NOVARTIS

Global Clinical Epidemiology

Non-interventional study protocol

QVA149A2402

Title	Multinational database cohort study to assess [redacted]
Protocol version identifier	v02
Date of last version of protocol	02 June 2014
EU PAS register number	Study not registered
Active substance	Indacaterol/glycopyrronium bromide (QVA149) (R03AL04)
Medicinal product	Ultibro® Breezhaler®
Product reference	QVA149
Procedure number	EMEA/H/C/002679
Marketing authorization holder(s)	Novartis Europharm Limited Wimblehurst Road Horsham West Sussex RH12 5AB United Kingdom
Joint PASS	No

Research questions and objectives	...[redacted]
Country (-ies) of study	The Netherlands, Spain, Denmark, Italy, United Kingdom (UK)
Author	...[redacted]

QPPV or delegate	Signature	02 June 2014 Date

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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
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
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
IPCI	Integrated Primary Care Information Project
ICS	Inhaled Corticosteroid
IR	Incidence Rate
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 Authorisation Safety
PASS	Post Authorisation 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
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]
Project leaders and principal investigators	...[redacted]
Sub-investigators	...[redacted]

Role	Person
MAH contact person .	...[redacted]
Scientific advisory committee	...[redacted]

4 Abstract

Title	Multinational database cohort study to assess RMP specified safety outcomes in association with indacaterol/glycopyrronium bromide in Europe
Version and date	v02; 02 June 2014
Name and affiliation of main author .	...[redacted]
Rationale and background	Indacaterol/glycopyrronium bromide (QVA149, registered as Ultibro® Breezhaler® and related products) is a once-daily, inhaled fixed-dose combination (FDC) of indacaterol maleate (QAB149, registered as Onbrez® Breezhaler® and related products) and glycopyrronium bromide (NVA237, registered as Seebri® Breezhaler® and related products®) for the treatment of chronic obstructive pulmonary disease (COPD). QVA149 has been approved by European Commission on September 19th 2013 and has been launched in the Netherlands on November, 2013. Although QVA149 has demonstrated a good safety profile in the clinical trials, Novartis proactively proposed – in the context of the QVA149 marketing authorization application – to conduct a post-authorization safety study (PASS) under real-world conditions. The proposal to conduct a PASS was endorsed by the Pharmacovigilance Risk Assessment Committee (PRAC) to assess ...[redacted] .
Research question and objectives	...[redacted]
Study design	A multinational, multi-database cohort study will be conducted in patients with COPD. Within this cohort, new users of QVA149 will be compared to new users of comparator drugs (i.e., single constituent long-acting β_2 agonist [LABA], long-acting muscarinic antagonist [LAMA], free combination of LAMA/LABA, LABA/inhaled corticosteroids [ICS], or LAMA/LABA/ICS or fixed dose combination of LABA+ICS with or without LAMA) based on secondary use of information derived from five electronic health care databases from various European countries (i.e., the Netherlands, Italy, the United Kingdom [UK], Denmark, and Spain).
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 the study drugs (QVA149, single constituent LABA, single constituent LAMA, free combination of LAMA/LABA, LABA/inhaled corticosteroids [ICS], or LAMA/LABA/ICS or fixed dose combination of LABA+ICS with or without LAMA).
Variables	...[redacted]

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.
Study size	All QVA149 users who meet the study inclusion criteria and their comparator patients will be used to assess the risk of the selected safety endpoints. Based upon the market projections, MAH (i.e., Novartis) is confident that it will be able to accrue a sample size of a minimum of 6,000 patients in the QVA149 treatment cohort.
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 cohorts. The crude incidence rates will only be estimated if at least 1,000 new QVA149 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 the different endpoints of interest among new users of QAV149 will be compared to the risk in the new users of comparators using Cox regression analysis. If numbers allow, the free combination of LAMA/ long-acting β_2 agonist [LABA] will serve as anchor comparator; In case of low numbers, LAMA will serve as anchor comparator. 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 QVA149 and other comparators until the endpoint of interest, end of study, disenrollment from the database or death, whichever comes first. The anchor drug will be used as reference category, and the HR of the events of interest will be estimated for all other treatment categories compared to this reference. In addition, a sensitivity analysis will be conducted only considering the first treatment episode during follow-up in patients naïve to both QVA149 and all of the comparator drugs. Finally, 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 Nov 2013 End of data collection: 30 April 2018 Interim report 1: 28 February 2015 Interim report 2: 30 November 2015 Interim report 3: 30 November 2016 Interim report 4: 30 November 2017

	Registration in the EU PAS register: After EMA approval of the protocol Final report of study results: 4th Calendar Quarter 2018

5 Amendments and updates

Table 5-1 Study protocol amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1		4. Abstract	Abstract was updated to reflect changes in the body of the protocol	Based on PRAC comments
2		6. Milestones	Date of final report of study results amended	Based on PRAC comments
3		8.1 Primary objectives	Primary Objectives clarified	Based on PRAC comments
4		8.2 Secondary objectives	Secondary objectives clarified	Based on PRAC comments
5		9.2.1 Study population and study cohorts	Limitations of databases in relation to choosen methodology clarified	Based on PRAC comments
6		Study period	Launch dates for Spain and Italy updated	Based on PRAC comments
7		9.2.4 Follow-up	Death added as end of follow-up	Based on PRAC comments
8		9.3.1 Endpoints of interest	Endpoints of interest + how these will be assessed have been updated and clarified	Based on PRAC comments
9		9.3.5. Demography, lifestyle factors and comorbidity	Updated now including glaucoma and urinary retention/BPH	Based on PRAC comments

10		9.5 Study size	Updated: - now including sample size assuming a 1:10 and 1:20 ratio for QVA149 vs comparator drugs - Individual database estimates have been corrected - Corrective measures in case identified users of QVA149 is lower than expected have been added	Based on PRAC comments
11		9.7.1 Yearly analysis for study reports	Treshold of RR of >3 has been clarified	Based on PRAC comments
12		9.7.2 Analysis	Updated now including analysis in strictly naive users + considering the complete follow-up where reference is anchor therapy	Based on SAC comments
13		9.9 Limitation of research methods	Have been updated including corrective measures in case of heterogeneity between Spanish and other databases	Based on PRAC comments
14		Annex 3	Endpoint definition, validation algorithm, comorbidity, exposure and concomitant medication updated	Based on PRAC comments regarding endpoints + review of disease codes by database partners

6 Milestones

Table 6-1 Study milestones

Milestone	Planned date
Start of data collection	01 November 2013
End of data collection	30 April 2018
Interim report 1	28 February 2015
Interim report 2	30 November 2015
Interim report 3	30 November 2016
Interim report 4	30 November 2017

Milestone	Planned date
Registration in the EU PAS register	After EMA approval of the protocol
Final report of study results	4th Calendar Quarter 2018

7 Rationale and background

According to GOLD (Global Initiative of Lung Disease), chronic obstructive pulmonary 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 co-morbidities contribute to the overall severity in individual patients. COPD is characterized by a progressive decline in lung function which cannot be reversed by treatment (Pauwels et al. 2001). COPD is a frequent disease and in Europe, the COPD prevalence rates range from 4-10% in the adult population (Halbert et al. 2006).

Bronchodilators are the mainstay of symptomatic management of COPD and include β2 agonists, anticholinergics (AC), methylxanthines and phosphodiesterase-4 inhibitors, used alone or in combination. Indacaterol/glycopyrronium bromide (QVA149, registered as Ultibro® Breezhaler® and related products) is a once-daily, inhaled fixed-dose combination (FDC) of indacaterol maleate (QAB149, registered as Onbrez® Breezhaler® and related products) and glycopyrronium bromide (NVA237, registered as Seebri® Breezhaler® and related products) is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). QVA149 has been approved by European Commission on September 19th 2013 and has been launched in the Netherlands on November, 2013. Indacaterol is a full agonist at the human β2-receptor, has a fast onset of action (5 min), and a long duration of action (24 hours). Indacaterol exhibits modest β1 and β3-adrenoceptor activity, similar to formoterol and salbutamol. Glycopyrronium bromide is a synthetic quaternary ammonium compound that acts as a competitive antagonist at the muscarinic acetylcholine receptor M1 to M5 with modest selectivity for receptor M1 and M3 and a relatively slow dissociation rate.

Current guidelines recommend management of stable COPD with a long-acting bronchodilator, either a long-acting β2 agonist (LABA) or a long-acting muscarinic antagonist (LAMA). Combining bronchodilators of different pharmacological classes is also suggested with the rationale of complementary bronchodilation, sustained effect and reduced risk of side effects compared to monotherapy (GOLD 2011). Clinical evidence supports this suggestion by showing greater improvement of various outcome measures with combination therapy (Cazzola et al. 2010; Wang et al. 2011; van der Molen et al. 2012).

Combining a long-acting beta2 agonist (LABA) with a long-acting muscarinic antagonist (LAMA) as concurrent therapy has been shown to significantly improve bronchodilation in COPD patients compared to the respective monotherapies (van Noord et al. 2010). This is expected to lead to improvement in dyspnea, health status/quality of life and COPD exacerbations compared to monotherapy.

Although QVA149 has demonstrated an acceptable safety profile in clinical trials (Decraemer 2013; Vogelmeier 2013; Welte 2013), in the context of the QVA149 marketing authorization application, the MAH (i.e., Novartis) proactively proposed to conduct a PASS in the post-marketing setting. The proposal to conduct PASS was endorsed by the Pharmacovigilance Risk Assessment Committee (PRAC) to assess risk management plan (RMP) specified safety outcomes in association with QVA149.

8 Research question and objectives

...[redacted]

8.1 Primary objectives

...[redacted]

8.2 Secondary objectives

...[redacted]

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 QVA149 for the treatment of COPD, will be defined as well as comparator cohorts, namely a new user cohort of single constituent LAMA, single constituent LABA, free combination of LAMA/LABA, LABA/ICS, or LAMA/LABA/ICS or fixed dose combination of LABA+ICS with or without LAMA. For the primary analysis, these cohorts will be followed from start of the first prescription until the end of treatment (switching or add-on therapy), end of study, any of the endpoints of interest, disenrollment from the database or death whichever comes first.

In a secondary analysis, the complete study follow-up of each patient will be taken into account, with treatment being used as a time-varying variable. This implies that patients will be followed from start of first prescription of QVA149 or comparator drug until the endpoint of interest, end of study, disenrollment from the database or death, whichever comes first. The anchor drug (i.e. as defined in Section 9.7.2.1.2) will be used as reference category, and the HR of the events of interest will be estimated for all other treatment categories compared to this reference. (for more details, see 'Sensitivity analyses', in Section 9.7.2.2.2).

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 cardiac arrhythmia.

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. Limitations of these databases are described in 9.4 and 9.9. In brief, as IPCI, HSD, THIN and SIDIAP are primary care databases; information on specialist prescribing, drug dispensing and actual drug intake is missing. Aarhus does have information on specialist prescribing and drug dispensing however dosing information is not available and this database lacks information on actual drug intake as well. In addition, co-factors such as smoking and BMI are not systematically reported in all databases. Finally, relevant endpoints and comorbidity are identified via disease codes. Misclassification could be a concern in case of inappropriate or insufficient coding. For all of the databases, validation studies have shown that coding is reliable in the databases and that these databases are suitable for pharmaco-epidemiological research. If free text is available, validation of endpoints will be conducted at the end of the study

From these databases, we will first select a population of patients ≥40 years of age with at least one year of valid database history and a recorded diagnosis of COPD (for the definition of COPD, see Annex 3.4 – COPD definition). Valid database history means that there is at least one year of database history for a patient. This means that the patient was registered with the GP since at least one year but also that the GP is providing data to the database for at least one year as well. 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 and having fulfilled the criteria for a diagnosis of COPD. Diagnoses of COPD may be searched in the entire available 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 2011). Especially as LABAs and LABAs+ICS are part of the comparator drugs and frequently used for the symptomatic treatment of asthma, it is important to overcome the risk of misclassification of COPD. If not, there is the potential of comparing the safety profile of QVA149 in patients with COPD versus the safety profile of LABAs in patients with asthma.

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

1. QVA149
2. A single ingredient LABA
3. A single ingredient LAMA
4. A free combination of LAMA/LABA
5. A free combination of LABA/ICS
6. A free combination of LAMA/LABA/ICS

7. A fixed dose combination of LABA+ICS with or without LAMA

Because of the size of the databases and the fact that the comparator groups are well established treatments in COPD, we assume a 1:4 ratio of QVA149 vs. comparator group.

New single ingredient or fixed drug combinations of LABA/LAMA/ICS coming onto the market during the course of the study will also be captured. The list of drugs as mentioned in Annex 3.5 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 apart for the secondary analysis (see also 9.7.2.2.2 – sensitivity analysis).

9.2.2 Study period

The study will cover patients' data from the first launch of QVA149 in one of the European countries of interest (i.e. November 2013) up to one year after inclusion of the last patient (for details, see Section 9.5 'Study size') in the new user cohort of QVA149. The end of the study is one year after inclusion of the last patient in the new user cohort of QVA149. Based on the size of the databases and the expected market uptake of QVA149, the end of the study is roughly estimated as approximately 4.5 years after drug launch, i.e. approximately end of April 2018 (estimated 1 year follow-up date of the last patient enrolled in the QVA149 cohort). During the study, the progress of identification of QVA149 within all databases will be monitored closely.

Planned dates for launch of QVA149 in the five countries are specified in Table 9-1.

Table 9-1 Launch dates for QVA149 in the five participating countries

Countries	Actual/Planned launch date
Denmark	November 2013
Italy	March 2014
Netherlands	November 2013
Spain	May 2014
United Kingdom	November 2014

9.2.3 In- and exclusion criteria

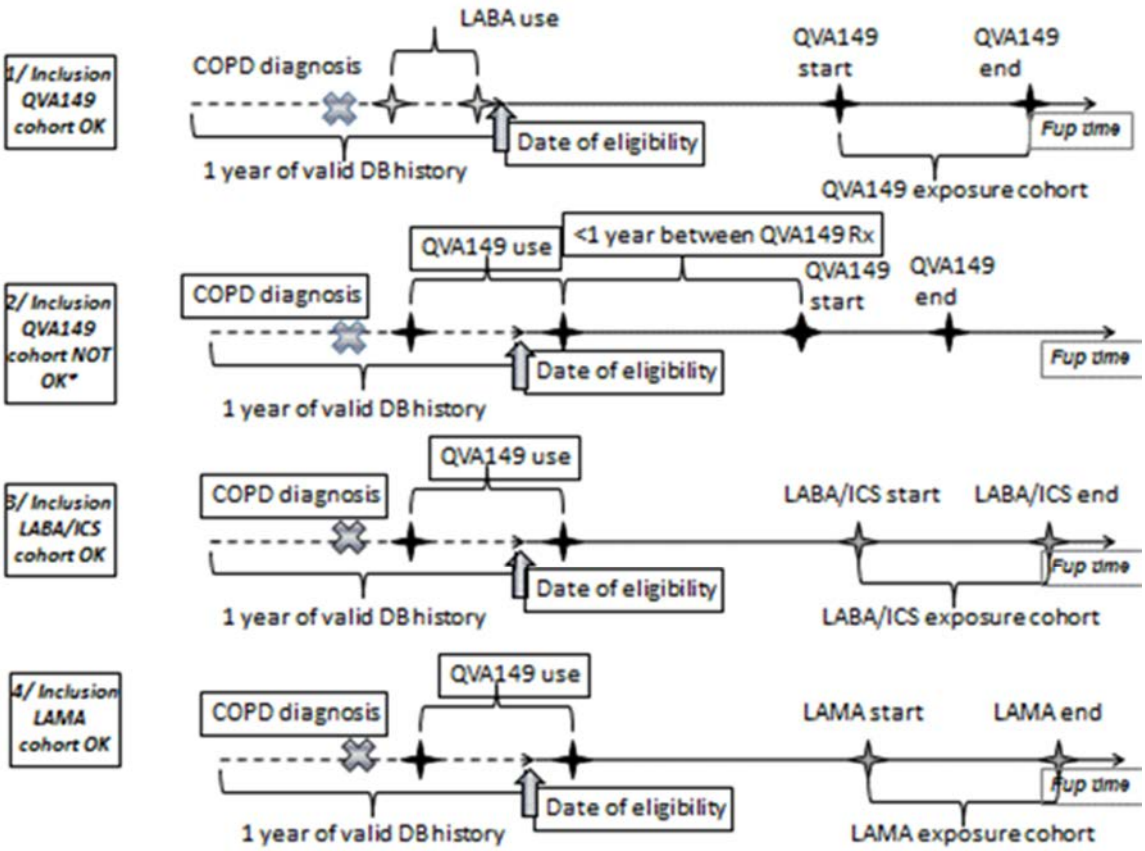
Inclusion criteria

All patients fulfilling the criteria for COPD diagnosis, 40 years or older, with at least one year of database history, and a first time prescription/dispensing for QVA149, or comparator drugs after 1st of November 2013 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 of the first prescription/dispensing of any of the drugs of interest or 3) who received the study drug of interest (QVA149 or comparator drugs) 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.

