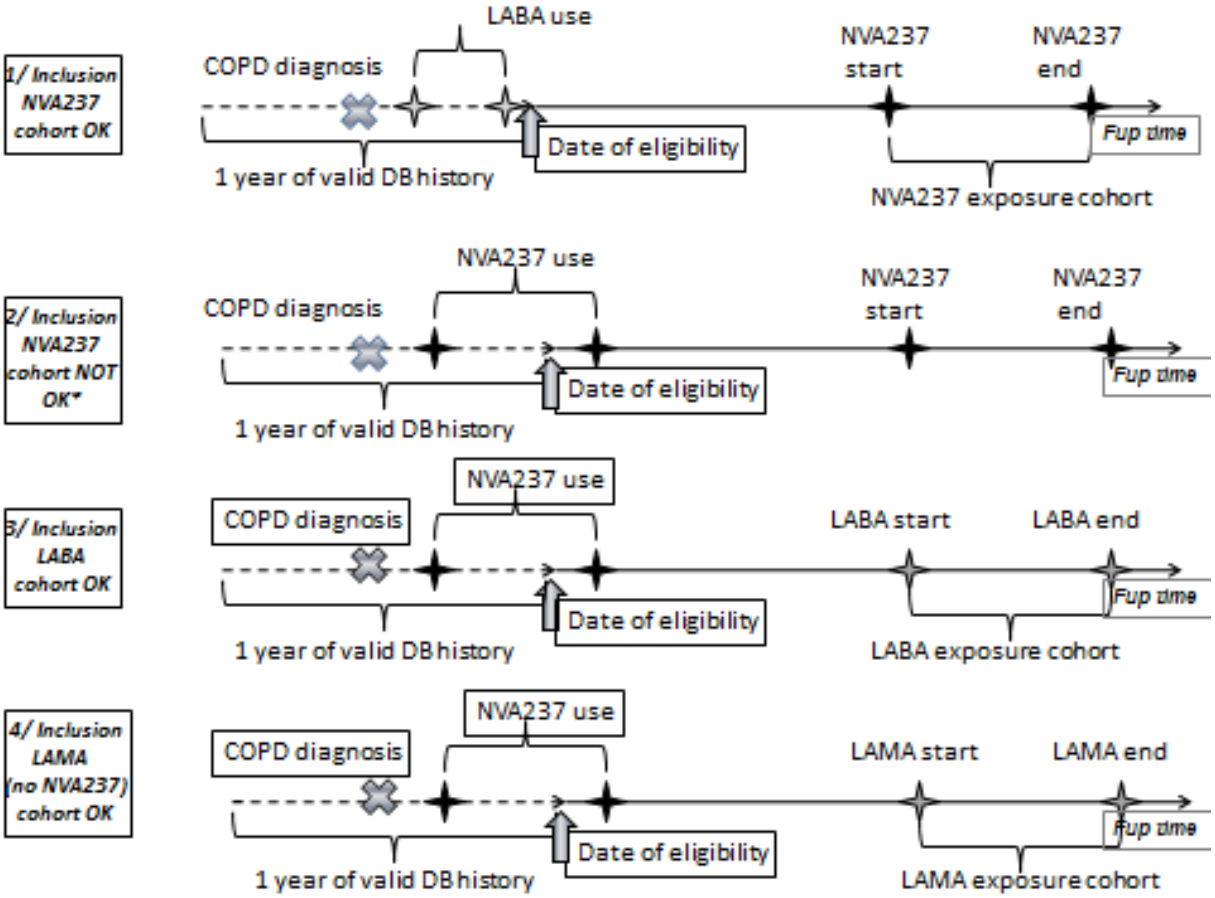
Exclusion criteria

Patients with 1) missing data on age or gender, 2) a recorded diagnosis of asthma only and thus, no recorded diagnosis of COPD prior to or within 6 months after the first prescription/dispensing of any of the drugs of interest or 3) who received the study drug of interest (NVA237, LAMA [excluding NVA237] or LABA) in the one year prior to the index date (= time of first prescription) of the respective study cohorts will be excluded (see Figure 9-1). Patients thus need to be treatment naïve to the exposure of interest for a minimum of one year. In addition, patients initiating both LABA and LAMA at the same time will be excluded from the study.

This is a non-interventional study using real-world data. Therefore, it was decided to not exclude patients with non-cardiovascular life-threatening conditions (=defined as patients with underlying cancer [excluding skin basal cell cancer as this is not a life-threatening condition]). In the final report, it will be discussed to what extent this patient category might have affected the final study results. In support of this discussion, a stratified analysis will be conducted in patients with and without non-cardiovascular life-threatening conditions. Underlying comorbidity of cancer, with the respective disease codes is described under Annex 8 – Comorbidity definition.

Figure 9-1 In- or exclusion in the study based on previous exposure of study drugs

(* In the second example, inclusion into the NVA237 would be OK if time window between date of eligibility and NVA237 start would be more than 1 year)



9.2.4 Follow-up

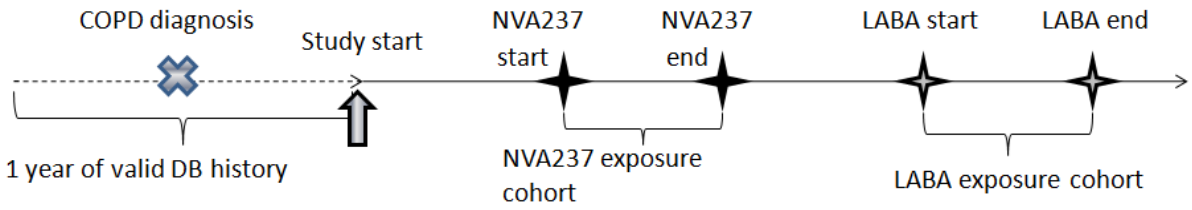
For the primary analysis, patients initiating NVA237 or any single ingredient comparator drug (LABA or LAMA [excluding NVA237]) will be followed from the time of first prescription (index date) until the earliest of (i) end of treatment episode +30 days, (ii) end of study or disenrollment from the database, (iii) any cardiovascular or cerebrovascular endpoint, or (iv) death.

End of treatment is defined as the discontinuation of use of NVA237, LAMA (excluding NVA237), or LABA for the respective treatment cohorts. This implies that follow-up, for the respective cohorts, ends when a patient discontinues, receives add-on therapy with another long acting bronchodilator, or switches treatment.

Upon discontinuation of one of the treatment cohorts, patients are still eligible to be enrolled in the other treatment cohorts (Figure 9-2).

The calculation of the end of treatment episode is further clarified under Section 9.3.2 – Exposure.

Figure 9-2 Eligibility to different exposure cohorts



9.3 Variables

9.3.1 Endpoints of interest

During exposure to the different study drugs of interest, patients will be followed for a new diagnosis of any of the following endpoints:

- Major cardiovascular events (MACE) including myocardial infarction and stroke, and hospitalizations due to acute coronary syndromes and/or heart failure
- Ischemic heart disease including myocardial infarction or angina pectoris
- Cardiac arrhythmia (atrial fibrillation/flutter, atrioventricular (AV) block, premature depolarization, sick sinus, supraventricular tachycardia and ventricular arrhythmia including ventricular tachycardia, ventricular fibrillation and Torsade de Pointes/Long QT syndrome)
- Cerebrovascular disorders (ischemic and hemorrhagic stroke, transient ischemic attack [TIA]
- Mortality (all cause)

The definitions of these endpoints are described under Annex 3 – Event definitions.

In all databases, mortality is well documented and death and date of death are one of the variables that are standardly recorded in the population table (demography table). In addition, the databases will be searched for death specific codes.

As each endpoint will be studied separately, patients who experience more than one endpoint during the study will be included in the analysis of each endpoint. In case of combined endpoints, patients will be censored upon the first event of interest. E.g. a patient diagnosed with atrial fibrillation and later diagnosed with ventricular tachycardia, will be censored at the date of the diagnosis of atrial fibrillation for the analysis of cardiac arrhythmia as endpoint. Disease outcomes which are part of the combined endpoints will not be studied separately,

e.g., there will be no separate analysis with hemorrhagic stroke as endpoint, TIA as endpoint or ischemic stroke as endpoint.

Prior to analysis, for each patient of the COPD cohort, all endpoints will be identified in the database based on searches on disease specific coding and free text. For those databases where free text is available (i.e. IPCI, HSD and SIDIAP), outcomes will be validated, blinded from exposure, by medical doctors, according to the event definition algorithm (see Annex 4 – Validation algorithm). These event definition algorithms will be part of the statistical analysis plan. This validation of the endpoints will only be done at the end of the study, in preparation of the final analysis.

As different data sources will be used with different coding dictionaries (International Classification of Primary Care [ICPC], International Classification of Disease 9th or 10th version [ICD-9, ICD-10] and READ codes) concepts of diseases will be mapped through the Unified Medical Language System (UMLS) for the different outcomes (see Annex 3 – Event definitions).

The identified codes as documented in the protocol-annexes will be carefully reviewed by all database partners prior to data extraction. As coding might change over time, relevant codes might be updated during the course of the project.

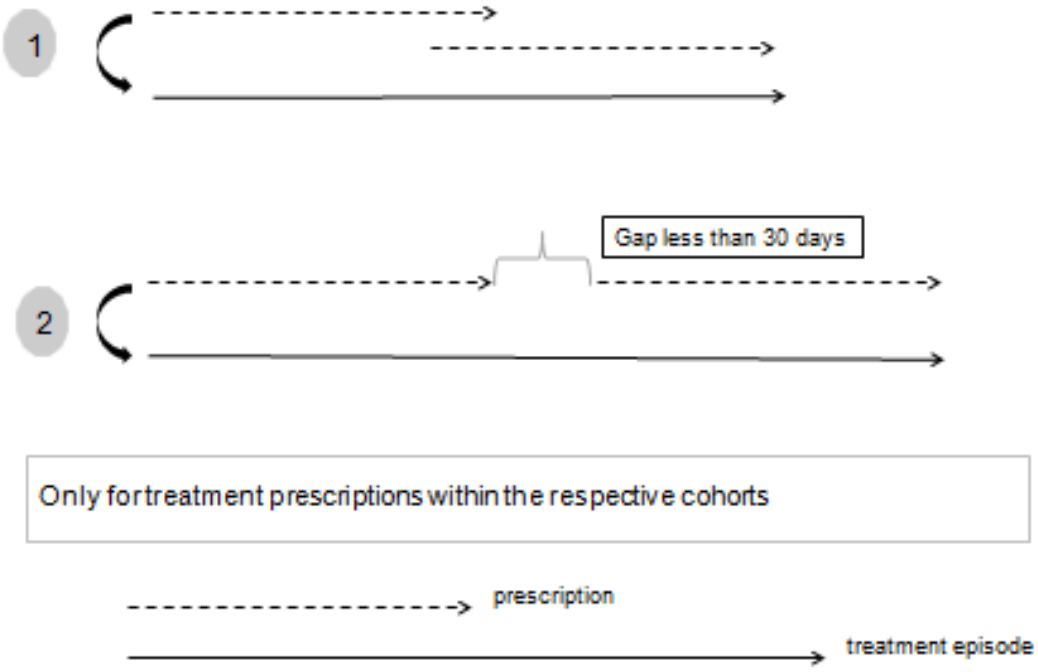
9.3.2 Exposure

Patients prescribed NVA237, LABA or LAMA (excluding NVA237) will be identified in the database by an automated search on the respective Anatomical Therapeutic Chemical classification system (ATC) codes, product names or Multilex codes of the prescription records in the respective databases (see Annex 5 – Exposure definition).

From these drug prescriptions, episodes of drug exposure will be created. First of all, for each drug prescription, the end date of the prescription is calculated based on the amount of drug prescribed and the actual dosing of the individual patient. For HSD and Aarhus, where information on dosing is always lacking and for the other databases, in case of missing dose, the total amount (per prescription) is divided by the recommended dosing according to the Summary of Product Characteristics (SmPC) of the respective drug. This duration of use is then added to the start date of the prescription resulting in an end date for each prescription.

From the individual prescriptions, episodes of use will be created taking into account potential overlap and gaps (Figure 9-3). If the subsequent prescription overlaps the previous prescription, the 2 prescriptions will be combined into 1 episode and the stop date of that episode will be the stop date of the second prescription ((1) in Figure 9-3). In case of a gap between 2 prescriptions, these prescriptions will only be combined into one episode if the duration of the gap is less than 30 days ((2) in Figure 9-3).

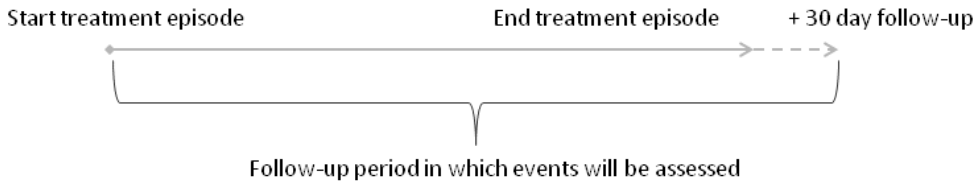
Figure 9-3 Creation of treatment episode for inhaled COPD therapies



Patients will be classified as "exposed" to study medication (NVA237, LABA, or LAMA excluding NVA237) for the duration of the first treatment episode plus 30 days.

In the primary analysis, patients who discontinue treatment and later restart will only be considered for their first episode of continuous use (+30 days) (Figure 9-4). The patient will be censored upon treatment stop date + 30 days of the exposure of interest. Subsequent treatment episodes of the exposure of interest will thus not be taken into account. To avoid misclassification of the endpoints, the 30 day extension window is not considered when treatment is discontinued because of switching to another treatment cohort.

Figure 9-4 Identification of period of follow-up



In a sensitivity analysis, as part of the final study report, we will repeat the analysis where the first treatment episode is extended to a window of 60 days.

9.3.3 COPD and COPD severity

First of all, from the source population of individuals, 40 years or older with at least 1 year of valid database history, a cohort of COPD patients will be defined.

COPD will be retrieved from the database by an automated search on COPD specific code (see Annex 6 – COPD definition and COPD severity).

In IPCI, HSD and SIDIAP, where free text is available, additional free text searches will be conducted. This additional validation will be done at the end of the study, in preparation of the final analysis. In those circumstances, patients will be considered as having COPD in case of clinical symptoms (dyspnea, chronic cough or sputum production) as registered in the electronic medical file of the patient, confirmed by spirometry (post-bronchodilator $FEV_1/FVC < 0.70$) or confirmed by the specialist (GOLD 2014).

Prior to the final analysis, for those databases where free text is available (IPCI, HSD and SIDIAP), COPD will be validated. A patient will only be considered as having COPD in case of at least 2 records (on different days) of COPD within maximum one year. The last record of the two will be used for COPD start, to avoid immortal time bias.

COPD severity is an important confounder and/or effect modifier in the association between the use of NVA237 or comparator drug and the risk of cardiovascular and/or cerebrovascular endpoints or mortality. It is thus important to quantify COPD severity where possible.

COPD severity will be assessed by spirometry, if corresponding data are available. If spirometry data are lacking or the date of spirometry dates back to more than 5 years prior to the index date, COPD severity will be categorised according to published algorithms (Soriano et al 2001, Eisner et al 2005, Curkendall et al 2006).

COPD severity will be assessed during the complete follow-up and the COPD severity closest to the index date will be considered as covariate in the analysis. For further details on COPD severity, see Annex 6 – COPD definition and COPD severity.

9.3.4 Concomitant drug use

Concomitant drug use will be assessed in the one year prior to the index date of the different exposure cohorts and will be considered as confounder or effect modifier in the analysis. The following classes of concomitant drugs will be considered:

Concomitant use of respiratory drugs

Information on the use of drugs for the treatment of COPD will be retrieved from the prescription records through an automated search on either ATC, product names or Multilex codes (see Annex 7 – Concomitant medication definition). The following types of bronchodilating and anti-inflammatory drugs will be considered as respiratory drugs:

- Single ingredient short acting muscarinic agents (SAMAs)
- Single-ingredient short acting β_2 agonists (SABAs)
- Inhaled corticosteroids (ICS)
- Xanthines
- Fixed combination therapy (LABA + ICS, anticholinergic agents + SABA)
- Oral β_2 agonists
- Leukotriene receptor antagonists (LTRA)
- Systemic corticosteroids (oral, intravenous or intramuscular administration)
- LABA
- LAMA
- Oral phosphodiesterase 4 (PDE-4) inhibitors

Other concomitant drug use

The following drugs will also be considered as they might be potential confounders or effect modifiers in the association between use of NVA237 or comparator drug and risk of cardiovascular or cerebrovascular outcomes. Exposure to these drugs, at index date, will be assessed via an automated search on either ATC, product names or Multilex codes (see Annex 7 – Concomitant medication definition)

- Central nervous system drugs (excluding drugs with anticholinergic effects)
  Use of opioids, hypnotics and sedatives, anxiolytics, antiepileptic drugs, serotonin reuptake inhibitors.

- Anticholinergic drugs
  Use of drugs with anticholinergic effects (antipsychotic drugs, tricyclic and tetracyclic antidepressant agents, disopyramide, antispasmodics, antiparkinsonian agents, cholinesterase inhibitors, atropine, H1-antihistamines, and anticholinergics for treatment of overactive bladder in patients with bladder outlet obstruction).

- Drugs affecting cerebrovascular and cardiovascular disease
  Use of systemic corticosteroids, NSAIDs, vitamin K antagonists, lipid lowering drugs, platelet aggregation inhibitors, nitrates, anti-arrhythmics, anti-diabetic drugs and anti-hypertensive drugs.

9.3.5 Demography, life style factors and comorbidity

- For all patients, information on gender and age (at time of index date) will be captured
- If available, information on smoking status will be retrieved from the databases, and patients will be classified as "current smoker", "past smoker", "non-smoker" or "smoking status unknown" at the time of the index date
- Duration of COPD (from date of diagnosis of COPD until index date)
- COPD severity at index date
- Number of COPD exacerbations requiring hospitalization or need of oral steroids in the year prior to the index date. Hospitalization will be assessed either via linkage with the hospital admission database (SIDIAP) or via use of COPD specific codes linked to hospitalization (Aarhus and THIN). For HSD and IPCI, hospitalization for COPD exacerbation is identified by linking COPD (exacerbation) with hospital referral or hospital discharge letters
- The number of GP (outpatient) office visits (excluding telephone requests for repeat prescriptions only) and home visits, in the year prior to the index date
- The number of prescriptions for each of the classes of the cardiovascular drugs, respiratory drugs, CNS drugs and analgesics in the year prior to the index date.
- Underlying comorbidity or "history of" at time of index date namely:
  - Asthma
  - Cardiovascular disease (hypertension, angina pectoris, myocardial infarction, cardiac arrhythmia (atrial fibrillation/flutter, atrioventricular (AV) block, premature depolarization, sick sinus, supraventricular tachycardia and ventricular arrhythmia including ventricular tachycardia, ventricular fibrillation and Torsade de Pointes/Long QT syndrome), heart failure)
  - Cerebrovascular disease (history of stroke and/or TIA at time of index date)
  - Metabolic disorders including diabetes mellitus, and hyperlipidemia
  - Lung cancer
  - Malignancies (excluding lung cancer)
  - Chronic kidney disease

Underlying comorbidity or history of above conditions will be identified via an automated search on disease specific codes (see Annex 3 – Event definition and Annex 8 – Comorbidity definition). As different data sources will be used with different coding dictionaries concepts of diseases will be mapped through the UMLS. The identified codes as documented in the

protocol-annexes will be reviewed by all databases owners prior to data-extraction. As coding might change over time, relevant codes might be updated during the course of the project.

Underlying comorbidity or 'history of' above mentioned conditions will be described as patient characteristics at time of entry into the specific study cohorts of interest. In addition, all factors as listed above will be considered as potential confounders in the association between the use of NVA237 or comparator drug and any of the outcomes of interest.

9.4 Data sources

This study will be conducted by using databases that comprise routine health care data. This will provide a reflection of real life circumstances and prescribing behaviors. The databases have been selected based on their geographic location, the availability of population based data on drugs, strength and indication plus their recognized reputation in the area of drug utilization and safety research. Multiple countries are included in order to provide international data and to guarantee a sufficient exposure to NVA237. All of the participating databases are part of the EU-ADR alliance, a stable collaboration framework for running drug safety studies in a federated manner, especially when the participation of several electronic health care record databases is required (Coloma et al 2013).

All of the chosen databases comply with European Union (EU) guidelines on the use of medical data for medical research and have been validated for pharmaco-epidemiological research (Vlug et al 1999, Lewis et al 2007, Ehrenstein, Antonsen, and Pedersen 2010, Cazzola et al 2011; Garcia-Gil Mdel et al 2011).

The data for this study will be retrieved from the databases listed below and will be analysed by EMC according to the Statistical Analysis Plan that has been reviewed and approved by Novartis.The databases will be THIN (UK), HSD (Italy), IPCI (Netherlands [NL]), the Aarhus University Prescription Database (DK), and SIDIAP (Spain). Table 9-2 provides an overview of the data. These databases have a mean follow-up ranging from 2.5 to 11 years. The databases are representative of the country-specific populations in terms of age and gender. The databases that will be used are primary care databases (except for the Aarhus database from Denmark, which is a prescription database) and available data are complete as they come from the general practitioner's (GP's) electronic primary care records. The primary care databases represent 3-13% of the country specific total population. The total number of persons in the source population encompassing all five databases will be around 12 million.

Table 9-2 Overview of databases

	NL	UK	DK	Italy	Spain
Name of the database	IPCI	THIN	Aarhus	HSD	SIDIAP
Type of database	MR	MR	ADM	MR	MR
Number of patients, *millions*	1.2	2.7	1.8	1.5	5.1
Date in	Yes	Yes	Yes	Yes	Yes
Date out	Yes	Yes	Yes	Yes	Yes
Date of death	Yes	Yes	Yes	Yes	Yes
Cause of death	Yes	Yes	Yes	No	No
Updates	Bi-annually	Monthly	Yearly (April)	Bi-annually: (30/06 and 31/12)	Yearly (April/May)
Prescriptions					
Outpatient Rx	Yes (specialist incomplete	Yes (specialist incomplete	Yes	Yes (specialist incomplete)	Yes (specialist incomplete)
Coding of drugs	ATC	BNF/Multilex code	ATC	ATC	ATC
Dosing regimen	Yes	Yes	No	Yes (incomplete)	Yes
Outcomes					
Hospitalisations	Yes	Yes	Yes	Yes	Yes
Outpatient diagnoses	Yes	Yes	No	Yes	Yes
Coding of disease	ICPC	READ	ICD-10	ICD-9 CM	ICD-10

9.4.1 IPCI Database

In 1992 the Integrated Primary Care Information Project (IPCI) was started by the Department of Medical Informatics of the Erasmus University Medical Center. IPCI is a longitudinal observational database that contains data from computer-based patient records of a selected group of general practitioners (GPs) throughout the Netherlands, who voluntarily chose to supply data to the database. Collaborating practices are located throughout the Netherlands and the collaborating GPs are comparable to other GPs in the country according to age and

gender. In the Netherlands, all citizens are registered with a GP practice, which forms the point of care and acts as a gatekeeper in a two-way exchange of information with secondary care. The medical records of each patient can therefore be assumed to contain all relevant medical information including medical findings and diagnosis from secondary care.

