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Global Clinical Epidemiology

Non-interventional study protocol

QVA149A2401

Title	Multinational, multi-database drug utilization study of indacaterol/glycopyrronium bromide in Europe
Protocol version identifier	v03
Date of last version of protocol	18 November 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	To estimate the use of QVA149 off-label and in the subpopulations with missing information mentioned in the risk management plan (RMP).
Counties of study	The Netherlands, Spain, Denmark, Italy, United Kingdom
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		18 November 2014
QPPV or delegate	Signature	Date

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2 List of abbreviations

ADM	Administrative
(A)MI	(Acute) Myocardial Infarction
ATC	Anatomical Therapeutic Chemical Classification
AV	Atrioventricular
BNF	British National Formulary
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
EMA	European Medicines Agency
EHR	Electronic Health Record
FDA	Food and Drug Administration
FDC	Fixed-Dose Combination
FEV_1	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 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 Corticosteroids
LABA	Long Acting β_2 Agonist
LAMA	Long Acting Muscarinic Antagonist
LTRA	Leukotriene receptor antagonist
MR	Medical record
NOS	Nothing specified
OTC	Over-the-counter
PASS	Post Authorisation Safety Study
PDE	Phosphodiesterase
PSUR	Periodic Safety Update Report
RRE	Remote Research Environment
PRAC	Pharmacovigilance Risk Assessment Committee
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
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4 Abstract

Title	Multinational, multi-database drug utilization study of indacaterol/glycopyrronium bromide in Europe
Version and date	v03; 18 November 2014
Name and affiliation of main author	[redacted], MD, PhD Erasmus MC [redacted] The Netherlands
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) 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. 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. This is expected to lead to improvement in dyspnea, health status/quality of life and COPD exacerbations compared to monotherapy. The "missing information" as per Risk Management Plan (RMP) includes use of QVA149 in patients with unstable, clinically significant cardiovascular conditions and long QT-syndrome, type I & II uncontrolled diabetes, use in patients with severe liver impairment, use in patients with moderate to severe kidney impairment, use in pregnancy and lactation, long-term use in COPD beyond 18 months, use in COPD not related to smoking or smoking exposure less than 10 pack years, use in pregnancy and lactation and use in patients with ethnic origin other than Caucasian and Asian. Therefore, in the context of the QVA149 marketing authorization application, the Pharmacovigilance Risk Assessment Committee (PRAC) endorsed marketing authorization holder's (i.e., Novartis) proposal to conduct a drug utilization study (DUS) to address aspects related to drug utilization, off-label use, and identification of patient groups, which have not yet or insufficiently been studied in the pivotal clinical trials of QVA149 (i.e., so called 'missing' outlined in the Risk Management Plan (RMP). This DUS will allow us to check whether QVA149 is prescribed according to the current labeling.
Research question and objectives	To estimate the use of QVA149 off-label and in the subpopulations with missing information mentioned in the risk management plan (RMP).
Study design	An exploratory, descriptive study will be conducted in new user cohorts of QVA149 with secondary use of data derived from five health care databases (from the Netherlands, Italy, United Kingdom [UK], Denmark and Spain).
Population	All patients registered in the respective electronic health care databases (see below- 'Data sources') with a minimum of one year of QVA149-free valid database history and with at least one prescription of inhaled QVA149.
Variables	QVA149 exposure and duration of use, switching patterns, demography, life

	style factors and COPD characteristics at time of first prescription of QVA149 (COPD severity & duration), indication of use of inhaled QVA149, prescribed dosage/posology, concomitant use of other respiratory/ anticholinergic drugs, underlying co-morbidities, and pregnancy or breast-feeding at initiation of QVA149.
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 and the Health Search CSD Longitudinal Patient Database (HSD) from Italy and the Aarhus University Prescription Database (Aarhus) from Denmark.
Study size	The actual sample size for the study will be determined by the market uptake of QVA149 in the above 5 countries. As this is a descriptive study where no hypothesis will be tested and because the actual number of subjects in the study is difficult to predict, Novartis plans to include a minimum of 3,000 patients overall within 3 years of drug launch.
Data analysis	Descriptive statistics will be used. Categorical data will be presented as counts (n) and proportions (%) along with (95% confidence intervals). For continuous data, the number of observations (n), mean, standard deviation, median (with interquartile range) will be presented. Yearly progress reports will be prepared containing country specific data. Only for the final analysis (end of study), pooled data will be presented.
Milestones	Start of data collection: 01 Nov 2013 End of data collection: 31 Oct 2016 Interim report 1: February 2015 Interim report 2: November 2015 (with PSUR) Registration in the EU PAS register: After EMA approval of the protocol Final report of study results: 31 Oct 2017

5 Amendments and updates

Table 5-1 Study protocol amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1		Milestones	Updated	Based on estimated PRAC review
2		8 Research questions and objectives	Primary and secondary objective clarified and updated	Based on PRAC comment
3		Table 9-1	Launch dates updated	Based on PRAC comment

4		9.3 Variables	Clarified and updated: - COPD severity added - Indication of use of antibiotics clarified - Switching pattern+analysis described - Timing of use of concomitant therapy clarified	Based on PRAC comment
5		9.5 Study Size		Based on PRAC comment
6		9.7 Analysis	Updated with regard to; - Analysis of switching - Handling of missing data - RMP activities	Based on PRAC comment
7		11. Management and reporting of AEs/ADRs	Updated	Based on PRAC comment
8		Annex 2 - ENCePP checklist for study protocols	Updated	Based on new page numbering
9		Annex 3 – additional information	Disease and comorbidity codes updated based on new drugs coming onto the market and input from databases	Update based on new drugs and code review by databases
10	30-Oct-2014	Table 9-6	Clarification that country estimates reflect population ≥ 40 years of age	Update based on PRAC's recommendation of 'points for consideration' no. 3
11	30-Oct-2014	9.9 Limitation of research methods	Discussion of the validity of the approach to obtain antibiotic use for treatment of LRTI and specification of category "other/unknown"	Update based on PRAC's recommendation of 'points for consideration' no.1

12	30-Oct-2014	9.9 Limitation of research methods	Discussion of potential misclassification of results for hepatic injury when using diagnosis code of "liver enzymes abnormal."	Update based on PRAC's recommendation of 'points for consideration' no. 2
13	30-Oct-2014	11 Management and reporting of adverse events/reactions	Re-wording according to PRAC's request.	Update based on PRAC's recommendation of 'points for consideration' no. 4
14	30-Oct-2014	9.3.9 Pregnancy or breast-feeding at initiation of QVA149	Pregnancy will be assessed within 274 days (= 9 months) before QVA149 initiation but also during first QVA149 use. Breast feeding will be assessed within 365 days before QVA149 but also during first QVA149 use.	

6 Milestones

Table 6-1 Study milestones

Milestone	Planned date
Start of data collection	01 Nov 2013
End of data collection	31 Oct 2016
Interim report 1	February 2015
Interim report 2	November 2015 (with PSUR)
Registration in the EU PAS register	After EMA approval of the protocol
Final report of study results	31 Oct 2017

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.

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.

The "missing information" as per Risk Management Plan (RMP) includes use of QVA149 in patients with unstable, clinically significant cardiovascular conditions and long QT-syndrome, type I & II uncontrolled diabetes, use in patients with severe liver impairment, use in patients with moderate to severe kidney impairment, use in pregnancy and lactation, long-term use in COPD beyond 18 months, use in COPD not related to smoking or smoking exposure less than 10 pack years, use in pregnancy and lactation and use in patients with ethnic origin other than Caucasian and Asian.

Therefore, in the context of the QVA149 marketing authorization application, the Pharmacovigilance Risk Assessment Committee (PRAC) endorsed MAH's proposal to conduct a drug utilization study (DUS) to address aspects related to drug utilization, off-label use, and identification of patient groups, which have not yet or insufficiently been studied in the pivotal clinical trials of QVA149 (i.e., so called 'missing' outlined in the Risk Management Plan (RMP).

This DUS will determine how often QVA149 is prescribed in a manner that does not follow the approved label.

8 Research question and objectives

In this post-authorization DUS, we will estimate use of QVA149 off-label and in the subpopulations with missing information mentioned in the RMP.

8.1 Primary objective

1. To determine the proportion of patients using QVA149 who do not meet the criteria specified in the QVA149 label ('off-label use') i.e., use of QVA149 in patients younger than 18 years or in patients without a diagnosis of COPD or in patients with asthma/asthma and COPD without concomitant use of inhaled corticosteroids (ICS)*

2. To determine the proportion of patients using QVA149 who have missing information as per RMP or high risk treatment conditions:
   a. To determine the proportion of patients using QVA149 with a history of the following conditions:
      - **Cardiovascular conditions:** unstable ischemic heart disease, congestive heart failure, myocardial infarction, cardiac arrhythmia (brady- and tachyarrhythmias), atrial flutter/fibrillation, cerebrovascular conditions (hemorrhagic or ischemic stroke, transient ischemic attack [TIA]) and hypertension
      - Long QT-syndrome or prolonged QT_c interval (>450 ms)
      - Diabetes mellitus
      - Glaucoma (narrow-angle glaucoma and others)
      - Bladder obstruction/urinary retention
      - Chronic renal failure
      - Liver disease
      - Pregnancy or breast-feeding at initiation of QVA149 (if available)
   b. To determine the proportion of new initiators of QVA149 with an uninterrupted use for more than one year
   c. To obtain long-term exposure data in patients using QVA149 continuously for more than 18 months

8.2 Secondary objective

As secondary objective, we want to describe the patient characteristics of new initiators of QVA149 in terms of:

- Demographics (age and gender)
- Indication (COPD, COPD and asthma [with or without ICS*], asthma [without COPD], other)
- COPD duration (from diagnosis of COPD until first prescription of QVA149)
- COPD disease severity
- COPD exacerbation (need of oral corticosteroids and/or hospitalization for COPD) in 1 year prior to first prescription of QVA149
- Smoking status at time of first prescription of QVA149
- Prescribed dosage/posology
- Duration of QVA149 exposure (in days)
- Switching patterns (switching to and from other treatments)
- Co-prescription with other respiratory drugs
- Concomitant use of other anticholinergic drugs

*Concomitant use of ICS is defined as at least one prescription of ICS within ± 90 days of index date.