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



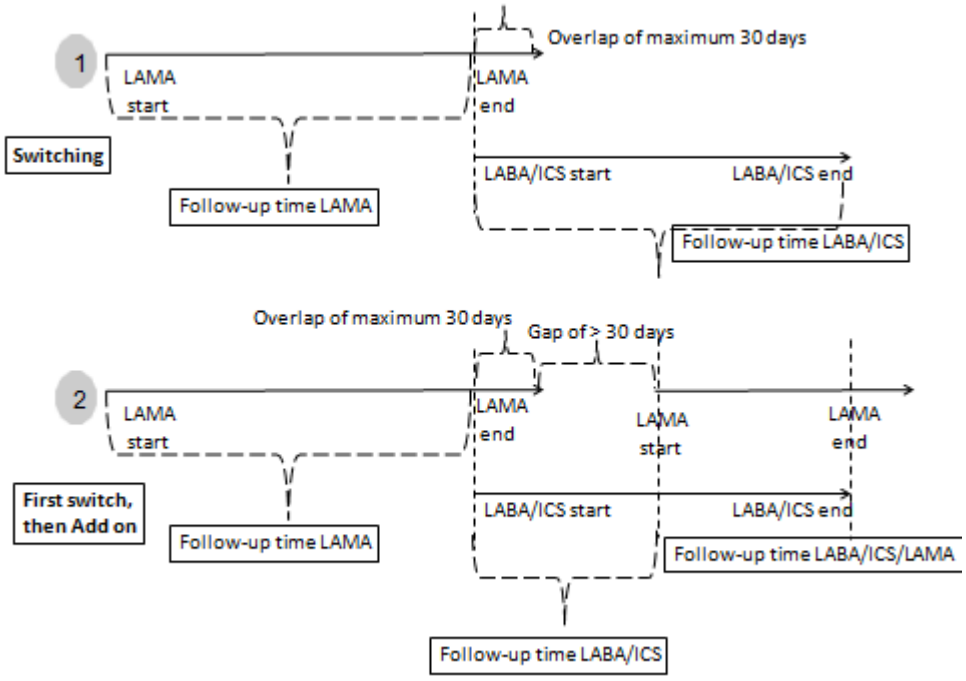
* In the second example, inclusion into the QVA149 would be OK if time window between date of eligibility and QVA149 start would be more than 1 year

9.2.4 Follow-up

For the primary analysis, patients initiating QVA149 or comparator drugs 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 study endpoint or (iv) death.

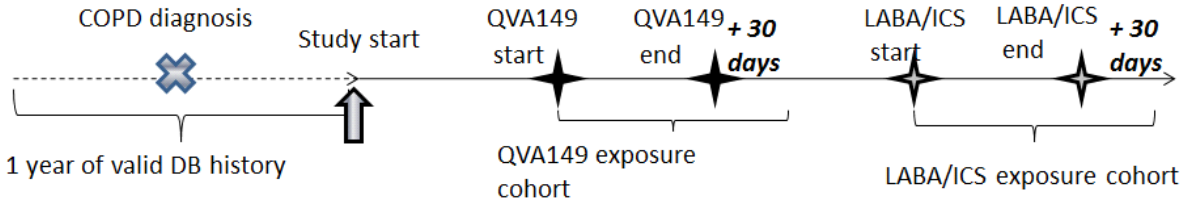
End of treatment is defined as the discontinuation of use of QVA149, or comparator drugs for the respective treatment cohorts. This implies that follow-up, for the respective cohorts, ends when a patient discontinues, switches treatment or initiates another comparator drug as add-on therapy (Figure 9-2). Switching is defined as start of another comparator drug with maximum overlap of prescriptions of 30 days. Add-on therapy is defined as start of prescriptions of comparator drugs combined with repeated prescriptions of first exposure cohort

Figure 9-2 Switching and add-on therapy



Upon discontinuation of one of the treatment cohorts, patients are still eligible to be enrolled in the other treatment cohorts (Figure 9-3).

Figure 9-3 Eligibility to different exposure cohorts



This implies that, if a patient switches from QVA149 to another comparator drug, this patient can enroll into the comparator cohort. Enrollment into the comparator cohort is only acceptable in case the patient was comparator drug exposure naïve in the one year prior to the index date.

If add-on therapy is initiated (Figure 9-2), follow-up of the initial exposure cohort discontinues and the combined use of the drugs of interest will contribute follow-up time to the combined drug categories of interest (free combination of LAMA/LABA, free combination of LABA/ICS, free combination of LAMA/LABA/ICS or fixed dose combination of LABA+ICS with or without LAMA). The calculation of the end of the treatment episodes is further clarified under "9.3.2- Exposure".

9.3 Variables

9.3.1 Endpoints of interest

...[redacted]

Prior to analysis, for each patient of the COPD cohort, all endpoints will be identified in the database based on searches for 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 3.2 – Validation algorithm). These event definition algorithms will be part of the statistical analysis plan. The validation of endpoints will only be done at the end of the study, in preparation of the final analysis. For each of the endpoints of interest, the date of the first disease-code specific entry within the database will serve as date of diagnosis of the endpoint and follow-up time will be censored upon that date. For chronic conditions such as angina pectoris or heart failure, patients will be considered as having a new endpoint of interest in case of hospitalization for unstable angina pectoris (= acute coronary syndrome) or heart failure. These events are captured either via event specific codes (e.g. admit heart failure emergency) and/or 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).

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 3.1 – Event definition).

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 (i.e ...[redacted]...
), patients will be censored
upon the first event of interest, e.g., a patient diagnosed with myocardial infarction and later diagnosed with stroke, will be censored at the date of the diagnosis of ...[redacted]
.

The identified codes, as documented in Annex 3.1 – Event definition, 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.

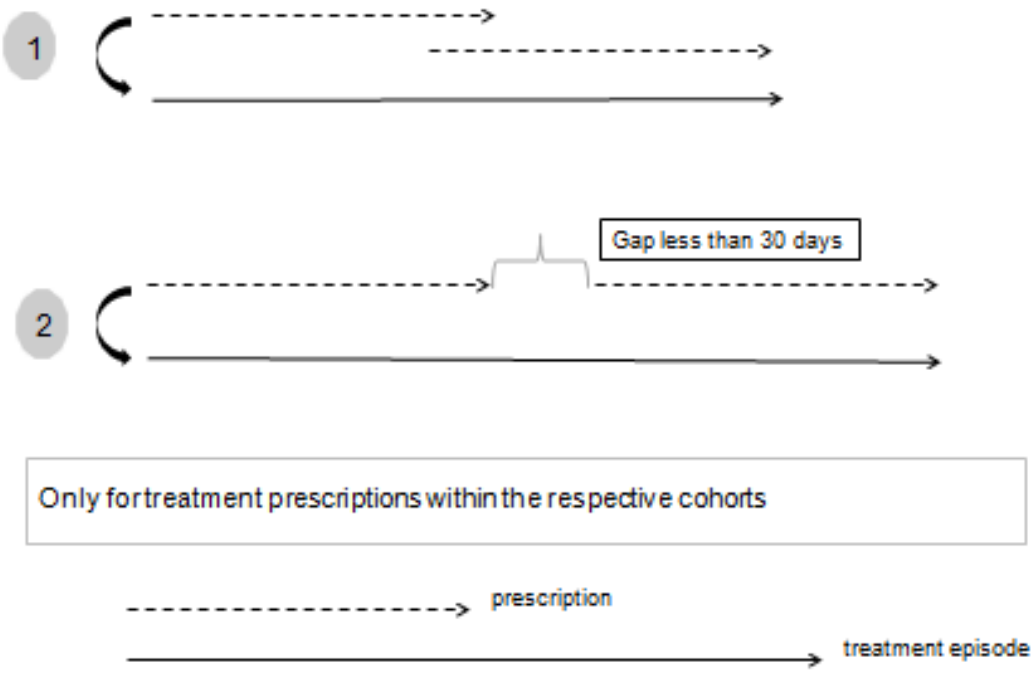
9.3.2 Exposure of interest

Patients prescribed QVA149, and comparator drugs will be identified in the database by an automated search on the respective anatomical therapeutic chemical classification system (ATC) codesor Multilex codes of the prescription records in the respective databases (see Annex 3.3 – 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 not available, 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 9-4). If the subsequent prescription overlaps the previous prescription, the two prescriptions will be combined into one episode and the stop date of that episode will be the stop date of the second prescription ((1) in Figure 9-4). In case of a gap between two prescriptions, these prescriptions will only be combined into one episode if the duration of the gap is less than 30 days. ((2) in Figure 9-4).

Figure 9-4 Creation of treatment episode for inhaled COPD therapies



Patients will be classified as "exposed" to study medication (QVA149 or comparator drugs) for the duration of the first treatment episode plus 30 days. This 30 days grace period was chosen as patients are considered not to be 100% compliant, especially in case of chronic therapy. In a sensitivity analysis, as part of the final study report, we will repeat the analysis where the first treatment episode is extended with a window of 60 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 9-5). 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 9-5 Identification of period of follow-up

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 3.4 – 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 electronical medical file of the patient, confirmed by spirometry (post-bronchodilator FEV1/FVC < 0.70) or confirmed by the specialist (GOLD 2011).

In addition, for all databases, prior to the final analysis, COPD will be categorized in "definite COPD" and "probable COPD". Patients will be considered to have "definite COPD" in case of at least two 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. Patients with only one record of COPD will be classified as "probable COPD".

COPD severity is an important confounder and/or effect modifier in the association between the use of QVA149 or comparator drug(s) and the risk of various outcomes of interest, specifically 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 available. If spirometry data is lacking or 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 3.4 – COPD definition and COPD severity.

9.3.4 Past use of drugs and concomitant drug use

9.3.4.1 Use of other 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 3.5 – Concomitant medication definition). Use of these drugs will be assessed in the one year prior to the index date and at index date. In addition, use of concomitant medication (respiratory drugs and other drugs) will be added as time-varying exposure in the Cox regression model (see Section 9.7 Data analysis). The following types of bronchodilating and/or anti-inflammatory drugs will be considered as respiratory drugs:

- Single ingredient short acting muscarinic antagonists (SAMAs)
- Single ingredient short acting β2 agonists (SABAs)
- ICS
- Xanthines
- Fixed combination therapy (LABA + ICS, anticholinergic agents + SABA)
- Oral β_2-agonists
- Leukotriene receptor antagonists (LTRAs)
- Systemic corticosteroids (oral, intravenous or intramuscular administration)
- Single ingredient LABA
- Single ingredient LAMA
- Oral phosphodiesterase 4 (PDE-4) inhibitors

9.3.4.2 Other drug use

The following drugs will also be considered as they might be potential confounders or effect modifiers in the association between use of QVA149 or comparator drug and the outcomes of interest. Exposure to these drugs, at index date and as time-varying exposure, will be assessed via an automated search on either ATC, product names or Multilex codes (see Annex 3.5 – Concomitant medication definition).

9.3.4.2.1 Central nervous system drugs (excluding drugs with anticholinergic effects)

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

9.3.4.2.2 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).

9.3.4.2.3 Drugs affecting cerebrovascular and cardiovascular disease

Use of systemic corticosteroids, NSAIDs, vitamin K antagonists, lipid lowering drugs, platelet aggregation inhibitors, nitrates, anti-arrhythmics, cardiac glycosides, anti-diabetic drugs and anti-hypertensive drugs.

9.3.5 Demography, life style factors and comorbidity

For all patients, information will be captured on:

- Age and gender (at time of index date)
- Smoking status (if available); 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 corticosteroids 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.
- Number of courses of antibiotics for the treatment of lower respiratory tract infections in the one year prior to the index date.
- 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.
- ...[redacted]

Underlying comorbidity or history of above conditions will be identified via an automated search on disease specific codes (see Annex 3.1 – Event definition and Annex 3.6 – 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 QVA149 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 QVA149. All of the participating databases are part of the ...[redacted], a stable collaboration framework for running drug safety studies in a federated manner, especially when the participation of several electronical health care record databases is required (...[redacted]).

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 et al. 2010; Cazzola et al. 2011; Garcia-Gil Mdel et al. 2011).

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 database characteristics including the available 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 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 in 2013.

Table 9-2 Overview of databases

	Netherlands	United Kingdom	Denmark	Italy	Spain
Name of the database	IPCI	THIN	Aarhus	HSD	SIDIAP

	Netherlands	United Kingdom	Denmark	Italy	Spain
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	2 times a year (January/July)	3 times a year	Yearly (April)	2 times a year: (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	Yes	Yes	Yes
Coding of disease	ICPC	READ	ICD-10	ICD-9 CM	ICD-10

ADM = Administrative; ATC = Anatomical Therapeutic Chemical; BNF = British National Formulary; ICD= International classification of disease, ICPC = International Classification of Primary Care; MR = Medical Records

9.4.1 IPCI database

In 1992 the Integrated Primary Care Information Project (IPCI) was started by the ...[redacted] . IPCI is a
longitudinal observational database that contains data from computer-based patient records of a selected group of 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 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 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 QVA149 and according to the dosing regimens of the respective SmPC for the other drugs. Around 50% of prescription dosage is also imputed by GPs.

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

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 UK. GPs 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 GPs' visits such as medical diagnoses and prescriptions written by the GPs, 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. 2007) 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, 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.

As this is a primary care database, information on specialist prescribing, drug dispensing and actual drug intake is missing. 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 et al. 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 pharmaco-epidemiological research (Sorensen et al. 1994).

Dose must be inferred from the strength, assuming a once daily administration for QVA149 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). Aarhus is listed under the ENCePP resources database (www.encepp.eu/encepp/resourcesDatabase.jsp).

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. The 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).

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

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

9.5 Study size

All QVA149 users who meet the study inclusion criteria and their comparator patients will be used to assess the risk of the selected safety endpoints. The actual sample size for the study will be largely affected by the market uptake of QVA149 in the source population. Because the actual number of subjects in the study is difficult to predict at the early planning stage, Novartis proposes to include minimum 6,000 patients in patients in the QVA149 treatment cohort. The following calculations provide examples of sample size in terms of number of patients (see Table 9-3).

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 et al. 2008; Dong Yaa-Hui 2012; Jara et al. 2012). For this reason, sample size estimates were calculated assuming an HR of 1.5 and 2. Considering the size of the databases and the fact that the comparator groups are well established treatments in COPD and QVA149 being new to market, we assume a 1:4 ratio of QVA149 vs. comparator drugs.

Table 9-3 Sample size and power calculation

Endpoints	Background IR*	Hazard ratio	Actual power	N Total	N QVA group	N Total	N QVA group	N Total	N QVA group
				1:4	1:4	1:10	1:10	1:20	1:20
[redacted]	0.01	1.5	0.8	38,050	7,610	70037	6,367	125,013	5,953
	0.0122	1.5	0.8	31,235	6,247	57,497	5,227	102,648	4,888
	0.0464	1.5	0.8	8,415	1,683	15,510	1,410	27,699	1,319
	0.0109	1.5	0.8	34,930	6,986	64,295	5,845	114,765	5,465
	0.0334	1.5	0.8	11,580	2,316	21,340	1,940	38,094	1,814
	0.00356	1.5	0.8	106,390	21,278	195,789	17,799	349,419	16,639
	0.00911	1.5	0.8	41,740	8,348	76,824	6,984	137,130	6,530
	0.01	2	0.8	10,395	2,079	18,315	1,665	32,067	1,527
	0.0122	2	0.8	8,535	1,707	15,037	1,367	26,334	1,254
	0.0464	2	0.8	2,315	463	4,092	372	7,161	341
	0.0109	2	0.8	9,545	1,909	16,819	1,529	29,442	1,402
	0.0334	2	0.8	3,175	635	5,610	510	9,828	468
	0.00356	2	0.8	29,035	5,807	51,117	4,647	89,460	4,260
	0.00911	2	0.8	11,400	2,280	20,086	1,826	35,154	1,674

Sample size calculation done with SAS 9.3 using Proc POWER two survival curves assuming 80% power 2-sided 0.05 alpha and 3 years of accrual time with no extra follow-up and a median censoring time of 180 days. Sources: (Cedrone et al. ; Gonzalez et al. 2009; Schneider et al. 2010; Jara et al. 2012).

	Netherlands	United Kingdom	Denmark	Italy	Spain
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	2 times a year (January/July)	3 times a year	Yearly (April)	2 times a year: (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	Yes	Yes	Yes
Coding of disease	ICPC	READ	ICD-10	ICD-9 CM	ICD-10

ADM = Administrative; ATC = Anatomical Therapeutic Chemical; BNF = British National Formulary; ICD= International classification of disease, ICPC = International Classification of Primary Care; MR = Medical Records

9.4.1 IPCI database

In 1992 the Integrated Primary Care Information Project (IPCI) was started by the v...[redacted] . IPCI is a
longitudinal observational database that contains data from computer-based patient records of a selected group of 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.

Table 9-5 Individual database estimates of QVA149 treated patients for the year 2017

Countries	Country estimate for 2017	Multiplier	Individual database estimate of QVA149 treated patients in 2017
UK	29,857	0.030	896
Italy	187,746	0.017	3,192
Spain	140,535	0.066	9,275
Denmark	6,031	0.153	922
Netherlands	15,278	0.062	947
Total	379,447	NA	15,232

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

The total estimate across all databases would sum up to over 15,200 patients. Under the assumption that 70% of the QVA149 treated patients will fulfill the in-/exclusion criteria, the total number of patients would correspond to over 10,600. Based on this conservative estimate, the MAH is confident that it will be able to accrue a sample size of a minimum of 6,000 patients in the QVA149 treatment cohort. If, at the time of the third interim report, the number of patients included in the study is below expectation, the possibility to include additional database sources will be considered.