The database contains information on about 1.2 million patients. This is the cumulative amount of patients who have ever been part of the dynamic cohort of patients who have been registered. The International Classification of Primary Care (ICPC) is the coding system for patient complaints and diagnoses, but diagnoses and complaints can also be entered as free text. Prescription data such as product name, quantity prescribed, dosage regimens, strength and indication are entered into the computer (Vlug et al 1999). The National Database of Drugs, maintained by the Royal Dutch Association for the Advancement of Pharmacy, enables the coding of prescriptions, according to the Anatomical Therapeutic Chemical (ATC) classification scheme recommended by the WHO (WHO 2008).

As this is a primary care database, information on specialist prescribing, drug dispensing and actual drug intake is missing.

IPCI is listed under the ENCePP resources database (www.encepp.eu/encepp/resourcesDatabase.jsp).

9.4.2 HSD CSD Longitudinal Patient Database

The Italian arm of the study will use the Health Search CSD Longitudinal Patient Database (HSD), a longitudinal observational database that is representative of the Italian general population. It was established in 1998 by the Italian College of General Practitioners (Filippi et al 2005). The HSD contains data from computer-based patient records from a selected group of GPs (covering a total of 1.5 million patients) located throughout Italy. These GPs voluntarily agreed to collect data for the database and attend specified training courses. The database includes information on the age, gender, and identification of the patient, and GP registration information, which is linked to prescription information, clinical events and diagnoses, hospital admission, and causes of death. All diagnoses are coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Drug names are coded according to the ATC classification system (WHO 2008). To be included in the study, GPs must have provided data for at least 1 year and meet standard quality criteria pertaining to: levels of coding, prevalence of well-known diseases, and mortality rates (Cricelli et al 2003). The HSD complies with EU, guidelines on the use of medical data for research. The HSD has been used as data source for a number of peer-reviewed publications on the prevalence of disease conditions, drug safety and prescription patterns in Italian primary care (Cazzola et al 2011). Approval for use of data is obtained from the Italian College of General Practitioners.

Dose must be inferred from the strength, assuming a once daily administration for NVA237 and according to the dosing regimens of the respective SmPC for the other drugs. Around 50% of prescription dosage is also imputed by GPs.

HSD is listed under the ENCePP resources database (www.encepp.eu/encepp/resourcesDatabase.jsp).

9.4.3 THIN Database

The Health Improvement Network (THIN) is a database of primary care medical records from the United Kingdom. General practitioners are trained to complete their medical records using the Vision general practice computer system (InPractice Systems, London, UK). This electronic record serves as the primary medical records for the practice.

Data recorded in THIN include demographics, details from general practitioners' visits such as medical diagnoses and prescriptions written by the general practitioners, diagnoses from specialist referrals and hospital admissions, some results of laboratory tests, some lifestyle characteristics and other measurements as taken in the practice. Within the database, diagnoses are recorded using READ codes. Prospective data collection for THIN began in September 2002, with electronic medical records that date back to 1985. In addition, practices may retrospectively enter significant medical events into the electronic medical record. Currently, the database has 2.7 million active patients registered. Recently a validation study was conducted by Lewis et al which concluded that "THIN data that are collected outside of the Clinical Practice Research Datalink (CPRD) appear as valid as the data collected as part of the CPRD (Lewis et al 2007).

As the primary aim of the collection of data in the THIN database is patient management, data will reflect only those events that are deemed to be relevant to patient's care. In addition; use of THIN data is not appropriate in studies where individual ethnicity, occupation, employment, and/or socio-economic status are important variables. As for all prescription databases, over-the-counter (OTC) drug use and non-compliance to medication prescriptions might be an issue. As the average follow-up within the THIN database is 5.5 years, the THIN database is not suitable to conduct long-term follow-up studies.

THIN is listed under the ENCePP resources database (www.encepp.eu/encepp/resourcesDatabase.jsp).

9.4.4 Aarhus Database

The Aarhus University Prescription Database comprises clinical and prescription data on the population of former North-Jutland, Aarhus, Rinkjebing and Viborg counties, which since 2007 are called the Central Denmark Region and the North Denmark Region. This population covers a total of 1.8 million inhabitants and is representative of the population of Denmark

(Ehrenstein, Antonsen, and Pedersen 2010). Data available on these subjects comprise their eligibility, dispensing data, hospitalizations and procedures and the population can also be linked to other National Danish registries. Dispensing data comprise the filled prescriptions for all ambulatory patients and contains information on name of the drug, ATC code, package identifier (strength and route of administration), and the date of refill. These data can be linked to the national registry of patients that comprises information on admissions to Danish somatic hospitals, emergency rooms and outpatient clinics, diagnosis codes and procedures are registered. These databases have been used in numerous studies and are proven valid for pharmacoepidemiological research (Sorensen and Larsen 1994).

Dose must be inferred from the strength, assuming a once daily administration for NVA237 and according the dosing regimens of the respective Summary of Product Characteristics of the other drugs. The main drawbacks of the Aarhus University Prescription Database are a lack of nationwide coverage and the absence of data of certain medication types (non-reimbursed drugs, OTC drugs or drugs dispensed directly to hospital patients or outpatient clinics).

9.4.5 SIDIAP Database

GPs play an essential role in the public health care system of Spain, as they are responsible for primary health care, long-term prescriptions and specialist and hospital referrals. The Spanish public health care system covers more than 98% of the population. SIDIAP Database comprises of electronic medical records of a representative sample of patients attended by GPs in Catalonia (North-East Spain), covering a population of more than 5.1 million patients (about 80% of the total of 7.5 million population of Catalonia) from 274 primary care practices with 3,414 participating GPs. The SIDIAP data comprises the clinical and referral events registered by primary care health professionals (GPs and nurses) and administrative staff in electronic medical records, comprehensive demographic information, prescription and corresponding pharmacy invoicing data, specialist referrals, primary care laboratory test results, and hospital admissions and their major outcomes. Health professionals gather this information using ICD-10 codes, and structured forms designed for the collection of variables relevant for primary care clinical management, such as country of origin, sex, age, height, weight, body mass index, tobacco and alcohol use, blood pressure measurements, blood and urine test results. Only GPs who meet quality control standards can participate in the SIDIAP database. Encoding personal and clinic identifiers ensures the confidentiality of the information in the SIDIAP Database. Recent reports have shown the SIDIAP data to be useful for epidemiological research (Garcia-Gil Mdel et al 2011).

SIDIAP is listed under the ENCePP resources database (www.encepp.eu/encepp/resourcesDatabase.jsp).

9.5 Study size

All NVA237 users who meet the study inclusion criteria and their comparator patients will be used to assess the risk of the selected cardio- and cerebrovascular outcomes and mortality. The actual sample size for the study will be largely affected by the market uptake of NVA237 in the source population. Because the actual number of subjects in the study is difficult to predict at the early planning stage, the following calculations provide examples of sample size in terms of number of patients.

This sample size calculation was repeated for different estimates of background IR of MACE and assuming a median duration of first treatment episode of NVA237 of 180 days, all based on information from literature (Breekveldt-Postma et al 2007, Jara et al 2012, Verhamme et al 2012 White et al 2013). Although there is conflicting evidence from the literature on the association between the use of LAMA (tiotropium) and the risk of cardiovascular events, those studies with positive associations, reported hazard ratios (HRs) varying from 1.5 to 2 and above (Singh, Loke, and Furberg 2008, Jara et al 2012, Dong et al 2013). For this reason, sample size estimates were calculated assuming an incidence rate ratio (IRR) of 1.5 and 2 (see Table 9-3 below).

Considering the size of the databases, and the fact that the comparator groups are well established treatments in COPD and NVA237 being new to market, we assume in the worst case a 1:4 ratio of NVA237 vs. LAMA, (excluding NVA237) or LABA. The sample size calculation was repeated assuming a 1:6 ratio and a 1:10 ratio which is more likely in view of the uptake of a new drug in the market.

Table 9-3 Sample size calculation

Outcome	Background IR (based on literature (Jara et al 2012, Verhamme et al 2012, White et al 2013)	Additional IR	IRR	NVA – comparator ratio	Number of NVA237-exposed patients needed
MACE	0.01	0.005	1.5	1:4	7610
	0.02	0.01	1.5	1:4	3832
	0.05	0.025	1.5	1:4	1565
	0.10	0.05	1.5	1:4	810
MACE	0.01	0.01	2	1:4	2079

Outcome	Background IR (based on literature (Jara et al 2012, Verhamme et al 2012, White et al 2013)	Additional IR	IRR	NVA – comparator ratio	Number of NVA237-exposed patients needed
	0.02	0.02	2	1:4	1049
	0.05	0.05	2	1:4	431
	0.10	0.10	2	1:4	225
MACE	0.01	0.005	1.5	1:6	6919
	0.02	0.01	1.5	1:6	3485
	0.05	0.025	1.5	1:6	1424
	0.10	0.05	1.5	1:6	738
MACE	0.01	0.01	2	1:6	1849
	0.02	0.02	2	1:6	933
	0.05	0.05	2	1:6	384
	0.10	0.10	2	1:6	201
MACE	0.01	0.005	1.5	1:10	6367
	0.02	0.01	1.5	1:10	3207
	0.05	0.025	1.5	1:10	1312
	0.10	0.05	1.5	1:10	680
MACE	0.01	0.01	2	1:10	1665
	0.02	0.02	2	1:10	841
	0.05	0.05	2	1:10	346
	0.10	0.10	2	1:10	181

IR = incidence rate; IRR = incidence rate ratio; MACE = major adverse cardiac event

Based on SAS Proc Power (Lakatos 1988, Cantor 2003)

Note: This sample size calculation does not take into account the loss of precision, when conducting a pooled analysis (meta-analysis approach)

Sample size calculation is based on a logrank test, with a power of 80% and a 2-sided test with a significance level of 0.05. Accrual time (= time between first patient and last patient entering the study) was set at 3 years and we assumed no additional follow-up time. Based on information from literature on the duration of LAMA treatment episodes, censoring was set after a median of 180 days, assuming most censoring will be caused by the end of treatment

period (Breekveldt-Postma et al 2007, Jara et al 2012, Verhamme et al 2013). Of course, patients will be followed-up for the complete duration of their treatment episode (thus even beyond 180 days if the treatment episode lasts longer).

In order to allow detecting an increased risk, if the risk is higher by at least a factor of two (incidence rate ratio, IRR=2), for an event with a background incidence rate of 10 per 1,000 person-years, and a worst case scenario of a 1:4 ratio of numbers of NVA237 vs. LAMA or LABA, the group of NVA users should consist of at least 2,079 persons with at least 10,395 persons for both the LAMA and the LABA cohort.

The sample size estimation procedure followed here is different from the previous approach used in the agreed study synopsis and the initially submitted PASS protocol (version 1.5). For the current sample size estimation approach, we included accrual period and duration of LAMA treatment episodes based upon literature information (Breekveldt-Postma 2007; Jara 2012; Verhamme 2013). Although the sample size estimated with the current approach (i.e. 2,079 patients) – which allows detecting an increased risk if the risk is higher by at least a factor of two – is considerably lower than the initially proposed 3,000 patients, we propose to include the originally proposed sample size of 3,000 to be consistent with the previously agreed study synopsis and the initially submitted PASS protocol (dated 11 December 2012).

Based on the projected market uptake of NVA237 and the coverage of the databases of the total (country specific) population, the following predictions can be made about the number of NVA237 users within the different databases:

Table 9-4 Individual database estimates of NVA237 treated patients for the year 2016

	Country estimate for 2016	Multiplicator	Individual database estimate of Seebri treated patients in 2016
UK	58,677	0.030	1,760
Italy	257,911	0.017	4,384
Spain	181,567	0.066	11,983
Denmark	19,420	0.153	2,971
Netherlands	20,745	0.062	1,286

NA=not applicable; *since COPD is mainly affecting ≥40 years old, corresponding multiplicator is used.

The total estimate across all databases would sum up to 22,386 patients. Under the assumption that 70% of the NVA237 treated patients will fulfill the in-/exclusion criteria, the total number of patients would correspond to 15,670. Based on these numbers, we are confident that we

will be able to accrue the proposed sample size of 3,000 patients in the NVA237 treatment cohort.

9.6 Data management

Data from the five different databases will be pooled after local extraction, validation and data-cleaning. Clearly, it is not possible to use one single data extraction algorithm for all the databases. They use different coding schemes (e.g. ICD9-CM and ICD10, ICPC, READ) and their content comes from different data sources (e.g., general practitioners' records, hospital discharge diagnoses, and death registries). To reconcile differences across terminologies a shared semantic foundation will be built for the definition of events under study by selecting disease concepts from the Unified Medical Language System (UMLS, V.2008AA), and set up a multi-step and iterative process for the harmonization of event data. The sequential steps of this process are shortly described below:

9.6.1 Identification of Unified Medical Language System (UMLS) concepts

A UMLS® concept is identified by a Concept Unique Identifier (CUI) and describes a single medical notion that can be expressed using different synonyms (terms). For each event, a medical definition will be created and, based on such definition relevant UMLS concepts are identified and projected into the database-specific terminologies (disease specific codes per event, COPD and comorbidity are described in Annex 3, Annex 6, and Annex 8, respectively) In addition, for those databases where free text is available, the labels of the codes are considered for free text search of the events.

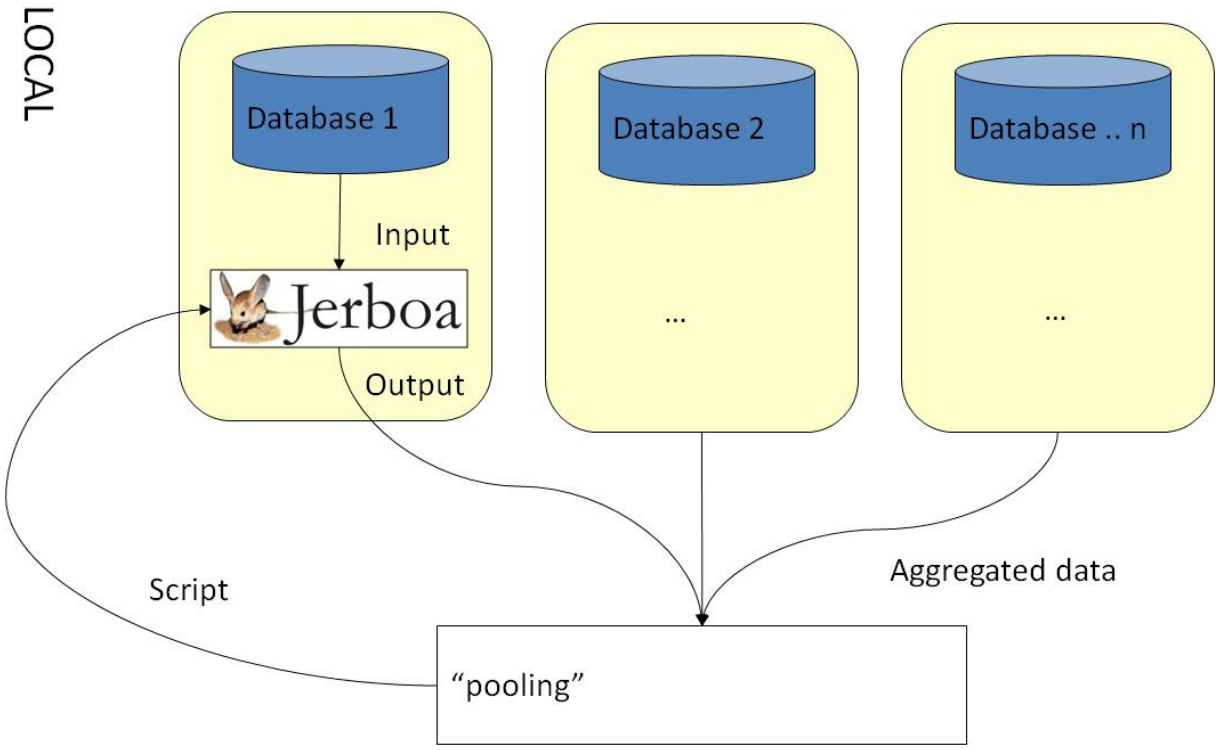
9.6.2 Definition of data extraction algorithm

Based on the relevant diagnostic codes and key words (for free text search), a data extraction algorithm will be constructed for each event based on the consensus of the data providers. This data extraction algorithm will then be implemented by all databases.

9.6.3 Event data extraction

Subsequently, each database extracts data using a common data model, i.e. standardized patient, drug, and event files linkable via a patient unique identifier. These files are managed locally by purpose-built software called Jerboa, which transforms the input files in de-identified aggregated output files. These output files are transmitted to a central secured environment (remote research environment) for pooling and further processing. Jerboa has been developed for the EU-ADR FP7-ICT project (www.EU-ADR-project.org) that combines health care data of 30 million individuals in Europe to detect adverse drug events. It has been used in many other EU funded projects (i.e. SOS: www.sos-nsaids-project.org; VAESCO: www.vaesco.net) and EMA tender protocols.

Figure 9-5 Model for data sharing and elaboration (obtained from www.EU-ADR-project.org)



9.6.4 Benchmarking of incidence rates of events

For each event we benchmark database-specific incidence rates (IRs) using Jerboa. The observed IRs are compared with IRs estimated from previous database studies and literature. Outliers are identified and further investigated in an iterative manner.

We have used this multi-step process successfully in several other European multi-database projects. It maximizes the involvement of the data providers in the study by utilizing their knowledge on the characteristics and the process underlying the data collection.

9.7 Data analysis

All analyses will be performed by [redacted], the coordinating center for this multi-database study. Data will be deposited in the remote research environment and participating partners can inspect the analysis by remotely accessing.

Further details of the analysis are described in the statistical analysis plan (SAP).

The endpoints of interests for both the yearly reports and the final report are the following:

- Major cardiovascular events (MACE) including myocardial infarction and stroke, and hospitalizations due to acute coronary syndromes and/or heart failure
- Ischemic heart disease including myocardial infarction or angina pectoris
- Cardiac arrhythmias (atrial fibrillation/flutter, atrioventricular (AV) block, premature depolarization, sick sinus, supraventricular tachycardia and ventricular arrhythmia including ventricular tachycardia, ventricular fibrillation and Torsade de Pointes/Long QT syndrome)
- Cerebrovascular disorders (ischemic and hemorrhagic stroke, transient ischemic attack [TIA]
- Mortality (all cause)

Definitions of these endpoints and validation algorithms are further described under Annex 3 – Event definition and Annex 4 – Validation algorithm.

9.7.1 Yearly analysis for study progress reports and yearly reports

Yearly progress reports and interim reports will be created with the first report scheduled one year after first launch (November 2012) of NVA237. These reports will include both data-specific information and pooled data. The reports will contain the following information:

- Number of patients in the different exposure cohorts (NVA237, LAMA [excluding NVA237] or LABA)
- Baseline characteristics in terms of comorbidity and concomitant drug use at time of index date of the different exposure cohorts. This will be described using contingency tables for categorical variables and mean, standard deviation (SD), and range for continuous variables
- Counts will be provided for the combined endpoints overall as well as for the single components of the endpoints (i.e. overall count for cerebrovascular disorder as well as separate count for stroke and TIA). With regard to cardiac arrhythmia, counts will be provided for i) cardiac arrhythmia overall, ii) for the individual components of cardiac arrhythmia, iii) for severe cardiac arrhythmia (atrial flutter/fibrillation, atrioventricular (AV) block and ventricular arrhythmia (ventricular tachycardia, ventricular fibrillation and Torsade de Pointes/Long QT syndrome) and iv) for other cardiac arrhythmia (premature depolarization, sick sinus and supraventricular tachycardia).
- Crude IRs of the combined endpoints of interest among the three different exposure cohorts

The IRs will only be calculated when the number of identified new NVA237 users is more than 1000 patients. If this number is not reached, the yearly progress reports will only provide numbers of exposed patients and baseline characteristics.

The yearly reports will not provide information on adjusted hazard ratios (HRs; see Section 9.7.2) as the manual validation of the COPD cohort and validation of the different endpoints of interest will only be conducted at the end of the study. This implies that no correction for multiple testing needs to be done for the final data analysis which is planned at the end of the study.

During the study conduct however, the safety of NVA237 will be closely monitored by reviewing the yearly IRs for the different endpoints of interest. If the crude IR of the pooled data of any of the endpoints for the NVA237 cohort is 3-fold higher than the IR among the comparator groups, this will be considered as a safety signal and a full analysis including controlling/adjustment for potential confounders and/or effect modifiers will be initiated. The full analysis will include the main analysis and secondary analyses (including relative risk estimates [as HRs with 95% confidence intervals {95% CIs}]) consisting of all analyses performed individually in each database as well as a pooled analysis, with test for heterogeneity etc. as outlined in more detail in the following Section 9.7.2.

9.7.2 Final analysis

The final analysis, consisting of an analysis on each database individually as well as a pooled analysis will be conducted at the end of the study (one year after inclusion of the 3000th patient in the new user cohort of NVA237). The final analysis will be conducted after manual validation of the COPD cohort (see Section 9.3.3 and the endpoints of interest (see Section 9.3.1)).

The final analysis consists of a main analysis and secondary analyses.

9.7.2.1 Main analysis

Demographic and baseline characteristics of exposure cohorts

Demographic and baseline characteristics of the patients initiating NVA237 or new users of LAMA and LABA will be described using contingency tables for categorical variables and mean, SD, and range for continuous variables in each database. Differences in demographic and baseline characteristics of NVA237 and the two comparator drug classes will be assessed via the non-parametric Mann-Whitney U test for continuous variables, and the Chi-square test for categorical variables.

Incidence rates and hazard ratios of different endpoints

To determine the risk of cardiovascular and cerebrovascular endpoints and mortality in new users of NVA237 and new users of LAMA (excluding NVA237) and new users of LABA (two comparator groups), the IRs with 95% CIs will be calculated using negative binomial distribution for each outcome of interest in the three treatment cohorts.

The relative risk (expressed as HR with 95% CI) will be estimated for users of NVA237 vs. new users of LABA and new users of LAMA (excluding NVA237) using Cox regression models (for each of the endpoints of interest). HRs will only be estimated in case of at least 5 events per exposure cohort. This analysis will be conducted considering 1) only the first treatment episode during follow-up (in this scenario, patients who switched to another exposure category will be excluded) or 2) all treatment episodes.