9 Research methods

9.1 Study design

An exploratory, descriptive study will be conducted in new user cohorts of QVA149 with secondary use of data derived from five health care databases from various European countries, namely the Netherlands, Italy, the United Kingdom (UK), Denmark and Spain.

From these databases, a new user cohort of QVA149 will be identified and patient characteristics at initiation of therapy will be described. These patient characteristics will be assessed either at the time of the first prescription or in a pre-defined period prior to the first prescription. More details are described in Section 9.3 Variables.

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 CSD Longitudinal Patient Database (HSD) from Italy, The Health Improvement Network (THIN) from the UK, the Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP) from Spain and the Aarhus University Prescription Database from Denmark. For more detailed information on the individual databases, see Section 9.4.

From these databases, we will first select a population of patients with at least 1 year of valid database history. This indeed 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. At least one year of database history is required in order to have minimal information on comorbidity and use of concomitant drugs.

The study population will comprise of all patients who newly initiated therapy with QVA149, as recorded in the databases. Initiation of therapy will be defined as a first prescription or dispensing of QVA149 preceded by at least 1 year of QVA149-free valid database history. The date of the first prescription of QVA149 will be defined as index date.

9.2.2 Study period

The study period will run from the first launch in any of the participating countries (November 2013) and ends when 3,000 patients have been included. As this is a descriptive study where no hypothesis will be tested, and because the actual number of subjects in the study is difficult to predict, MAH plans to include a minimum of 3,000 patients initiating QVA149 overall (including all databases). Based on the QVA149 market uptake, it is assumed that by November 2016 latest, 3,000 new QVA149 users will be included (see also Section 9.5 Study size).

Planned dates for launch of QVA149 in the five countries are as follows:

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

Countries	Planned/Actual 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

Patients with a first prescription or dispensing of QVA149 preceded by at least 1 year of QVA149-free valid database history will be included in the study. No other exclusion criteria will be applied in the study.

9.2.4 Follow-up

Patients initiating QVA149 will be followed from time of first prescription until the earliest of (i) end of treatment, (ii) end of study, (iii) disenrollment from the database or (iv) death.

9.3 Variables

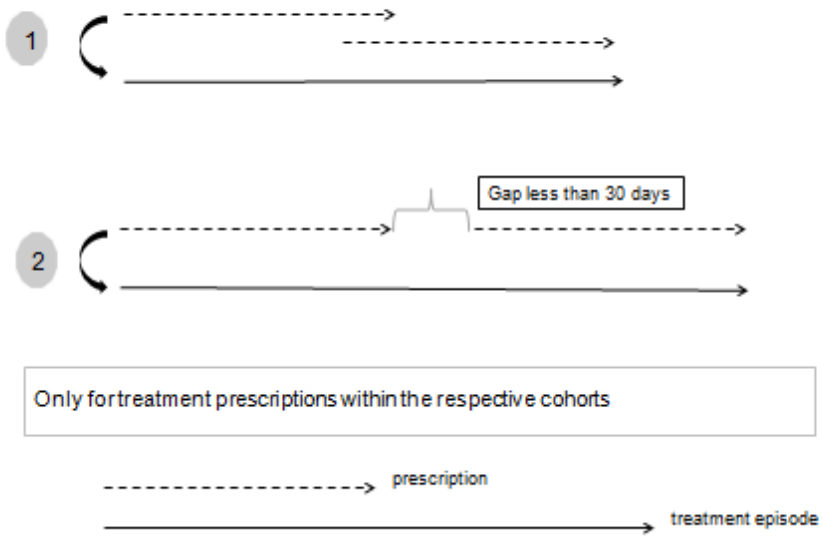
9.3.1 QVA149 exposure and duration of use

Patients prescribed QVA149 will be identified in the databases by an automated search on the respective Anatomical Therapeutic Chemical (ATC) classification system codes, product names and/or Multilex codes from the prescription records (see Annex 3.2 – Exposure and concomitant medication definition).

From the 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 regimen of the individual patient. If dosing is missing, the total amount (per prescription) is divided by the recommended dosing according to the SmPC of the respective drug. This duration of use is then added to the start date of the prescription resulting in a stop date for each prescription.

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

Figure 9-1 Creation of treatment episode for QVA149



For this study, only patient characteristics at the start of the first treatment episode will be described.

From this study cohort, all QVA149 patients with uninterrupted use of more than 365 days will be identified and the proportion among the total of patients initiating QVA149 will be described.

9.3.2 Demography, life style factors and COPD characteristics prior to or at time of first prescription, as recorded in the databases

- For all patients, information on gender and age (at time of first prescription of QVA149) will be captured.
- If available, information on smoking status will be retrieved from the databases, and patients will be classified as “current smoker”, “past smoker”, “non-smoker” or “smoking status unknown” at the time of first prescription. If available, information on smoking pack-years will be provided as well.
- Duration of COPD (from date of diagnosis of COPD until date of first prescription)
- Number of COPD exacerbations requiring hospitalization (including ER visits for reasons of COPD exacerbation) or need of oral steroids in the year prior to the index date. Hospitalization will be retrieved either via linkage with hospital admission/discharge database (SIDIAP and Aarhus), combination of COPD codes (see Annex 3.1 – Indication of use and co-morbidity definition) with information from hospital referral and discharge letters) (HSD and IPCI) or combination of disease codes with source codes (hospital discharge letters) (THIN).

- COPD severity at time of first prescription (see Annex 3.1 – Indication of use and co-morbidity definition)
- Number of courses of antibiotics for the treatment of lower respiratory tract infections in the one year prior to the index date. If the indication of use is missing in the prescription file, a search will be conducted for disease diagnosis codes of pneumonia, acute bronchitis or COPD exacerbation at the time of the prescription of the antibiotic in order to determine if the prescription data can be used in this analysis.

9.3.3 Indication of use of inhaled QVA149

For each patient initiating treatment with QVA149, the indication of use will be assessed. Indication of use will be defined either as:

- COPD
- COPD and asthma (with and without ICS)
- Asthma (without COPD)
- Other (no COPD nor asthma recorded in database)

The indication of use will be identified in the database based on disease specific coding.

As different data sources will be used with different coding dictionaries (ICPC, ICD-9, ICD-10, Read codes) concepts of disease will be mapped through the Unified Medical Language System (UMLS) (see Annex 3.1 – Indication of use and co-morbidity definition).

This indication of use will be retrieved either directly from the drug prescription or drug dispensing records. If missing, the indication of use will be retrieved from the patient's medical file ("journal") where disease codes of asthma and/or COPD will be searched for. For COPD, the complete medical record will be searched for COPD specific codes. For asthma, the medical record file will be reviewed with recorded date of entry maximum one year prior to the index date. If QVA149 is prescribed for other reasons than COPD or asthma, the respective disease codes will be provided.

9.3.4 Prescribed dosage/posology

Each delivered dose of QVA149 contains 110 µg of indacaterol maleate equivalent to 85 µg of indacaterol and 54 µg of glycopyrronium bromide equivalent to 43 µg of glycopyrronium. The recommended dose is the inhalation of the content of one capsule once daily using the Ultibro® Breezhaler® inhaler or related products.

Although it is expected that patients use QVA149 once daily, for this study, we will register the frequency of use as following based on the patient specific dosing regimen (if available):

1. Once daily
2. Every other day
3. Twice daily
4. Other (all other dosing regimens)

For databases that do not have the dosing regimen recorded we cannot assess prescribed dosage (e.g., Aarhus, and HSD).

9.3.5 Switching patterns (switching to and from other treatments)

Switching patterns of QVA149 will also be evaluated. Patients could either switch to another drug, or start a prescription with another drug as add-on therapy.

Switching will involve the following:

1. Switching from QVA149 to single use LABA (or vice versa)
2. Switching from QVA149 to single use LAMA (or vice versa)
3. Switching from QVA149 to loose combination of LABA and LAMA (or vice versa)
4. Switching from QVA149 to combination of LABA+ICS (either fixed or loose) (or vice versa)
5. Switching from QVA149 to loose combination of LAMA+ICS (or vice versa)
6. Switching from QVA149 to combination of LABA, LAMA and ICS (LABA+ICS either fixed or loose) (or vice versa)

Switching will be defined as a prescription of any of the drugs as listed above (QVA149, LABA (single use), LAMA (single use), combination of LABA and LAMA, combination of LABA+ICS (fixed or loose) and combination of LABA, LAMA and ICS). A patient will be defined as a switcher in case a patient is on a treatment with a respiratory drug and receives a prescription of any of the drugs as listed above and the initial treatment is not repeated within 1 month of the end of the previous treatment episode. Switching to loose combination therapy will only be considered if both devices are initiated on the same day.
In the example as described in Figure 9-2, a patient prescribed QVA149 is considered as a switcher as prescriptions of QVA149 are no longer continued and treatment of LABA/ICS is initiated.