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, and hospital discharge diagnoses). 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 3.1, Annex 3.4 and Annex 3.6 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.

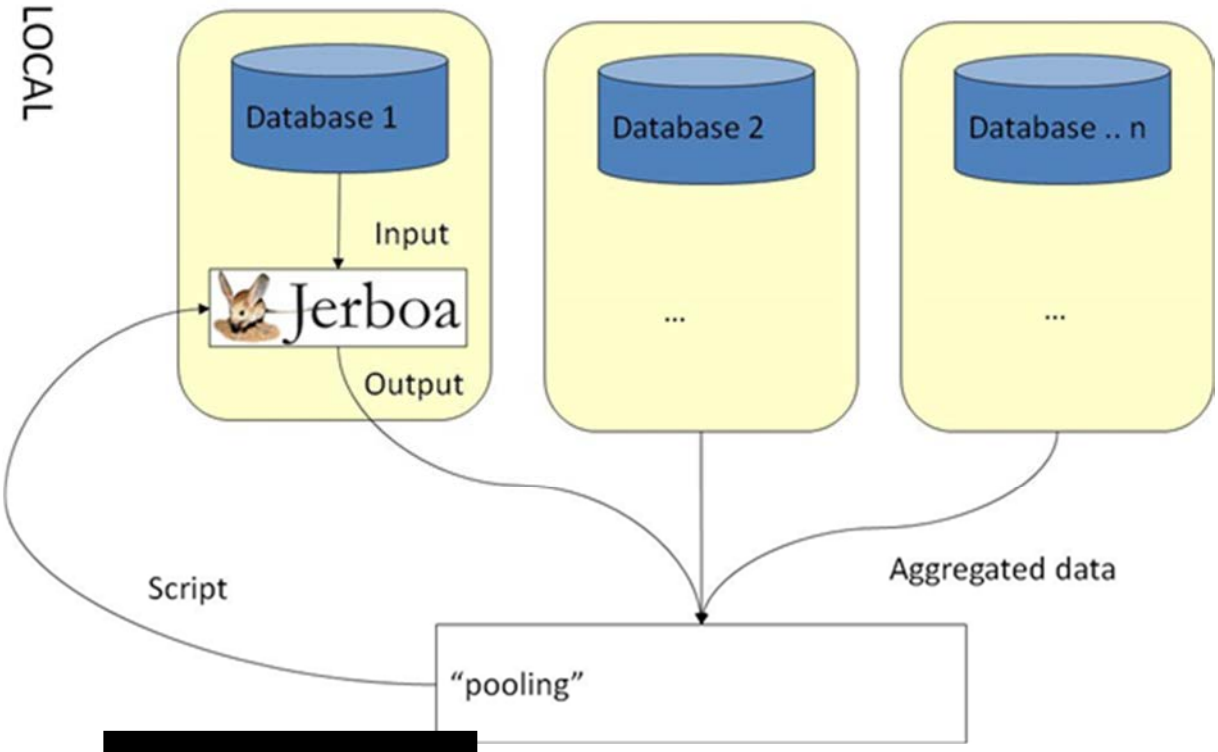
9.6.2 Definition of data extraction algorithm

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 [redacted] 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 9-6 Model for data sharing and elaboration



Source: [redacted]

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 and scientific lead 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 described in Section 9.3.1. Definitions of these endpoints and validation algorithms are further described under Annex 3.1 – Event definition and Annex 3.2 – Validation algorithm.

9.7.1 Yearly analysis for study progress reports

Yearly progress reports/ interim reports will be created with the first report scheduled one year after first launch of QVA149 (November 2013). These reports will include both data-specific information and pooled data. These reports will contain the following information:

- Number of patients in the different exposure cohorts (QVA149, comparator drugs)
- Baseline characteristics in terms of comorbidity and concomitant drug use at time of index data of the different exposure cohorts. This will be described using contingency tables for categorical variables and mean, standard deviation (SD), range for continuous variables
- Crude incidence rates (IRs) of the endpoints of interest among the different exposure cohorts

The crude incidence rates (database specific and pooled) will only be estimated if at least 1,000 new QVA149 users have been enrolled. 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 study conduct however, the safety of QVA149 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 QVA149 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 (see Section 9.7.2).

9.7.2 Final analysis

The final analysis, consisting of an analysis on each database individually and a pooled analysis, will be conducted at the end of the study (one year after inclusion of the 6000th patient in the new user cohort of QVA149). 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

9.7.2.1.1 Demographic and baseline characteristics of exposure cohorts

Demographic and baseline characteristics of the patients initiating QVA149 or comparator drugs 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 QVA149 and comparator drugs will be assessed via the non-parametric Mann-Whitney U test for continuous variables, and the Chi-square test for categorical variables.

9.7.2.1.2 Incidence rates and hazard ratios of different endpoints

To determine the risk of various endpoints in new users of QVA149 and new users of comparator drugs, IRs with 95% confidence intervals (CI) will be calculated using negative binomial distribution for each outcome of interest in the different treatment cohorts.

The relative risk (expressed as hazard ratio [HR] with 95% CI) will be estimated for new users of QVA149 vs. new users of comparator drugs 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 first treatment episodes of each drug.

If numbers allow, the free combination of LAMA/ long-acting β2 agonist [LABA] will serve as anchor comparator; In case of low numbers, LAMA will serve as anchor comparator.

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

- Age
- Gender
- Smoking history (“current smoker”, “past smoker”, “non-smoker” or “smoking status unknown”. Number of pack-years will be provided if available.
- 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-days 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 QVA149.

First, a logistic regression model will be built to estimate propensity scores to be treated with QVA149 instead of the comparator drugs using the below covariates:

- Age (at index date)
- Gender
- COPD severity
- Concomitant drug use (see Section 9.3.4 and Annex 3.5 for codes)
- Comorbidity (see Section 9.3.5 and Annex 3.6 for codes)
- Smoking (see Section 9.3.5)

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

9.7.2.1.3 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 I2 value will be recorded, with I2 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. In addition, in case of heterogeneity between Spain's SIDIAP (which is expected to contribute the highest number of patients to this study) and the other databases, a meta-analysis will be conducted on all databases excluding SIDIAP.

9.7.2.1.4 Handling of missing data

Smoking

Information on smoking status might be incomplete in these electronical 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 analyses 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 QVA149 (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).

COPD severity

COPD severity will be assessed by spirometry, if available. If spirometry data is lacking, COPD severity will be categorised according to published algorithms (Soriano et al. 2001; Eisner et al. 2005; Curkendall et al. 2006). For further details on COPD severity, see Annex 3.4 – COPD definition and COPD severity.

9.7.2.1.5 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 (adjusted) 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

9.7.2.2.1 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 or hemorrhagic stroke or TIA at the index date.

For all endpoints, stratified analyses will be conducted by:

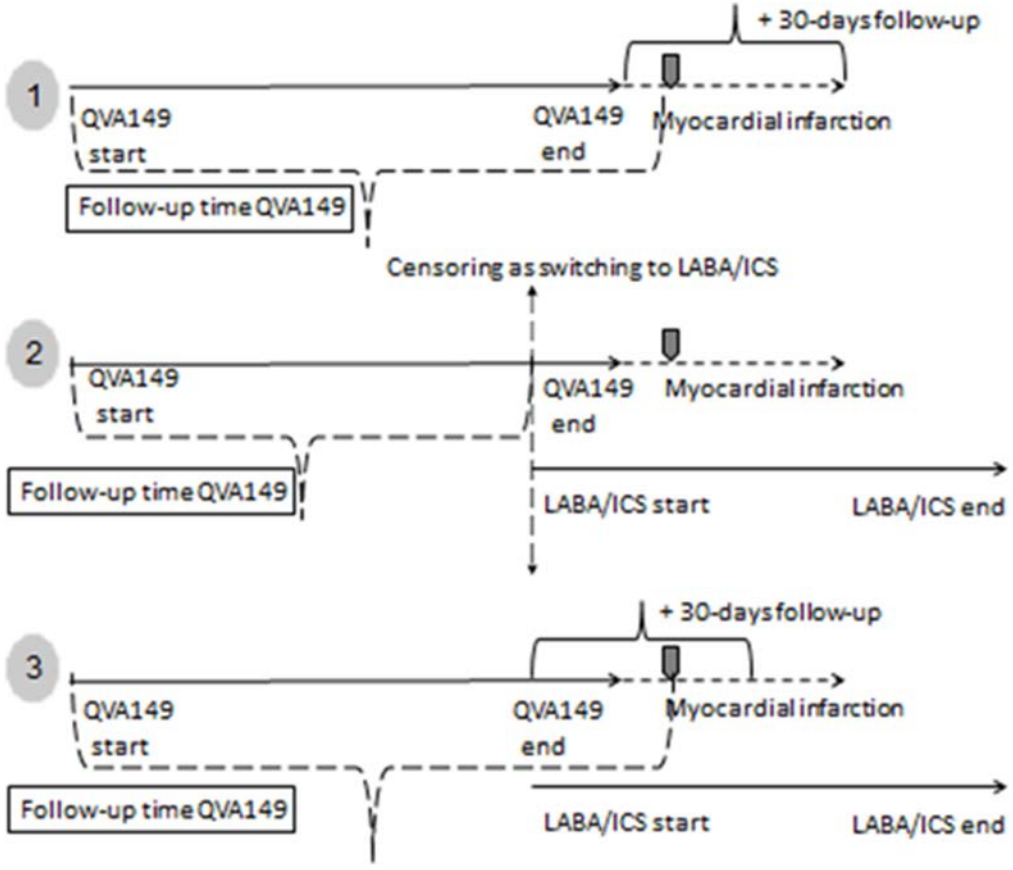
- Gender
- Age group (≥40-<65, ≥65-<75, ≥75 years)
- COPD severity status
- Inhaled corticosteroid use (at least one prescription of ICS ± 90 days of index date)
- Patients with probable and definite COPD (see 9.3.3 COPD and COPD severity)

The purpose of stratified analyses is to determine the modifying effect of co-morbidities on the risk of study 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.

9.7.2.2.2 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 9-7 – 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 9.7 – 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 9-7 – third scenario).

Figure 9-7 Different scenarios of follow-up for first episode of exposure

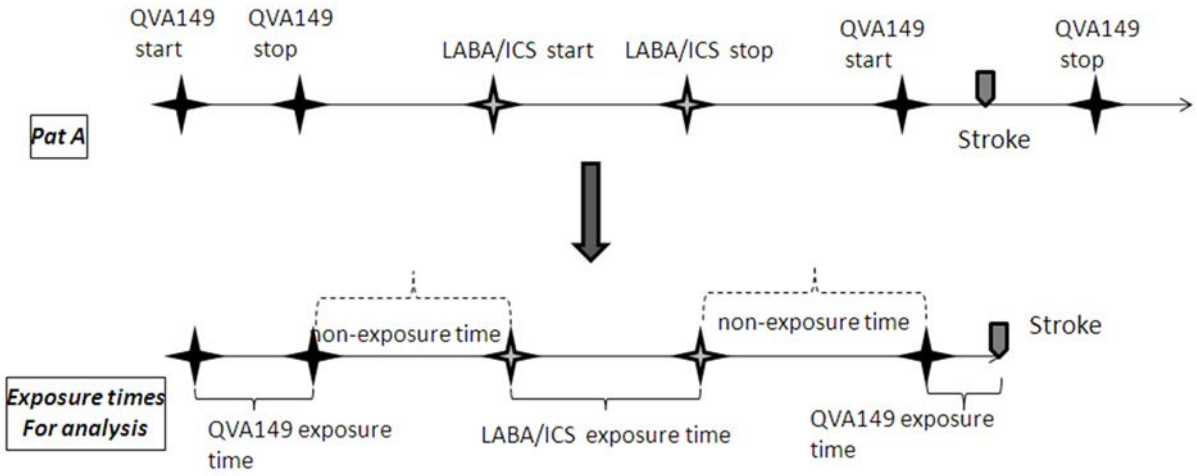


The use of a 30-day window after drug discontinuation to define "current exposure" is common in pharmaco-epidemiological research within COPD (Verhamme et al. 2013). In a sensitivity analysis, this follow-up window after drug discontinuation will be extended from 30 to 60 days.

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 minimum 60 days.

To analyze the complete follow-up of each patient from start of first treatment onwards, treatment will be used as time-varying variable. For this analysis, all subsequent episodes with or without treatment will be taken into account. Patients will be followed from start of first prescription of QVA149 or comparator drug, until the endpoint of interest, end of study, disenrollment from the database or death, whichever comes first. Each change of treatment will give a change in the exposure category. "No treatment" will also be one of the categories of the exposure variable. The anchor drug (i.e., as defined in Section 9.7.2.1.2) will be used as reference category, and the HR of the events of interest will be estimated for all other treatment categories compared to this reference. (Figure 9-8).

Figure 9-8 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 QVA149 and all comparator drugs. (thus no use of QVA149 or any of the comparator drugs) 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 Pharmaco-epidemiology Practice (GPP) (Epstein 2005) and according to the ENCePP code of conduct (EMA 2010).

All database partners have experience in conducting pharmaco-epidemiological research and research is done by researchers trained in pharmaco-epidemiology; In addition; the databases are representative of the respective countries and database specific disease prevalence rates are in line with what has been published before.

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. life style factors such as smoking, BMI, race) 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 QVA149 and comparator drugs 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 prescription 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 pharmaco-epidemiological research. For those databases where free text is available (IPCI, HSD and SIDIAP), validation of endpoints will be conducted and comparison of incidence rates of endpoints among databases will allow checking for internal and external validity.

For all databases, apart from 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 to the patient's care. In addition, specialist information is incomplete in majority of the databases. The only database that captures all prescriptions is Aarhus. So for Aarhus there is information on drug dispensing, not only for drugs prescribed by the GP but also for drugs prescribed by the specialist. The other databases are primary care databases, so they do not capture prescriptions of the specialist. However, in all of these countries (UK, Italy, Spain and the Netherlands), the GP is the gatekeeper of care and prescriptions initiated by the specialist are continued by the GP.

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.

As SIDIAP is expected to contribute the highest number of patients on QVA149, it will be important to assess whether this could have distorted/biased the overall results. In the case of heterogeneity of results between the Spanish and other database study populations, a meta-analysis will be conducted on all database populations excluding then SIDIAP population.

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.

10 Protection of human subjects

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

All 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 [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 [redacted] 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.

The protocols will be reviewed by the Institutional Review Boards of the respective databases. As this is a non-interventional observational study, there is no need for ethical approval in the Netherlands, UK, Denmark and Italy. For SIDIAP (Spain), both the scientific committee for SIDIAP studies and the local ethics committee will evaluate the protocol before the study can be carried out.

In addition, a scientific advisory committee 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.

Suggested members of the scientific advisory committee are the following:

[redacted]

Regulatory and ethical compliance

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2008), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (von Elm et al. 2008), and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct' (EMA 2010).

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 for disseminating and communicating study results

As the study progresses, Novartis will submit to EMA interim reports as well as a final study report as per the due dates mentioned in the RMP.. 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

Not applicable

Annex 2 - ENCePP checklist for study protocols

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

London, 25 July 2011

Doc.Ref. EMA/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) 1.1.2 The objectives of the study?	☒	☐	☐	15-16

Section 1: Research question	Yes	No	N/A	Page Number(s)
	☒	☐	☐	16-17
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)	☒	☐	☐	18-19
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?	☒	☐	☐	18
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	19
2.2.2 Age and sex?	☒	☐	☐	19-20
2.2.3 Country of origin?	☒	☐	☐	18
2.2.4 Disease/indication?	☒	☐	☐	19
2.2.5 Co-morbidity?	☒	☐	☐	27-28
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)	☒	☐	☐	19-20

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?	☒	☐	☐	22
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	17
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)	☒	☐	☐	33-35, 37-42
3.4 Is sample size considered?	☒	☐	☐	32-35
3.5 Is statistical power calculated?	☒	☐	☐	32-35

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 practice prescribing, claims data, self-report, face-to-face interview, etc)	☒	☐	☐	18-19, 20-22, 23-25
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)	☒	☐	☐	22
4.1.3 Covariates?	☒	☐	☐	25-28
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)	☒	☐	☐	18-19, 20-22, 23-25
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	22
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	25-28
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	35-37
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☒	☐	☐	35-37
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	23-24
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	35-37

Comments:
Respective codes for drug exposure, endpoints and comorbidities are described in the annexes of the protocol (page 56-147)

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	☒	☐	☐	18-19, 20-22, 23-25

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)	☒	☐	☐	18-19, 20-22, 23-25
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	18-19, 20-22, 23-25
5.4 Is exposure classified based on biological mechanism of action?	☒	☐	☐	18-19, 20-22, 23-25
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?	☒	☐	☐	22
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)	☒	☐	☐	22,56-99

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?	☒	☐	☐	43-44
7.1.2 Information biases?	☒	☐	☐	43-44
(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)	☒	☐	☐	38-39
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	38-39

Section 7: Biases and Effect modifiers	Yes	No	N/A	Page Number(s)
7.4 Does the protocol address other limitations?	☒	☐	☐	43-44

Comments:

Section 8: Analysis plan	Yes	No	N/A	Page Number(s)
8.1 Does the plan include measurement of absolute effects?	☒	☐	☐	37-42
8.2 Is the choice of statistical techniques described?	☒	☐	☐	37-42
8.3 Are descriptive analyses included?	☒	☐	☐	38
8.4 Are stratified analyses included?	☒	☐	☐	40
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	☒	☐	☐	38-39
8.5.2 Effect modifiers?	☒	☐	☐	38-39
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	☒	☐	☐	38-39
8.6.2 Effect modification?	☒	☐	☐	40

Comments:

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)	☒	☐	☐	35-36
9.2 Are methods of quality assurance described?	☒	☐	☐	42-43
9.3 Does the protocol describe quality issues related to the data source(s)?	☒	☐	☐	42-43
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	32-35
9.5 Does the protocol specify timelines for				
9.5.1 Study start?	☒	☐	☐	14-15
9.5.2 Study progress? (e.g. end of data collection, other milestones)	☒	☐	☐	14-15
9.5.3 Study completion?	☒	☐	☐	14-15
9.5.4 Reporting? (i.e. interim reports, final study report)	☒	☐	☐	14-15
9.6 Does the protocol include a section to document	☒	☐	☐	13-14

Section 9: Quality assurance, feasibility and reporting	Yes	No	N/A	Page Number(s)
future amendments and deviations?				
9.7 Are communication methods to disseminate results described?	☒	☐	☐	45
9.8 Is there a system in place for independent review of study results?	☒	☐	☐	44

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?	☒	☐	☐	44
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
10.3 Have data protection requirements been described?	☒	☐	☐	35-36,44

Comments:

Name of the coordinating study entity: [redacted]

Name of (primary) lead investigator: [redacted]

Date: 02/June/2014

Signature: [redacted]

Annex 3 - Additional information

Annex 3.1 - Event definition

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.