To control for potential confounding, the following covariates (all measured at the index date) will be included in the final model:

- Age (at index date)
- Gender
- Smoking history ("current smoker", "past smoker", "non-smoker" or "smoking status unknown")
- COPD severity
- Hospitalization for COPD
- Duration of COPD
- Calendar year (year of index date)
- Number of GP visits in the one year prior to the index date
- All potential confounding factors. To assess confounding, all covariates that change the crude HR by more than 5% will be included in the final model. The factors that will be considered are all drugs and co-morbidities specified under Section 9.3.4 and Section 9.3.5.

Use of concomitant medication (respiratory drugs and other drugs) will be added as time-varying exposure in the Cox regression model. Time-varying exposure will be assessed by dividing the treatment follow-up in 30-day windows and assessing drug exposure in each of these windows.

In addition, to control for confounding by indication, the analysis will be repeated adjusting for the propensity score assigned to NVA237.

First, a logistic regression model will be built to estimate propensity scores to be treated with NVA237 instead of the comparator using the covariates listed below:

- Age (at index date)
- Gender
- COPD severity
- Concomitant drug use (see protocol Section 9.3.4; Annex 7 for codes)
- Comorbidity (see protocol Section 9.3.5; Annex 8 for codes)
- Smoking (see protocol Section 9.3.5)

Stratified Cox models will be fitted using deciles of the propensity scores as strata (Huybrechts et al 2012).

Pooled analysis

All analyses will at first be performed for each database separately and the heterogeneity between databases will be examined. Statistical heterogeneity across databases will be tested by using a Cochran's Q statistic. For this test, a p-value of 0.05 (2-sided) and below will be considered to indicate heterogeneity. To measure the degree of heterogeneity an I^2 value will be recorded, with I^2 values above 75% representing a high level of heterogeneity.

To account for the heterogeneity between databases, a meta-analysis with random effects will be used for the combined analysis of the results of the databases separately.

In addition, a pooled analysis will be done by combining the data sources on patient-level with adjustment as described for the analysis of the individual databases.

Handling of missing data

Smoking

Information on smoking status might be incomplete in these electronic health care databases. In a first analysis, patients will be classified as "current smoker", "past smoker", "non-smoker" or "smoking status unknown" at the time of the index date.

Next, a sensitivity analysis will be done, first attributing all patients in the category "unknown" as non-smokers, and secondly attributing all patients in the category "unknown" as smokers. If this will give different estimates for the HR of NVA237 (difference > 5%), imputation for missing information on smoking will be done. To compare the distribution of smokers (before and after imputation), appropriate prospective COPD cohorts, covering each geographic region, will be identified at the time of the analysis (Lokke et al 2006, van Durme et al 2009).

Correction for multiple testing

Although yearly progress reports will be prepared, there will be no need for correction for multiple testing as these yearly reports will not contain information on hazard ratios.

In addition, as all analyses have been predefined, there will be no need for adjustment for multiple comparisons.

9.7.2.2 Secondary analyses

Stratified analysis

To determine the modifying effect of co-morbidities on the risk of cardiovascular and cerebrovascular endpoints, a stratified Cox regression analysis will be conducted in patients with or without medical history of cardiovascular or cerebrovascular disease.

Patients with a medical history of cardiovascular disease will be patients with a history of hypertension, heart failure, cardiac arrhythmia and ischemic heart disease at the index date.

Patients with a medical history of cerebrovascular disease will be patients with a history of ischemic, hemorrhagic stroke or TIA at the index date.

In addition, stratified analyses will be conducted by:

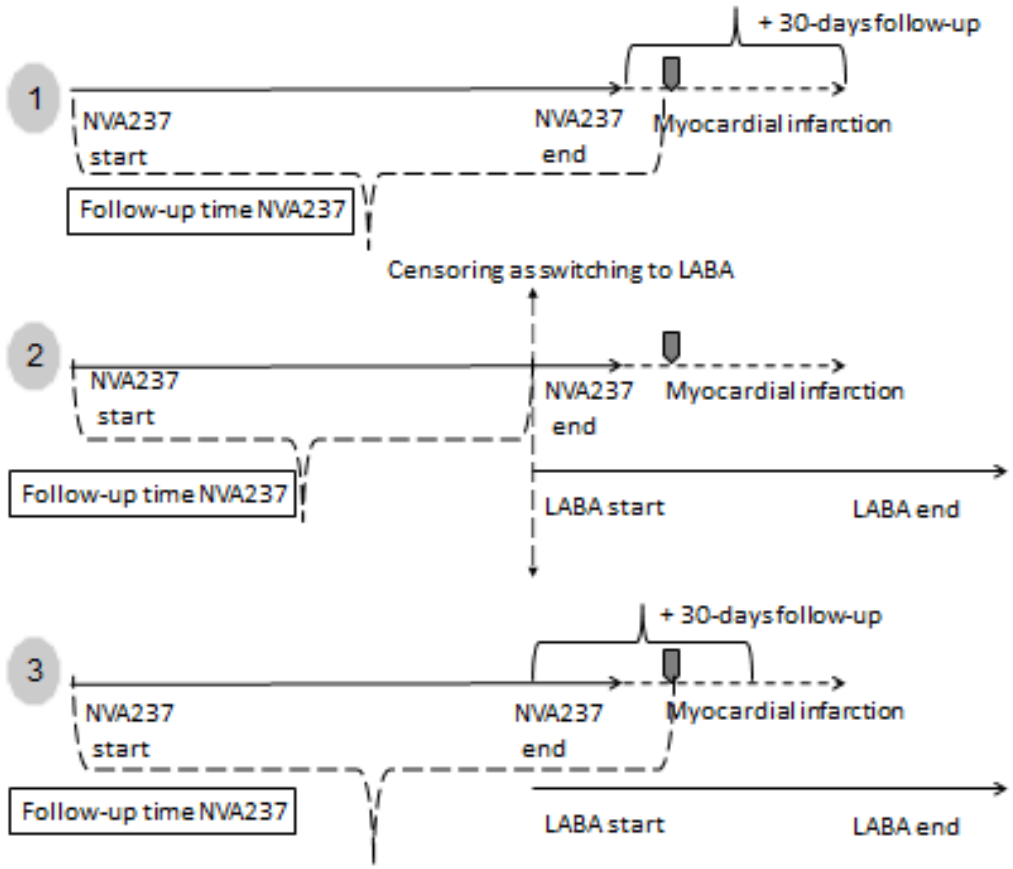
- Gender
- age group (≥40-<65, ≥65-<75, ≥75 years)
- COPD severity status
- Patients with and without non-cardiovascular life-threatening conditions (stratification as a minimum will include patients with underlying cancer [excluding skin basal cell cancer as this is not a life-threatening condition]. Other conditions will be considered as appropriate depending upon the data obtained during the study)

The purpose of stratified analyses is to determine the modifying effect of co-morbidities on the risk of cardiovascular and cerebrovascular endpoints. Stratified analyses will result in lower sample sizes for the individual strata with the risk of loss of power as compared to the un-stratified analysis.

Sensitivity analyses

For the primary analysis and for each of the different treatment cohorts, patients are only followed during the first episode of exposure. A 30-day window after last estimated drug intake is added as patients might not be fully compliant and to control for late effect upon treatment discontinuation (see Figure 9-6 – first scenario). To avoid misclassification of the endpoints, the 30 day extension window is not considered when treatment is discontinued because of switching to or add-on of another treatment and thus follow-up is censored upon discontinuation or add-on therapy (see Figure 9-6 – second scenario). In a sensitivity analysis, events occurring in the 30 days window upon switching or add-on therapy will be attributed to the first treatment episode (see Figure 9-6 – third scenario).

Figure 9-6 Different scenarios of follow-up for first episode of exposure



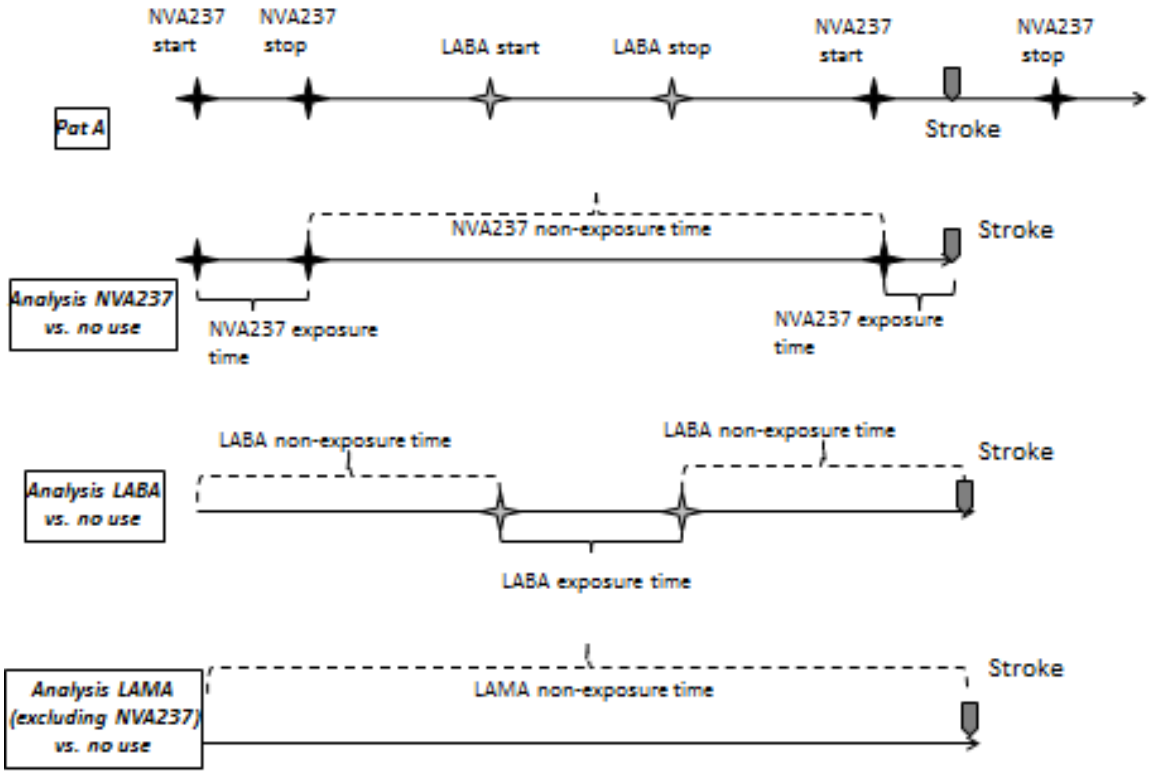
The use of a 30-day window after drug discontinuation to define "current exposure" is common in pharmacoepidemiological research within COPD (Verhamme et al 2013). In a sensitivity analysis, this follow-up window after drug discontinuation will be extended from 30 to 60 days.

Upon discontinuation of one of the treatment cohorts, patients are still eligible to be enrolled in the other treatment cohorts. In a sensitivity analysis, switching to another cohort will only be allowed when the window between treatment discontinuation of first cohort and treatment initiation of second cohort is a minimum of 60 days.

To analyze the complete follow-up of each patient from start of first treatment onwards, treatment with NVA237, LAMA (excluding NVA237) or LABA will be used as time-varying exposure variables. For this analysis, subsequent cardio- or cerebrovascular episodes of interest with or without treatment will be taken into account. Patients will be followed from start of first prescription of NVA237, LABA or LAMA (excluding NVA237) until the endpoint of interest, end of study, disenrollment from the database or death, whichever comes first. For this analysis, the HR of the events of interest will be estimated for NVA237 vs. no

use of NVA237. This analysis will be repeated for LAMA (excluding NVA237) vs. no use of LAMA (excluding NVA237) and LABA vs. no use of LABA (Figure 9-7).

Figure 9-7 Sensitivity analysis where complete follow-up of patients is used for the respective analysis



In addition, a sensitivity analysis will be conducted only considering the first treatment episode during follow-up in patients naïve to both NVA237 and all of the comparator drugs. (thus no use of NVA237 or LABA or LAMA) in the one year prior to the first treatment episode since study start)

9.8 Quality control

The study will be conducted according to the guidelines for Good Pharmacoepidemiology Practice (GPP) (Epstein 2005) and according to the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) code of conduct (EMA 2010). All programs will be programmed according to agreed coding standards and will be validated by double programming or source code review with second programmer involvement. Only

validated software (SAS version 9.2, SAS Institute Inc., Cary, NC) will be used for statistical analyses.

9.9 Limitations of the research methods

The limitations of this study will be mainly due to the availability and level of detail of data. Not all potential confounders (e.g. lifestyle factors such as smoking, body mass index [BMI]) are contained in (all) databases or are available at all in any database (e.g. physical activity, socio-economic status, and race), and not all variables contain the information in desired detail. Particularly, information on the prescribed dose and duration of a prescription is not contained in all databases and has to be estimated, which might lead to misclassification of exposure. Misclassification of NVA237 and comparative LAMA (excluding NVA237) and LABA is less of a concern as these drugs are prescribed according to a fixed dose only.

All of the databases, apart from the Aarhus University Prescription Database, have information on prescriptions only and not on dispensing or actual drug intake. This implies that we do not know whether the patient actually took the drug – however, it is known that adherence to drugs is highest at initiation of therapy, thus the risk of misclassification of exposure is less of a concern in a new user design.

Misclassification of endpoints as well as confounders is possible. Most of the databases only contain information on underlying diseases based on disease codes. For the different databases that will be used, validation studies have shown that coding is reliable in the databases and that these databases are suitable for pharmacoepidemiological research. For the databases in which free text is available (IPCI, HSD and SIDIAP), validation of endpoints will be conducted. Comparison of IRs of endpoints across databases will allow investigation of internal and external validity.

For all databases, apart from the Aarhus University Prescription Database, it should be noted that the primary aim of data collection is patient management and not medical research. This implies that only events are collected which are deemed to be relevant for the patient's care.

Some of the databases (Aarhus, IPCI, THIN and SIDIAP) have a mean follow-up of 2.5-6 years hindering the conduct of long-term follow-up studies.

Finally, there are differences in timing of data updates in the various databases (medical records are continuously updated, administrative databases are updated only once per year in most instances). However, as data extraction will be repeated during the course of the study, this should allow for "up-to-date data" at study end.

9.10 Other aspects

Not applicable.

10 Protection of human subjects

For this study, participants from various EU member states will process personal data from individuals which are collected in national/regional electronic health record databases. Due to the sensitive nature of these 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 of the databases used in this study are currently 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.

According to these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which will generate non identifiable data with less detailed information that will be pooled across databases.

The output files are stored in the central Remote Research Environment (RRE) [redacted]. These output files do not contain any data that allows identification of subjects included in the study. In fact each record is completely anonymous and does not contain any identifier key. Starting from this, the RRE implements further security measures in order to ensure a high level of stored data protection, according to the article 34 of legislative decree 196/2003 and article 22 of Regulation (EC) 45/2001.

In addition, a scientific advisory committee (SAC) will be installed to guarantee scientific soundness of the study and in addition will follow-up on the progress and the appropriate conduct of the study. This scientific advisory committee will also be involved in the review of the yearly progress and interim reports.

Members of the scientific advisory committee are the following:

- Prof Dr [redacted], Canada
- Prof Dr [redacted], Belgium
- Dr [redacted], USA

11 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 reporting of adverse drug reactions from secondary use of data (such as electronic health care databases). Reports of adverse events/reactions will not be provided on an individual case level; only aggregated safety results, i.e. the overall association between an exposure and an outcome will be reported in the final study report.

12 Plans of disseminating and communicating study results

As the study progresses, Novartis will submit the interim reports and final study report to EMA. The study progress and interim results will be reported in yearly intervals following first launch in Europe (with PSUR).

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

In order to allow EMA to review in advance the results and interpretations to be published, Novartis will communicate to the Agency the final manuscript of an article within two weeks after first acceptance for publication.

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Annex 1 List of stand-alone documents

None.

Annex 2 ENCePP checklist for study protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

London, 25 July 2011

Doc.Ref. EMEA/540136/2009

ENCePP Checklist for Study Protocols (Revision 1)

Adopted by the ENCePP Steering Group on 19/08/2011

The purpose of the Checklist developed by ENCePP is to stimulate consideration of important epidemiological principles when designing a pharmacoepidemiological or pharmacovigilance study and writing a study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. ENCePP welcomes innovative designs and new methods of research. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each of the questions of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

Section 1: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the formulation of the research question clearly explain:				
1.1.1 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)	☒	☐	☐	23-24
1.1.2 The objectives of the study?	☒	☐	☐	24
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	25-26
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☐	☒	☐	
1.2.3 if applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Is the source population described?	☒	☐	☐	25-26
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	26
2.2.2 Age and sex?	☒	☐	☐	27

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.2.3 Country of origin?	☒	☐	☐	25
2.2.4 Disease/indication?	☒	☐	☐	25-26
2.2.5 Co-morbidity?	☒	☐	☐	34
2.2.6 Seasonality?	☐	☐	☒	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	27

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	29-30
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	24-25
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	45-46
3.4 Is sample size considered?	☒	☐	☐	40-43
3.5 Is statistical power calculated?	☒	☐	☐	40-43

Comments:

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: 4.1.1 Exposure? (e.g. pharmacy dispensing, general	☒	☐	☐	30-32

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
practice prescribing, claims data, self-report, face-to-face interview, etc)				
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc)	☒	☐	☐	29-30
4.1.3 Covariates?	☒	☐	☐	32-35
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	30-32
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	29-30
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	32-35
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	34, 36-39
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☒	☐	☐	34, 36-39
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	30, 36-39
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	43-44

Comments:Respective codes for drug exposure, endpoints and comorbidities are described in the annexes of the protocol (page 67-164)

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and	☒	☐	☐	30-32

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
categorising exposure)				
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	30-32
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	30-32
5.4 Is exposure classified based on biological mechanism of action?	☒	☐	☐	30-32
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	29-30; 67-96
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	29-30; 67-96

Comments:

Section 7: Biases and Effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address:				
7.1.1 Selection biases?	☒	☐	☐	25-27
7.1.2 Information biases?	☒	☐	☐	52

Section 7: Biases and Effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)				
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	46-47
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	48-49
7.4 Does the protocol address other limitations?	☒	☐	☐	52

Comments:

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☒	☐	☐	45-48
8.2 Is the choice of statistical techniques described?	☒	☐	☐	47-49
8.3 Are descriptive analyses included?	☒	☐	☐	45-46
8.4 Are stratified analyses included?	☒	☐	☐	48-49
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	☒	☐	☐	46-47
8.5.2 Effect modifiers?	☒	☐	☐	49
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	☒	☐	☐	46-47
8.6.2 Effect modification?	☒	☐	☐	49

Comments:

Information on the analysis is also documented in the Statistical Analysis Plan of this study (see separate document)

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	43-44
9.2 Are methods of quality assurance described?	☒	☐	☐	51-52
9.3 Does the protocol describe quality issues related to the data source(s)?	☒	☐	☐	52
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	40-43
9.5 Does the protocol specify timelines for				
9.5.1 Study start?	☒	☐	☐	22
9.5.2 Study progress? (e.g. end of data collection, other milestones)	☒	☐	☐	22
9.5.3 Study completion?	☒	☐	☐	22
9.5.4 Reporting? (i.e. interim reports, final study report)	☒	☐	☐	22
9.6 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	16-21
9.7 Are communication methods to disseminate results described?	☒	☐	☐	54
9.8 Is there a system in place for independent review of study results?	☒	☐	☐	53

Comments:

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	53
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
10.3 Have data protection requirements been described?	☒	☐	☐	53-54; 43-44

Comments:

Name of the coordinating study entity[1]: [redacted]

Name of (primary) lead investigator[2]: [redacted]

Date: 18 December 2014

Signature: _____

[1] A legal person, institution or organisation which takes responsibility for the design and/or the management of a study. The (primary) lead investigator is the person authorised to represent the coordinating study entity.

[2] A person with the scientific background and experience required for the conduct of a particular pharmacoepidemiological or pharmacovigilance study. The lead investigator is responsible for the conduct of a study at a study site. If a study is conducted at several study sites by a team of investigators, the (primary) lead investigator is the investigator who has overall responsibility for the study across all sites.

Annex 3 Event definitions

Note: The identified codes as documented in this annex will be reviewed by all databases prior to data-extraction. As coding might change over time, relevant codes might be updated during the course of the project.

Annex 3.1 Major cardiovascular events

MACE includes the following events:

- Myocardial infarction
- Stroke
- Hospitalization due to acute coronary syndrome and/or heart failure.

The definitions of myocardial infarction and stroke (and relevant disease codes) are described under Annex 3.1.1 and Annex 3.1.3.

Hospitalization due to acute coronary syndrome is defined as patients being hospitalized for reasons of 1) unstable angina pectoris or 2) myocardial infarction (ST segment elevation or non-ST segment elevation). The definition and disease specific codes for (unstable) angina pectoris and myocardial infarction are described under annexes 1.

Patients will be identified within the different databases based on a combination of disease specific codes for either unstable angina pectoris or myocardial infarction in combination with codes related to hospitalization. Hospitalization will be retrieved either via linkage with hospital admission/discharge database (SIDIAP and Aarhus), combination of disease codes with information from hospital referral and discharge letters) (HSD and IPCI) or combination of disease codes with source codes (hospital discharge letters) (THIN).

Hospitalization due to heart failure is defined as patients hospitalized for reasons of heart failure. The definition and disease specific codes for heart failure are described under annex 1.

Patients will be identified within the different databases based on a combination of disease specific codes for heart failure in combination with codes related to hospitalization. Hospitalization will be retrieved either via linkage with hospital admission/discharge database (SIDIAP and Aarhus), combination of disease codes with information from hospital referral and discharge letters) (HSD and IPCI) or combination of disease codes with source codes (hospital discharge letters) (THIN).

Annex 3.1.1 Myocardial infarction

Definition of acute myocardial infarction (AMI)

Myocardial infarction is defined as necrosis of the myocardium caused by an obstruction of the blood supply to the heart (coronary circulation). Blockage of a coronary artery deprives the heart muscle of blood and oxygen, causing injury to the heart muscle Therefore, acute myocardial infarction is defined by the evidence of myocardial necrosis - in a clinical setting consistent with a) myocardial ischemia, including ST elevation b) myocardial infarction and c) non-ST elevation myocardial infarction. In this study, an acute MI event will be ascertained using specific diagnoses codes for acute transmural myocardial infarction, acute subendocardial myocardial infarction, or unspecified acute myocardial infarction (Thygesen et al 2012).

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of myocardial infarction.

Codes used for identification of myocardial infarction

Terms	ICD10	ICD9CM	Read Codes	ICPC
Cardiac infarction	I22*			
Cardiac infarction	I21*			
Acute myocardial infarction	I21*	410.*	G30z.	K75
Acute myocardial infarction, unspecified	I21.9	410.9		
Myocardial infarction (acute) NOS	I21.3	410		
Acute myocardial infarction, unspecified site, episode of care unspecified		410.90		
AMI NOS, unspecified		410.90		
Acute myocardial infarction, sub endocardial infarction		410.7		
Old myocardial infarction[#]	I25.2	412		
Healed myocardial infarction[#]			G32..11	
Old myocardial infarction[#]			G32..00	
Subsequent/recurrent myocardial infarction	I22		G35..	
Subsequent myocardial infarction of unspecified site	I22.9		Gyu36	
Subsequent myocardial infarction of other sites	I22.8		Gyu35 G353.	
Subsequent myocardial infarction of	I22.0		G350.	