Within the analysis, the proportion of QVA149 patients previously on LABA, LAMA, loose combination of LABA and LAMA, LABA+ICS (fixed or loose), LAMA+ICS or LABA+LAMA+ICS at the time of first prescription of QVA149 will be summarized. Similarly, the proportion of patients on the non-QVA therapies that switched to QVA149 will also be summarized.

Figure 9-2 QVA149 switching

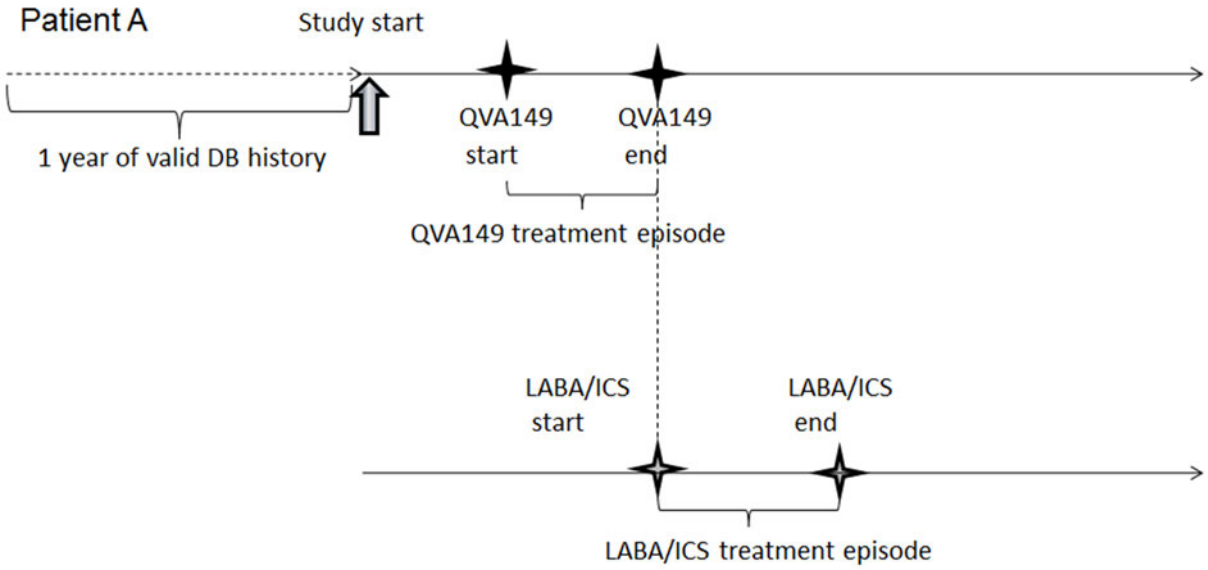
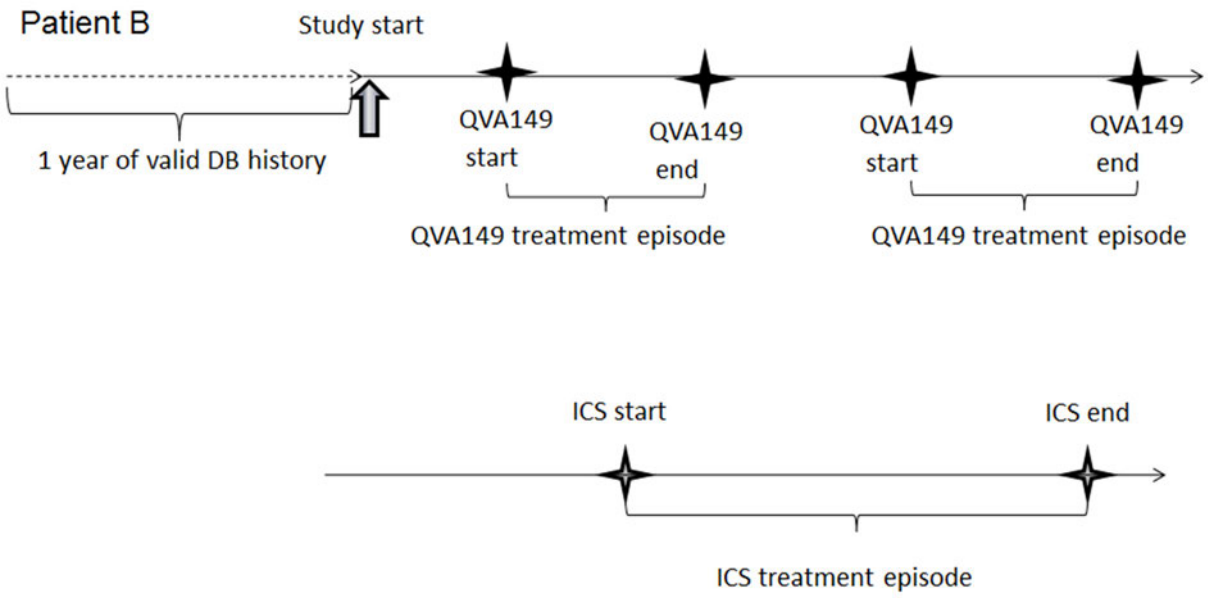


Figure 9-3 describes add-on therapy where treatment with QVA149 is further continued but treatment with ICS is added.

Figure 9-3 QVA149 add on therapy



9.3.6 Previous and concomitant use of other respiratory drugs

Information on the use of respiratory drugs will be retrieved from the prescription records and will be assessed in the 6 months prior to the index date (including drugs initiated at index date). These drugs will be retrieved via an automated search on either ATC or Multilex codes

(see Annex 3.2 – Exposure and concomitant medication definition). The following types of bronchodilating and anti-inflammatory drugs will be considered as respiratory drugs:

1. Short acting muscarinic agents (SAMAs)
2. Single-ingredient LAMAs
3. Single-ingredient SABA
4. Single-ingredient LABA
5. Inhaled corticosteroids (ICS)
6. Xanthines
7. Fixed combination therapy ((LABA + inhaled corticosteroids, SAMA (anticholinergic agents) + SABA))
8. Oral β2-agonists
9. Leukotriene receptor antagonists (LTRAs)
10. Systemic corticosteroids
11. Oral phosphodiesterase- 4 (PDE-4) inhibitors

9.3.7 Previous and concomitant use of other anticholinergic drugs

Information on the concomitant use of other anticholinergic drugs will be retrieved from the prescription records and will be assessed in the 6 months prior to the index date (including drugs initiated at index date). These drugs will be retrieved via an automated search on either ATC or Multilex codes (see Annex 3.2 – Exposure and concomitant medication definition).

The following types of drugs will be considered as anticholinergic drugs:

1. Antipsychotic drugs
2. Tricyclic and tetracyclic antidepressant agents
3. Disopyramide
4. Antispasmodics
5. Antiparkinsonian agents
6. Cholinesterase inhibitors
7. Atropine
8. H1-antihistamines
9. Anticholinergics for treatment of overactive bladder in patients with bladder outlet obstruction

9.3.8 Underlying co-morbidities

Underlying co-morbidities will be assessed during the complete database history prior to the index date (start of first prescription of QVA149). Underlying co-morbidity will be identified via an automated search on disease specific codes (see Annex 3.1 – Indication of use and co-morbidity definition).

Co-morbidities of interest are the following:

- Cardiovascular conditions: unstable ischemic heart disease, congestive heart failure, myocardial infarction, cardiac arrhythmia ((brady- and tachyarrhythmias), atrial

flutter/fibrillation, cerebrovascular conditions (hemorrhagic or ischemic stroke, transient ischemic attack [TIA]) and hypertension
- Long QT-syndrome or prolonged QT_c interval (>450 ms)
- Diabetes mellitus
- Glaucoma (narrow-angle glaucoma and others)
- Bladder obstruction/urinary retention
- Chronic renal failure
- Liver disease

9.3.9 Pregnancy or breast-feeding at initiation of QVA149

Information on pregnancy or breast-feeding at initiation of QVA149 will only be provided for those databases (THIN and IPCI) that capture this information via specific codes or free text search. Codes for pregnancy and/or breast feeding are described under Annex 3.1–Pregnancy and breast-feeding. For Aarhus, pregnancy is captured through linkage with the Danish birth register.

Pregnancy will be assessed within 274 days (= 9 months) before QVA149 initiation and during first treatment episode. Breast-feeding will be assessed within 365 days before QVA149 initiation and during the first treatment episode. Frequencies for pregnancy and breast-feeding will be reported separately for prior to QVA149 initiation vs. during first treatment episode of QVA149.

9.4 Data sources

This study will be conducted by using databases that comprise routine health care data. This will provide an unbiased 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 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 sufficient exposure to QVA149. All of the participating databases are part of the EU-ADR alliance, a stable collaboration framework for running drug safety studies in a federated manner, especially when the participation of several electronic health care record databases is required (EU-ADR 2012).

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 (NL), the Aarhus University Prescription Database (DK) and SIDIAP (Spain). Table 9-2 provides an overview of key elements of these databases. The total number of persons in the source population will be around 12 million as of 2013.