Major cardiovascular events

MACE include the following:

- ***myocardial infarction***
- ***stroke***
- ***hospitalisation due to acute coronary syndrome and/or heart failure***.

The definition of myocardial and stroke (and relevant disease codes) are described under item 2 and 4 of this annex

Hospitalisation 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).

Hospitalisation 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).

Ischemic heart disease

Ischemic heart disease or myocardial ischemia, is a disease characterized by ischemia of the heart muscle, usually due to atherosclerosis of the coronary arteries.

For this study, ischemic heart disease as endpoint encompasses angina pectoris (both stable and unstable) but excludes myocardial infarction. Myocardial infarction is considered as separate endpoint.

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 ischemia 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.

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		411.*	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	
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	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			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	
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

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.

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	G32..00	
Healed myocardial infarction[#]			G32..11	
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 anterior wall	I22.0		G350.	
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			

Terms	ICD10	ICD9CM	Read Codes	ICPC
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.	
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			G384.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
myocardial infarction				
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 angina pectoris as underlying comorbidity

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 et al. 2008).

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

Terms	ICD10	ICD9CM	Read Codes	ICPC
Hypertensive heart disease with (congestive) heart failure	I11.0	402.01 402.91	G21z011	
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 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	

Terms	ICD10	ICD9CM	Read Codes	ICPC
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

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 haemorrhage (intracerebral) or infarction (i.e. ischemic) and stroke not specified as haemorrhage 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.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Stroke, not specified as hemorrhage or	I64			
Stroke NOS	I63.9			K90
Intracerebral haemorrhage		431	G61..	
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	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			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	
			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			G683.00	
Sequelae of stroke, not specified as haemorrhage or infarction[#]		438.*	G68X.00/Gyu6C00	
Cerebral infarction due unspecified occlusion/stenosis of pre-cerebral arteries		433.*	G6W..00/Gyu6300	
			G6X..00/Gyu6G00	
Cerebral infarction due to unspecified occlusion/stenosis of cerebral arteries		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

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 et al. 2009).

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

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 stroke as underlying comorbidity

Cardiac arrhythmia

Cardiac arrhythmia as endpoint will consist of tachyarrhythmia and bradyarrhythmia. For this study, tachyarrhythmia will encompass small QRS tachyarrhythmia and broad QRS tachyarrhythmia.

Small QRS tachyarrhythmia consists of supraventricular tachycardia, re-entry tachycardia and atrial flutter or fibrillation. Broad QRS tachyarrhythmia consists of ventricular arrhythmia: ventricular tachycardia, ventricular fibrillation and “Torsade de pointes”. The definition of atrial flutter and fibrillation is described above.

For this study, bradyarrhythmia will consist of atrioventricular block.

Finally, premature depolarization will also be captured as endpoint and will consist of atrial, junctional and ventricular premature depolarization.

Small QRS tachycardia

- **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 et al. 2010).

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

- **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 et al. 2010).

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

Terms	ICD10	ICD9CM	Read Codes	ICPC
ECG: atrial fibrillation			3272.	
H/O: atrial fibrillation[#]			14AN.00	
Atrial fibrillation resolved[#]			212R.00	
Atrial fibrillation monitoring			662S.00	
			6A9..00	
			8HTy.00	
			9hF1.00	
			9Os..	

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

- **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).

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	
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

Broad QRS tachycardia

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 et al. 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 et al. 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 et al. 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).

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	I45.81	426.82	X202	
ECG: Q-T interval prolonged			32K3.00	

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).

Terms	ICD10	ICD9CM	Read Codes	ICPC
Sick sinus syndrome	149.5 I47.2E		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).

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.	
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.	
ECG: heart block			329..00	

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).

Terms	ICD10	ICD9CM	Read codes	ICPC
Extrasystole	I49.4	427.6	G576z00	K80
	I49.40		G576011	
	I49.49			
Supraventricular extrasystole		427.61	G576100	K80.01
Ventricular extrasystole	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	
ECG: extrasystole			3262.00	
ECG: ventricular ectopics			3263.00	

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

Glaucoma (narrow angle glaucoma and other))

Definition of narrow angle glaucoma

Narrow angle glaucoma, also called acute angle closure glaucoma or closed angle glaucoma, is a rare type of glaucoma in which symptoms usually come on suddenly. Unlike most glaucoma, people with narrow angle glaucoma usually have severe symptoms including pain, blurry vision, redness and nausea. Some people also complain of seeing halos around lights.

Narrow angle glaucoma is caused by an acute blockage of the drainage canal where fluid normally flows freely out of the eye. A buildup of fluid causes a sudden increase in intraocular pressure.

Narrow angle glaucoma requires a quick diagnosis and rapid treatment, as significantly decreased vision or blindness can result within hours (Casson et al. 2012).

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

Terms	ICD10	ICD9CM	Read Codes	ICPC
Anatomical narrow angle borderline glaucoma		365.02	F450200	
Acute angle-closure glaucoma	H40.21	365.22	F452	F93.02
Primary angle-closure glaucoma	H40.2		F452.00	
Closed angle glaucoma			F452.11	
Primary angle-closure glaucoma			F452..	
Glaucoma due to chamber angle anomaly			F454000	

Definitions of other glaucoma

Open-angle glaucoma, the most common form of glaucoma, accounting for at least 90% of all glaucoma cases: It is caused by the slow clogging of the drainage canals, resulting in increased eye pressure. In contrast to narrow angle glaucoma, it has as wide and open angle between the iris and cornea. Open angle glaucoma develops slowly and is a lifelong condition and often has symptoms and eye damage that are not immediately noticed.

In normal tension glaucoma, the optic nerve is damaged even though the eye pressure is not very high.

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

Terms	ICD10	ICD9CM	Read Codes	ICPC
glaucoma	H40-H42.9	365	F45	F93

Terms	ICD10	ICD9CM	Read Codes	ICPC
Glaucoma - absolute			F404211	
Glaucomatocyclitic crises			F442100	
[X]Glaucoma			FyuG.00	

Bladder obstruction/urinary retention/BPH

Definition of bladder obstruction/urinary retention

Urinary retention describes a bladder that does not empty completely or does not empty at all. Historically, urinary retention has been classified as either acute or chronic the latter is generally classified as high pressure or low pressure according to the bladder filling pressure on urodynamic (Verhamme et al. 2008).

Bladder outlet obstruction (BOO) is a blockage at the base of the bladder that reduces or prevents the flow of urine into the urethra, the tube that carries urine out of the body.Bladder outlet obstruction (BOO) can have many different causes, including benign prostatic hyperplasia (BPH), bladder stones, bladder tumors (cancer), pelvic tumors (cervix, prostate, uterus, rectum) and urethral stricture (scar tissue)

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

Terms	ICD10	ICD9CM	Read Codes	ICPC
Urinary Retention	R33	788.2 788.20	R082..	U05.02
Cannot pass urine - retention			1A32.00	
Acute retention of urine			R0822	
Retention symptoms			1A32.11	
Micturition stream poor			1A33.00	
Hesitancy			1A34.00	
Hesitancy of micturition			1A34.11	
BOO - Bladder outflow obstruction			K160.13	
Bladder outflow obstruction			K165200	
Bladder neck obstruction	N32.0	596.0		

Definition of BPH

Benign prostatic hyperplasia (BPH) is a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone. The enlarged gland has been proposed to contribute to the overall lower urinary tract symptoms (LUTS) complex via at least two routes: (1) direct bladder outlet obstruction (BOO) from enlarged tissue (static component) and (2) from increased smooth muscle tone and resistance within the enlarged gland (dynamic component). Voiding symptoms have often been attributed to the physical presence of BOO. Detrusor overactivity is thought to be a contributor to the storage symptoms seen in LUTS.[Juliao, 2012 #127]

Terms	ICD10	ICD9CM	Read Codes	ICPC
Benign prostatic hypertrophy/ Benign prostatic hyperplasia	N40	600.0	XE0e6 K20*	Y85

Terms	ICD10	ICD9CM	Read Codes	ICPC
Prostatic hyperplasia			K20z.	
			K200.	
Benign neoplasm of prostate			B7C2.00	

Diabetes mellitus

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 (based on lab results):

A1C ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*

OR

2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/l).

*In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing.

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
Diabetes mellitus due to underlying condition	E08			
Unspecified diabetes mellitus	E14			
diabetes NOS	E11			

Terms	ICD10	ICD9CM	Read Codes	ICPC
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	

For those databases where information on lab results are available (THIN, HSD, SIDIAP and IPCI), a new diagnosis of diabetes mellitus will be made based on either the presence of diabetes mellitus disease codes and abnormal lab results (HbA1c, fasting plasma glucose, glucose tolerance test).

Bronchospasm

Definition of bronchospasm

Bronchospasm is an abnormal contraction of the smooth muscle of the bronchi, resulting in an acute narrowing and obstruction of the respiratory airway. A cough with generalized wheezing usually indicates this condition. For this study, we are interested in bronchospasm as a result of administration of QVA149. As bronchospasm is much related to the indication of use, (paradoxical) bronchospasms will only be identified in those databases that allow free text validation (HSD, IPCI and SIDIAP). A free text search and a search on codes for bronchospasms will be done, maximum in the 1 month after start of QVA149 and the comparator drugs. For those patients where potential hits have been identified, the complete medical file will be reviewed and only bronchospasms occurring short (within 1 hour) after administration of QVA149 (or comparators) will be considered. This manual validation will be conducted blinded to the treatment exposure.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Acute bronchospasm	J98.01	519.11		
Dyspnea/shortness of breath				R02

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.

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 3.2 - Validation algorithm

Validation of coronary events: myocardial infarction and ischemic heart disease

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

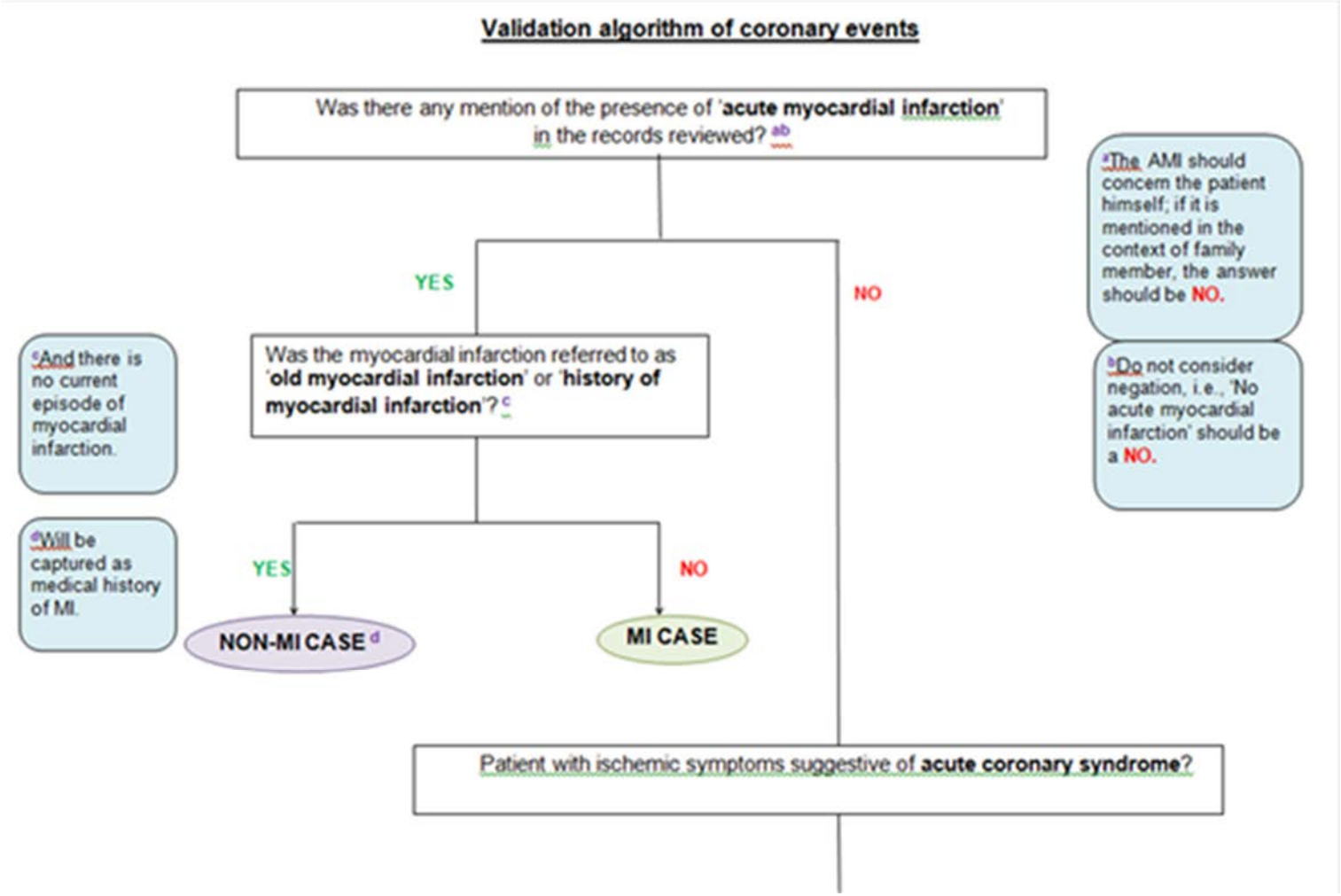
- Myocardial infarction
- Ischemic heart disease (stable and unstable angina pectoris)

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 3.1.

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).