Terms	ICD10	ICD9CM	Read Codes	ICPC
anterior wall				
Subsequent myocardial infarction of inferior wall	I22.1		G351.]	
Subsequent acute sub endocardial myocardial infarction	I22.2			
Subsequent non transmural myocardial infarction NOS	I22.2			
Subsequent myocardial infarction (acute) NOS	I22.9			
Re-infarction of myocardium			G35..	
Acute sub endocardial myocardial infarction	I21.4			
Acute myocardial infarction, sub endocardial infarction, episode of care unspecified		410.70		
Non transmural myocardial infarction	I21.4			
Acute myocardial infarction, of antero lateral wall		410.0	G300.	
Acute antero septal myocardial infarction			G3011	
Acute inferior myocardial infarction		410.4	G308.00	
Acute myocardial infarction, true posterior wall infarction		410.6		
True posterior myocardial infarction			G306.	
Acute myocardial infarction, of inferoposterior wall		410.3	G303.]	
Other specified anterior myocardial infarction			G301.]	
Acute transmural myocardial infarction of unspecified site	I21.3		Gyu34 G30X.00	
Acute transmural myocardial infarction of anterior wall	I21.0 122.0			
Acute transmural myocardial infarction of inferior wall	I21.1 I21.19 122.1			
Acute transmural myocardial infarction of other sites	I21.2 I21.29 122.8			
ECG: old myocardial infarction[#]			3232.	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Anterior myocard. infarct NOS		410.8	G301z	
Other acute myocardial infarct			G30y.	
Other acute myocardial inf.NOS			G30yz	
Inferior myocard. infarct NOS			G308.	
Acute myocardial infarction, of infero lateral wall		410.2	G302.	
Acute lateral myocardial infarction		410.5		
Lateral myocardial infarct NOS			G305.]	
Acute widespread myocardial infarction			X200S	
Acute posterior myocardial infarction		410.60 410.61 410.62		
Posterior myocard. infarct NOS			G304.]	
Silent myocardial infarct			G30..17	
ECG: myocardial infarction			323..	
ECG: myocardial infarct NOS			323Z.	
Postoperative sub endocardial myocardial infarction			G384.00	
Postoperative myocardial infarction			G38z.00	
Acute anterior myocardial infarction		410.1		
Acute Q wave myocard infarct			G309.00	
Acute myocardial infarction, sub endocardial infarction		410.71 410.72		
Non-Q wave myocardial infarction NOS	I21.4 I22.2			
Non-ST elevation (NSTEMI) myocardial infarction	I21.4 I22.2			
History of MI[#]			14A3.00 14A4.00 14AH.00 14AT.00	K76.02
Diabetes mellitus insulin-glucose infuse acute myocardial infarct			889A.00	

[#] not for acute event, will only be considered for myocardial infarction as underlying comorbidity

Annex 3.1.2 Angina pectoris

Definition of Angina pectoris

Angina pectoris: According to the guidelines of the European Heart Association; angina pectoris is described as chest discomfort due to myocardial ischaemia associated with coronary artery disease. Anginal symptoms are regarded as stable if they have been occurring over several weeks without major deterioration. They typically occur in conditions associated with increased myocardial oxygen consumption. Angina is said to be unstable if pre-existing angina worsens abruptly for no apparent reason or when new angina develops at a relatively low work load or at rest (Fox et al 2006).

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of angina pectoris.

Codes used for identification of angina pectoris

Terms	ICD10	ICD9CM	Read Codes	ICPC
Angina pectoris	I20*	413*	G33..	K74
Angina pectoris, unspecified	I20.9	413.9	G33z.	
Angina of effort	I20.8			
Anginal syndrome	I20.9			
Cardiac angina	I20.9			
Ischemic chest pain	I20.9		G33z400	
Ischaemic heart disease			G3...00	
			G3...13	
Dressler's syndrome			G310.11	
			G31y.00	
			G34..00	
			G3y..00	
			G3z..00	
			Gyu3.00	
			Gyu3000	
Stenocardia			G33z1	
Unstable angina	I20.0		G311.00	K74.01
			G311.13	
			G311100	
			G330000	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Crescendo angina	I20.0		G311.11	
Intermediate coronary syndrome	I20.0	411.1		K76.01
Acute coronary syndrome				
			G311500	
			G33z000	
Angina at rest			G311.14	
			G311200	
Impending infarction			G311.12	
			G311000	
			G311011	
			G311z00	
			G312.00	
			G31y100	
			G31y200	
			G31y300	
			G31yz00	
Worsening angina			G311400	
Angina pectoris with documented spasm	I20.1		G31y000	
			G332.00	
Nocturnal angina			G330000	
Stable angina			G33z700	
Other forms of angina pectoris	I20.8		Gyu30	
Exercise induced angina			G33z300	
Refractory angina			G311300	
Frequency of angina			187..00	
H/O angina pectoris[#]			14A5.	
			14AJ.00	
Canadian Cardiovascular Society classification of angina			388E.00	
Cardiovascular Limitations and			388F.00	
Angina self-management plan agreed			661M000	
Angina self-management plan re			661N000	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Angina control			662K.00	
			662K000	
			662K100	
			662K200	
			662K300	
			662Kz00	
Antianginal therapy			8B27.00	
Coronary artery bypass graft operation planned			8L40.00	
Coronary angioplasty planned			8L41.00	
Other chronic ischaemic heart disease			G34..	

[#] not for acute event, will only be considered for angina pectoris as underlying comorbidity

Annex 3.1.3 Stroke

Definition of stroke

Stroke is defined as rapidly developed clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death), with no apparent cause other than a vascular origin: it includes patients presenting clinical signs and symptoms suggestive of intracerebral haemorrhage or cerebral ischemic necrosis. It does not include transient cerebral ischemia or stroke events in cases of blood disease (e.g. leukemia, polycythaemia vera), brain tumour or brain metastases. Secondary stroke caused by trauma should also be excluded.

In this study, a stroke event is defined as any form of stroke due to hemorrhage (intracerebral) or infarction (i.e. ischemic) and stroke not specified as hemorrhage or infarction. Potential cases of acute stroke will be ascertained by specific and unspecific diagnosis codes (Goldstein et al 2011).

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of stroke.

Codes used for identification of stroke

Terms	ICD10	ICD9CM	Read Codes	ICPC
Stroke, not specified as hemorrhage or	I64			
Stroke NOS	I63.9			K90

Terms	ICD10	ICD9CM	Read Codes	ICPC
Intracerebral haemorrhage	I61	431	G61..	
Non-traumatic subarachnoidal bleeding	I60	430	G60..	
Cerebrovascular accident (CVA)			G66..13	
Stroke and cerebrovascular accident unspecified			G66..00	
Stroke NOS			G66..12	
Sequelae of stroke, not specified as hemorrhage or infarction	I69	342*	Gyu6C	
Brain stem stroke syndrome	G46.3		G663.	
Cerebellar stroke syndrome	G46.4		G664.	
Other and unspecified intracranial haemorrhage	I62	432.*	G62..00	
			G62z.00	
Cerebral infarction	I63		G64..	
Personal history of stroke#			ZV125	
Sequelae of stroke NOS#	I69.3			
H/O: Stroke#			14A7.00	
			14A7.11	
			14A7.12	
			14AK.00	
Cerebral infarct due to thrombosis of precerebral arteries		433*	G63y000	
			G63y000	
Personal history of transient# ischemic attack (TIA), and cerebral infarction without residual deficits	Z86.73	V12.54		
Management/monitoring of stroke			661M700	
			661N700	
			662e.00	
			662e.11	
			662M.00	
			662M100	
			662M200	
			662o.00	
			9Om..00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			9Om0.00	
			9Om1.00	
			9Om2.00	
			9Om3.00	
			9Om4.00	
Delivery of rehabilitation for stroke			7P24200	
Stroke referral			8HBJ.00	
			8HTQ.00	
			8IEC.00	
Seen in stroke clinic			9N0p.00	
Quality indicators stroke			9h2..00	
			9h21.00	
			9h22.00	
Sequelae of cerebral infarction[#]		438.*	G683.00	
Sequelae of stroke, not specified as haemorrhage or infarction[#]			G68X.00/Gyu6C00	
Cerebral infarction due unspecified occlusion/stenosis of pre-cerebral arteries		433.*	G6W..00/Gyu6300	
Cerebral infarction due to unspecified occlusion/stenosis of cerebral arteries			G6X..00/Gyu6G00	
		434.*		
[X]Other cerebral infarction			Gyu6400	
[X]Occlusion and stenosis of other cerebral arteries			Gyu6600	
Discharge from stroke service			ZLEP.00	
Hemiplegia and hemiparesis		342.*		
Acute, but ill-defined, cerebrovascular disease		436.*		

[#] not for acute event, will only be considered for stroke as underlying comorbidity

Annex 3.1.4 Transient ischemic attack (TIA)

Definition of transient ischemic attack

TIA is a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction (Easton 2009).

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of TIA.

Codes used for identification of transient ischemic attack

Terms	ICD10	ICD9CM	Read Codes	ICPC
Transient cerebral ischemic attack, unspecified	G45.9			
TIA - Transient ischemic attack	G45	435.*	G65..12	K89
H/O: TIA			14AB.00	
			ZV12D00	
Amaurosis fugax			F423600	
Retinal transient arterial occlusion NOS			F423700	
Other transient cerebral ischemic attacks and related syndromes	G45.8		Fyu55	
Personal history of transient ischemic attack (TIA), and cerebral infarction without residual deficits[#]		V12.54		
Transient ischaemic attack clinical management plan			8CRB.00	
Transient cerebral ischaemia			G65..00	
Drop attack			G65..11	
Other transient cerebral ischaemia			G65y.00	
Transient cerebral ischaemia NOS			G65z.00	
Impending cerebral ischaemia			G65z000	
Intermittent cerebral ischaemia			G65z100	
Transient cerebral ischaemia NOS			G65zz00	

[#] not for acute event, will only be considered for TIA as underlying comorbidity

Annex 3.1.5 Cardiac arrhythmia

Cardiac arrhythmia as endpoint will consist of the following: atrial flutter/fibrillation, malignant ventricular arrhythmia (ventricular tachycardia, ventricular fibrillation and "Torsade de pointes"), long QT-syndrome, atrio-ventricular (AV) block, supraventricular tachycardia, sick sinus syndrome and premature depolarization. The definitions and relevant disease codes are described below:

Definition of atrial flutter and fibrillation is described below (Annex 3.1.6 and Annex Annex 3.1.7).

Malignant ventricular arrhythmia

Malignant ventricular arrhythmia consists of ventricular fibrillation, ventricular tachycardia and Torsade de pointes. (Bigger 1983).

Ventricular tachycardia is a rapid heartbeat that originates in one of the ventricles of the heart. To be classified as tachycardia, the heart rate is usually at least 100 beats per minute (Zipes 2006).

Ventricular fibrillation is a very rapid, uncoordinated, ineffective series of contractions throughout the ventricles of the heart. Unless stopped, these chaotic impulses are fatal (Zipes 2006).

Torsade de pointes is an uncommon and distinctive form of polymorphic ventricular tachycardia (VT) characterized by a gradual change in the amplitude and twisting of the QRS complexes around the isoelectric line. Torsade de pointes, is associated with a prolonged QT interval, which may be congenital or acquired. Torsade usually terminates spontaneously but frequently recurs and may degenerate into ventricular fibrillation (Zipes 2006).

The following concepts of ventricular arrhythmia (ventricular tachycardia, ventricular fibrillation and Torsade de pointes) have been mapped through the Unified Medical Language System (UMLS).

Codes used for identification of malignant ventricular arrhythmia

Terms	ICD10	ICD9CM	Read Codes	ICPC
Ventricular tachycardia	I47.2		G571.11	K79.02
Paroxysmal ventricular tachycardia		427.1	G571.00	
ECG: ventricular tachycardia			3282.	
Ventricular fibrillation and flutter	I49.0	427.4	G574.	
ECG: ventricular fibrillation			3282.00	

Long QT syndrome

Long QT syndrome (LQTS) is a congenital disorder characterized by a prolongation of the QT interval on electrocardiograms (ECGs) and a propensity to ventricular tachyarrhythmias, such as Torsade de Pointes, which may lead to syncope, cardiac arrest, or sudden death.

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of long QT syndrome.

Codes used for identification of long QT syndrome

Terms	ICD10	ICD9CM	Read Codes	ICPC
Long QT syndrome	I45.81	426.82	X202	
	I47.2E			
ECG: Q-T interval prolonged			32K3.00	

Sick Sinus Syndrome

Sick Sinus Syndrome is characterized by dysfunction of the sinoatrial (SA) node that is often secondary to senescence of the SA node and surrounding atrial myocardium. It is characterized by chronic SA node dysfunction, a sluggish or absent SA nodal pacemaker after electrical electroversion, frequently depressed escape pacemakers, and/or atrioventricular (AV) nodal conduction disturbances. These abnormalities can result in profound sinus bradycardia, sinus pauses, sinus arrest, SA nodal exit block, and inappropriate responses to physiological demands during exercise or stress.

The following concepts of Sick Sinus Syndrome have been mapped through the Unified Medical Language System (UMLS).

Codes used for identification of sick sinus syndrome

Terms	ICD10	ICD9CM	Read Codes	ICPC
Sick sinus syndrome	149.5		G57y300	K79.02

Atrioventricular block

Atrioventricular (AV) block is a partial or complete interruption of impulse transmission from the atria to the ventricles. The most common cause is idiopathic fibrosis and sclerosis of the conduction system. Diagnosis is by ECG; symptoms and treatment depend on degree of block (first, second or third degree AV block), but treatment, when necessary, usually involves pacing.

The following concepts of atrioventricular block have been mapped through the Unified Medical Language System (UMLS).

Codes used for identification of atrioventricular block

Terms	ICD10	ICD9CM	Read Codes	ICPC
Atrioventricular block, first degree	I44.0	426.11	G561311	
Atrioventricular block, complete	I44.2	426.0	G560.	
Third degree atrioventricular block			G560.	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Atrioventricular block, second degree	I44.1		G561400	
Other and unspecified atrioventricular block	I44.3	426.1	Gyu5U	
Unspecified atrioventricular block	I44.3	426.10	G561z	K84.02
			G5610	
Atrioventricular and left bundle-branch block	I44			
Mobitz (type) II atrioventricular block		426.12	G5612	
Other second degree atrioventricular block		426.13		
ECG: complete atrioventricular block			3298.	
Partial atrioventricular block			G561.	
ECG: partial atrioventricular block			3294.	
ECG: partial atrioventricular block - 2:1			3295.	
ECG: partial atrioventricular block - 3:1			3296.	

Premature depolarization

Premature depolarization will include atrial premature depolarization, junctional premature depolarization and ventricular premature depolarization.

The following concepts of premature depolarization have been mapped through the Unified Medical Language System (UMLS).

Codes used for identification of premature depolarization

Terms	ICD10	ICD9CM	Read codes	ICPC
Extra systole	I49.4	427.6	G576z00	K80
	I49.40		G576011	
	I49.49			
Supraventricular extra systole		427.61	G576100	K80.01
Ventricular extra systole	I49.3		G576500	K80.02
			G576200	
Atrial premature depolarization	I49.1		G576300	
Junctional premature depolarization	I49.2		G576400	
[X]Other and unspecified premature depolarization			Gyu5Z00	
ECG: ectopic beats		427.6	326..00	

Terms	ICD10	ICD9CM	Read codes	ICPC
ECG: extra systole			3262.00	
ECG: ventricular ectopics			3263.00	
ECG: atrial ectopics			3264.00	
ECG: ectopic beats NOS			326Z.00	
Ectopic beats			G576.00	
Premature beats			G576.11	
Ectopic beats unspecified			G576000	

Supraventricular tachycardia

Supraventricular tachycardia (SVT) is a condition presenting as a rapid heart rhythm originating at or above the atrioventricular node. Supraventricular tachycardias can be contrasted with the potentially more dangerous ventricular tachycardias—rapid rhythms that originate within the ventricular tissue.

Although "SVT" can be due to any supraventricular cause, the term is most often used to refer to a specific example, paroxysmal supraventricular tachycardia (PSVT), two common types being atrioventricular reciprocating tachycardia and AV nodal reentrant tachycardia.

The following concepts of sinus tachycardia have been mapped through the Unified Medical Language System (UMLS).

Codes used for identification of supraventricular tachycardia

Terms	ICD10	ICD9CM	Read Codes	ICPC
supraventricular tachycardia	I47.1			K79.01
paroxysmal supraventricular tachycardia		427.0		
paroxysmal tachycardia	147			K79
paroxysmal tachycardia, unspecified	147.9			
re-entry ventricular arrhythmia	147.0			
Wolf Parkinson White syndrome	145.6			
History of supraventricular tachycardia[#]			14AQ.00	
ECG: supraventricular arrhythmia			327..00	
Paroxysmal supraventricular tachycardia			G570.00	
ECG: paroxysmal atrial tachy.			3274.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
ECG: supraventric. arryth. NOS			327Z.00	
Wolff-Parkinson-White syndrome			G567400	
Paroxysmal atrial tachycardia			G570000	
Paroxysmal atrioventricular tachycardia			G570100	
Paroxysmal atrioventricular tachycardia			G570100	
Paroxysmal junctional tachycardia			G570200	
Paroxysmal nodal tachycardia			G570300	
Paroxysmal supraventricular tachycardia NOS			G570z00	
Supraventricular tachycardia NOS			G57y900	
Re-entry ventricular arrhythmia			G57yA00	

[#] not for acute event, will only be considered for SVT as underlying comorbidity

Annex 3.1.6 Atrial flutter

Definition of atrial flutter

Atrial flutter (AFL) is an abnormal heart rhythm that occurs in the atria of the heart. When it first occurs, it is usually associated with a fast heart rate or tachycardia (beats over 100 per minute). On ECG, AFL is defined as presence of flutter waves (Camm 2010).

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of atrial flutter.

Codes used for identification of atrial flutter

Terms	ICD10	ICD9CM	Read Codes	ICPC
Atrial flutter		427.32	G5731	
Atrial fibrillation and flutter	I48	427.3	G573.	K78
Atrial fibrillation and flutter NOS			G573z	
Unspecified atrial fibrillation and atrial flutter	I48.9			
Type I atrial flutter	I48.3			
Type II atrial flutter	I48.4			
Atypical atrial flutter	I48.4			
Unspecified atrial flutter	I48.92			

Terms	ICD10	ICD9CM	Read Codes	ICPC
ECG: atrial flutter			3273.00	
History of atrial flutter[#]			14AR.00	

[#] not for acute event, will only be considered for atrial flutter as underlying comorbidity

Annex 3.1.7 Atrial fibrillation

Definition of atrial fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in 1–2% of the general population. It is often associated with palpitations, fainting, chest pain, or congestive heart failure. By definition, the heart rate will be greater than 100 beats per minute. According to the ESC guidelines, the ECG shows absence of P waves, with disorganized electrical activity in their place, and irregular R-R intervals due to irregular conduction of impulses to the ventricles (Camm 2010).

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of atrial fibrillation.

Codes used for identification of atrial fibrillation

Terms	ICD10	ICD9CM	Read Codes	ICPC
Atrial fibrillation		427.31	G5730	
Atrial fibrillation and flutter	I48	427.3	G573.	K78
Atrial fibrillation and flutter NOS			G573z	
Unspecified atrial fibrillation and atrial flutter	I48.9			
AF - Paroxysmal atrial fibrillation			G573200	K79.01
Chronic atrial fibrillation[#]	I48.2			
Persistent atrial fibrillation[#]	I48.1		G573500	
Permanent atrial fibrillation[#]	I48.2		G573400	
Non-rheumatic atrial fibrillation			G573300	
ECG: atrial fibrillation			3272.	
H/O: atrial fibrillation[#]			14AN.00	
Atrial fibrillation resolved			212R.00	
Atrial fibrillation monitoring			662S.00	
			6A9..00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			8HTy.00	
			9hF1.00	
			9Os..	

[#] not for acute event, will only be considered for atrial fibrillation as underlying comorbidity

Annex 3.1.8 Heart failure

Definition of heart failure

HF is a syndrome in which the patients should have the following features: symptoms of HF, typically shortness of breath at rest or during exertion, and/or fatigue; signs of fluid retention such as pulmonary congestion or ankle swelling; and objective evidence of an abnormality of the structure or function of the heart at rest A clinical response to treatment directed at HF alone is not sufficient for the diagnosis, but is helpful when the diagnosis remains unclear after appropriate diagnostic investigations. Patients with HF would usually be expected to show some improvement in symptoms and signs in response to those treatments from which a relatively fast symptomatic improvement could be anticipated (e.g. diuretic or vasodilator administration) (Dickstein 2008).

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for heart failure.

Codes used for identification of heart failure

Terms	ICD10	ICD9CM	Read Codes	ICPC
Heart failure	I50	428*	G58..	K77
Heart failure, unspecified	I50.9	428.9		
Congestive heart failure	I50.0	428.0	G580.00	
Congestive heart disease	I50.9			
Left ventricular failure	I50.1	428.1	G581.00	
Acute heart failure			G582.	
			G5800	
Admit heart failure emergency			8H2S.00	
Chronic congestive heart failure[#]			G5801	
H/O: heart failure[#]			14A6.00	
			14AM.00	
Hypertensive heart disease with (congestive) heart failure	I11.0	402.01	G21z011	
		402.91		

Terms	ICD10	ICD9CM	Read Codes	ICPC
Hypertensive heart and renal disease with (congestive) heart failure	I13.0	402.11	G232.00	
Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	I13.2	404.01 404.91		
Heart failure confirmed			1O1..00	
Heart failure resolved[#]			2126400	
Heart failure management			661M500	
			661N500	
New York Heart Association classification - class II			662g.00	
New York Heart Association classification - class III			662h.00	
New York Heart Association classification - class IV			662i.00	
New York Heart Assoc classification heart failure symptoms			ZRad.00	
Heart failure monitoring			662p.00	
			662T.00	
			662W.00	
			679W100	
			679X.00	
			67D4.00	
			8CL3.00	
			8CMK.00	
Cardiac failure therapy			8B29.00	
Heart failure follow-up			8HBE.00	
			8Hg8.00	
			8HgD.00	
			8HHb.00	
			8HHz.00	
			8Hk0.00	
			8HTL.00	
			8IB8.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			8IE0.00	
			8IE1.00	
			9N0k.00	
			9N2p.00	
Heart failure quality indicators			9hH..00	
			9hH0.00	
			9hH1.00	
Cardiomegaly			G5y3.00	
Post cardiac operation heart failure NOS			G5y4z00	
Heart failure confirmed via echography			G5yy900	
			G5yyA00	
			G5yyC00	
Heart transplant failure and rejection			SP08400	
Heart failure as a complication of care			SP11111	

[#] not for acute event, will only be considered for heart failure as underlying comorbidity

Annex 3.1.9 Mortality (all-cause)

Definition of mortality (all-cause)

Mortality will be assessed in the database either from the population table (death date and identification of death as reason for end of database follow-up) or via death specific codes. The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of death.