Table 9-2 Overview of databases

Country	NL	UK	DK	IT	Spain
Name of the database	IPCI	THIN	Aarhus	HSD- Thales	SIDIAP
Type of database	MR	MR	ADM	MR	MR
# patients, millions	1.2	2.7	1.8	1.5	5.1
Age categories	All	All	All	>15 years	>15 years
Date in	Yes	Yes	Yes	Yes	Yes
Date out	Yes	Yes	Yes	Yes	Yes
Cause of death	Yes	Yes	Yes	No	No
Updates	Two times a year (January/July)	3 Times a year	Yearly (April)	Three 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; ICPC = International Classification of Primary Care; MR = Medical Records

Within these databases, hospitalization will be retrieved either via linkage with hospital admission/discharge database (SIDIAP and Aarhus), combination of disease codes (see Annex 3.1 - Indication of use and co-morbidity definition) with information from hospital referral and discharge letters (HSD and IPCI) or combination of disease codes with source codes (hospital discharge letters) (THIN).

9.4.1 IPCI Database

In 1992 the Integrated Primary Care Information Project (IPCI) was started by the Department of Medical Informatics of the Erasmus University Medical Center. IPCI is a longitudinal observational database that contains data from computer-based patient records of a selected group of general practitioners (GPs) throughout The Netherlands, who voluntarily chose to supply data to the database. Collaborating practices are located throughout The Netherlands and the collaborating GPs are comparable to other GPs in the country according to age and gender. In the Netherlands, all citizens are registered with a GP practice, which forms the point of care and acts as a gatekeeper in a two-way exchange of information with secondary care. The medical records of each patient can therefore be assumed to contain all relevant

medical information including medical findings and diagnosis from secondary care. The IPCI database is representative for the Dutch population regarding age and gender (Voordouw et al. 2004).

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

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

Around 50% of the prescribed daily dosages are also imputed by GPs.

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

9.4.3 THIN Database

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

Data recorded in THIN include demographics, details from 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, over-the-counter (OTC) drug use and non-compliance to medication prescriptions might be an issue. As the average follow-up within the THIN database is 5.5 years, the THIN database is not suitable to conduct long-term follow-up studies.

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 (Ehrenstein et al. 2010).

Dose must be inferred from the strength, assuming a once daily administration for QVA149 and according the dosing regimens of the respective SmPC of the other drugs. The main drawbacks of the Aarhus University Prescription Database are a lack of nationwide coverage and the absence of data of certain medication types (non-reimbursed drugs, OTC drugs or drugs dispensed directly to hospital patients or outpatient clinics).

9.4.5 SIDIAP Database

GPs play an essential role in the public health care system of Spain, as they are responsible for primary health care, long-term prescriptions and specialist and hospital referrals. The Spanish public health care system covers more than 98% of the population. SIDIAP Database comprises of electronic medical records of a representative sample of patients attended by GPs in Catalonia (North-East Spain), covering a population of more than 5.1 million patients (about 80% of the total of 7.5 million population of Catalonia) from 274 primary care practices with 3,414 participating GPs. The SIDIAP data comprises the clinical and referral events registered by primary care health professionals (GPs and nurses) and administrative staff in electronic medical records, comprehensive demographic information, prescription and corresponding pharmacy invoicing data, specialist referrals, primary care laboratory test results, and hospital admissions and their major outcomes. Health professionals gather this information using ICD-10 codes, and structured forms designed for the collection of variables relevant for primary care clinical management, such as country of origin, sex, age, height, weight, body mass index, tobacco and alcohol use, blood pressure measurements, blood, and urine test results. All GPs 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

The study size of this drug utilization study will consist of the sum of new initiators of QVA149 derived from each database. As this is a descriptive study where no hypothesis will be tested, and because the actual number of subjects in the study is difficult to predict, we will include a minimum of 3,000 patients initiating QVA149 overall (including all databases). The justification for the sample size of 3,000 is as follows:

9.5.1 Statistical procedure characteristics for off-label use

Off-label use will be monitored utilizing a conjugate Bayesian binomial-beta model. In statistics, Bayesian inference is a method of inference in which the so called Bayes' rule is used to update the probability estimate for a hypothesis as additional evidence becomes available. In monitoring the threshold for off-label use, the probability for the off-label use to exceed a certain threshold will be estimated based on the available data. The conjugate binomial-beta model is commonly used for estimating proportions. Conjugate models are

computationally convenient, since they yield posteriors in the same distributional family as the priors and are also conceptually straightforward as they allow a direct interpretation of the distribution parameters as functions of the data.

The following thresholds will be considered in the study:

1. The probability for off-label use in asthma and mixed asthma/COPD without ICS co-medication to exceed the proportion of 15% should be below 90%
2. The probability for off-label use in a pure asthmatic population to exceed the proportion of 8% should also be below 90%

Exceeding the thresholds of 90% in either case constitutes a trigger for risk minimization activities.

Utilizing the historical data from German IMS-Disease Analyzer (DA) database for the free combination of LAMA & LABA (N=30,711; asthma only- 7.0% (n=2,145); Asthma only & COPD with Asthma not on ICS – 10.3% (n=3,163): Source: IMS-DA database, Germany; data on file), allowing for a contribution of historical data with 10% of the sample size, inclusion of 3,000 patients into the study yields the following characteristics for the statistical procedure using decision rule for detecting of off-label use:

Table 9-3 Statistical procedure characteristics

Off-label population	Type 1 error	Power
Asthma	6%	99%
COPD with asthma without ICS (mixed)	2%	82%

Note: Null hypothesis off label use: 8% (asthma) and 15% (mixed) respectively
Note: Alternative hypothesis of label use: 10% (asthma) and 17% (mixed) respectively

The statistical procedure described above shows good characteristics with the proposed sample size of 3,000. Therefore, the proposed sample size of 3,000 is considered sufficient to describe off-label use of QVA149 in this study.

9.5.2 Estimation of two-sided confidence intervals for co-morbidities: Exact (Clopper-Pearson) method

Two-sided confidence intervals (CIs) for background prevalence of co-morbidities listed in the table below were estimated using the exact (Clopper-Pearson) method. This estimation was based upon the proposed overall sample size of 3,000.

Table 9-4 Estimated two-sided 95% confidence intervals per co-morbidity (N=3,000)

Co-morbidity	Background prevalence (%)*	Estimated 95% CI
Cerebrovascular disease	4.2	3.51 - 4.98
Myocardial Infarction	4.8	4.06 - 5.63
Chronic liver disease	5.0	4.25 - 5.84
Glaucoma	5.3	4.53 - 6.16
Chronic renal failure	6.3	5.46 - 7.23
Heart Failure	7.2	6.30 - 8.18
Cardiac arrhythmia	7.2	6.30 - 8.18

Co-morbidity	Background prevalence (%)*	Estimated 95% CI
Ischemic heart disease	8.4	7.43 - 9.45
Diabetes mellitus	12.2	11.05 - 13.42
Atrial fibrillation	13.0	11.82 - 14.26
QTC prolongation	13.4	12.20 – 14.67
Hypertension	27.4	25.81 – 29.03

Source: *We used conservative estimates of background prevalence: (Suruki et al. 2009; Feary et al. 2010; Schneider et al. 2010; Cazzola et al. 2012; Divo et al. 2012; Garcia-Olmos et al. 2013)

Based upon this estimation, a sample size of 3,000 produces a two-sided 95% CI of 3.51 - 4.98 when the background percentage is 4.2. Similarly, a sample size of 3,000 produces a two-sided 95% CI of 25.81 - 29.03 when the background percentage is 27.4% (see Table 9-4 for details). Therefore, MAH believes that the proposed sample size of 3,000 is sufficient to describe the use of QVA149 in patients with different cardiovascular or other co-morbidities (including missing information).

The numbers presented below in Table 9-5 represent estimates of population coverage by individual database:

Table 9-5 Population coverage by individual database

Database	Population coverage in overall country population (%)*
THIN-UK	6.0
HSD–Italy	3.0-5.0
SIDIAP–Spain**	12.8
Aarhus–Denmark	30.0
IPCI–Netherlands	12.0

*2012 Eurostat population estimates

** SIDIAP – Spain: 80% of the population from Catalonia, which represents 16% of the overall Spanish population

The actual study size will be affected by the market uptake of QVA149 in the countries of interest. Based on the projected market uptake of QVA149 and the coverage of the databases of the total (country specific) population, the following estimates can be made about the potential number of QVA149 users within the different databases.

Table 9-6 Individual database estimates of QVA149 treated patients for the year 2015

	Country estimate** for 2015	Population coverage in overall country population (%)	Individual database estimate of QVA149 treated patients by 2015
UK	4,462	6.0	268
Italy	87,904	3.0-5.0*	2,637
Spain	76,740	12.8	9,822
Denmark	2,455	30.0	737
Netherlands	7,653	12.0	918
Total	**179,214**	N/A	**14,382**

*Conservative population coverage of 3.0% is used for estimation. **Country estimates reflect population ≥ 40 years of age (i.e., no further multiplicator is necessary).

The total estimate across all databases would sum up to 14,382 patients. Under the assumption that 80% of the QVA149 treated patients will fulfill the in-/exclusion criteria, the total number of patients would correspond to 11,506. Based on these conservative estimates, MAH is confident that it will be able to accrue the proposed sample size of 3,000 patients in the QVA149 treatment cohort within three years.

The number of patients enrolled to QVA149 will be assessed yearly in view of the preparation of the annual progress and interim reports. The study will be discontinued when the number of patients enrolled exceeds 3,000. If, at time of the second year interim report, the number of patients on QVA149 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 obtained from each database for every interim analysis and for final analysis. Thus obtained data 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 co morbidities 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 co-morbidity 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 co-morbidity of interest, 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 for COPD and co-morbidity are described in Annex 3.1 - Indication of use and co-morbidity definition).