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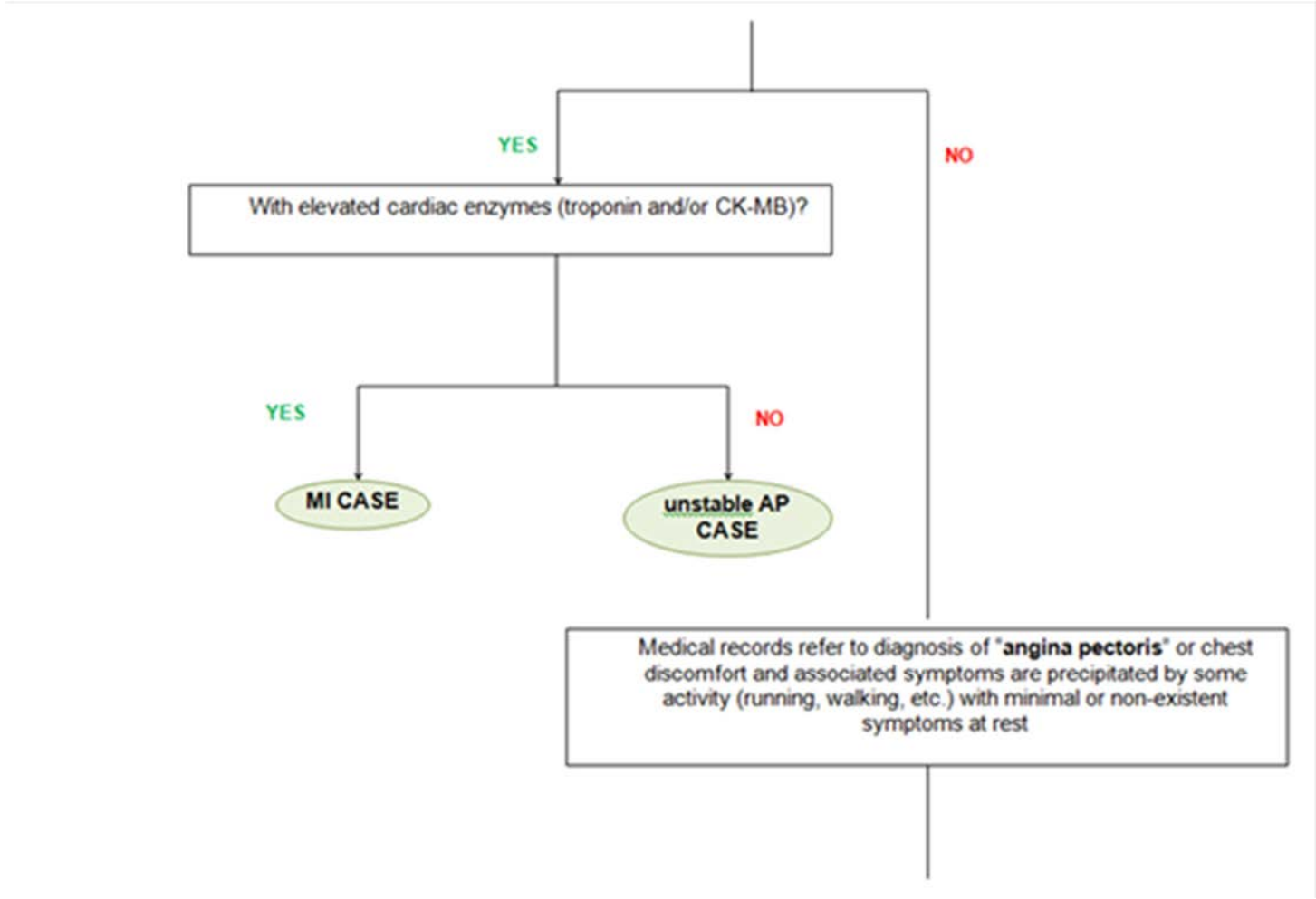

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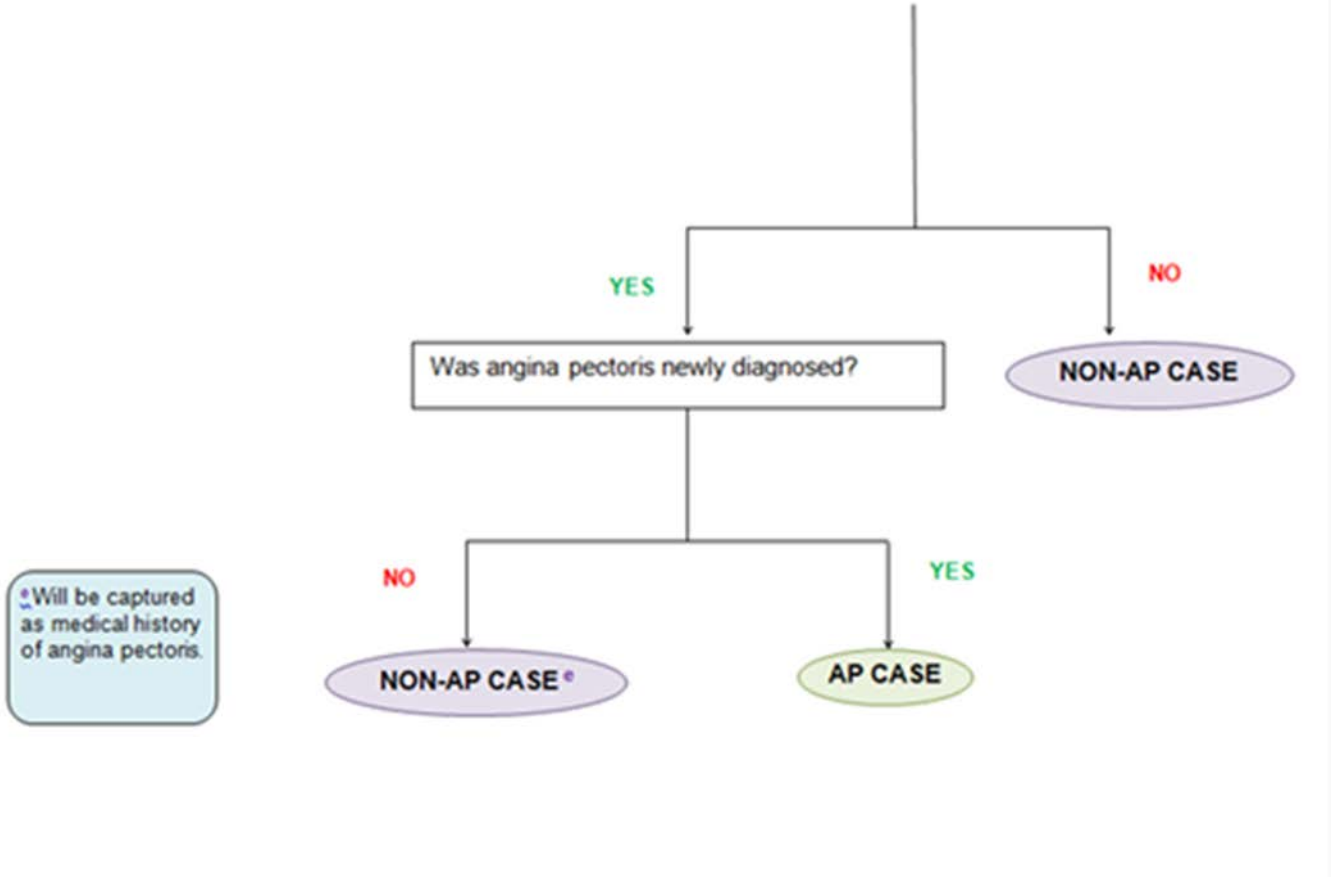


Validation of cerebrovascular events: stroke and TIA

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

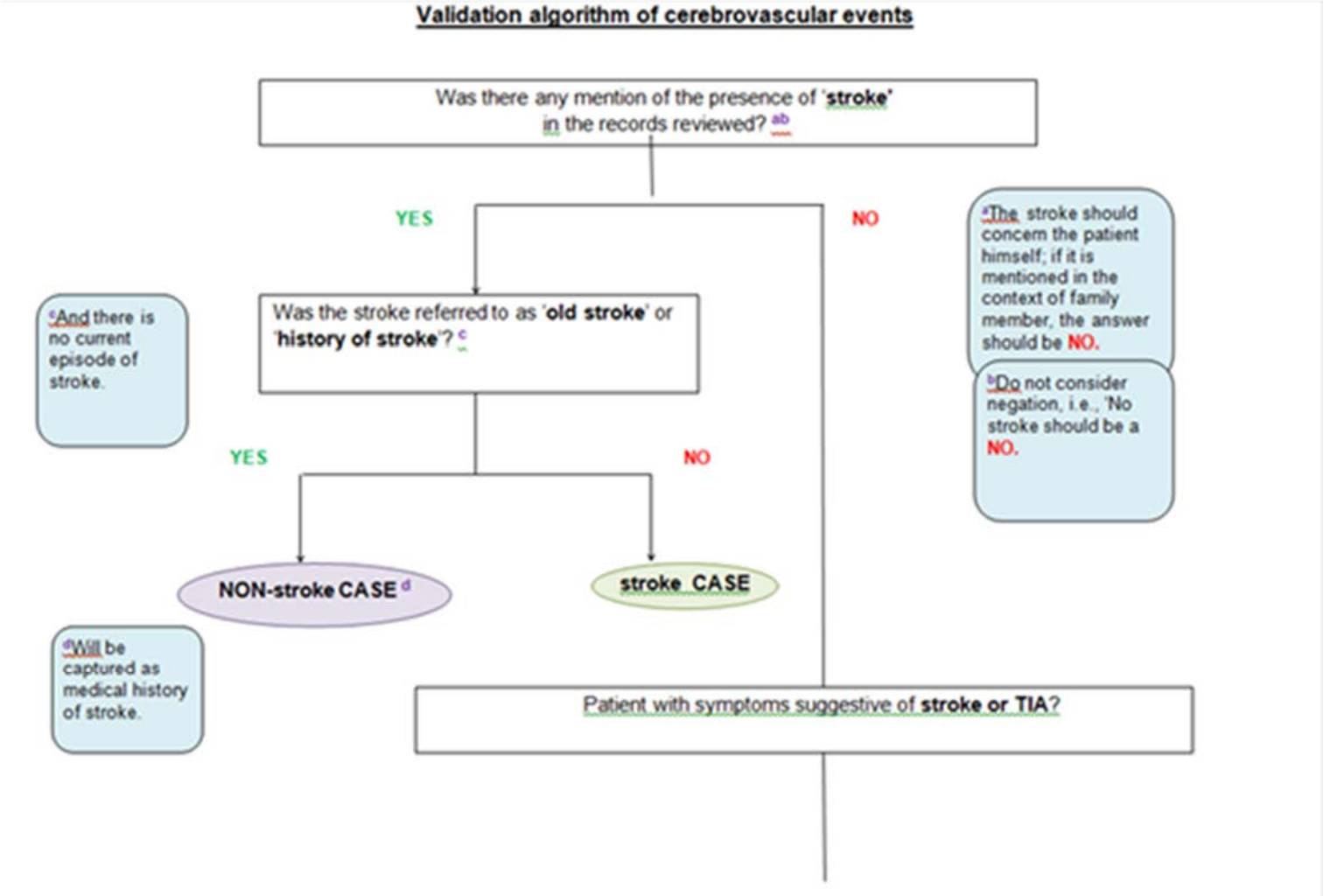
- Stroke (both hemorrhagic and ischemic)
- TIA (transient ischemic attack)

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 3.1.

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).



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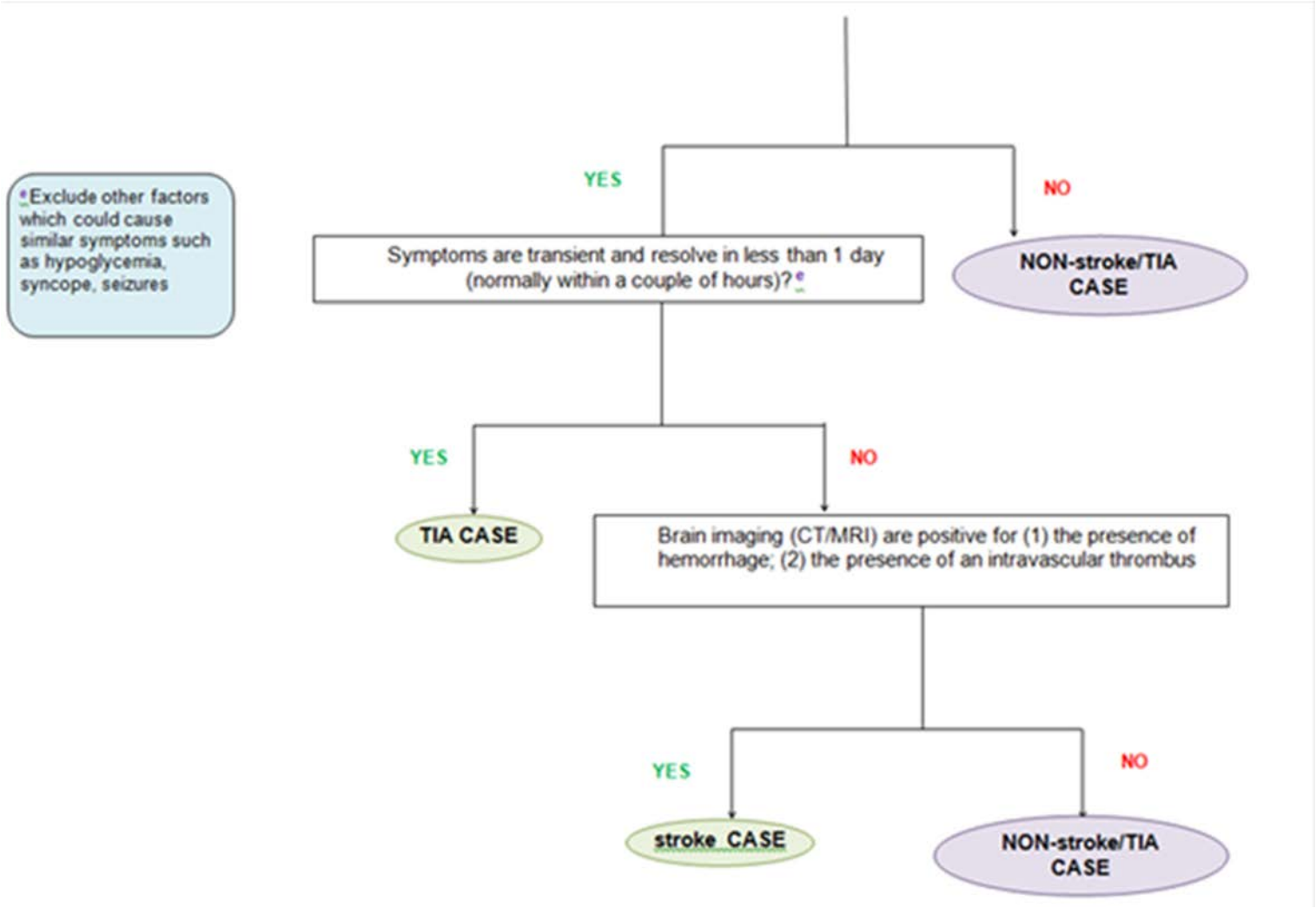


Validation of cardiac arrhythmia

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

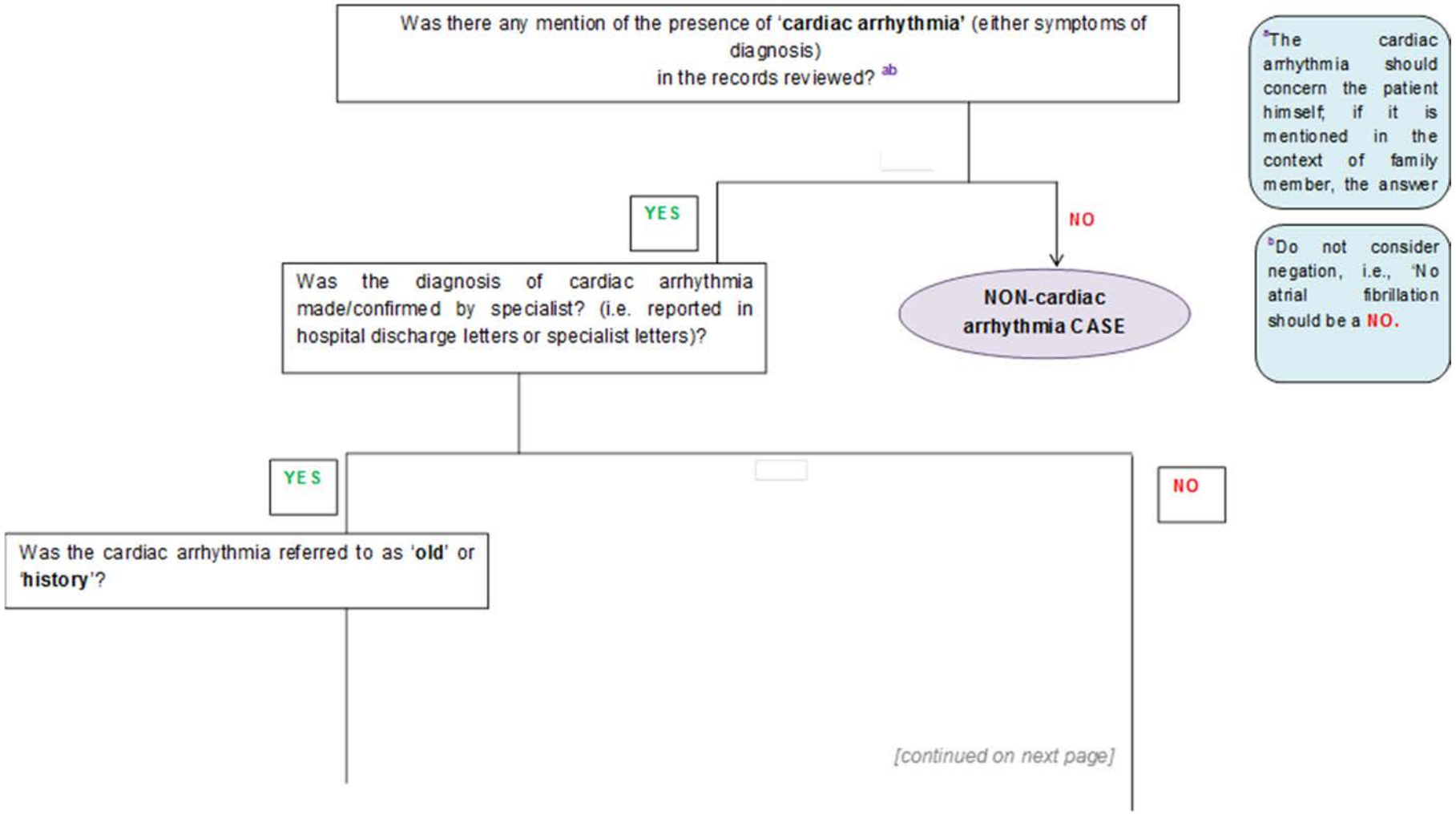
- atrial flutter/fibrillation
- supraventricular tachycardia
- ventricular tachycardia
- ventricular fibrillation
- “Torsade de pointes”
- AV block
- sick sinus syndrome