Codes used for identification of mortality

Terms	ICD10	ICD9CM	Read Codes	ICPC
Dead			XM01Y	A96
Died			XE1hB	
Death				
Has died				
Dead NOS			22JZ.	
Instantaneous death	R96.0	798.1	R211.	
			XM1AY	

			Ua1q3
Unattended death	R98	798.9	R213.
Unattended death NOS			R213z
Sudden cardiac death, so described	I46.1		G5751
Other sudden death, cause unknown	R96	798	RyuC1
			R21..
			R21z.
			XM1Ac
Death occurring less than 24 hours from onset of symptoms, not otherwise explained	R96.1	798.2	R212.
			R212z

Annex 4 Validation algorithm

Annex 4.1 Validation of coronary events: myocardial infarction and (unstable) angina pectoris

Within this protocol, we have the following endpoints related to coronary diseases:

- Acute coronary syndrome (hospitalization for myocardial infarction and unstable angina pectoris)
- Myocardial infarction
- Angina pectoris

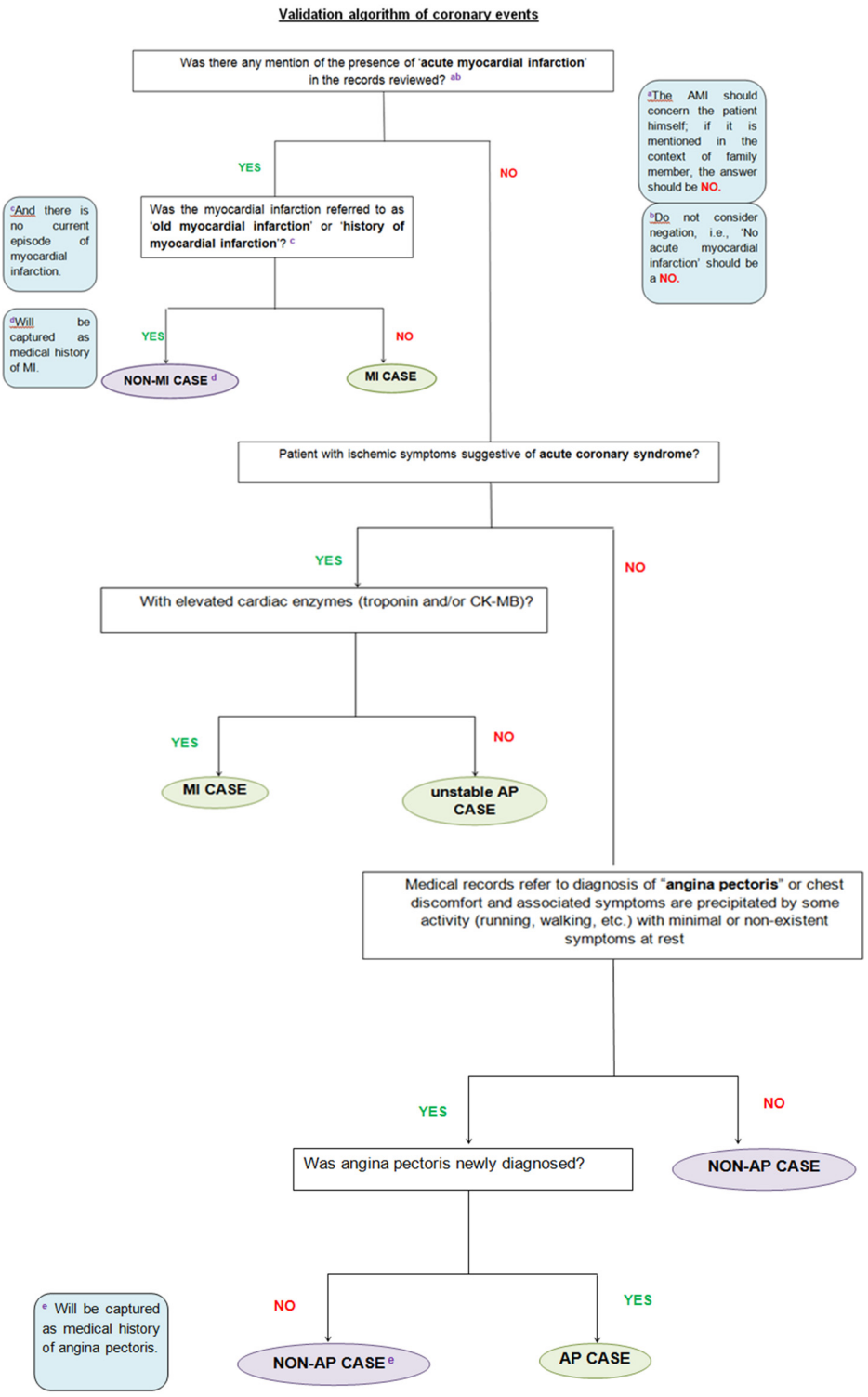
For those databases where free text is available (SIDIAP, IPCI and HSD), first of all, a broad free text search + disease code search will be conducted to retrieve all potential hits related to coronary events. The disease specific codes related to (unstable) angina pectoris and myocardial infarction are described in Annex 3.

The free text search will include the following (translated to the original language):

- “Myocardial” AND “infarction”
- “Heart” AND “attack”
- “ST” AND “elevation”
- “Troponin”
- “CABG”
- “PTCA”
- “Pardee” AND “waves”
- “Thrombolysis”
- “Retrosternal” AND “pain”
- “Heart enzymes” AND “elevated”

- "Angina pectoris"
- "Pain" AND "radiation" AND "left arm"
- "coronary"

All potential hits will be manually reviewed by medical doctors (one for each database), blinded to exposure according to the following algorithm. (see below)


Validation algorithm of coronary events
Was there any mention of the presence of 'acute myocardial infarction' in the records reviewed? ab
YES
NO
[a]The AMI should concern the patient himself; if it is mentioned in the context of family member, the answer should be NO.
[b]Do not consider negation, i.e., 'No acute myocardial infarction' should be a NO.
Was the myocardial infarction referred to as 'old myocardial infarction' or 'history of myocardial infarction'? c
[c]And there is no current episode of myocardial infarction.
[d]Will be captured as medical history of MI.
YES
NO
NON-MI CASE d
MI CASE
Patient with ischemic symptoms suggestive of acute coronary syndrome?
YES
NO
With elevated cardiac enzymes (troponin and/or CK-MB)?
YES
NO
MI CASE
unstable AP CASE
Medical records refer to diagnosis of "angina pectoris" or chest discomfort and associated symptoms are precipitated by some activity (running, walking, etc.) with minimal or non-existent symptoms at rest
YES
NO
Was angina pectoris newly diagnosed?
NON-AP CASE
NO
YES
[e] Will be captured as medical history of angina pectoris.
NON-AP CASE e
AP CASE

Annex 4.2 Validation of cerebrovascular events: stroke and TIA

Within this protocol, we have the following endpoints related to cerebrovascular events:

- Stroke (both hemorrhagic and ischemic)
- TIA (transient ischemic attack)

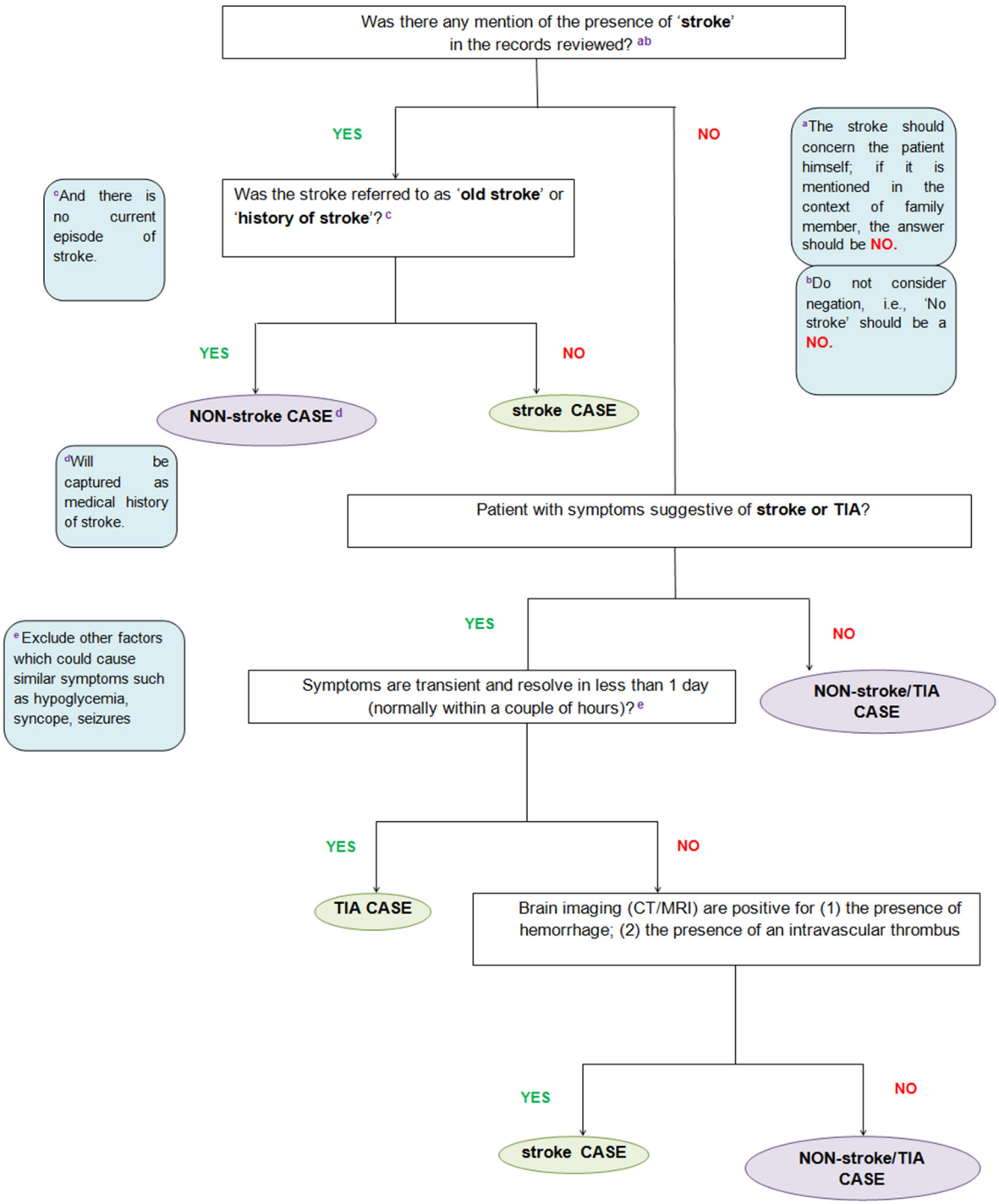
For those databases where free text is available (SIDIAP, IPCI and HSD), first of all a broad free text search + disease code search will be conducted to retrieve all potential hits related to cerebrovascular events. The disease specific codes related to stroke and TIA are described in Annex 3.

The free text search will include the following (translated to the original language):

- "Stroke"
- "TIA"
- "cerebral" AND "bleeding"
- "cerebral" AND "infarction"
- "brain" AND "infarction"
- "brain" AND "bleeding"
- "CVA"
- "parese"
- "paralysis"
- "apoplexy" and "brain"
- "aphasia"

All potential hits will be manually reviewed by medical doctors (one for each database), blinded to exposure according to the following algorithm. (see below)

Validation algorithm of cerebrovascular events



Annex 4.3 Validation of cardiac arrhythmia

Within this protocol, we have the following endpoints related to cardiac tachyarrhythmia:

- atrial flutter/fibrillation
- supraventricular tachycardia
- ventricular tachycardia
- ventricular fibrillation
- "Torsade de pointes/Long QT syndrome"
- AV block
- sick sinus syndrome
- Premature depolarisation

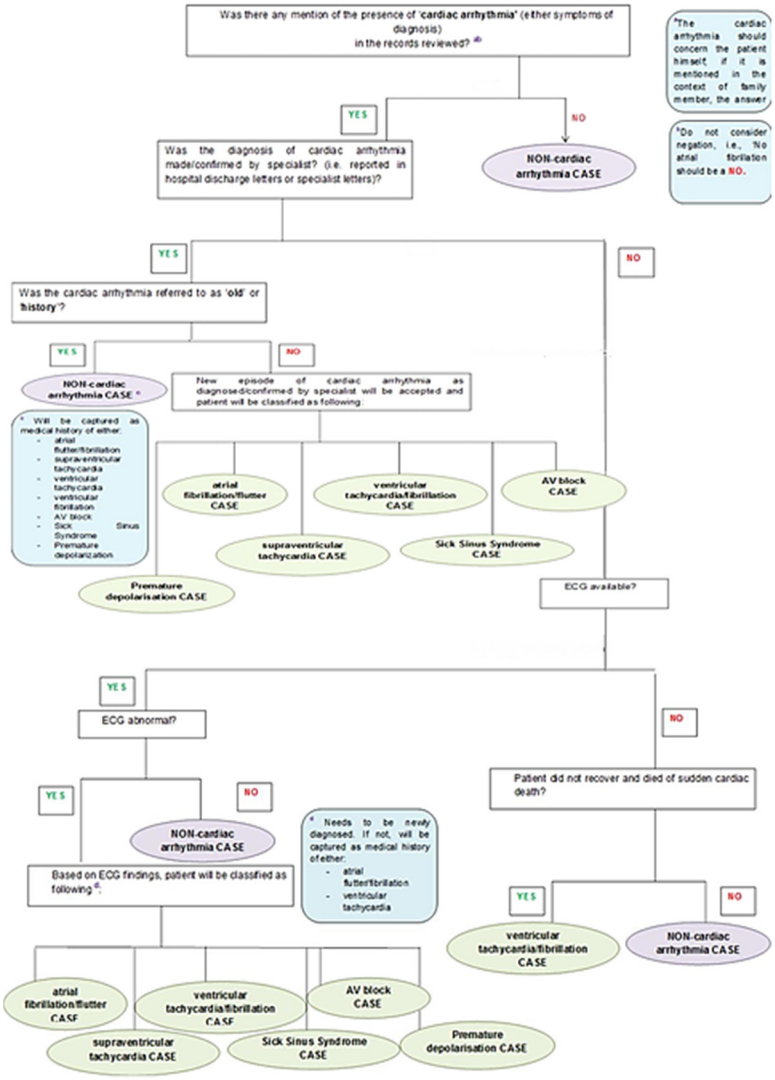
For those databases where free text is available (SIDIAP, IPCI and HSD), first of all a broad free text search + disease code search will be conducted to retrieve all potential hits related to cardiac arrhythmia. The disease specific codes related to cardiac arrhythmia are described in Annex 3.

The free text search will include the following (translated to the original language):

- "atrial" and "fibrillation"
- "atrial" and "flutter"
- "ventricular" AND "fibrillation"
- "ventricular" AND "tachycardia"
- "cardiac" AND "arrhythmia"
- "torsade de pointes"
- "QT" AND "prolongation"
- "AV" AND "block"
- "atrio" AND "block"
- "atrio" AND "ventricular"
- "Mobitz"
- "Wenkenbach"
- "Wolff" AND "Parkinson"

- "WPW"
- "SSS"
- "sick" AND "sinus"
- "extrasystole"
- "ectopic"
- "premature" AND "depolarization"

All potential hits will be manually reviewed by medical doctors (one for each database), blinded to exposure according to the following algorithm. (see below)



Annex 4.4 Validation of heart failure

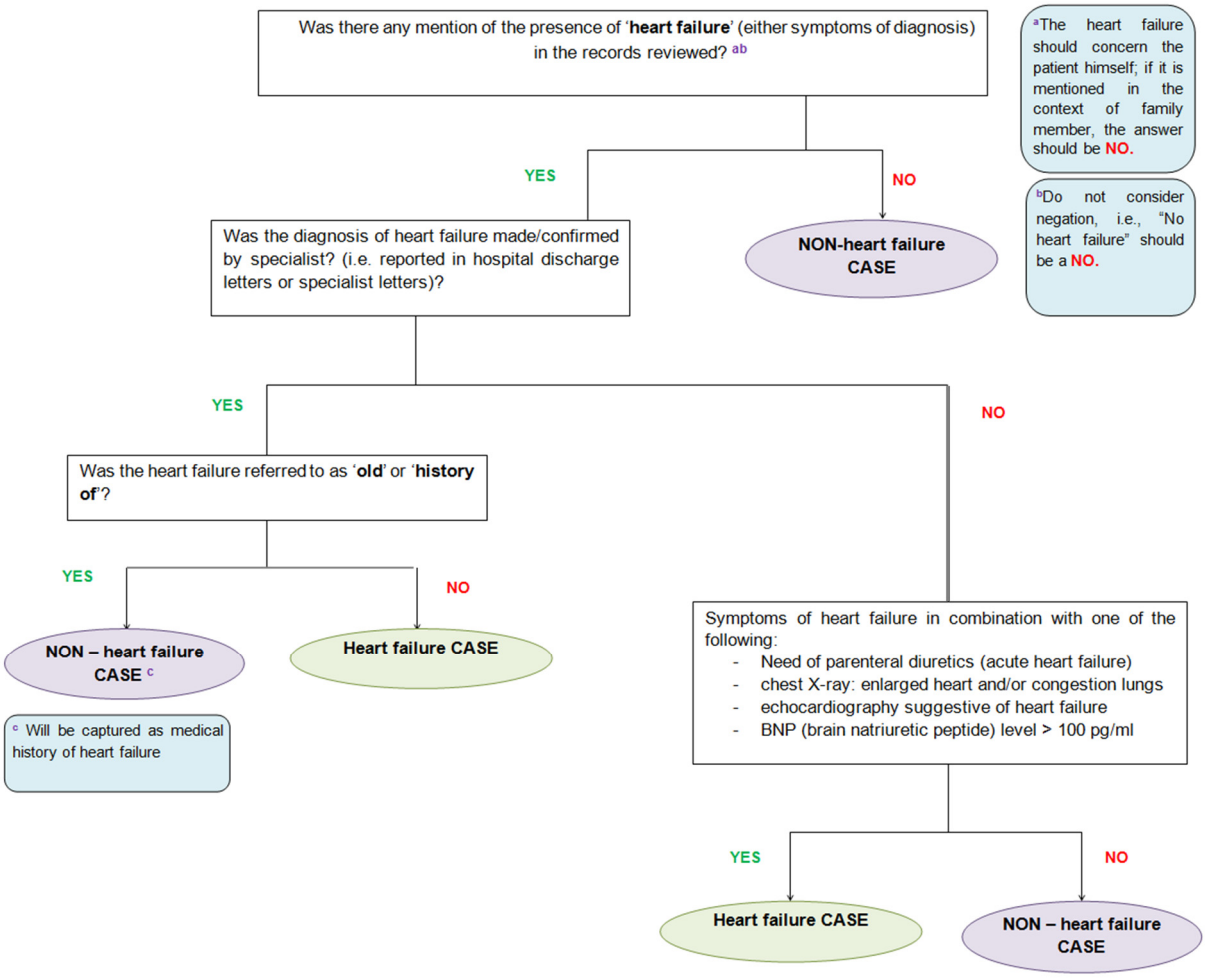
For those databases where free text is available (SIDIAP, IPCI and HSD), first of all a broad free text search + disease code search will be conducted to retrieve all potential hits related to heart failure. The disease specific codes related to heart failure are described in Annex 3.

The free text search will include the following (translated to the original language):

- "heart" AND "failure"
- "NYHA"
- "cardiomegaly"
- "lung" AND "edema"
- "forward" AND "failure"
- "backward" AND "failure"
- "anasarca"
- "hepatomegaly"
- "ankle" AND "swollen"
- "natriuretic" AND "peptide"
- "cardiac" AND "asthma"

All potential hits will be manually reviewed by medical doctors (one for each database), blinded to exposure according to the following algorithm. (see below)

Validation algorithm of heart failure



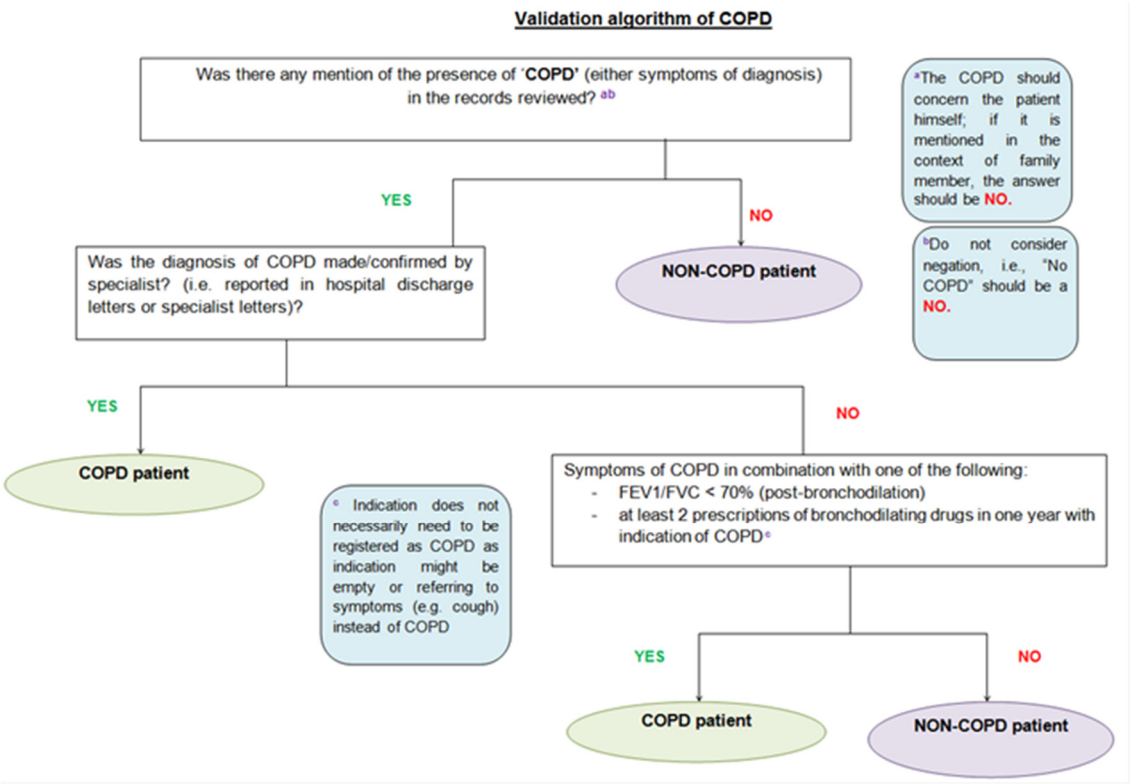
Annex 4.5 Validation of COPD

For those databases where free text is available (SIDIAP, IPCI and HSD), first of all a broad free text search + disease code search will be conducted to retrieve all potential hits related to COPD. The disease specific codes related to COPD are described in Annex 6.