9.6.2 Definition of data extraction algorithm

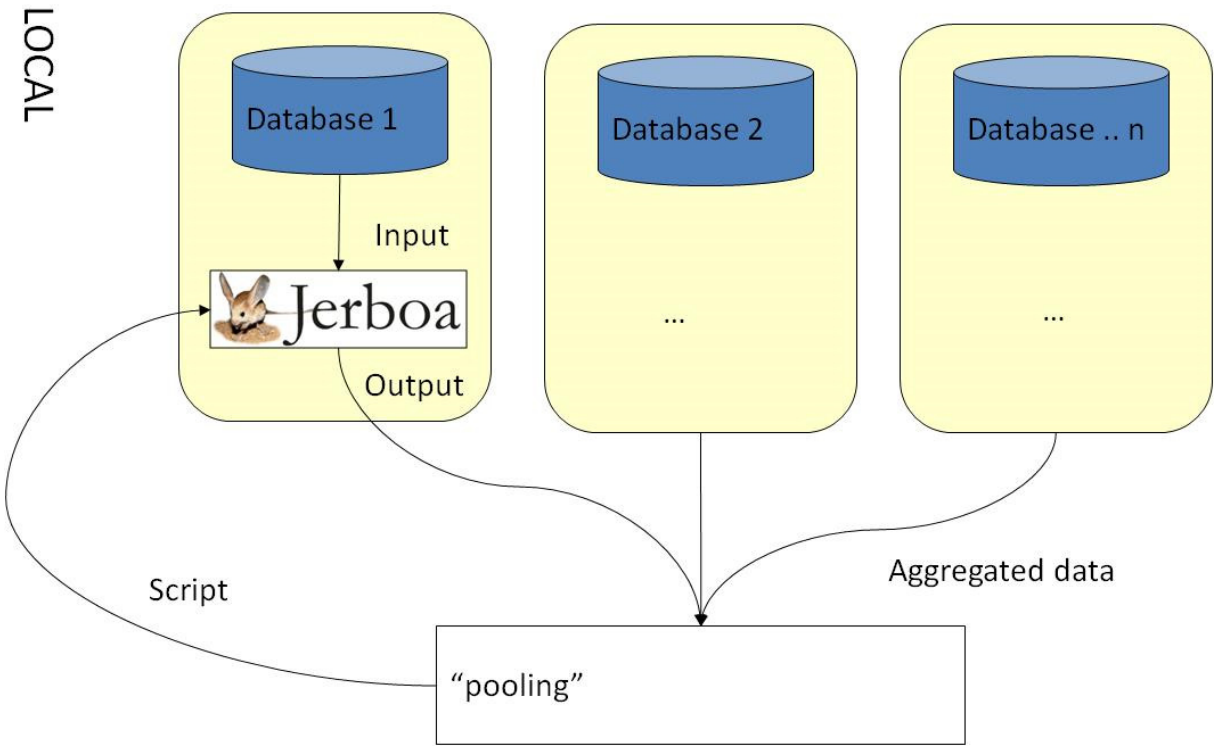
Based on the relevant diagnostic codes, a data extraction algorithm will be constructed for each co-morbidity of interest, based on the consensus of the data providers. This data extraction algorithm will then be implemented by all databases.

9.6.3 Event data extraction and pooling

Subsequently, each database extracts data using a common data model, i.e., standardized patient, drug, and co-morbidity files linkable via a patient unique identifier. These files are managed locally by purpose-built software called Jerboa, which transforms the input files in de-identified aggregated output files. These output files are transmitted to a central secured environment (remote research environment) for pooling and further processing. Jerboa has

been developed for the EU-ADR FP7-ICT project (www.EU-ADR-project.org) that combines health care data of 30 million individuals in Europe to detect adverse drug events. It has been used in many other EU funded projects (i.e. SOS: www.sos-nsaids-project.org; VAESCO: www.vaesco.net) and EMA tender protocols.

Figure 9-4 Model for data sharing and elaboration (obtained from www.EU-ADR-project.org)



9.6.4 Benchmarking of disease prevalence rates

For each co-morbidity of interest, we benchmark database-specific prevalence rates using Jerboa. The observed prevalence rates are compared with prevalence rates 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 process underlying the data collection.

9.7 Data analysis

The study will not test any a priori hypothesis.

All analyses will be performed by the Department of Medical Informatics of the ErasmusMC, the coordinating center for this multi-database study.

Descriptive statistics will be used and categorical data will be presented in counts (n) and proportions (%) with 95% confidence intervals (95% CIs). 95% CIs will be calculated either

based on the normal distribution or based on the binomial distribution. For continuous data, the number of observations (n), mean, standard deviation and median (with inter-quartile range) will be presented.

Switching characteristics will be described by counts, proportions and 95% CI both from switching from QVA149 to another respiratory drug (LABA, LAMA, LABA+ICS, loose combination LABA+LAMA, loose combination LABA+ICS, loose combination LAMA+ICS or triple therapy) and vice versa.

As mentioned before, off-label use will be monitored utilizing a conjugate Bayesian binomial-beta model. In statistics, Bayesian inference is a method of inference in which the so called Bayes' rule is used to update the probability estimate for a hypothesis as additional evidence becomes available. In monitoring the threshold for off-label use, the probability for the off-label use to exceed a certain threshold will be estimated based on the available data. The conjugate binomial-beta model is commonly used for estimating proportions. Conjugate models are computationally convenient, since they yield posteriors in the same distributional family as the priors and are also conceptually straightforward as they allow a direct interpretation of the distribution parameters as functions of the data.

The following thresholds will be considered in the study:

1. The probability for off-label use in asthma and mixed asthma/COPD without ICS co-medication to exceed the proportion of 15% should be below 90%
2. The probability for off-label use in a pure asthmatic population to exceed the proportion of 8% should also be below 90%

In accordance with the RMP, exceeding the thresholds of 90% in either case will constitute a trigger for risk minimization activities. Additionally, results from post-hoc analyses of the study data as well as data from routine pharmacovigilance and safety signal detection will be used to assess the need for additional risk minimization activities.

Yearly progress reports will be prepared containing the information as described above. For the yearly progress reports, data will be presented by country only. The pooled analysis will only be conducted at the end of the study for the preparation of the final report.

All patients have at least a minimum database history of 1 year prior to cohort entry meaning that risk of missing data is low (unless not reported such as smoking status). Covariates for which info might be missing are the following; smoking status, indication of use of QVA149, COPD severity (through spirometry), date of COPD diagnosis and lab data (e.g. liver enzymes). If missing, the number and proportion of missing data (per item) will be reported within the interim and final study reports, As this is a DUS, no imputation for missing data will be conducted.

For the final report, data will be presented by country, by calendar year (to evaluate trends over time) and in addition will be pooled across the different databases.

9.8 Quality control

The study will be conducted according to the guidelines for Good Pharmaco-epidemiology Practice (GPP) (ISPE 2008) and according to the ENCePP code of conduct (EMA 2010).

All programs will be programmed according to agreed coding standards and will be validated by double programming or source code review with second programmer involvement.

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

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 covariates (e.g. smoking) are registered in (all) databases 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 exposure is less of a concern as these drugs are prescribed according to a fixed dose.

All of the databases, apart from the Aarhus University Prescription Database, only have information on prescription and not on dispensing or actual drug intake. This implies that it is not known whether the patient actually took the drug – however, as adherence to drugs is highest at initiation of therapy, the risk of misclassification of exposure is less of a concern in a new user design. This study includes data from GPs, however, the specialist information is incomplete in the majority of the databases. Specialist prescriptions will be missing in most of the databases apart from Aarhus and IPCI (for a subset). However, in all of the countries, the GP plays a gatekeeper role for patient care implying that prescriptions, as initiated by the specialist, will be continued by the GP.

The indication of use will not be available in all databases. Indeed, only IPCI captures the indication of use within the prescription files, however, also for IPCI, this is not 100% complete. If missing, the indication of use will be assessed by checking for relevant disease codes (COPD and/or asthma) prior to and on the index date. The validity of this approach will depend on appropriate COPD/asthma coding. If respiratory symptoms are coded instead of disease coding, there is the potential of misclassification of COPD and asthma. For this reason, if indication of use is categorized as “other”, the file of the respective patients will be searched for disease codes at the time of QVA149 prescribing. This list of used disease/symptom codes will be part of the interim report. The same principle holds for the indication of use of antibiotics and systemic steroids. Again in this instance, the validity of the approach will depend on appropriate coding of antibiotics for LRTI/acute bronchitis/COPD exacerbation and appropriate coding of systemic corticosteroids for COPD exacerbation. To capture scenarios where coding for antibiotic use and systemic corticosteroids is missing or found to refer to indications other than LRTI and COPD exacerbations, respectively, the indication of use will be captured as “other/unknown.” There is the potential to underestimate the “indication of interest” in case of inappropriate or non-coding.

Hepatic impairment will be assessed through a search on disease codes relevant to hepatic impairment. These disease codes also include abnormality of liver enzymes. There is the potential of misclassification of hepatic impairment as abnormal liver enzymes might also occur in patients without hepatic impairment. (e.g., drug induced, heart failure)

In all of the databases, for reasons of patient confidentiality, information on race/ethnicity is missing.