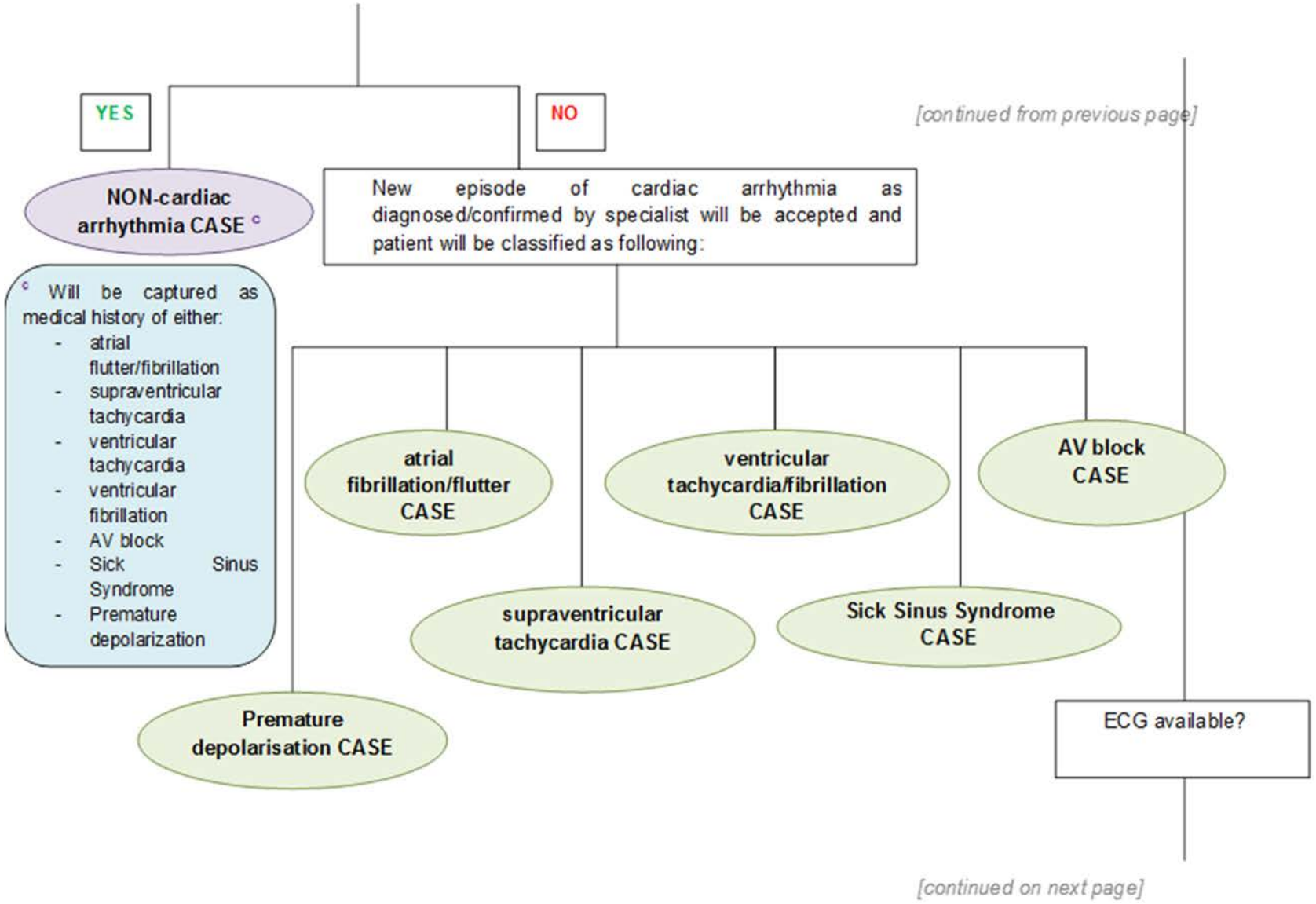
For those databases where free text is available (SIDIAP, IPCI and HSD), first of all a broad free text search + disease code search will be conducted to retrieve all potential hits related to cardiac arrhythmia. The disease specific codes related to cardiac arrhythmia are described in Annex 3.1.

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”
- “QTc” 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)


Was there any mention of the presence of 'cardiac arrhythmia' (either symptoms of diagnosis) in the records reviewed? ab
YES
NO
NON-cardiac arrhythmia CASE
Was the diagnosis of cardiac arrhythmia made/confirmed by specialist? (i.e. reported in hospital discharge letters or specialist letters)?
YES
NO
Was the cardiac arrhythmia referred to as 'old' or 'history'?
[continued on next page]
aThe cardiac arrhythmia should concern the patient himself, if it is mentioned in the context of family member, the answer
bDo not consider negation, i.e., 'No atrial fibrillation should be a NO.


YES
NO
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NON-cardiac arrhythmia CASE c
New episode of cardiac arrhythmia as diagnosed/confirmed by specialist will be accepted and patient will be classified as following:
c Will be captured as medical history of either:
- atrial flutter/fibrillation
- supraventricular tachycardia
- ventricular tachycardia
- ventricular fibrillation
- AV block
- Sick Sinus Syndrome
- Premature depolarization
atrial fibrillation/flutter CASE
ventricular tachycardia/fibrillation CASE
AV block CASE
supraventricular tachycardia CASE
Sick Sinus Syndrome CASE
Premature depolarisation CASE
ECG available?
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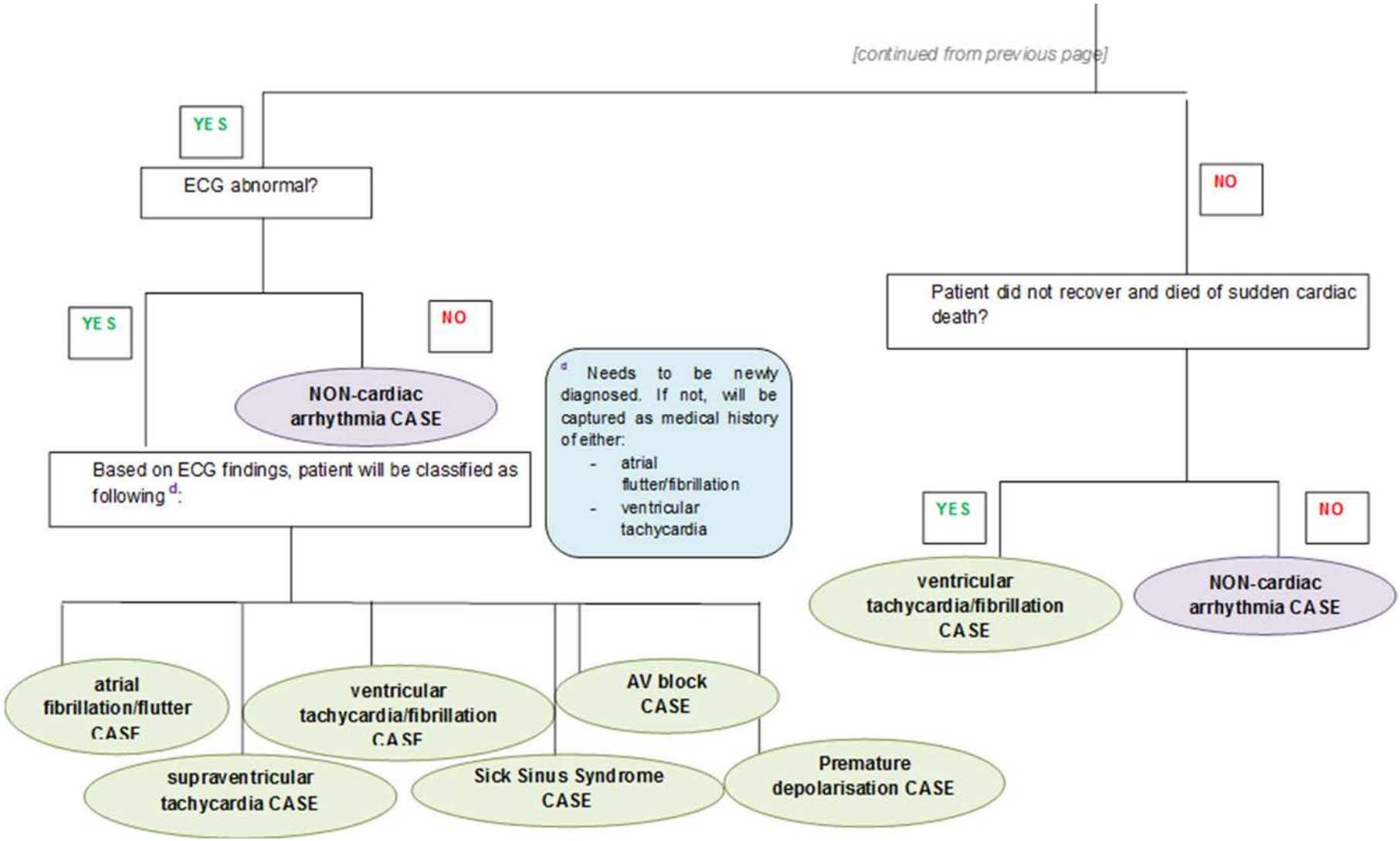
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YES
ECG abnormal?
NO
Patient did not recover and died of sudden cardiac death?
YES
NO
NON-cardiac arrhythmia CASE
[d] Needs to be newly diagnosed. If not, will be captured as medical history of either:
- atrial flutter/fibrillation
- ventricular tachycardia
Based on ECG findings, patient will be classified as following [d]:
YES
NO
ventricular tachycardia/fibrillation CASE
NON-cardiac arrhythmia CASE
atrial fibrillation/flutter CASE
ventricular tachycardia/fibrillation CASE
AV block CASE
supraventricular tachycardia CASE
Sick Sinus Syndrome CASE
Premature depolarisation CASE

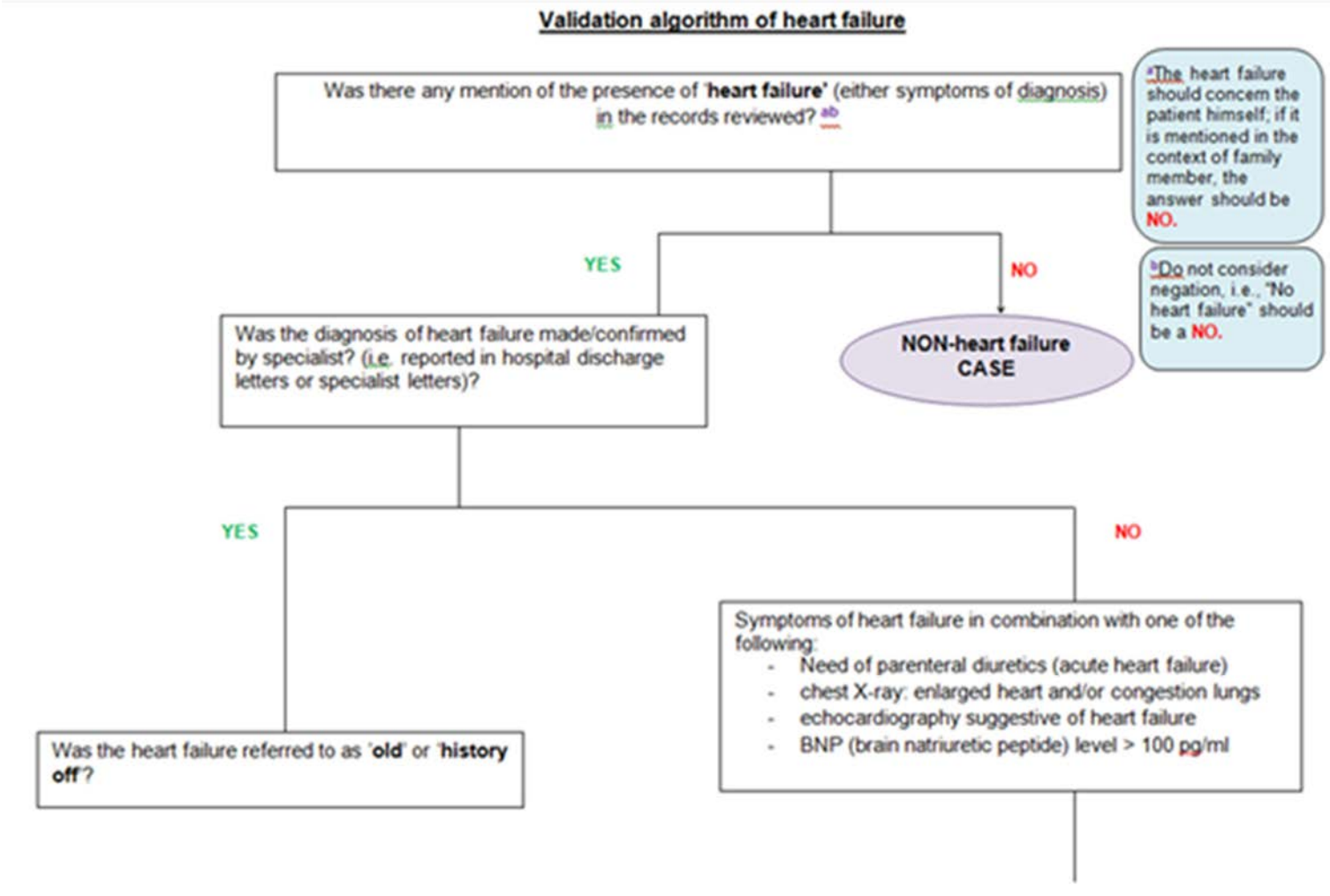
Validation of heart failure

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 3.1.

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)



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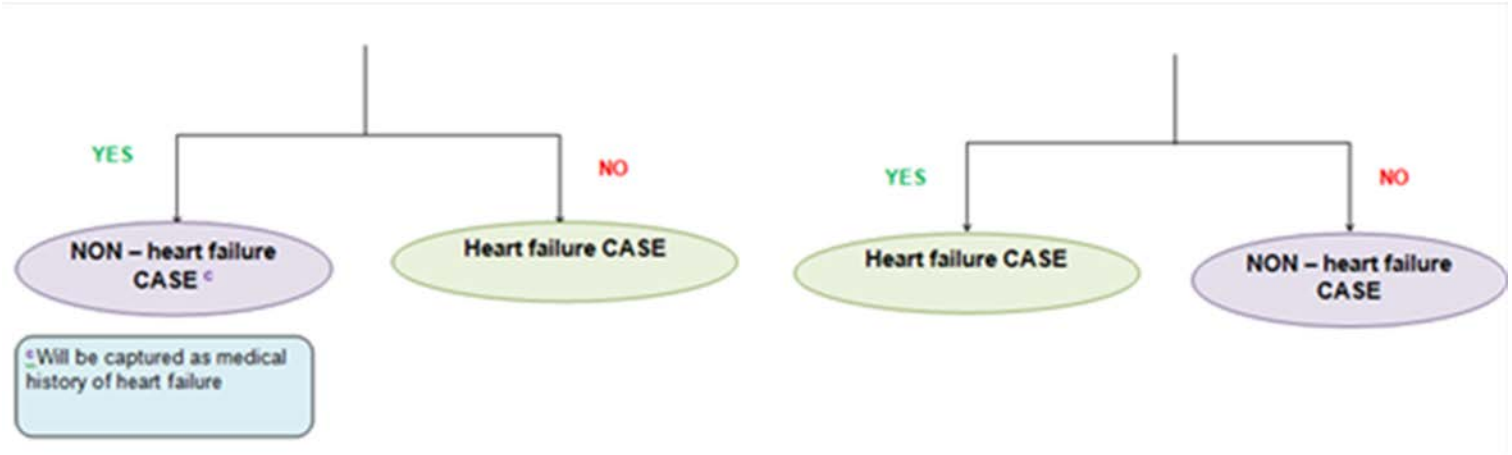


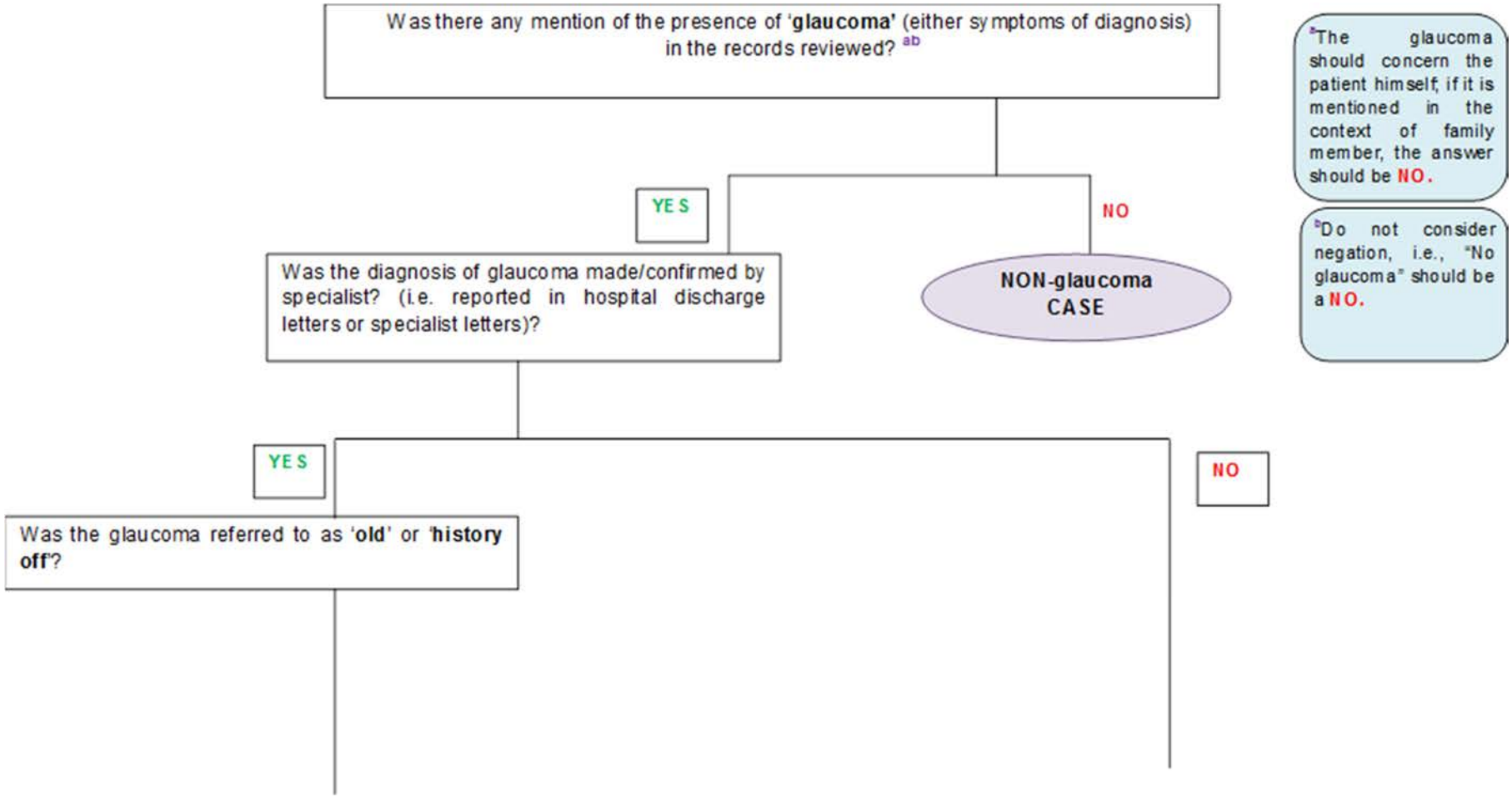
Validation of glaucoma (narrow angle glaucoma and other)

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 glaucoma. The disease specific codes related to glaucoma are described in Annex 3.1.