The free text search will include the following (translated to the original language):

- "COPD"
- "chronic" AND "obstructive"
- "GOLD" AND "class"
- "tiffenau"
- "FEV1"
- "emphysema"
- "chronic" AND "bronchitis"

All potential hits will be manually reviewed by medical doctors (one for each database), blinded to exposure according to the following algorithm. (see below)



Annex 5 Exposure definition

	ATC code	multilex id code
NVA237	R03BB06	to be defined (via THIN)
LAMA		
tiotropium	R03BB04	84357998 84358998 85051998 85052998 85053998 85054998 89235998 93457998
aclidinium bromide	R03BB05	to be defined (via THIN)
LABA		
Salmeterol	R03AC12	84908998 84911998 84912998 84915998 86320998 86321998 93181996 93181997 93181998 93182996 93182997 93182998

Formoterol	R03AC13	86529998 86530998 88487998 88488998 88490997 88490998 90942998 90943998
Indacaterol	R03AC18	82082998 82083998 82122998 82124998
Olodaterol	R03AC19	to be defined (via THIN)

Annex 6 COPD definition

Definition of COPD

According to GOLD (Global initiative of lung disease), COPD is a common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients. A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production and/or a history of exposure to risk factors for the disease. Spirometry is required to make the diagnosis in this clinical context; the presence of a postbronchodilator FEV1/FVC < 0.70 confirms the presence of persistent airflow limitation and thus of COPD. (GOLD 2014)

COPD will be identified within the databases both by COPD disease specific codes and via free text search for those databases where free text is available. The COPD validation algorithm has been described in Annex 4.5 – Validation of COPD.

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of COPD.

Terms	ICD10	ICD9CM	Read Codes	ICPC

Terms	ICD10	ICD9CM	Read Codes	ICPC
Chronic obstructive pulmonary disease, unspecified	J44.9			R95
Chronic obstructive lung disease			H3...	
Chronic obstructive airways disease			H3z..	
Other chronic obstructive pulmonary disease	J44			
Other specified chronic obstructive pulmonary disease	J44.8		Hyu31	
Other specified chronic obstructive airways disease			H3y..	
Chronic obstructive pulmonary disease with acute exacerbation, unspecified	J44.1		X101i	
Mild chronic obstructive pulmonary disease			XaEIV	
Moderate chronic obstructive pulmonary disease			XaEIW	
Severe chronic obstructive pulmonary disease			XaEIY	
chronic obstructive pulmonary disease and allied conditions		490-496.99		
Chronic obstructive pulmonary disease with acute lower respiratory infection	J44.0		H3y0.	

COPD severity

COPD severity will be assessed at the index date for the three different exposure cohorts on the basis of spirometry data or on the basis of a severity classification if spirometry is not available.

- If spirometry is available:

Severity of COPD will be determined by spirometry, according to GOLD guidelines:

I. Mild COPD (GOLD stage I): $FEV_1/FVC<70\%$ and FEV_1 predicted > 80%

II. Moderate COPD (GOLD stage II): $FEV_1/FVC<70\%$ and $50\%<FEV_1\leq 80\%$ predicted

III. Severe COPD (GOLD stage III): $FEV_1/FVC<70\%$ and $30\%<FEV_1\leq 50\%$ predicted

IV. Very severe COPD (GOLD stage IV): $FEV_1/FVC<70\%$ and $FEV_1\leq 30\%$ predicted or $FEV_1<50\%$ predicted and chronic respiratory failure.

The most recently performed spirometry prior to the index date (for all 3 cohorts) will be considered. If date of spirometry is more than 5 years prior to the index date, COPD severity will be assessed by proxy (see below)

In addition, in accordance with the updated GOLD guidelines (GOLD 2014), patients will be further stratified upon the previous history of exacerbations (no, one or ≥ two exacerbations in the year prior to the index date [time of first prescription]).(GOLD 2014) A moderate COPD exacerbation is defined as need for oral corticosteroids and/or systemic antibiotics for COPD. A severe COPD exacerbation is defined as hospitalisation because of COPD exacerbation.

Since the COPD Assessment Test (CAT) is not performed routinely in clinical practice, and since a CAT score < 10 occurs only in the setting of screening programs in general populations, all patients will be considered as COPD GOLD B or D patients: COPD GOLD B if FEV1 > 50% AND a history of ≤ 1 exacerbation in the previous year; COPD GOLD D if FEV1 ≤ 50% OR a history of ≥ 2 exacerbations in the previous year.

- If spirometry is not available:

COPD severity will be categorised according to published literature on COPD severity scores using data from GP or health care databases. (Soriano 2001; Eisner 2005; Curkendall 2006) The COPD severity assessed closed to the index date (for all 3 cohorts) will be considered.

1. Mild: Patients initially diagnosed with COPD
2. Moderate: Patients on regular treatment (defined as at least 2 prescriptions of the same drug group within 6 months) with inhaled/oral bronchodilators, xanthines or combination therapy. Patients are considered to have moderate COPD from the time of the second prescription on.
3. Severe: Patients with any of the following:
   - hospitalized for COPD during the past 365 days (prior to the index date)
   - requiring 3 or more courses of antibiotics for the treatment of respiratory infections in the past 365 days (prior to the index date)

- 2 or more courses of systemic corticosteroids for the treatment of COPD exacerbations in the past 365 days (prior to the index date)
- long term use of systemic corticosteroids in the past 365 days for the treatment of COPD (prior to the index date)

4. Very severe: Patients requiring chronic oxygen therapy.

Annex 7 Concomitant medication definition

Concomitant use of respiratory drugs

Short acting anticholinergic agents

R03BB01 Ipratropium bromide

Single-ingredient SABA

R03AC02 Salbutamol

R03AC03 Terbutaline

R03AC04 Fenoterol

Inhaled corticosteroids (ICS)

R03BA01 Beclometasone

R03BA02 Budesonide

R03BA03 Flunisolide

R03BA04 Betamethasone

R03BA05 Fluticasone

R03BA06 Triamcinolone

R03BA07 Mometasone

R03BA08 Ciclesonide

Xanthines

R03DA01 Diprophylline

R03DA02 Choline theophyllinate

R03DA03 Proxyphylline

R03DA04 Theophylline

R03DA05 Aminophylline

R03DA06 Etamiphylline

R03DA07 Theobromine

R03DA08 Bamifylline

R03DA09 Acefylline piperazine

R03DA10 Bufylline

R03DA11 Doxofylline

R03DA20 Combinations of xanthines

R03DA51 Diprophylline, combinations

R03DA54 Theophylline, combinations excluding psycholeptics

R03DA55 Aminophylline, combinations

R03DA57 Theobromine, combinations

R03DA74 Theophylline, combinations with psycholeptics

Fixed combination therapy (LABA + inhaled corticosteroids, anticholinergic agents + SABA)

R03AK01 Epinephrine and other drugs for obstructive airway diseases

R03AK02 Isoprenaline and other drugs for obstructive airway diseases

R03AK03 Fenoterol and other drugs for obstructive airway diseases

R03AK04 Salbutamol and other drugs for obstructive airway diseases

R03AK05 Reproterol and other drugs for obstructive airway diseases

R03AK06 Salmeterol and fluticasone

R03AK07 Formoterol and budesonide

R03AK08 Formoterol and beclomethasone

R03AK09 Formoterol and momethasone

R03AK10 Vilanterol and fluticasone furoate

R03AK11 Formoterol and fluticasone

Oral ß2-agonists

R03CC02 Salbutamol

R03CC03 Terbutaline

R03CC04 Fenoterol

R03CC05 Hexoprenaline

R03CC06 Isoetarine

R03CC07 Pirbuterol

R03CC08 Procaterol

R03CC09 Tretoquinol

R03CC10 Carbuterol

R03CC11 Tulobuterol

R03CC12 Bambuterol

R03CC13 Clenbuterol

R03CC14 Reproterol

R03CC53 Terbutaline, combinations

QR03CC90 Clenbuterol, combinations

Leukotriene receptor antagonists (LTRA)

R03DC01 Zafirlukast

R03DC02 Pranlukast

R03DC03 Montelukast

R03DC04 Ibudilast

Other concomitant drug use

Central nervous system drugs (excl drugs with anticholinergic effects)

Use of opioids, hypnotics and sedatives, anxiolytics, antiepileptic drugs, serotonin reuptake inhibitors.

Opioids

N02AA Natural opium alkaloids

N02AA01 Morphine

N02AA02 Opium

N02AA03 Hydromorphone

N02AA04 Nicomorphine

N02AA05 Oxycodone

N02AA08 Dihydrocodeine

N02AA09 Diamorphine

N02AA10 Papaveretum

N02AA51 Morphine, combinations

N02AA55 Oxycodone, combinations

N02AA58 Dihydrocodeine, combinations

N02AA59 Codeine, combinations excluding psycholeptics

N02AA79 Codeine, combinations with psycholeptics

N02AB Phenylpiperidine derivatives

N02AB01 Ketobemidone

N02AB02 Pethidine

N02AB03 Fentanyl

N02AB52 Pethidine, combinations excluding psycholeptics

QN02AB53 Fentanyl, combinations excluding psycholeptics

N02AB72 Pethidine, combinations with psycholeptics

QN02AB73 Fentanyl, combinations with psycholeptics

N02AC Diphenylpropylamine derivatives

N02AC01 Dextromoramide

N02AC03 Piritramide

N02AC04 Dextropropoxyphene

N02AC05 Bezitramide

N02AC52 Methadone, combinations excluding psycholeptics

N02AC54 Dextropropoxyphene, combinations excluding psycholeptics

N02AC74 Dextropropoxyphene, combinations with psycholeptics

N02AD Benzomorphan derivatives

N02AD01 Pentazocine

N02AD02 Phenazocine

N02AE Oripavine derivatives

N02AE01 Buprenorphine

QN02AE90 Etorphine

QN02AE99 Oripavine derivatives, combinations

Morphinan derivatives

N02AF01 Butorphanol

N02AF02 Nalbuphine

N02AG Opioids in combination with antispasmodics

N02AG01 Morphine and antispasmodics

N02AG02 Ketobemidone and antispasmodics

N02AG03 Pethidine and antispasmodics

N02AG04 Hydromorphone and antispasmodics

N02AX Other opioids

N02AX01 Tilidine

N02AX02 Tramadol

N02AX03 Dezocine

N02AX05 Meptazinol

N02AX06 Tapentadol

N02AX52 Tramadol, combinations

Hypnotics and sedatives

N05CA Barbiturates, plain

N05CA01 Pentobarbital

N05CA02 Amobarbital

N05CA03 Butobarbital

N05CA04 Barbital

N05CA05 Aprobarbital

N05CA06 Secobarbital

N05CA07 Talbutal

N05CA08 Vinylbital

N05CA09 Vinbarbital

N05CA10 Cyclobarbital

N05CA11 Heptabarbital

N05CA12 Reposal

N05CA15 Methohexital

N05CA16 Hexobarbital

N05CA19 Thiopental

N05CA20 Ethallobarbital

N05CA21 Allobarbital

N05CA22 Proxibarbal

N05CB Barbiturates, combinations

N05CB01 Combinations of barbiturates

N05CB02 Barbiturates in combination with other drugs

N05CC Aldehydes and derivatives

N05CC01 Chloral hydrate

N05CC02 Chloralodol

N05CC03 Acetylglycinamide chloral hydrate

N05CC04 Dichloralphenazone

N05CC05 Paraldehyde

N05CD Benzodiazepine derivatives

N05CD01 Flurazepam

N05CD02 Nitrazepam

N05CD03 Flunitrazepam

N05CD04 Estazolam

N05CD05 Triazolam

N05CD06 Lormetazepam

N05CD07 Temazepam

N05CD08 Midazolam

N05CD09 Brotizolam

N05CD10 Quazepam

N05CD11 Loprazolam

N05CD12 Doxefazepam

N05CD13 Cinolazepam

QN05CD90 Climazolam

N05CE Piperidinedione derivatives

N05CE01 Glutethimide

N05CE02 Methyprylon

N05CE03 Pyrithyldione

N05CF Benzodiazepine related drugs

N05CF01 Zopiclone

N05CF02 Zolpidem

N05CF03 Zaleplon

N05CF04 Eszopiclone

N05CH Melatonin receptor agonists

N05CH01 Melatonin

N05CH02 Ramelteon

N05CM Other hypnotics and sedatives

N05CM01 Methaqualone

N05CM02 Clomethiazole

N05CM03 Bromisoval

N05CM04 Carbromal

N05CM05 Scopolamine

N05CM06 Propiomazine

N05CM07 Triclofos

N05CM08 Ethchlorvynol

N05CM09 Valerianae radix

N05CM10 Hexapropymate

N05CM11 Bromides

N05CM12 Apronal

N05CM13 Valnoctamide

N05CM15 Methylpentynol

N05CM16 Niaprazine

N05CM18 Dexmedetomidine

QN05CM90 Detomidine

QN05CM91 Medetomidine

QN05CM92 Xylazine

QN05CM93 Romifidine

QN05CM94 Metomidate

N05CX Hypnotics and sedatives in combination, excluding barbiturates

N05CX01 Meprobamate, combinations

N05CX02 Methaqualone, combinations

N05CX03 Methylpentynol, combinations

N05CX04 Clomethiazole, combinations

N05CX05 Emepronium, combinations

N05CX06 Dipiperonylaminoethanol, combinations

Anxiolytics

N05BA Benzodiazepine derivatives

N05BA01 Diazepam

N05BA02 Chlordiazepoxide

N05BA03 Medazepam

N05BA04 Oxazepam

N05BA05 Potassium clorazepate

N05BA06 Lorazepam

N05BA07 Adinazolam

N05BA08 Bromazepam

N05BA09 Clobazam

N05BA10 Ketazolam

N05BA11 Prazepam

N05BA12 Alprazolam

N05BA13 Halazepam

N05BA14 Pinazepam

N05BA15 Camazepam

N05BA16 Nordazepam

N05BA17 Fludiazepam

N05BA18 Ethyl loflazepate

N05BA19 Etizolam

N05BA21 Clotiazepam

N05BA22 Cloxazolam

N05BA23 Tofisopam

N05BA56 Lorazepam, combinations

N05BB Diphenylmethane derivatives

N05BB01 Hydroxyzine

N05BB02 Captodiame

N05BB51 Hydroxyzine, combinations

N05BC Carbamates

N05BC01 Meprobamate

N05BC03 Emylcamate

N05BC04 Mebutamate

N05BC51 Meprobamate, combinations

N05BD Dibenzo-bicyclo-octadiene derivatives

N05BD01 Benzoctamine

N05BE Azaspirodecanedione derivatives

N05BE01 Buspirone

N05BX Other anxiolytics

N05BX01 Mephenoxalone

N05BX02 Gedocarnil

N05BX03 Etifoxine

Antiepileptics

N03AA Barbiturates and derivatives

N03AA01 Methylphenobarbital

N03AA02 Phenobarbital

N03AA03 Primidone

N03AA04 Barbexaclone

N03AA30 Metharbital

N03AB Hydantoin derivatives

N03AB01 Ethotoin

N03AB02 Phenytoin

N03AB03 Amino(diphenylhydantoin) valeric acid

N03AB04 Mephenytoin

N03AB05 Fosphenytoin

N03AB52 Phenytoin, combinations

N03AB54 Mephenytoin, combinations

N03AC Oxazolidine derivatives

N03AC01 Paramethadione

N03AC02 Trimethadione

N03AC03 Ethadione

N03AD Succinimide derivatives

N03AD01 Ethosuximide

N03AD02 Phensuximide

N03AD03 Mesuximide

N03AD51 Ethosuximide, combinations

N03AE Benzodiazepine derivatives

N03AE01 Clonazepam

N03AF Carboxamide derivatives

N03AF01 Carbamazepine

N03AF02 Oxcarbazepine

N03AF03 Rufinamide

N03AF04 Eslicarbazepine

N03AG Fatty acid derivatives

N03AG01 Valproic acid

N03AG02 Valpromide

N03AG03 Aminobutyric acid

N03AG04 Vigabatrin

N03AG05 Progabide

N03AG06 Tiagabine

N03AX Other antiepileptics

N03AX03 Sultiame

N03AX07 Phenacemide

N03AX09 Lamotrigine

N03AX10 Felbamate

N03AX11 Topiramate

N03AX12 Gabapentin

N03AX13 Pheneturide

N03AX14 Levetiracetam

N03AX15 Zonisamide

N03AX16 Pregabalin

N03AX17 Stiripentol

N03AX18 Lacosamide

N03AX19 Carisbamate

N03AX21 Retigabine

N03AX22 Perampanel

N03AX30 Beclamide

QN03AX90 Imepitoin

Serotonin reuptake inhibitors

N06AB Selective serotonin reuptake inhibitors

N06AB02 Zimelidine

N06AB03 Fluoxetine

N06AB04 Citalopram

N06AB05 Paroxetine

N06AB06 Sertraline

N06AB07 Alaproclate

N06AB08 Fluvoxamine

N06AB09 Etoperidone

N06AB10 Escitalopram

Anticholinergic drugs

Antipsychotic drugs

N05AA Phenothiazines with aliphatic side-chain

N05AA01 Chlorpromazine

N05AA02 Levomepromazine

N05AA03 Promazine

N05AA04 Acepromazine

N05AA05 Trifluprom azine

N05AA06 Cyamemazine

N05AA07 Chlorproethazine

N05AB Phenothiazines with piperazine structure

N05AB01 Dixyrazine

N05AB02 Fluphenazine

N05AB03 Perphenazine

N05AB04 Prochlorperazine

N05AB05 Thiopropazate

N05AB06 Trifluoperazine

N05AB07 Acetophenazine

N05AB08 Thioproperazine

N05AB09 Butaperazine

N05AB10 Perazine

N05AC Phenothiazines with piperidine structure

N05AC01 Periciazine

N05AC02 Thioridazine

N05AC03 Mesoridazine

N05AC04 Pipotiazine

N05AD Butyrophenone derivatives

N05AD01 Haloperidol

N05AD02 Trifluperidol

N05AD03 Melperone

N05AD04 Moperone

N05AD05 Pipamperone

N05AD06 Bromperidol

N05AD07 Benperidol

N05AD08 Droperidol

N05AD09 Fluanisone

QN05AD90 Azaperone

N05AE Indole derivatives

N05AE01 Oxypertine

N05AE02 Molindone

N05AE03 Sertindole

N05AE04 Ziprasidone

N05AF Thioxanthene derivative

N05AF01 Flupentixol

N05AF02 Clopenthixol

N05AF03 Chlorprothixene

N05AF04 Thiothixene

N05AF05 Zuclopenthixol

N05AG Diphenylbutylpiperidine derivatives

N05AG01 Fluspirilene

N05AG02 Pimozide

N05AG03 Penfluridol

N05AH Diazepines, oxazepines, thiazepines and oxepines

N05AH01 Loxapine

N05AH02 Clozapine

N05AH03 Olanzapine

N05AH04 Quetiapine

N05AH05 Asenapine

N05AH06 Clotiapine

QN05AK Neuroleptics, in tardive dyskinesia

N05AL Benzamides

N05AL01 Sulpiride

N05AL02 Sultopride

N05AL03 Tiapride

N05AL04 Remoxipride

N05AL05 Amisulpride

N05AL06 Veralipride

N05AL07 Levosulpiride

N05AN Lithium

N05AN01 Lithium

N05AX Other antipsychotics

N05AX07 Prothipendyl

N05AX08 Risperidone

N05AX10 Mosapramine

N05AX11 Zotepine

N05AX12 Aripiprazole

N05AX13 Paliperidone

N05AX14 Iloperidone

QN05AX90 Amperozide

Tricyclic and tetracyclic antidepressant agents

N06AA Non-selective monoamine reuptake inhibitors

N06AA01 Desipramine

N06AA02 Imipramine

N06AA03 Imipramine oxide

N06AA04 Clomipramine

N06AA05 Opipramol

N06AA06 Trimipramine

N06AA07 Lofepramine

N06AA08 Dibenzepin

N06AA09 Amitriptyline

N06AA10 Nortriptyline

N06AA11 Protriptyline

N06AA12 Doxepin

N06AA13 Iprindole

N06AA14 Melitracen

N06AA15 Butriptyline

N06AA16 Dosulepin

N06AA17 Amoxapine

N06AA18 Dimetacrine

N06AA19 Amineptine

N06AA21 Maprotiline

N06AA23 Quinupramine

N06AX Other antidepressants

N06AX01 Oxitriptan

N06AX02 Tryptophan

N06AX03 Mianserin

N06AX04 Nomifensine

N06AX05 Trazodone

N06AX06 Nefazodone

N06AX07 Minaprine

N06AX08 Bifemelane

N06AX09 Viloxazine

N06AX10 Oxaflozane

N06AX11 Mirtazapine

N06AX12 Bupropion

N06AX13 Medifoxamine

N06AX14 Tianeptine

N06AX15 Pivagabine

N06AX16 Venlafaxine

N06AX17 Milnacipran

N06AX18 Reboxetine

N06AX19 Gepirone

N06AX21 Duloxetine

N06AX22 Agomelatine

N06AX23 Desvenlafaxine

N06AX24 Vilazodone

N06AX25 Hyperici herba

N06AX90 Selegiline

Disopyramide

C01BA03 Disopyramide

Antispasmodics

A03AA Synthetic anticholinergics, esters with tertiary amino group

A03AA01 Oxyphencyclimine

A03AA03 Camylofin

A03AA04 Mebeverine

A03AA05 Trimebutine

A03AA06 Rociverine

A03AA07 Dicycloverine

A03AA08 Dihexyverine

A03AA09 Difemerine

A03AA30 Piperidolate

A03AB Synthetic anticholinergics, quaternary ammonium compounds

A03AB01 Benzilone

A03AB02 Glycopyrronium

A03AB03 Oxyphenonium

A03AB04 Penthienate

A03AB05 Propantheline

A03AB06 Otilonium bromide

A03AB07 Methantheline

A03AB08 Tridihexethyl

A03AB09 Isopropamide

A03AB10 Hexocyclium

A03AB11 Poldine

A03AB12 Mepenzolate

A03AB13 Bevonium

A03AB14 Pipenzolate

A03AB15 Diphemanil

A03AB16 (2-benzhydryloxyethyl)diethyl-methylammonium iodide

A03AB17 Tiemonium iodide

A03AB18 Prifinium bromide

A03AB19 Timepidium bromide

A03AB21 Fenpiverinium

A03AB53 Oxyphenonium, combinations

QA03AB90 Benzetimide

QA03AB92 Carbachol

QA03AB93 Neostigmin

Anti-Parkinson drugs

N04A Anticholinergic agents

N04AA Tertiary amines

N04AA01 Trihexyphenidyl

N04AA02 Biperiden

N04AA03 Metixene

N04AA04 Procyclidine

N04AA05 Profenamine

N04AA08 Dexetimide

N04AA09 Phenglutarimide

N04AA10 Mazaticol

N04AA11 Bornaprine

N04AA12 Tropatepine

N04AB Ethers chemically close to antihistamines

N04AB01 Etanautine

N04AB02 Orphenadrine (chloride)