Co-morbidity will be assessed via disease specific codes. If disease coding is inconsistent or differential, this could result diagnostic bias. Validation studies have shown that coding is reliable in the databases being used and that these databases are suitable for pharmaco-epidemiological research.

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.

For all databases, the average follow-up ranges between 3-5 years (Aarhus University Prescription Database – 15 years of follow-up) hindering the conduct of long term follow-up studies. For this study, as we want to assess off-label use of QVA149, we did not define a minimum age and will also include patients younger than 18 years. However, in Spain and Italy, primary care of children is organized via primary care pediatricians meaning that data in HSD and SIDIAP is only collected on patients older than 15 years.

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

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

The output files are stored in the central Remote Research Environment (RRE) of the Erasmus MC. These output files do not contain any data that allow identification of subjects included in the study. In fact, each record is completely anonymous and does not contain any identifier key. Starting from this, the RRE implements further security measures in order to ensure a high level of stored data protection, according with 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 consisting of three external experts will be constituted to guarantee scientific soundness of the study and also to follow-up on the progress and the appropriate conduct of the study. The members of the scientific advisory committee will be involved in review of the data and preparation of the reports (yearly and final).

Suggested members of the scientific advisory committee are the following:

- Prof Dr [redacted], [redacted], UK
- Prof Dr [redacted], [redacted], Belgium.
- Dr [redacted], USA

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 expedited reporting of adverse drug reactions from studies with secondary use of data (such as electronic health care databases). As far as possible, given the limitations of the study design (see section 9.9 "Limitations of research methods"), all adverse events/reactions should be summarised in the final study report.

12 Plans of disseminating and communicating study results

As the study progresses 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 national competent authorities to review in advance the results and interpretations to be published, the marketing authorization holder will communicate to the Agency and the competent authorities of the Member States in which the product is authorized, the final manuscript of the 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 MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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)	☒	☐	☐	11-12
1.1.2 The objectives of the study?	☒	☐	☐	14-16
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)	☒	☐	☐	15-16
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?	☒	☐	☐	15
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	16
2.2.2 Age and sex?	☐	☒	☐	
2.2.3 Country of origin?	☒	☐	☐	15
2.2.4 Disease/indication?	☒	☐	☐	18
2.2.5 Co-morbidity?	☒	☐	☐	21-22
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)	☒	☐	☐	15

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?	☒	☐	☐	14-15
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	15
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)	☐	☐	☒	
3.4 Is sample size considered?	☒	☐	☐	26-29
3.5 Is statistical power calculated?	☒	☐	☐	26-29

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)	☒	☐	☐	16-17
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)	☐	☐	☒	
4.1.3 Covariates?	☒	☐	☐	17-18, 21-22,20
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)	☒	☐	☐	16-17, 18-20
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)				17-18, 21-

Section 4: Data sources	Yes	No	N/A	Page Number(s)
	☒	☐	☐	22
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	18, 29-31, 48-86
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☐	☐	☒	
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	16-17
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	22-26, 29-31

Comments:

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 categorising exposure)	☒	☐	☐	16-17, 18-20
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)	☒	☐	☐	16-17, 18-20
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	16-17, 18-20
5.4 Is exposure classified based on biological mechanism of action?	☒	☐	☐	16-17, 18-20
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)

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?	☐	☐	☒	
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)	☐	☐	☒	

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?	☒	☐	☐	33-34
7.1.2 Information biases?	☒	☐	☐	33-34
(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)	☐	☐	☒	
7.3 Does the protocol address known effect modifiers?	☐	☐	☒	
(e.g. collection of data on known effect modifiers, anticipated direction of effect)				
7.4 Does the protocol address other limitations?	☒	☐	☐	33-34

Comments:

Section 8: Analysis plan	Yes	No	N/A	Page Number(s)
8.1 Does the plan include measurement of absolute effects?	☐	☐	☒	
8.2 Is the choice of statistical techniques described?	☒	☐	☐	31-32

Section 8: Analysis plan	Yes	No	N/A	Page Number(s)
8.3 Are descriptive analyses included?	☒	☐	☐	31-32
8.4 Are stratified analyses included?	☐	☒	☐	
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	☐	☐	☒	
8.5.2 Effect modifiers?	☐	☐	☒	
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	☐	☐	☒	
8.6.2 Effect modification?	☐	☐	☒	

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)	☒	☐	☐	29-31
9.2 Are methods of quality assurance described?	☒	☐	☐	32
9.3 Does the protocol describe quality issues related to the data source(s)?	☒	☐	☐	32
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	26-29
9.5 Does the protocol specify timelines for				
9.5.1 Study start?	☒	☐	☐	12
9.5.2 Study progress? (e.g. end of data collection, other milestones)	☒	☐	☐	12
9.5.3 Study completion?	☒	☐	☐	12
9.5.4 Reporting? (i.e. interim reports, final study report)	☒	☐	☐	12
9.6 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	11
9.7 Are communication methods to disseminate results described?	☒	☐	☐	35

Section 9: Quality assurance, feasibility and reporting	Yes	No	N/A	Page Number(s)
9.8 Is there a system in place for independent review of study results?	☒	☐	☐	34

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?	☒	☐	☐	34
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
10.3 Have data protection requirements been described?	☒	☐	☐	29-31, 34

Comments:

Name of the coordinating study entity: Department of Medical Informatics, ErasmusMC

Name of (primary) lead investigator: [redacted]

Date: 02/June/2014

Signature: _____

Annex 3 - Additional information

Annex 3.1 - Indication of use and co-morbidity 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.

COPD

According the 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 co-morbidities 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).

Not all patients with chronic bronchitis of emphysema (often a radiology finding) do have a diagnosis of COPD (postbronchodilator FEV1/FVC < 0.70). In this DUS, we are interested in the indication of use of QVA149. As GPs often use the terms COPD, chronic bronchitis and emphysema interchangeably, we will also consider disease specific codes for chronic bronchitis and emphysema.

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

Terms	ICD10	ICD9CM	Read Codes	ICPC
			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	
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	
Chronic bronchitis		491*	H31..00	R91
Simple and mucopurulent chronic bronchitis	J41			
Unspecified chronic bronchitis	J42			
Simple chronic bronchitis			H310.00	
Simple chronic bronchitis NOS			H310z00	
Mucopurulent chronic bronchitis			H311.00	
Purulent chronic bronchitis			H311000	
Fetid chronic bronchitis			H311100	
Mucopurulent chronic bronchitis NOS			H311z00	
Obstructive chronic bronchitis			H312.00	
Chronic wheezy bronchitis			H312011	
Emphysematous bronchitis			H312100	
Mixed simple and mucopurulent chronic bronchitis			H313.00	
Other chronic bronchitis			H31y.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Other chronic bronchitis NOS			H31yz00	
Chronic bronchitis NOS			H31z.00	
Bronchitis, not specified as acute or chronic	J40	490		
Emphysema	J43	492*	H32..00	R95
interstitial emphysema		518.1		
Compensatory emphysema		518.2		
Chronic bullous emphysema			H320.00	
Segmental bullous emphysema			H320000	
Zonal bullous emphysema			H320100	
Giant bullous emphysema			H320200	
Bullous emphysema with collapse			H320300	
Chronic bullous emphysema NOS			H320z00	
Panlobular emphysema			H321.00	
Centrilobular emphysema			H322.00	
Other emphysema			H32y.00	
Acute vesicular emphysema			H32y000	
Atrophic (senile) emphysema			H32y100	
MacLeod's unilateral emphysema			H32y200	
Other emphysema NOS			H32yz00	
Emphysema NOS			H32z.00	

COPD severity will be assessed at the index date 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 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]). 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 will be considered.

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

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	
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		493.11		

Terms	ICD10	ICD9CM	Read Codes	ICPC
asthmaticus				
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	
			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	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			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 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	

Terms	ICD10	ICD9CM	Read Codes	ICPC
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	
			9OJA.00	
			9OJA.11	
			9OJZ.00	
Patient in asthma study			9Q21.00	

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.

Ischemic heart disease encompasses angina pectoris (both stable and unstable). The definition of angina pectoris and myocardial infarction with their respective disease codes are explained below.

Angina pectoris

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

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

Terms	ICD10	ICD9CM	Read Codes	ICPC
Angina pectoris	I20*	413*	G33..	K74
Angina pectoris, unspecified	I20.9	413.9	G33z.	
Angina of effort	I20.8			
Anginal syndrome	I20.9			
Cardiac angina	I20.9			
Ischemic chest pain	I20.9		G33z400	
Ischaemic heart disease			G3...00	
			G3...13	
Dressler's syndrome			G310.11	
			G31y.00	
			G34..00	
			G3y..00	
			G3z..00	
			Gyu3.00	
			Gyu3000	
Stenocardia			G33z1	
Unstable angina	I20.0		G311.00	K74.01
			G311.13	
			G311100	
			G330000	
Crescendo angina	I20.0		G311.11	
Intermediate coronary syndrome	I20.0	411.1		K76.01
Acute coronary syndrome				
			G311500	
			G33z000	
Angina at rest			G311.14	
			G311200	
Impending infarction			G311.12	
			G311000	
			G311011	
			G311z00	
			G312.00	
			G31y100	
			G31y200	
			G31y300	
			G31yz00	
Worsening angina			G311400	
Angina pectoris with documented spasm	I20.1		G31y000	
			G332.00	
Nocturnal angina			G330000	
Stable angina			G33z700	
Other forms of angina pectoris	I20.8		Gyu30	

Terms	ICD10	ICD9CM	Read Codes	ICPC
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..	