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

- “glaucoma”
- “narrow” AND “angle”
- “occular” AND “pressure”
- “acute” AND “red” AND “eye”

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



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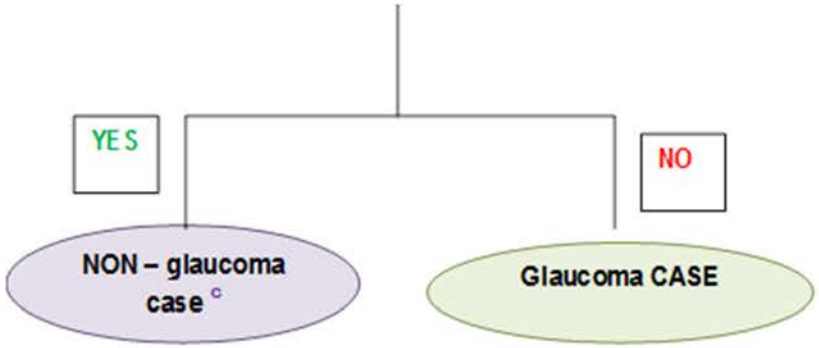
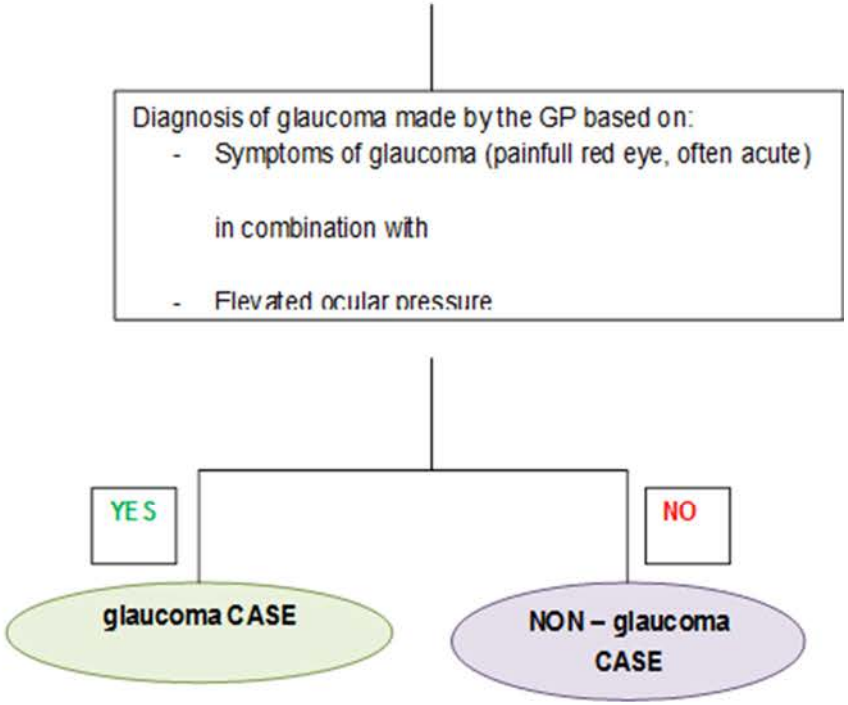




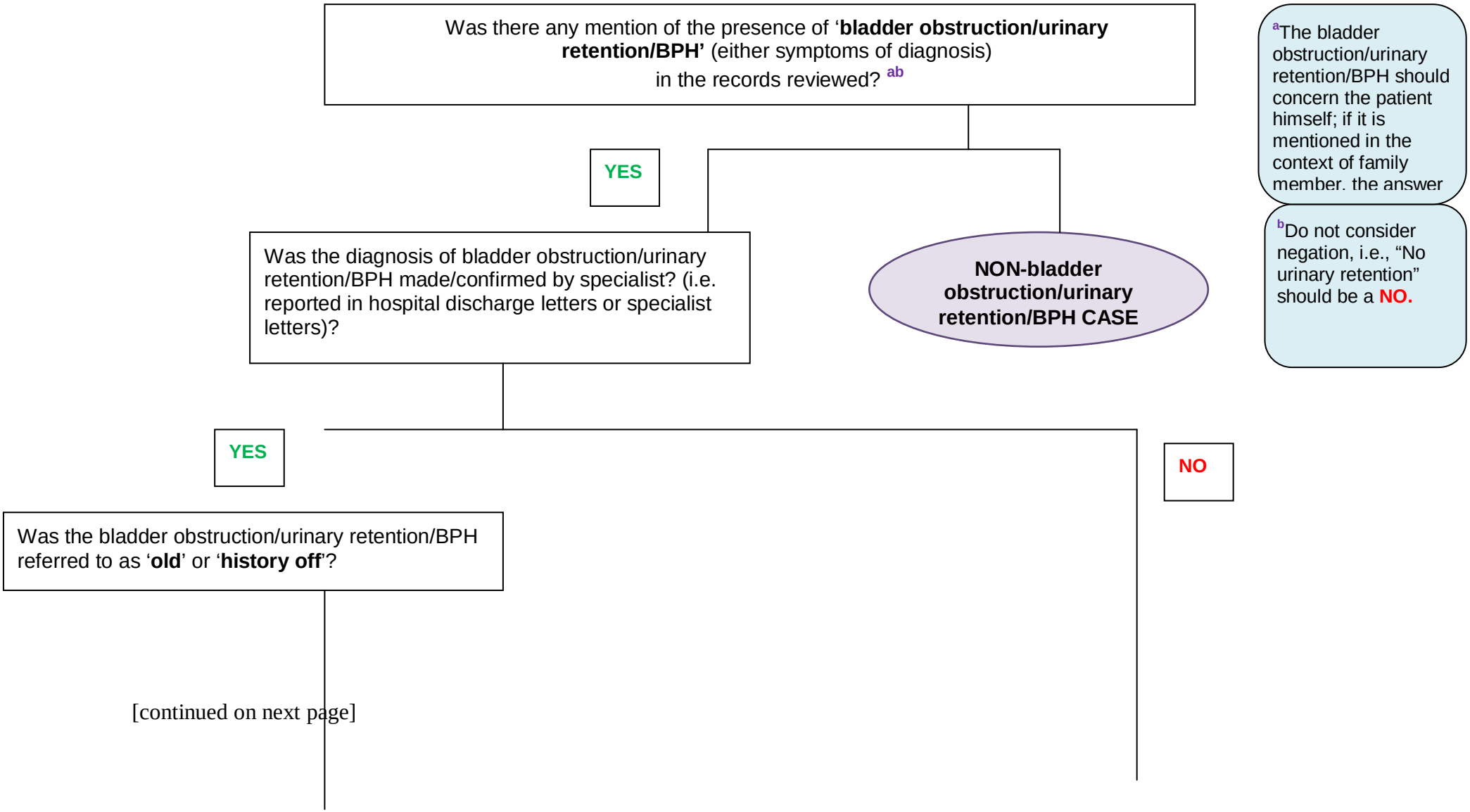
Validation of bladder obstruction/urinary retention/BPH

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 bladder obstruction/urinary retention. The disease specific codes related to bladder obstruction/urinary retention are described in Annex 3.1.

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

- "bladder" AND "outflow"
- "urinary" AND "retention"
- "overflow" AND "incontinence"
- "bladder" AND "residue"
- bladder" AND "retention"
- prostate" AND "hyperplasia"
- "BPH"
- "TURP" or "prostatectomy"

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



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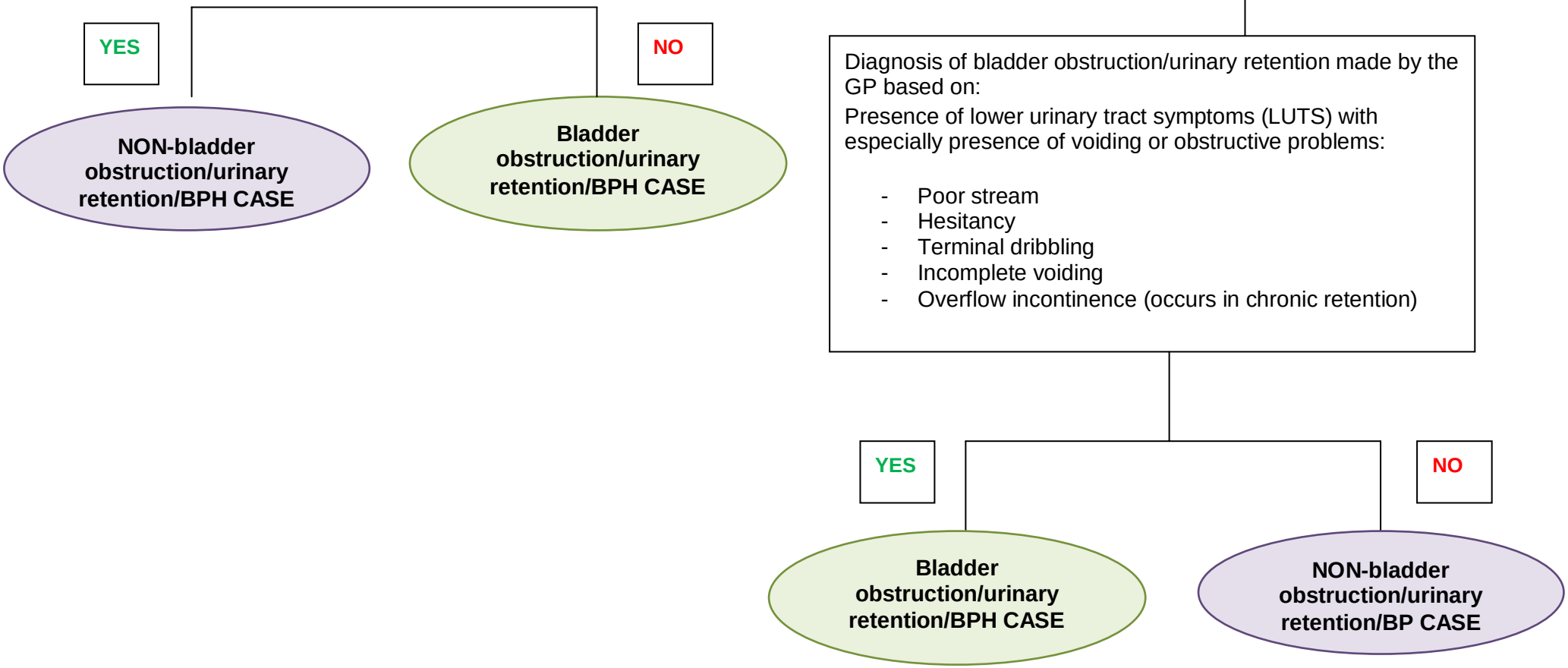


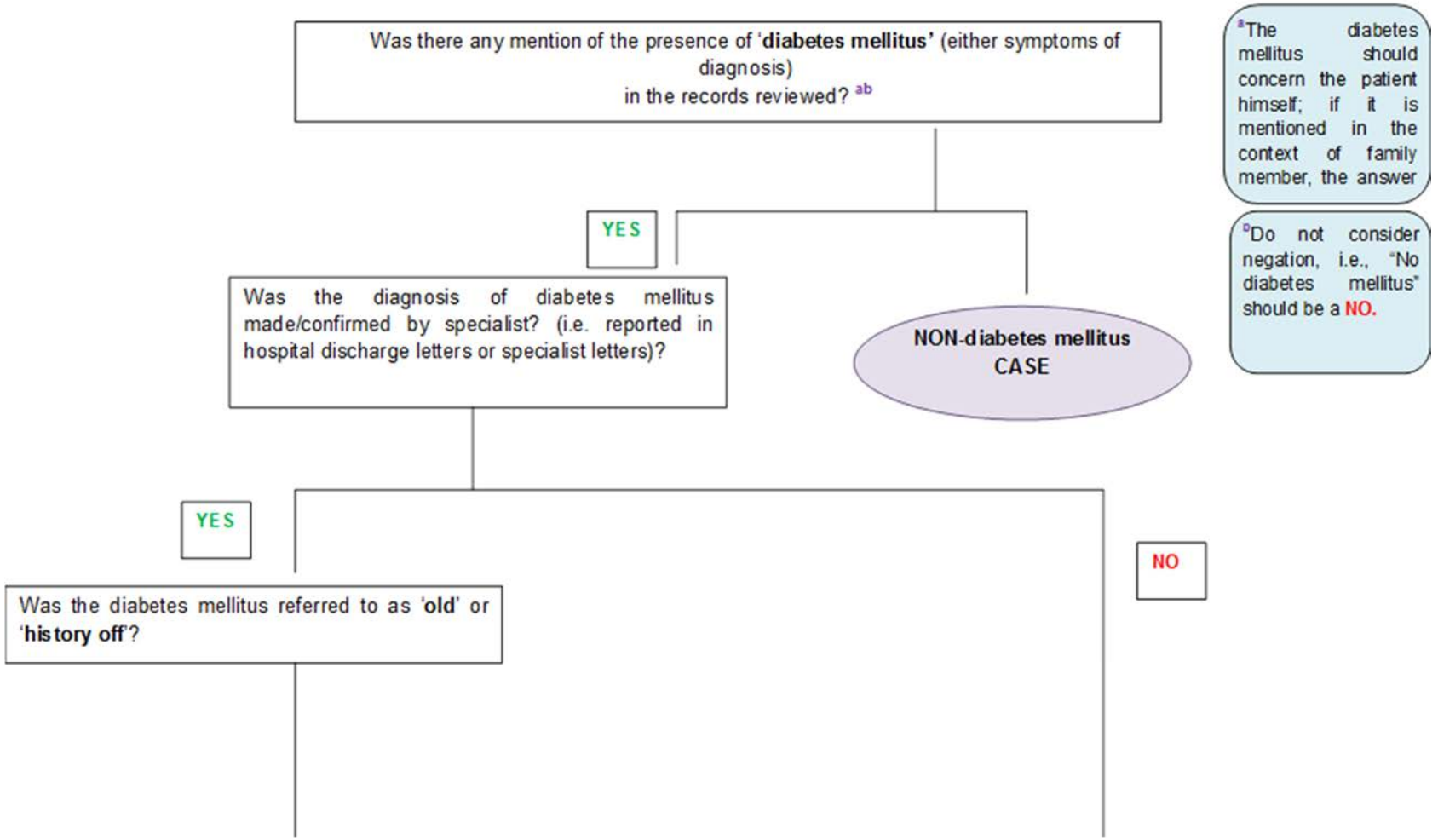
Validation of diabetes mellitus

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 diabetes mellitus. The disease specific codes related to diabetes mellitus are described in Annex 3.1.