N04AC Ethers of tropine or tropine derivatives

N04AC01 Benzatropine

N04AC30 Etybenzatropine

Choline-esterase inhibitors

N07AA Anticholinesterases

N07AA01 Neostigmine

N07AA02 Pyridostigmine

N07AA03 Distigmine

N07AA30 Ambenonium

N07AA51 Neostigmine, combinations

Atropine

A03BA01 Atropine

H1-antihistamines

R06AA Aminoalkyl ethers

R06AA01 Bromazine

R06AA02 Diphenhydramine

R06AA04 Clemastine

R06AA06 Chlorphenoxamine

R06AA07 Diphenylpyraline

R06AA08 Carbinoxamine

R06AA09 Doxylamine

R06AA52 Diphenhydramine, combinations

R06AA54 Clemastine, combinations

R06AA56 Chlorphenoxamine, combinations

R06AA57 Diphenylpyraline, combinations

R06AA59 Doxylamine, combinations

R06AB Substituted alkylamines

R06AB01 Brompheniramine

R06AB02 Dexchlorpheniramine

R06AB03 Dimetindene

R06AB04 Chlorphenamine

R06AB05 Pheniramine

R06AB06 Dexbrompheniramine

R06AB07 Talastine

R06AB51 Brompheniramine, combinations

R06AB52 Dexchlorpheniramine, combinations

R06AB54 Chlorphenamine, combinations

R06AB56 Dexbrompheniramine, combinations

R06AC Substituted ethylene diamines

R06AC01 Mepyramine

R06AC02 Histapyrrodine

R06AC03 Chloropyramine

R06AC04 Tripelennamine

R06AC05 Methapyrilene

R06AC06 Thonzylamine

R06AC52 Histapyrrodine, combinations

R06AC53 Chloropyramine, combinations

R06AD Phenothiazine derivatives

R06AD01 Alimemazine

R06AD02 Promethazine

R06AD03 Thiethylperazine

R06AD04 Methdilazine

R06AD05 Hydroxyethylpromethazine

R06AD06 Thiazinam

R06AD07 Mequitazine

R06AD08 Oxomemazine

R06AD09 Isothipendyl

R06AD52 Promethazine, combinations

R06AD55 Hydroxyethylpromethazine, combinations

R06AE Piperazine derivatives

R06AE01 Buclizine

R06AE03 Cyclizine

R06AE04 Chlorcyclizine

R06AE05 Meclozine

R06AE06 Oxatomide

R06AE07 Cetirizine

R06AE09 Levocetirizine

R06AE51 Buclizine, combinations

R06AE53 Cyclizine, combinations

R06AE55 Meclozine, combinations

R06AK Combinations of antihistamines

R06AX Other antihistamines for systemic use

R06AX01 Bamipine

R06AX02 Cyproheptadine

R06AX03 Thenalidine

R06AX04 Phenindamine

R06AX05 Antazoline

R06AX07 Triprolidine

R06AX08 Pyrrobutamine

R06AX09 Azatadine

R06AX11 Astemizole

R06AX12 Terfenadine

R06AX13 Loratadine

R06AX15 Mebhydrolin

R06AX16 Deptropine

R06AX17 Ketotifen

R06AX18 Acrivastine

R06AX19 Azelastine

R06AX21 Tritoqualine

R06AX22 Ebastine

R06AX23 Pimethixene

R06AX24 Epinastine

R06AX25 Mizolastine

R06AX26 Fexofenadine

R06AX27 Desloratadine

R06AX28 Rupatadine

R06AX29 Bilastine

R06AX53 Thenalidine, combinations

R06AX58 Pyrrobutamine, combinations

Anticholinergics for treatment of overactive bladder

G04BD Urinary antispasmodics

G04BD01 Emepronium

G04BD02 Flavoxate

G04BD03 Meladrazine

G04BD04 Oxybutynin

G04BD05 Terodiline

G04BD06 Propiverine

G04BD07 Tolterodine

G04BD08 Solifenacin

G04BD09 Trospium

G04BD10 Darifenacin

G04BD11 Fesoterodine

Drugs affecting cerebrovascular and cardiovascular disease

Systemic glucocorticosteroids

H02AB Glucocorticoids

H02AB01 Betamethasone

H02AB02 Dexamethasone

H02AB03 Fluocortolone

H02AB04 Methylprednisolone

H02AB05 Paramethasone

H02AB06 Prednisolone

H02AB07 Prednisone

H02AB08 Triamcinolone

H02AB09 Hydrocortisone

H02AB10 Cortisone

H02AB11 Prednylidene

H02AB12 Rimexolone

H02AB13 Deflazacort

H02AB14 Cloprednol

H02AB15 Meprednisone

H02AB17 Cortivazol

QH02AB30 Combinations of glucocorticoids

QH02AB56 Prednisolone, combinations

QH02AB57 Prednisone, combinations

QH02AB90 Flumetasone

NSAIDs

M01AA Butylpyrazolidines

M01AA01 Phenylbutazone

M01AA02 Mofebutazone

M01AA03 Oxyphenbutazone

M01AA05 Clofezone

M01AA06 Kebuzone

QM01AA90 Suxibuzone

QM01AA99 Combinations

M01AB Acetic acid derivatives and related substances

M01AB01 Indometacin

M01AB02 Sulindac

M01AB03 Tolmetin

M01AB04 Zomepirac

M01AB05 Diclofenac

M01AB06 Alclofenac

M01AB07 Bumadizone

M01AB08 Etodolac

M01AB09 Lonazolac

M01AB10 Fentiazac

M01AB11 Acemetacin

M01AB12 Difenpiramide

M01AB13 Oxametacin

M01AB14 Proglumetacin

M01AB15 Ketorolac

M01AB16 Aceclofenac

M01AB17 Bufexamac

M01AB51 Indometacin, combinations

M01AB55 Diclofenac, combinations

M01AC Oxicams

M01AC01 Piroxicam

M01AC02 Tenoxicam

M01AC04 Droxicam

M01AC05 Lornoxicam

M01AC06 Meloxicam

M01AC56 Meloxicam, combinations

M01AE Propionic acid derivatives

M01AE01 Ibuprofen

M01AE02 Naproxen

M01AE03 Ketoprofen

M01AE04 Fenoprofen

M01AE05 Fenbufen

M01AE06 Benoxaprofen

M01AE07 Suprofen

M01AE08 Pirprofen

M01AE09 Flurbiprofen

M01AE10 Indoprofen

M01AE11 Tiaprofenic acid

M01AE12 Oxaprozin

M01AE13 Ibuproxam

M01AE14 Dexibuprofen

M01AE15 Flunoxaprofen

M01AE16 Alminoprofen

M01AE17 Dexketoprofen

M01AE18 Naproxcinod

M01AE51 Ibuprofen, combinations

M01AE52 Naproxen and esomeprazole

M01AE53 Ketoprofen, combinations

M01AE56 Naproxen and misoprostol

QM01AE90 Vedaprofen

QM01AE91 Carprofen

QM01AE92 Tepoxalin

M01AG Fenamates

M01AG01 Mefenamic acid

M01AG02 Tolfenamic acid

M01AG03 Flufenamic acid

M01AG04 Meclofenamic acid

QM01AG90 Flunixin

M01AH Coxibs

M01AH01 Celecoxib

M01AH02 Rofecoxib

M01AH03 Valdecoxib

M01AH04 Parecoxib

M01AH05 Etoricoxib

M01AH06 Lumiracoxib

QM01AH90 Firocoxib

QM01AH91 Robenacoxib

QM01AH92 Mavacoxib

QM01AH93 Cimicoxib

M01AX Other anti-inflammatory and antirheumatic agents, non-steroids

M01AX01 Nabumetone

M01AX02 Niflumic acid

M01AX04 Azapropazone

M01AX05 Glucosamine

M01AX07 Benzydamine

M01AX12 Glucosaminoglycan polysulfate

M01AX13 Proquazone

M01AX14 Orgotein

M01AX17 Nimesulide

M01AX18 Feprazone

M01AX21 Diacerein

M01AX22 Morniflumate

M01AX23 Tenidap

M01AX24 Oxaceprol

M01AX25 Chondroitin sulfate

M01AX26 Avocado and soyabean oil, unsaponifiables

QM01AX52 Niflumic acid, combinations

M01AX68 Feprazone, combinations

QM01AX90 Pentosan polysulfate

QM01AX91 Aminopropionitrile

QM01AX99 Combinations

Vit K antagonists

B01AA Vitamin K antagonists

B01AA01 Dicoumarol

B01AA02 Phenindione

B01AA03 Warfarin

B01AA04 Phenprocoumon

B01AA07 Acenocoumarol

B01AA08 Ethyl biscoumacetate

B01AA09 Clorindione

B01AA10 Diphenadione

B01AA11 Tioclomarol

B01AA12 Fluindione

Lipid lowering drugs

C10AA HMG CoA reductase inhibitors

C10AA01 Simvastatin

C10AA02 Lovastatin

C10AA03 Pravastatin

C10AA04 Fluvastatin

C10AA05 Atorvastatin

C10AA06 Cerivastatin

C10AA07 Rosuvastatin

C10AA08 Pitavastatin

C10AB Fibrates

C10AB01 Clofibrate

C10AB02 Bezafibrate

C10AB03 Aluminium clofibrate

C10AB04 Gemfibrozil

C10AB05 Fenofibrate

C10AB06 Simfibrate

C10AB07 Ronifibrate

C10AB08 Ciprofibrate

C10AB09 Etofibrate

C10AB10 Clofibride

C10AB11 Choline fenofibrate

C10AC Bile acid sequestrants

C10AC01 Colestyramine

C10AC02 Colestipol

C10AC03 Colextran

C10AC04 Colesevelam

C10AD Nicotinic acid and derivatives

C10AD01 Niceritrol

C10AD02 Nicotinic acid

C10AD03 Nicofuranose

C10AD04 Aluminium nicotinate

C10AD05 Nicotinyl alcohol (pyridylcarbinol)

C10AD06 Acipimox

C10AD52 Nicotinic acid, combinations

C10AX Other lipid modifying agents

C10AX01 Dextrothyroxine

C10AX02 Probucol

C10AX03 Tiadenol

C10AX05 Meglutol

C10AX06 Omega-3-triglycerides

C10AX07 Magnesium pyridoxal 5-phosphate glutamate

C10AX08 Policosanol

C10AX09 Ezetimibe

C10AX10 Alipogene tiparvovec

C10AX11 Mipomersen

C10B Lipid modifying agents, combinations

C10BA HMG CoA reductase inhibitors in combination with other lipid modifying agents