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,		410.90		

Terms	ICD10	ICD9CM	Read Codes	ICPC
unspecified site, episode of care unspecified				
AMI NOS, unspecified		410.90		
Acute myocardial infarction, sub endocardial infarction		410.7		
Old myocardial infarction	I25.2	412		
Healed myocardial infarction			G32..11	
Old myocardial infarction			G32..00	
Subsequent/recurrent myocardial infarction	I22		G35..	
Subsequent myocardial infarction of unspecified site	I22.9		Gyu36	
Subsequent myocardial infarction of other sites	I22.8		Gyu35 G353.	
Subsequent myocardial infarction of 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			
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	I21.0			

Terms	ICD10	ICD9CM	Read Codes	ICPC
of anterior wall	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 myocardial infarction			G384.00	
Postoperative myocardial infarction			G38z.00	
Acute anterior myocardial infarction		410.1		
Acute Q wave myocard infarct			G309.00	
Acute myocardial infarction, sub endocardial infarction		410.71 410.72		
Non-Q wave myocardial infarction NOS	I21.4 122.2			
Non-ST elevation (NSTEMI) myocardial infarction	I21.4 122.2			
History of MI			14A3.00 14A4.00 14AH.00 14AT.00	K76.02
Diabetes mellitus insulin-glucose infuse acute myocardial infarct			889A.00	

Cardiac arrhythmia

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

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	

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 European Socitey of Cardiology (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	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Permanent atrial fibrillation	I48.2		G573400	
Non-rheumatic atrial fibrillation			G573300	
ECG: atrial fibrillation			3272.	
H/O: atrial fibrillation			14AN.00	
Atrial fibrillation resolved			212R.00	
Atrial fibrillation monitoring			662S.00	
			6A9..00	
			8HTy.00	
			9hF1.00	
			9Os..	

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	

Malignant ventricular arrhythmia

Malignant ventricular arrhythmia consists of ventricular fibrillation, ventricular tachycardia and Torsade de pointes ventricular tachycardia in the long QT syndrome (Bigger 1983).

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

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

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

Terms	ICD10	ICD9CM	Read Codes	ICPC
Long QT syndrome	I45.81	426.82	X202	
	147.2E			
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		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 G5610	K84.02
Atrioventricular and left bundle-branch block	I44			
Mobitz (type) II atrioventricular block		426.12	G5612	
Other second degree atrioventricular block		426.13		
ECG: complete atrioventricular block			3298.	
Partial atrioventricular block			G561.	
ECG: partial atrioventricular block			3294.	
ECG: partial atrioventricular block - 2:1			3295.	
ECG: partial atrioventricular block - 3:1			3296.	

Premature depolarization

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

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

Terms	ICD10	ICD9CM	Read codes	ICPC
Extrasystole	I49.4 I49.40 I49.49	427.6	G576z00 G576011	K80
Supraventricular extrasystole		427.61	G576100	K80.01
Ventricular extrasystole	I49.3		G576500 G576200	K80.02

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

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	
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		

Terms	ICD10	ICD9CM	Read Codes	ICPC
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	
Heart failure confirmed via echography			G5yy900	
			G5yyA00	
			G5yyC00	
Heart transplant failure and rejection			SP08400	
Heart failure as a complication of care			SP11111	

Cerebrovascular events

For this study, a cerebrovascular event encompasses stroke and TIA. The definitions of stroke and TIA and their respective disease codes are described below.

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 subarachnoid haemorrhage, 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 (subarachnoid, 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	I69.4		Gyu6C	
Brain stem stroke syndrome	G46.3		G663.	
Cerebellar stroke syndrome	G46.4		G664.	
Other and unspecified intracranial haemorrhage	162	432.*	G62..00 G62z.00	
Cerebral infarction	163		G64..	
Personal history of stroke			ZV125	
Sequelae of stroke NOS	I69.3			
H/O: Stroke			14A7.00 14A7.11 14A7.12 14AK.00	
Cerebral infarct due to thrombosis of precerebral arteries		433*	G63y000 G63y000	
Personal history of transient ischemic attack (TIA), and cerebral infarction	Z86.73	V12.54		

Terms	ICD10	ICD9CM	Read Codes	ICPC
without residual deficits				
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		438.*	G683.00	
Sequelae of stroke, not specified as haemorrhage or infarction			G68X.00/Gyu6C00	
Cerebral infarction due unspecified occlusion/stenosis of pre-cerebral arteries		433.*	G6W..00/Gyu6300	
			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.*		

NOS - Not otherwise specified.

Transient Ischemic Attack (TIA)

TIA is a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than 1 hour, and without evidence of 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	

H/O – History 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 et al. 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
Chronic kidney disease	N18 N18.9	585.9 583* 585* 586*	1Z1.. K05..13	U99

Terms	ICD10	ICD9CM	Read Codes	ICPC
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	
Chronic kidney disease, stage 4 (severe)	N18.4	585.4	1Z13.00	
			1Z1H.00	
			1Z1H.11	
			1Z1J.00	
			1Z1J.11	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			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 V56.0 V56.8	7L1.. SP06B00 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, 996.81 250.4x	SP08300 SP08C00 SP08D00 SP08E00 SP08F00 SP08G00 SP08H00	

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

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 et al. 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.

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).

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* 788.20 600*	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	

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..00	F93
Glaucoma - absolute			F404211	
Glaucomatocyclitic crises			F442100	
[X]Glaucoma			FyuG.00	

Hepatic impairment

Hepatic function decreases with age, but due to the high capacity of the liver this is considered not to change the pharmacokinetics to a clinically relevant extent. Liver disease, however, is known to be a common cause of altered pharmacokinetics of drugs. Hepatic function can be decreased through different pathophysiological mechanisms. Worldwide, chronic infections with hepatitis B or C are the most common causes of chronic liver disease, whereas in the western world, chronic and excessive alcohol ingestion is one of the major causes of liver disease. Other causes are uncommon diseases such as primary biliary cirrhosis, primary sclerosing cholangitis and autoimmune chronic active hepatitis. Ongoing destruction of the liver parenchyma in chronic liver diseases ultimately leads to liver cirrhosis and the development of portal hypertension. However, even if liver cirrhosis is established, the residual metabolic function of the liver may be rather well preserved for many years because of regeneration of hepatocytes. Clinical symptoms related to hepato-cellular failure and portal hypertensions are most importantly ascites, oesophageal varices and encephalopathy. Serum markers of liver failure are low serum albumin and a prothrombin deficiency. Serum bilirubin as well as other liver tests may or may not be affected to a varying degree, e.g. depending on the liver disease (cholestatic versus hepatocellular). Liver cirrhosis is irreversible in nature,

but progression can be modified by e.g. abstinence of alcohol in alcohol liver cirrhosis (EMA 2005).

Terms	ICD10	ICD9CM	Read Codes	ICPC
Liver enzymes abnormal	R94.5	794.8	44G2.	
	R74		R148.	
			44D2.	
			44G3100	
			44G4100	
			44H5100	
			44H5200	
			R148.00	
Hepatic failure, unspecified	K72.9			
Liver failure			7L1f.00	
			7L1fy00	
			7L1fz00	
			J625.00	
			J625.11	
			J62y.11	
			J62y.12	
			J62y.13	
Cirrhosis; liver	K74.60	571.5	J615..	D97
Hepatic failure, unspecified				
Nonspecific elevation of levels of transaminase or LDH		790.4		
Inflammatory liver disease, unspecified	K75.9			
Hepatitis NOS		573.3	J633.	
Hepatitis unspecified				
Unspecified viral hepatitis	B19	070	A70z.	D72
Viral hepatitis	B19.9		A70..	
			A72x000	
			A785200	
			AyuB..	
			J63..	
Chronic hepatitis, unspecified	K73.9	571.4	J614..	
			J614y	
Alcoholic cirrhosis or fibrosis	K70.2			
	K70.3			
	K70.4			
Primary or secondary biliary cirrhosis	K74.3			
	K74.4			
	K74.5			
History of hepatitis			141E.00	
			141F.00	
			2126700	
H/O: liver disease			14C5.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Hepatitis A - current infection			2J23.00	
Chronic hepatitis			9kR..00	
			9kR..11	
Hepatitis screening positive			9kV..00	
			9kV..11	
			9kZ..00	
			9kZ..11	
Sequelae of viral hepatitis			AE23.00	
			AyuJ900	
Acute liver failure			J600011	
Acute hepatitis - noninfective			J600100	
Necrosis of liver			J600z00	
			J601.00	
Cirrhosis and chronic liver disease			J61..	
Other sequelae of chronic liver			J62y.00	
[X]Diseases of the liver			Jyu7..	
Liver transplant failure and rejection			SP08600	
Liver failure as a complication of care			SP14211	

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

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			
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	

Pregnancy and breast feeding

Information on breast feeding and pregnancy will be retrieved from IPCI and THIN via specific ICPC or READ codes. Information on pregnancy in Aarhus is derived via linkage with the birth register