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

- "diabetes" AND NOT "insipidus"

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



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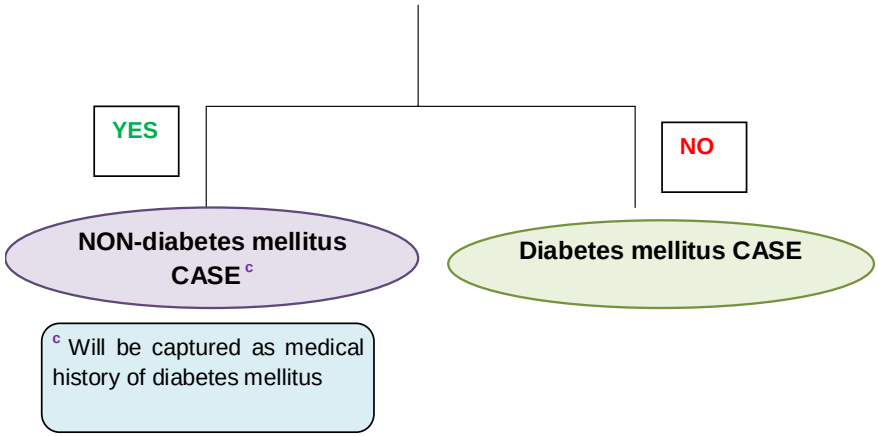
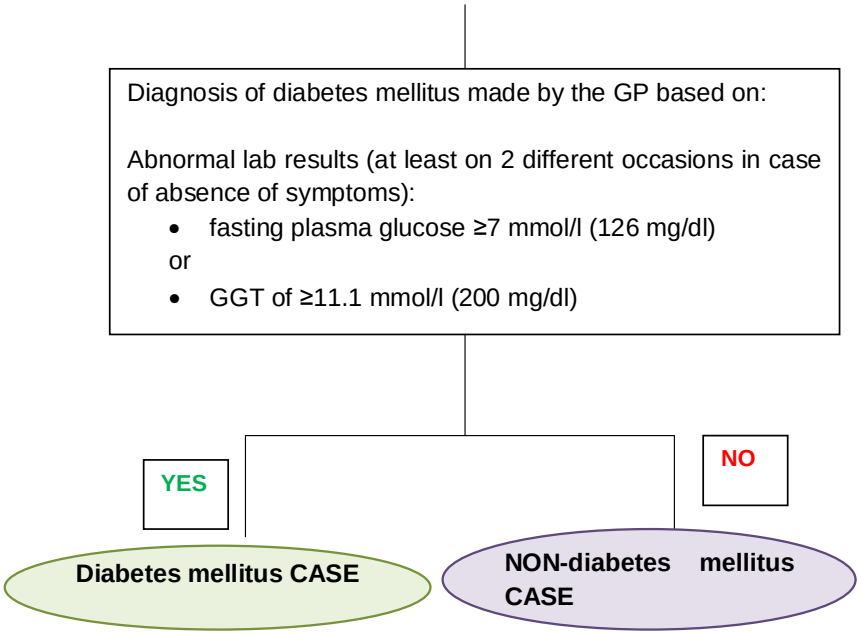




Validation of bronchospasm

For this study, we are interested in bronchospasm as a result of administration of QVA149. As bronchospasm is much related to the indication of use, (paradoxical) bronchospasms will only be identified in those databases that allow free text validation (HSD, IPCI and SIDIAP). A free text search and a search on codes for bronchospasms will be done. These codes or free text need to be recorded maximum in the one month after start of QVA149 or the comparator drugs.

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

- "bronchus" AND "spasm"
- "paradoxical" AND "spasm"
- "paradoxical" AND "dyspnea"

For those patients where potential hits have been identified, the complete medical file will be reviewed and only bronchospasms occurring short (within one hour) after administration of QVA149 (or comparators) will be considered. This manual validation will be conducted blinded to the treatment exposure.

Validation of COPD

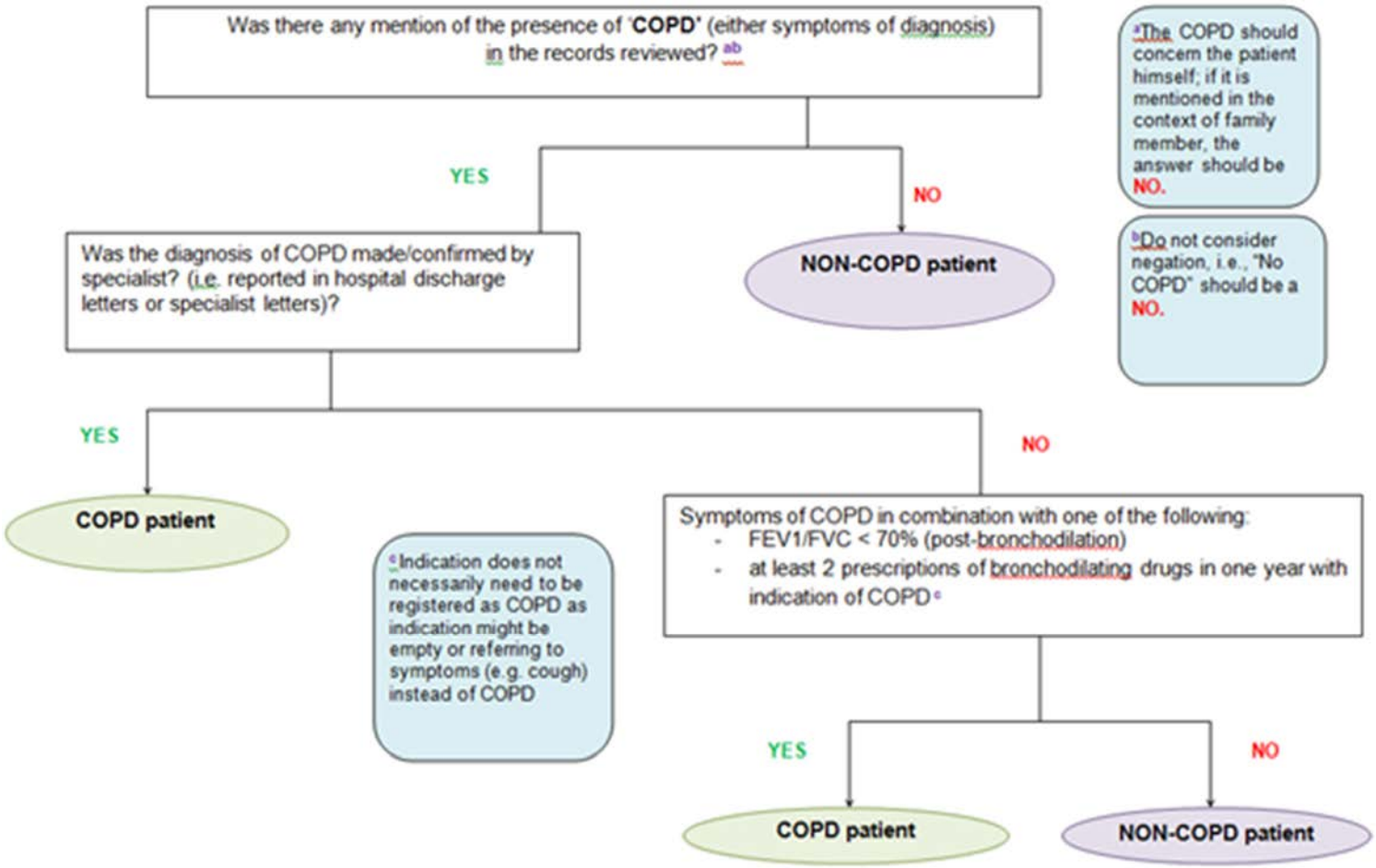
For those databases where free text is available (SIDIAP, IPCI and HSD), first of all a broad free text search + disease code search will be conducted to retrieve all potential hits related to COPD. The disease specific codes related to COPD are described in Annex 3.4.

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).

Validation algorithm of COPD



Annex 3.3 - Exposure definition

This list will be updated whenever new respiratory drugs come to the market.

	ATC code
QVA149	R03AL04
LAMA	
Tiotropium	R03BB04
Aclidinium bromide	R03BB05
Glycopyrronium bromide	R03BB06
LABA	
Salmeterol	R03AC12
Formoterol	R03AC13
Indacaterol	R03AC18
Olodaterol	R03AC19
LABA+ICS	
Salmeterol+fluticasone	R03AK06
Formoterol+budesonide	R03AK07
Formoterol+beclomethasone	R03AK08
Formoterol+mometasone	R03AK09
Vilanterol+fluticasone furoate	R03AK10
Formoterol+fluticasone	R03AK11
ICS (always in combination with LABA and/or LAMA)	
Beclometasone	R03BA01
Budesonide	R03BA02
Flunisolide	R03BA03
Betamethasone	R03BA04
Fluticasone	R03BA05
Triamcinolone	R03BA06
Mometasone	R03BA07
Ciclesonide	R03BA08

Annex 3.4 - 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 2011).

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 3.2 – Validation algorithms.

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
Chronic obstructive pulmonary disease, unspecified	J44.9			R95
Chronic airway obstruction		496.*		
Obstructive chronic bronchitis		491.2*	H312z00	
Chronic obstructive lung disease			H3...00	
Chronic obstructive airways disease			H3...11 H3z..00	
Other chronic obstructive pulmonary disease	J44			
Other specified chronic obstructive pulmonary disease	J44.8		Hyu31 H3z..11	
Chronic obstruct pulmonary dis with acute lower respiratory infection			H3y0.00	
Chronic obstructive pulmonary disease with acute exacerbation, unspecified	J44.1		H3y1.00	
Chronic obstructive pulmonary disease monitoring			66YB.00 66YB000 66YB100 66YD.00	
Mild chronic obstructive pulmonary disease			H36..00	
Moderate chronic obstructive pulmonary disease			H37..00	
Severe chronic obstructive pulmonary disease			H38..00	
Very severe chronic obstructive pulmonary disease			H39..00	
End stage chronic obstructive airways disease			H3A..00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Chronic obstructive pulmonary disease with acute lower respiratory infection	J44.0		H3y0.00	
COPD exacerbation			66Yd.00	
			66Ye.00	
			66Yf.00	
			8H2R.00	
			H3y1.00	
			H312200	
Chronic obstructive pulmonary disease disturbs sleep			66Yg.00	
Chronic obstructive pulmonary disease does not disturb sleep			66Yh.00	
Attends respiratory support group			66YH.00	
COPD self-management plan given			66YI.00	
Multiple COPD emergency hospitalisations			66Yi.00	
Chronic obstructive pulmonary disease follow-up/monitoring			66YL.00	
			66YL.11	
			66YL.12	
			66YM.00	
			66YS.00	
			66YT.00	
COPD quality indicators			9h5..00	
			9h51.00	
			9h52.00	

COPD severity will be assessed at the index date for the 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:

1. Mild COPD (GOLD stage I): $FEV_1/FVC<70\%$ and FEV_1 predicted > 80%
2. Moderate COPD (GOLD stage II): $FEV_1/FVC<70\%$ and $50\%<FEV_1\leq80\%$ predicted
3. Severe COPD (GOLD stage III): $FEV_1/FVC<70\%$ and $30\%<FEV_1\leq50\%$ predicted
4. Very severe COPD (GOLD stage IV): $FEV_1/FVC<70\%$ and $FEV_1\leq30\%$ predicted or $FEV_1<50\%$ predicted and chronic respiratory failure.

The most recently performed spirometry prior to the index date (for all exposure cohorts) will be considered. In addition, in accordance with the updated GOLD guidelines (updated (GOLD 2011)), 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, 2011) 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.

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 et al. 2001; Eisner et al. 2005; Curkendall et al. 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 bronchodilators (excluding short acting 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 3.5 - Concomitant medication definition

Concomitant use of respiratory drugs

- Short acting anticholinergic agents
  R03BB01 Ipratropium bromide
- Single-ingredient SABA
  R03AC02 Salbutamol
  R03AC03 Terbutaline
  R03AC04 Fenoterol
- 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 (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
- Oral ß$_2$-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
N02AB53 Fentanyl, combinations excluding psycholeptics
N02AB72 Pethidine, combinations with psycholeptics
N02AB73 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
N02AE90 Etorphine
N02AE99 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

N05CD90 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
N05CM90 Detomidine
N05CM91 Medetomidine
N05CM92 Xylazine
N05CM93 Romifidine
N05CM94 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
N03AX90 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 Triflupromazine
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
N05AD90 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
N05AK 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
N05AX90 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
A03AB90 Benzetimide
A03AB92 Carbachol
A03AB93 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
  H02AB30 Combinations of glucocorticoids
  H02AB56 Prednisolone, combinations

H02AB57 Prednisone, combinations
H02AB90 Flumetasone

- NSAIDs
  M01AA Butylpyrazolidines
  M01AA01 Phenylbutazone
  M01AA02 Mofebutazone
  M01AA03 Oxyphenbutazone
  M01AA05 Clofezone
  M01AA06 Kebuzone
  M01AA90 Suxibuzone
  M01AA99 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
M01AE90 Vedaprofen
M01AE91 Carprofen
M01AE92 Tepoxalin
M01AG Fenamates
M01AG01 Mefenamic acid
M01AG02 Tolfenamic acid
M01AG03 Flufenamic acid
M01AG04 Meclofenamic acid
M01AG90 Flunixin
M01AH Coxibs
M01AH01 Celecoxib
M01AH02 Rofecoxib
M01AH03 Valdecoxib
M01AH04 Parecoxib
M01AH05 Etoricoxib
M01AH06 Lumiracoxib
M01AH90 Firocoxib

M01AH91 Robenacoxib
M01AH92 Mavacoxib
M01AH93 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
M01AX52 Niflumic acid, combinations
M01AX68 Feprazone, combinations
M01AX90 Pentosan polysulfate
M01AX91 Aminopropionitrile
M01AX99 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 Eritrityl 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 Eritrityl 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

- Cardiac glycosides
  C01AA01 Acetyldigitoxin
  C01AA02 Acetyldigoxin
  C01AA03 Digitalis leaves
  C01AA04 Digitoxin
  C01AA05 Digoxin
  C01AA06 Lanatoside C
  C01AA07 Deslanoside
  C01AA08 Metildigoxin
  C01AA09 Gitoformate
  C01AA52 Acetyldigoxin, combinations
- 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
C07AA90 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 3.6 - Comorbidity definition

History of any of the endpoints of interest will also be considered as comorbidity. These events are described in Annex 3.1. 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 et al. 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	

Terms	ICD10	ICD9CM	Read Codes	ICPC
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 asthmaticus		493.01		
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	
Resolved asthma			2126200	
Induced asthma			173A.00	
			173c.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			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 unsatisfactory			663p.00	
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				

Terms	ICD10	ICD9CM	Read Codes	ICPC
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	
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	
Asthma monitoring			9OJ..00	
			9OJ..11	
			9OJ1.00	
			9OJ2.00	
			9OJ3.00	
			9OJ4.00	
			9OJ5.00	
			9OJ6.00	
			9OJ7.00	
			9OJ8.00	
			9OJ9.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			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. (2007)

	Blood pressure (mmHg)				
Other risk factors, OD or Disease	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors, MS, OD or Diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Established CV or renal disease	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

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
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	

Terms	ICD10	ICD9CM	Read Codes	ICPC
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 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			X40Vm	T93.04
Familial combined hyperlipidaemia				
Hyper apo beta lipoproteinaemia				
Other hyperlipidemia	E78.4	272.4	Cyu8D	
hypercholesterolaemia	E78.0	272.0	XE11S	T93.01
			C320z	

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 m^2)
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

Terms	ICD10	ICD9CM	Read Codes	ICPC
Chronic kidney disease	N18 N18.9	585.9 583* 585* 586*	1Z1.. K05..13	U99
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 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	

Terms	ICD10	ICD9CM	Read Codes	ICPC
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, 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..	
			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,	SP08300	

Terms	ICD10	ICD9CM	Read Codes	ICPC
		996.81	SP08C00	
		250.4x	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:

GFR = 141 X min(Scr/κ,1)α X max(Scr/κ,1)-1.209 X 0.993Age X 1.018 [if female] X 1.159 [if black]

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	C34.9	162	Xa0KG	R84
Malignant neoplasm of bronchus and lung		162.9	B22..	
			Byu20	
			XE1vc	
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	C34.3	162.5	B224.	

Terms	ICD10	ICD9CM	Read Codes	ICPC
or lung			B224z	
Malignant neoplasm of other parts of bronchus or lung		162.8	B22y.	
Malignant neoplasm overlapping bronchus and lung sites	C34.8		B225.	
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
Malignancy	C* (excluding lung cancer)			
Malignant neoplasm without specification of site	C80	199	ByuC8 XE20H B59..	A79
Cancer			X78ef	
Malignant neoplasm				
Malignant neoplasm of bladder	C67	188	B49..	U76
Malignant neoplasm of breast	C50-C50.9		Byu6.	X76
Breast cancer			X78WM	
Malignant tumor of breast			XE1zL	
Malignant neoplasm of colon	C18	153	B13..	D75
Malignant tumour of colon			XE1xd XE1vV	
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
Malignant neoplasm of cervix uteri	C53	180	XE1vi B41z.	X75
Malignant neoplasm of stomach	C16	151	X78gA	D74
Gastric cancer			XE1vR XE1xJ B11z.	
Malignant neoplasm of vagina	C52	184.0	B450.	
Malignant neoplasm of oropharynx	C10	146	B06..	
Malignant neoplasm of nasopharynx	C11	147	B07..	

Terms	ICD10	ICD9CM	Read Codes	ICPC
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.	
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..	
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