C10BA01 Lovastatin and nicotinic acid

C10BA02 Simvastatin and ezetimibe

C10BA03 Pravastatin and fenofibrate

C10BX HMG CoA reductase inhibitors, other combinations

C10BX01 Simvastatin and acetylsalicylic acid

C10BX02 Pravastatin and acetylsalicylic acid

C10BX03 Atorvastatin and amlodipine

C10BX04 Simvastatin, acetylsalicylic acid and ramipril

Platelet aggregation inhibitors

B01AC Platelet aggregation inhibitors excluding heparin

B01AC01 Ditazole

B01AC02 Cloricromen

B01AC03 Picotamide

B01AC04 Clopidogrel

B01AC05 Ticlopidine

B01AC06 Acetylsalicylic acid

B01AC07 Dipyridamole

B01AC08 Carbasalate calcium

B01AC09 Epoprostenol

B01AC10 Indobufen

B01AC11 Iloprost

B01AC13 Abciximab

B01AC15 Aloxiprin

B01AC16 Eptifibatide

B01AC17 Tirofiban

B01AC18 Triflusal

B01AC19 Beraprost

B01AC21 Treprostinil

B01AC22 Prasugrel

B01AC23 Cilostazol

B01AC24 Ticagrelor

B01AC30 Combinations

B01AC56 Acetylsalicylic acid and esomeprazole

Nitrates

C01DA Organic nitrates

C01DA02 Glyceryl trinitrate

C01DA04 Methylpropylpropanediol dinitrate

C01DA05 Pentaerithrityl tetranitrate

C01DA07 Propatylnitrate

C01DA08 Isosorbide dinitrate

C01DA09 Trolnitrate

C01DA13 Erityrityl tetranitrate

C01DA14 Isosorbide mononitrate

C01DA20 Organic nitrates in combination

C01DA38 Tenitramine

C01DA52 Glyceryl trinitrate, combinations

C01DA54 Methylpropylpropanediol dinitrate, combinations

C01DA55 Pentaerithrityl tetranitrate, combinations

C01DA57 Propatylnitrate, combinations

C01DA58 Isosorbide dinitrate, combinations

C01DA59 Trolnitrate, combinations

C01DA63 Erityrityl tetranitrate, combinations

C01DA70 Organic nitrates in combination with psycholeptics

Anti-arrhythmics

C01BA Antiarrhythmics, class Ia

C01BA01 Quinidine

C01BA02 Procainamide

C01BA03 Disopyramide

C01BA04 Sparteine

C01BA05 Ajmaline

C01BA08 Prajmaline

C01BA12 Lorajmine

C01BA51 Quinidine, combinations excluding psycholeptics

C01BA71 Quinidine, combinations with psycholeptics

C01BB Antiarrhythmics, class Ib

C01BB01 Lidocaine

C01BB02 Mexiletine

C01BB03 Tocainide

C01BB04 Aprindine

C01BC Antiarrhythmics, class Ic

C01BC03 Propafenone

C01BC04 Flecainide

C01BC07 Lorcainide

C01BC08 Encainide

C01BD Antiarrhythmics, class III

C01BD01 Amiodarone

C01BD02 Bretylium tosilate

C01BD03 Bunaftine

C01BD04 Dofetilide

C01BD05 Ibutilide

C01BD06 Tedisamil

C01BD07 Dronedarone

C01BG Other antiarrhythmics, class I and III

C01BG01 Moracizine

C01BG07 Cibenzoline

C01BG11 Vernakalant

Anti-hypertensive drugs

C03AA Thiazides, plain

C03AA01 Bendroflumethiazide

C03AA02 Hydroflumethiazide

C03AA03 Hydrochlorothiazide

C03AA04 Chlorothiazide

C03AA05 Polythiazide

C03AA06 Trichlormethiazide

C03AA07 Cyclopenthiazide

C03AA08 Methyclothiazide

C03AA09 Cyclothiazide

C03AA13 Mebutizide

C03AA56 Trichlormethiazide, combinations

C03AB Thiazides and potassium in combination

C03AB01 Bendroflumethiazide and potassium

C03AB02 Hydroflumethiazide and potassium

C03AB03 Hydrochlorothiazide and potassium

C03AB04 Chlorothiazide and potassium

C03AB05 Polythiazide and potassium

C03AB06 Trichlormethiazide and potassium

C03AB07 Cyclopenthiazide and potassium

C03AB08 Methyclothiazide and potassium

C03AB09 Cyclothiazide and potassium

C03AH Thiazides, combinations with psycholeptics and/or analgesics

C03AH01 Chlorothiazide, combinations

C03AH02 Hydroflumethiazide, combinations

C03AX Thiazides, combinations with other drugs

C03AX01 Hydrochlorothiazide, combinations

C03B Low-ceiling diuretics, excluding thiazides

C03BA Sulfonamides, plain

C03BA02 Quinethazone

C03BA03 Clopamide

C03BA04 Chlortalidone

C03BA05 Mefruside

C03BA07 Clofenamide

C03BA08 Metolazone

C03BA09 Meticrane

C03BA10 Xipamide

C03BA11 Indapamide

C03BA12 Clorexolone

C03BA13 Fenquizone

C03BA82 Clorexolone, combinations with psycholeptics

C03BB Sulfonamides and potassium in combination

C03BB02 Quinethazone and potassium

C03BB03 Clopamide and potassium

C03BB04 Chlortalidone and potassium

C03BB05 Mefruside and potassium

C03BB07 Clofenamide and potassium

C03BC Mercurial diuretics

C03BC01 Mersalyl

C03BD Xanthine derivatives

C03BD01 Theobromine

C03BK Sulfonamides, combinations with other drugs

C03BX Other low-ceiling diuretics

C03BX03 Cicletanine

C03C High-ceiling diuretics

C03CA Sulfonamides, plain

C03CA01 Furosemide

C03CA02 Bumetanide

C03CA03 Piretanide

C03CA04 Torasemide

C03CB Sulfonamides and potassium in combination

C03CB01 Furosemide and potassium

C03CB02 Bumetanide and potassium

C03CC Aryloxyacetic acid derivatives

C03CC01 Etacrynic acid

C03CC02 Tienilic acid

C03CD Pyrazolone derivatives

C03CD01 Muzolimine

C03CX Other high-ceiling diuretics

C03CX01 Etozolin

C03D Potassium-sparing agents

C03DA Aldosterone antagonists

C03DA01 Spironolactone

C03DA02 Potassium canrenoate

C03DA03 Canrenone

C03DA04 Eplerenone

C03DB Other potassium-sparing agents

C03DB01 Amiloride

C03DB02 Triamterene

C03E Diuretics and potassium-sparing agents in combination

C03EA Low-ceiling diuretics and potassium-sparing agents

C03EA01 Hydrochlorothiazide and potassium-sparing agents

C03EA02 Trichlormethiazide and potassium-sparing agents

C03EA03 Epitizide and potassium-sparing agents

C03EA04 Altizide and potassium-sparing agents

C03EA05 Mebutizide and potassium-sparing agents

C03EA06 Chlortalidone and potassium-sparing agents

C03EA07 Cyclopenthiazide and potassium-sparing agents

C03EA12 Metolazone and potassium-sparing agents

C03EA13 Bendroflumethiazide and potassium-sparing agents

C03EA14 Butizide and potassium-sparing agents

C03EB High-ceiling diuretics and potassium-sparing agents

C03EB01 Furosemide and potassium-sparing agents

C03EB02 Bumetanide and potassium-sparing agents

C07A Beta blocking agents

C07AA Beta blocking agents, non-selective

C07AA01 Alprenolol

C07AA02 Oxprenolol

C07AA03 Pindolol

C07AA05 Propranolol

C07AA06 Timolol

C07AA07 Sotalol

C07AA12 Nadolol

C07AA14 Mepindolol

C07AA15 Carteolol

C07AA16 Tertatolol

C07AA17 Bopindolol

C07AA19 Bupranolol

C07AA23 Penbutolol

C07AA27 Cloranolol

C07AA57 Sotalol, combinations

QC07AA90 Carazolol

C07AB Beta blocking agents, selective

C07AB01 Practolol

C07AB02 Metoprolol

C07AB03 Atenolol

C07AB04 Acebutolol

C07AB05 Betaxolol

C07AB06 Bevantolol

C07AB07 Bisoprolol

C07AB08 Celiprolol

C07AB09 Esmolol

C07AB10 Epanolol

C07AB11 S-atenolol

C07AB12 Nebivolol

C07AB13 Talinolol

C07AB52 Metoprolol, combinations

C07AB57 Bisoprolol, combinations

C07AG Alpha and beta blocking agents

C07AG01 Labetalol

C07AG02 Carvedilol

C07B Beta blocking agents and thiazides

C07BA Beta blocking agents, non-selective, and thiazides

C07BA02 Oxprenolol and thiazides

C07BA05 Propranolol and thiazides

C07BA06 Timolol and thiazides

C07BA07 Sotalol and thiazides

C07BA12 Nadolol and thiazides

C07BA68 Metipranolol and thiazides, combinations

C07BB Beta blocking agents, selective, and thiazides

C07BB02 Metoprolol and thiazides

C07BB03 Atenolol and thiazides

C07BB04 Acebutolol and thiazides

C07BB06 Bevantolol and thiazides

C07BB07 Bisoprolol and thiazides

C07BB12 Nebivolol and thiazides

C07BB52 Metoprolol and thiazides, combinations

C07BG Alpha and beta blocking agents and thiazides

C07BG01 Labetalol and thiazides

C07C Beta blocking agents and other diuretics

C07CA Beta blocking agents, non-selective, and other diuretics

C07CA02 Oxprenolol and other diuretics

C07CA03 Pindolol and other diuretics

C07CA17 Bopindolol and other diuretics

C07CA23 Penbutolol and other diuretics

C07CB Beta blocking agents, selective, and other diuretics

C07CB02 Metoprolol and other diuretics

C07CB03 Atenolol and other diuretics

C07CB53 Atenolol and other diuretics, combinations

C07CG Alpha and beta blocking agents and other diuretics

C07CG01 Labetalol and other diuretics

C07D Beta blocking agents, thiazides and other diuretics

C07DA Beta blocking agents, non-selective, thiazides and other diuretics

C07DA06 Timolol, thiazides and other diuretics

C07DB Beta blocking agents, selective, thiazides and other diuretics

C07DB01 Atenolol, thiazides and other diuretics

C07E Beta blocking agents and vasodilators

C07EA Beta blocking agents, non-selective, and vasodilators

C07EB Beta blocking agents, selective, and vasodilators

C07F Beta blocking agents and other antihypertensives

C07FA Beta blocking agents, non-selective, and other antihypertensives

C07FA05 Propranolol and other antihypertensives

C07FB Beta blocking agents, selective, and other antihypertensives

C07FB02 Metoprolol and other antihypertensives

C07FB03 Atenolol and other antihypertensives

C07FB07 Bisoprolol and other antihypertensives

C08C Selective calcium channel blockers with mainly vascular effects

C08CA Dihydropyridine derivatives

C08CA01 Amlodipine

C08CA02 Felodipine

C08CA03 Isradipine

C08CA04 Nicardipine

C08CA05 Nifedipine

C08CA06 Nimodipine

C08CA07 Nisoldipine

C08CA08 Nitrendipine

C08CA09 Lacidipine

C08CA10 Nilvadipine

C08CA11 Manidipine

C08CA12 Barnidipine

C08CA13 Lercanidipine

C08CA14 Cilnidipine

C08CA15 Benidipine

C08CA16 Clevidipine

C08CA55 Nifedipine, combinations

C08CX Other selective calcium channel blockers with mainly vascular effects

C08CX01 Mibefradil

C08D Selective calcium channel blockers with direct cardiac effects

C08DA Phenylalkylamine derivatives

C08DA01 Verapamil

C08DA02 Gallopamil

C08DA51 Verapamil, combinations

C08DB Benzothiazepine derivatives

C08DB01 Diltiazem

C08E Non-selective calcium channel blockers

C08EA Phenylalkylamine derivatives

C08EA01 Fendiline

C08EA02 Bepridil

C08EX Other non-selective calcium channel blockers

C08EX01 Lidoflazine

C08EX02 Perhexiline

C08G Calcium channel blockers and diuretics

C08GA Calcium channel blockers and diuretics

C08GA01 Nifedipine and diuretics

C09A ACE inhibitors, plain

C09AA ACE inhibitors, plain

C09AA01 Captopril

C09AA02 Enalapril

C09AA03 Lisinopril

C09AA04 Perindopril

C09AA05 Ramipril

C09AA06 Quinapril

C09AA07 Benazepril

C09AA08 Cilazapril

C09AA09 Fosinopril

C09AA10 Trandolapril

C09AA11 Spirapril

C09AA12 Delapril

C09AA13 Moexipril

C09AA14 Temocapril

C09AA15 Zofenopril

C09AA16 Imidapril

C09B ACE inhibitors, combinations

C09BA ACE inhibitors and diuretics

C09BA01 Captopril and diuretics

C09BA02 Enalapril and diuretics

C09BA03 Lisinopril and diuretics

C09BA04 Perindopril and diuretics

C09BA05 Ramipril and diuretics

C09BA06 Quinapril and diuretics

C09BA07 Benazepril and diuretics

C09BA08 Cilazapril and diuretics

C09BA09 Fosinopril and diuretics

C09BA12 Delapril and diuretics

C09BA13 Moexipril and diuretics

C09BA15 Zofenopril and diuretics

C09BB ACE inhibitors and calcium channel blockers

C09BB02 Enalapril and lercanidipine

C09BB03 Lisinopril and amlodipine

C09BB04 Perindopril and amlodipine

C09BB05 Ramipril and felodipine

C09BB06 Enalapril and nitrendipine

C09BB07 Ramipril and amlodipine

C09BB10 Trandolapril and verapamil

C09BB12 Delapril and manidipine

C09C Angiotensin II antagonists, plain

C09CA Angiotensin II antagonists, plain

C09CA01 Losartan

C09CA02 Eprosartan

C09CA03 Valsartan

C09CA04 Irbesartan

C09CA05 Tasosartan

C09CA06 Candesartan

C09CA07 Telmisartan

C09CA08 Olmesartan medoxomil

C09CA09 Azilsartan medoxomil

C09D Angiotensin II antagonists, combinations

C09DA Angiotensin II antagonists and diuretics

C09DA01 Losartan and diuretics

C09DA02 Eprosartan and diuretics

C09DA03 Valsartan and diuretics

C09DA04 Irbesartan and diuretics

C09DA06 Candesartan and diuretics

C09DA07 Telmisartan and diuretics

C09DA08 Olmesartan medoxomil and diuretics

C09DB Angiotensin II antagonists and calcium channel blockers

C09DB01 Valsartan and amlodipine

C09DB02 Olmesartan medoxomil and amlodipine

C09DB04 Telmisartan and amlodipine

C09DB05 Irbesartan and amlodipine

C09DB06 Losartan and amlodipine

C09DX Angiotensin II antagonists, other combinations

C09DX01 Valsartan, amlodipine and hydrochlorothiazide

C09DX02 Valsartan and aliskiren

C09DX03 Olmesartan medoxomil, amlodipine and hydrochlorothiazide

C09X Other agents acting on the renin-angiotensin system

C09XA Renin-inhibitors

C09XA01 Remikiren

C09XA02 Aliskiren

C09XA52 Aliskiren and hydrochlorothiazide

C09XA53 Aliskiren and amlodipine

C09XA54 Aliskiren, amlodipine and hydrochlorothiazide

Anti-diabetic drugs

A10A Insulins and analogues

A10AB Insulins and analogues for injection, fast-acting

A10AB01 Insulin (human)

A10AB02 Insulin (beef)

A10AB03 Insulin (pork)

A10AB04 Insulin lispro

A10AB05 Insulin aspart

A10AB06 Insulin glulisine

A10AB30 Combinations

A10AC Insulins and analogues for injection, intermediate-acting

A10AC01 Insulin (human)

A10AC02 Insulin (beef)

A10AC03 Insulin (pork)

A10AC04 Insulin lispro

A10AC30 Combinations

A10AD Insulins and analogues for injection, intermediate-acting combined with fast-acting

A10AD01 Insulin (human)

A10AD02 Insulin (beef)

A10AD03 Insulin (pork)

A10AD04 Insulin lispro

A10AD05 Insulin aspart

A10AD30 Combinations

A10AE Insulins and analogues for injection, long-acting

A10AE01 Insulin (human)

A10AE02 Insulin (beef)

A10AE03 Insulin (pork)

A10AE04 Insulin glargine

A10AE05 Insulin detemir

A10AE30 Combinations

A10AF Insulins and analogues for inhalation

A10AF01 Insulin (human)

A10B Blood glucose lowering drugs, excluding insulins

A10BA Biguanides

A10BA01 Phenformin

A10BA02 Metformin

A10BA03 Buformin

A10BB Sulfonamides, urea derivatives

A10BB01 Glibenclamide

A10BB02 Chlorpropamide

A10BB03 Tolbutamide

A10BB04 Glibornuride

A10BB05 Tolazamide

A10BB06 Carbutamide

A10BB07 Glipizide

A10BB08 Gliquidone

A10BB09 Gliclazide

A10BB10 Metahexamide

A10BB11 Glisoxepide

A10BB12 Glimepiride

A10BB31 Acetohexamide

A10BC Sulfonamides (heterocyclic)

A10BC01 Glymidine

A10BD Combinations of oral blood glucose lowering drugs

A10BD01 Phenformin and sulfonamides

A10BD02 Metformin and sulfonamides

A10BD03 Metformin and rosiglitazone

A10BD04 Glimepiride and rosiglitazone

A10BD05 Metformin and pioglitazone

A10BD06 Glimepiride and pioglitazone

A10BD07 Metformin and sitagliptin

A10BD08 Metformin and vildagliptin

A10BD09 Pioglitazone and alogliptin

A10BD10 Metformin and saxagliptin

A10BD11 Metformin and linagliptin

A10BF Alpha glucosidase inhibitors

A10BF01 Acarbose

A10BF02 Miglitol

A10BF03 Voglibose

A10BG Thiazolidinediones

A10BG01 Troglitazone

A10BG02 Rosiglitazone

A10BG03 Pioglitazone

A10BH Dipeptidyl peptidase 4 (DPP-4) inhibitors

A10BH01 Sitagliptin

A10BH02 Vildagliptin

A10BH03 Saxagliptin

A10BH04 Alogliptin

A10BH05 Linagliptin

A10BX Other blood glucose lowering drugs, excluding insulins

A10BX01 Guar gum

A10BX02 Repaglinide

A10BX03 Nateglinide

A10BX04 Exenatide

A10BX05 Pramlintide

A10BX06 Benfluorex

A10BX07 Liraglutide

A10BX08 Mitiglinide

A10BX09 Dapagliflozin

A10X Other drugs used in diabetes

A10XA Aldose reductase inhibitors

A10XA01 Tolrestat

Annex 8 Comorbidity definition

History of any of the endpoints of interest will also be considered as comorbidity. These events are described in Annex 3. In addition, the following diseased will also be captured under comorbidity:

Definition of asthma

According to the GINA (Global initiative for Asthma) guidelines, asthma is a disorder defined by its clinical, physiological and pathological characteristics. The predominant feature of the clinical history is episodic shortness of breath, particularly at night often accompanied by cough. (Bateman 2008)

The following concepts of disease have been mapped through the UMLS for the outcomes of asthma.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Asthma	J45*	493.*	H33..	R96
Asthma, unspecified	J45.9	493.90	H33z	
Nonallergic asthma	J45.1	493.1	H331z	
Intrinsic asthma			H331z	
Mixed asthma	J45.8		H332.	
Atopic asthma	J45			
extrinsic allergic asthma	J45	493.0	H330z	
Predominantly allergic asthma	J45.0			
Confirmed asthma			1O2..00	
Extrinsic asthma with asthma attack		493.02	663d.00 663m.00	
Intrinsic asthma + attack		493.12		
Number of asthma exacerbations in past year			663y.00	
Emergency admission, asthma			8H2P.00	
Status asthmaticus	J46	493.91		
Extrinsic asthma with status		493.01		

Terms	ICD10	ICD9CM	Read Codes	ICPC
asthmaticus				
Intrinsic asthma NOS		493.10		
Intrinsic asthma with status asthmaticus		493.11		
chronic obstructive asthma		493.2		
Other forms of asthma		493.8		
Asthma severity			663V.00	
Mild asthma			663V100	
Moderate asthma			663V200	
Severe asthma			663V300	
Asthma management			661M100	
			661N100	
Asthma monitoring			663..11	
Asthma monitoring due			66YE.00	
Asthma management plan given			663U.00	
Change in asthma management plan			66Y5.00	
Step up change in asthma management plan			66Y9.00	
Step down change in asthma man			66YA.00	
Asthma annual review			66YJ.00	
Asthma follow-up			66YK.00	
Asthma monitoring by nurse			66YQ.00	
Asthma monitoring by doctor			66YR.00	
Patient has a written asthma personal action plan			8CMA000	
Asthma clinical management plan			8CR0.00	
History of asthma			14B4.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Resolved asthma			2126200	
Induced asthma			173A.00	
			173c.00	
			173d.00	
			1780.00	
			1781.00	
			1782.00	
			1783.00	
			1784.00	
			1785.00	
			1786.00	
			1787.00	
			1788.00	
			1789.00	
			178A.00	
			178B.00	
Asthma and exercise			663e.00	
			663e000	
			663e100	
			663f.00	
			663w.00	
			663x.00	
Asthma currently dormant			663h.00	
Asthma currently active			663j.00	
Asthma treatment compliance satisfactory			663n.00	
Asthma treatment compliance			663p.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
unsatisfactory				
Asthma disturbing sleep			663N.00	
Asthma causing night waking			663N000	
Asthma disturbs sleep weekly			663N100	
Asthma disturbs sleep frequently			663N200	
Asthma not disturbing sleep			663O.00	
Asthma never disturbs sleep			663O000	
Asthma night-time symptoms			66YP.00	
Asthma causes night time symptoms			66Yq.00	
Asthma causes symptoms most nights			66Yr.00	
Asthma never causes night symptoms			66Ys.00	
Asthma limits activities 1 to 2 times per month			663P000	
Asthma limits activities 1 to 2 times per week			663P100	
Asthma limits activities most days			663P200	
Asthma not limiting activities			663Q.00	
Asthma causes night symptoms 1 to 2 times per month			663r.00	
Asthma never causes daytime symptoms			663s.00	
Asthma causes daytime symptoms 1 to 2 times per month			663t.00	
Asthma causes daytime symptoms 1 to 2 times per week			663u.00	
Asthma causes daytime symptoms			663v.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Asthma prophylactic medication used			663W.00	
Asthma medication review			8B3j.00	
Absent from work or school due to asthma			66YC.00	
Number days absent from school due to asthma in past 6 month			66Yu.00	
Health education - asthma			679J.00	
Health education - asthma self management			679J000	
Health education - structured asthma discussion			679J100	
Health education - structured patient focused asthma discuss			679J200	
Asthma control			8793.00	
			8794.00	
			8795.00	
			8796.00	
			8797.00	
			8798.00	
Asthma quality indicators			9hA..00	
			9hA1.00	
			9hA2.00	
Seen in asthma clinic			9N1d.00	
Seen in school asthma clinic			9N1d000	
Asthma outreach clinic			9NI8.00	
Under care of asthma specialist nurse			9NNX.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Asthma monitoring			9OJ..00	
			9OJ..11	
			9OJ1.00	
			9OJ2.00	
			9OJ3.00	
			9OJ4.00	
			9OJ5.00	
			9OJ6.00	
			9OJ7.00	
			9OJ8.00	
			9OJ9.00	
			9OJA.00	
			9OJA.11	
			9OJZ.00	
Patient in asthma study			9Q21.00	

Definition of Arterial Hypertension

According to the European Society of Hypertension (ESH) and European Society of Cardiology (ESC) Guidelines for the Management of Arterial Hypertension, a patient is defined as having hypertension when the systolic blood pressure is above 140 mm Hg and the diastolic blood pressure is above 90 mm Hg. (ESH/ESC 2007)

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for arterial hypertension.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Hypertensive diseases	I10-I15.9	401-405.99	Gyu2.	
high blood pressure	I10		XE0Ub	
			XM02V	
High blood pressure disorder			XE0Ub	
Uncomplicated hypertension				K86

Terms	ICD10	ICD9CM	Read Codes	ICPC
Hypertension with involvement target organs				K87
Renovascular hypertension	I15.0			
Secondary hypertension	I15	405	G24..	
Secondary hypertension, unspecified	I15.9		G24z.	
Malignant essential hypertension		401.0	G200.	
Essential (primary) hypertension	I10	401	XE0Uc	
Hypertension NOS		401.9	XE0Ud	
Benign hypertension		401.1	G201.	
Other secondary hypertension	I15.8	405.99	Gyu20	
Malignant secondary hypertension		405.0	G240.	
		405.09	G240z	
Benign secondary hypertension		405.1	G241	
		405.19	G241z	
Malignant hypertension			Xa3fQ	

Definition of Diabetes mellitus

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels.

The vast majority of cases of diabetes fall into two broad etiopathogenetic categories (discussed in greater detail below). In one category, type 1 diabetes, the cause is an absolute deficiency of insulin secretion. Individuals at increased risk of developing this type of diabetes can often be identified by serological evidence of an autoimmune pathologic process occurring in the pancreatic islets and by genetic markers. In the other, much more prevalent category, type 2 diabetes, the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response.(ADA 2012)

Criteria for the diagnosis of diabetes

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for diabetes mellitus.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Diabetes mellitus	E10-E14.9	250	C10..]	T90
Unspecified diabetes mellitus	E14			
diabetes NOS	E11			
Insulin-dependent diabetes mellitus	E10		X40J4	
Non-insulin-dependent diabetes mellitus	E11		X40J5	
Diabetes mellitus with ketoacidosis			C101. C101z	
Diabetes with renal manifestations		250.4	X30Kk XE10G C104z	
Nephrotic syndrome in diabetes mellitus			K01x1	
Diabetes with neurological manifestations		250.6	X00Ag	
Diabetes mellitus with neuropathy				
Unspecified diabetes mellitus without complications	E14.9	250.0	C100. C100z	
Secondary diabetes mellitus		249	X40JA	
Diabetic polyneuropathy	G63.2	357.2	AB/XE15k	
Diabetes with ophthalmic manifestations		250.5	C105. C105z	
Unspecified diabetes mellitus with unspecified complications	E14.8	250.9	C10z. C10zz	

Definition of hyperlipidemia/dyslipidemia

Dyslipidemia is defined as an elevation of plasma cholesterol, triglycerides (TGs), or both, or a low high-density lipoprotein level that contributes to the development of atherosclerosis. Causes may be primary (genetic) or secondary. Diagnosis is by measuring plasma levels of total cholesterol, TGs, and individual lipoproteins.

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for hyperlipidemia.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Mixed hyperlipidaemia	E78.2	272.2	XE11U	T93.03
Fam hyperlipoproteinaemia IIb Familial combined hyperlipidaemia Hyperapobetalipoproteinaemia			X40Vm	T93.04
Other hyperlipidemia	E78.4	272.4	Cyu8D	
hypercholesterolaemia	E78.0	272.0	XE11S C320z	T93.01

Definition of chronic kidney disease

Chronic kidney disease is defined as either kidney damage or glomerular filtration rate <60 mL/min/1.73 m2 for at least 3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies (Levey 2012).

The different stages of chronic kidney disease are described in the table below:

Stage	Description	GFR (mL/min/1.73 m2)
1	Kidney damage with normal or ↑ GFR	≥ 90
2	Kidney damage with mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	< 15 or dialysis

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for the outcomes of chronic kidney disease.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Chronic kidney disease	N18	585.9	1Z1..	U99
	N18.9	583*	K05..13	
		585*		
		586*		
Hypertensive chronic kidney disease	I12	403		
Chronic kidney disease, Stage I		585.1	1Z10.00	
			1Z17.00	
			1Z18.00	
			1Z18.11	
			K051.00	
End stage renal disease		585.6	K050.00	
			K0D..00	
Chronic kidney disease, Stage 5		585.5	1Z14.00	
			1Z1K.00	
			1Z1K.11	
			1Z1L.00	
			1Z1L.11	
			K055.00	
Hypertensive chronic kidney disease, malignant		403.0		
Hypertensive heart and chronic kidney disease	I13	404		
Chronic kidney disease, stage 2 (mild)	N18.2	585.2	1Z11.00	
			1Z19.00	
			1Z19.11	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			1Z1A.00	
			1Z1A.11	
			K052.00	
Chronic kidney disease, stage 3 (moderate)	N18.3	585.3	1Z12.00	
			1Z15.00	
			1Z16.00	
			1Z1B.00	
			1Z1B.11	
			1Z1C.00	
			1Z1C.11	
			1Z1D.00	
			1Z1D.11	
			1Z1E.00	
			1Z1E.11	
			1Z1F.00	
			1Z1F.11	
			1Z1G.00	
			1Z1G.11	
			K053.00	
Chronic kidney disease, stage 4 (severe)	N18.4	585.4	1Z13.00	
			1Z1H.00	
			1Z1H.11	
			1Z1J.00	
			1Z1J.11	
			K054.00	
Hypertensive heart and chronic kidney disease, malignant		404.0		
		403.xx,		

Terms	ICD10	ICD9CM	Read Codes	ICPC
		404.xx		
Renal failure	N17-N19.9	586	D215.00	
			D215000	
			K05..00	
			K05..12	
			K050.00	
			K06..00	
			K06..12	
Other chronic renal failure	N18.8		Kyu21	
Chronic kidney diseases monitoring/self-management			661M200	
			661N200	
			66i..00	
			6AA..00	
			9Ni9.00	
			9Ot..00	
			9Ot0.00	
			9Ot1.00	
			9Ot2.00	
			9Ot3.00	
			9Ot4.00	
Dialysis		V45.1	7L1..	
		V56.0	SP06B00	
		V56.8	Z1A..	
			Z91A.00	
			Z91A100	
			ZV45100	
			ZV56..	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			ZVu3G00	
CKD quality indicators			9hE..00	
			9hE0.00	
			9hE1.00	
Predicted stage chronic kidney			9Ot5.00	
Renal impairment			K060.00	
Impaired renal function			K060.11	
Acute-on-chronic renal failure			K0E..00	
Kidney transplantation		V42.0, 996.81	SP08300	
		250.4x	SP08C00	
			SP08D00	
			SP08E00	
			SP08F00	
			SP08G00	
			SP08H00	

If available, kidney function will be derived from the lab results (calculation of glomerular filtration rate = creatinine clearance) using the following formula:

Where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1 (Levey 2009).

Based on the actual value of the GFR, it will be possible to describe the stage of chronic kidney disease. In addition, code specific terms by stage (see above) will be used.

Definition of Lung cancer

The definition of lung cancer is a cancer (malignancy) that originates in the tissues of the lungs or the cells lining the airways. Lung cancer originates when normal lung cells become abnormal, usually after a series of mutations, and begin to divide out of control.

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for lung cancer.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Lung cancer Malignant neoplasm of bronchus and lung	C34.9	162 162.9	Xa0KG B22.. Byu20 XE1vc	R84
Oat cell carcinoma of			X78QO	
Small cell carcinoma of lung			X78QN	
Secondary malignant neoplasm of lung	C78.0	197.0	B570	
Non-small cell lung cancer			X78QS	
Malignant neoplasm of hilus of lung			B2211	
Malignant neoplasm of upper lobe of lung			B2221	
Malignant neoplasm of middle lobe of lung			B2231	
Malignant neoplasm of lower lobe of lung			B2241	
Malignant neoplasm of upper lobe, bronchus or lung	C34.1	162.3	B222z XE1vb	
Malignant neoplasm of middle lobe, bronchus or lung	C34.2	162.4	B223. B223z	
Malignant neoplasm of lower lobe, bronchus or lung	C34.3	162.5	B224. B224z	
Malignant neoplasm of other parts of bronchus or lung		162.8	B22y.	
Malignant neoplasm overlapping bronchus and lung sites	C34.8		B225.	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Personal history of malignant neoplasm of lung			ZV101	

Definition of cancer

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for cancer.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Malignant neoplasm without specification of site	C80	199	ByuC8 XE20H B59..	A79
Cancer Malignant neoplasm			X78ef	
Malignant neoplasm of bladder	C67	188	B49..	U76
Malignant neoplasm of breast Breast cancer Malignant tumor of breast	C50-C50.9		Byu6. X78WM XE1zL	X76
Malignant neoplasm of colon Malignant tumour of colon	C18	153	B13.. XE1xd XE1vV	D75
Malignant neoplasm of larynx	C32	161	B21.. XE1yD	
Carcinoma of the rectum			XE1vW X78OK	
Malignant neoplasm of skin	C44		Byu43 X78gs B33z.	S77
Malignant neoplasm of thyroid gland	C73	193	B53..	T71

Terms	ICD10	ICD9CM	Read Codes	ICPC
Malignant neoplasm of cervix uteri	C53	180	XE1vi B41z.	X75
Malignant neoplasm of stomach Gastric cancer	C16	151	X78gA XE1vR XE1xJ B11z.	D74
Malignant neoplasm of vagina	C52	184.0	B450.	
Malignant neoplasm of oropharynx	C10	146	B06..	
Malignant neoplasm of nasopharynx	C11	147	B07..	
Malignant neoplasm of pharynx	C14	149.0	X78fO	
Malignant neoplasm of duodenum	C17	152.0	/B120.	
Malignant neoplasm of caecum	C18.0	153.4	XE1vU	
Malignant neoplasm of peritoneum	C48.2	158.9	Byu57 X78Pq	
Malignant neoplasm of trachea	C33	162.0	B220.	
Malignant neoplasm of pleura	C38.4	163	B23..	
Bone cancer			XE1vd	
Malignant neoplasm of liver	C22	155	Xa97q B152.	
Malignant neoplasm of intestinal tract, part unspecified	C26.0	159.0	Byu12 X78gK B1z0.	
Malignant neoplasm of pancreas	C25	157	B17.. XE1y5	D76
Malignant neoplasm of vertebral column	C41.2		B302.	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Malignant neoplasm of prostate	C61	185	B46..	Y77
Malignant neoplasm of oesophagus	C15	150.9	B10.. X78g3 XE1vQ	
Malignant neoplasm of ovary	C56	183.0	B440.	
Malignant neoplasm of uterus	C55	179	B43..	
Malignant melanoma of skin	C43	172	Byu41 B32..	S77.03
Malignant neoplasm of brain	C71	191	B51z. XE2vS	N74
Malignant tumor of kidney	C64	189.0	X78iu	U75
Hodgkin's disease	C81	201	B61.. XaC2n BBjA.	B72
Leukemia	C95	208	BBr00 X78e2	B73