Terms	Read Codes	ICPC

Terms	Read Codes	ICPC
Serum pregnancy test positive	4453.00	
Urine pregnancy test positive	4654.00	
Pregnancy associated plasma protein A level	4Q3N.00	
Pregnancy associated plasma protein A multiple of median	4Q3N000	
IUD failure - pregnant	615C.00	
Pregnant, IUD failure	615C.11	
Pregnant, diaphragm failure	6166.00	
Pregnant, sheath failure	6174.00	
Pregnant	62...	W78
	ZV..	W79
Pregnancy advice	67A..00	
Curettage of term pregnancy NE	7E07111	
Suction termination of pregnancy	7E08400	
Vacuum termination of pregnancy	7E08411	
Termination of pregnancy NEC	7E08600	W83
Pregnancy operations	7F...12	
Pregnancy prophylactic therapy	8B68.00	
	8B7..11	
	8B74.00	
	8B75.00	
Complications of pregnancy, childbirth and the puerperium	L....00	W03
	Ly...00	W05
	Lz...00	W17
		W18
		W28
		W29
		W70
		W71
		W72
		W73
		W75
		W76
		W77
		W80
		W81
Termination of pregnancy	L05..12	W82
	L095.00	
	L097.00	
Other specified pregnancy with abortive outcome	L0y..00	
	L0z..00	
Pregnancy complications	L1...	
Risk factors in pregnancy	L2...	W84

Terms	Read Codes	ICPC
Caesarean section – pregnancy	L398200	
Venous complications during pregnancy	L41..	W77
Nipple complications during pregnancy	L46..	
Pregnancy, childbirth and puerperium observations	Z2...	W91
		W92
		W93
		W96
		W99
Lactation established	62PD.00	
Obstetric breast and lactation	L46..	W19
		W20
Lactation management	Z2B5.00	W94
		W94
		W95
Establishing lactation	Z2B5400	
Promotion of lactation	Z2B5412	
Dietary advice for lactation	ZC2L.11	

Annex 3.2 - Exposure and concomitant medication definition

Exposure medication definition

	ATC code	Multilex id code
QVA149	R03AL04	to be defined (will be provided by THIN)

Concomitant use of respiratory drugs

- Short acting anticholinergic agents
  R03BB01 Ipratropium bromide
- Long-acting anticholinergic agents
  R03BB04 Tiotropium bromide
  R03BB05 Aclidinium bromide
  R03BB06 Glycopyrronium bromide
- Single-ingredient short-acting β2 agonists
  R03AC02 Salbutamol
  R03AC03 Terbutaline
  R03AC04 Fenoterol
- Long-acting β_2 agonists
  R03AC12 Salmeterol
  R03AC13 Formoterol
  R03AC18 Indacaterol
  R03AC19 Olodaterol
- Inhaled corticosteroids (ICS)
  R03BA01 Beclometasone
  R03BA02 Budesonide
  R03BA03 Flunisolide
  R03BA04 Betamethasone
  R03BA05 Fluticasone
  R03BA06 Triamcinolone
  R03BA07 Mometasone
  R03BA08 Ciclesonide
- Xanthines
  R03DA01 Diprophylline
  R03DA02 Choline theophyllinate
  R03DA03 Proxyphylline
  R03DA04 Theophylline
  R03DA05 Aminophylline
  R03DA06 Etamiphylline
  R03DA07 Theobromine

R03DA08 Bamifylline
R03DA09 Acefylline piperazine
R03DA10 Bufylline
R03DA11 Doxofylline
R03DA20 Combinations of xanthines
R03DA51 Diprophylline, combinations
R03DA54 Theophylline, combinations excluding psycholeptics
R03DA55 Aminophylline, combinations
R03DA57 Theobromine, combinations
R03DA74 Theophylline, combinations with psycholeptics

- Fixed combination therapy (LABA + inhaled corticosteroids, anticholinergic agents + SABA)
  R03AK01 Epinephrine and other drugs for obstructive airway diseases
  R03AK02 Isoprenaline and other drugs for obstructive airway diseases
  R03AK03 Fenoterol and other drugs for obstructive airway diseases
  R03AK04 Salbutamol and sodium glomolycate
  R03AK05 Reproterol and and sodium glomolycate
  R03AK06 Salmeterol and fluticasone
  R03AK07 Formoterol and budesonide
  R03AK08 Formoterol and beclomethasone
  R03AK09 Formoterol and mometasone
  R03AK10 Vilanterol and fluticsasone furoate
  R03AK11 Formoterol and fluticasone
- 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

Concomitant use of drugs with anticholinergic action

- 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
QN05AD90 Azaperone
N05AE Indole derivatives
N05AE01 Oxypertine
N05AE02 Molindone
N05AE03 Sertindole
N05AE04 Ziprasidone
N05AF Thioxanthene derivative
N05AF01 Flupentixol
N05AF02 Clopenthixol
N05AF03 Chlorprothixene
N05AF04 Thiothixene
N05AF05 Zuclopenthixol
N05AG Diphenylbutylpiperidine derivatives
N05AG01 Fluspirilene
N05AG02 Pimozide
N05AG03 Penfluridol
N05AH Diazepines, oxazepines, thiazepines and oxepines
N05AH01 Loxapine
N05AH02 Clozapine
N05AH03 Olanzapine
N05AH04 Quetiapine
N05AH05 Asenapine
N05AH06 Clotiapine
QN05AK Neuroleptics, in tardive dyskinesia
N05AL Benzamides
N05AL01 Sulpiride
N05AL02 Sultopride
N05AL03 Tiapride
N05AL04 Remoxipride
N05AL05 Amisulpride
N05AL06 Veralipride
N05AL07 Levosulpiride
N05AN Lithium
N05AN01 Lithium
N05AX Other antipsychotics
N05AX07 Prothipendyl
N05AX08 Risperidone
N05AX10 Mosapramine
N05AX11 Zotepine

N05AX12 Aripiprazole
N05AX13 Paliperidone
N05AX14 Iloperidone
QN05AX90 Amperozide

- Tricyclic and tetracyclic antidepressant agents
  N06AA Non-selective monoamine reuptake inhibitors
  N06AA01 Desipramine
  N06AA02 Imipramine
  N06AA03 Imipramine oxide
  N06AA04 Clomipramine
  N06AA05 Opipramol
  N06AA06 Trimipramine
  N06AA07 Lofepramine
  N06AA08 Dibenzepin
  N06AA09 Amitriptyline
  N06AA10 Nortriptyline
  N06AA11 Protriptyline
  N06AA12 Doxepin
  N06AA13 Iprindole
  N06AA14 Melitracen
  N06AA15 Butriptyline
  N06AA16 Dosulepin
  N06AA17 Amoxapine
  N06AA18 Dimetacrine
  N06AA19 Amineptine
  N06AA21 Maprotiline
  N06AA23 Quinupramine
  N06AX Other antidepressants
  N06AX01 Oxitriptan
  N06AX02 Tryptophan
  N06AX03 Mianserin
  N06AX04 Nomifensine
  N06AX05 Trazodone
  N06AX06 Nefazodone
  N06AX07 Minaprine
  N06AX08 Bifemelane
  N06AX09 Viloxazine
  N06AX10 Oxaflozane
  N06AX11 Mirtazapine
  N06AX12 Bupropion

N06AX13 Medifoxamine
N06AX14 Tianeptine
N06AX15 Pivagabine
N06AX16 Venlafaxine
N06AX17 Milnacipran
N06AX18 Reboxetine
N06AX19 Gepirone
N06AX21 Duloxetine
N06AX22 Agomelatine
N06AX23 Desvenlafaxine
N06AX24 Vilazodone
N06AX25 Hyperici herba
N06AX90 Selegiline

- Disopyramide
  C01BA03 Disopyramide
- Antispasmodics
  A03AA Synthetic anticholinergics, esters with tertiary amino group
  A03AA01 Oxyphencyclimine
  A03AA03 Camylofin
  A03AA04 Mebeverine
  A03AA05 Trimebutine
  A03AA06 Rociverine
  A03AA07 Dicycloverine
  A03AA08 Dihexyverine
  A03AA09 Difemerine
  A03AA30 Piperidolate
  A03AB Synthetic anticholinergics, quaternary ammonium compounds
  A03AB01 Benzilone
  A03AB02 Glycopyrronium
  A03AB03 Oxyphenonium
  A03AB04 Penthienate
  A03AB05 Propantheline
  A03AB06 Otilonium bromide
  A03AB07 Methantheline
  A03AB08 Tridihexethyl
  A03AB09 Isopropamide
  A03AB10 Hexocyclium
  A03AB11 Poldine
  A03AB12 Mepenzolate
  A03AB13 Bevonium

A03AB14 Pipenzolate
A03AB15 Diphemanil
A03AB16 (2-benzhydryloxyethyl) diethyl-methylammonium iodide
A03AB17 Tiemonium iodide
A03AB18 Prifinium bromide
A03AB19 Timepidium bromide
A03AB21 Fenpiverinium
A03AB53 Oxyphenonium, combinations
QA03AB90 Benzetimide
QA03AB92 Carbachol
QA03AB93 Neostigmin

- Anti Parkinson drugs
  N04A Anticholinergic agents
  N04AA Tertiary amines
  N04AA01 Trihexyphenidyl
  N04AA02 Biperiden
  N04AA03 Metixene
  N04AA04 Procyclidine
  N04AA05 Profenamine
  N04AA08 Dexetimide
  N04AA09 Phenglutarimide
  N04AA10 Mazaticol
  N04AA11 Bornaprine
  N04AA12 Tropatepine
  N04AB Ethers chemically close to antihistamines
  N04AB01 Etanautine
  N04AB02 Orphenadrine (chloride)
  N04AC Ethers of tropine or tropine derivatives
  N04AC01 Benzatropine
  N04AC30 Etybenzatropine
- Choline-esterase inhibitors
  N07AA Anticholinesterases
  N07AA01 Neostigmine
  N07AA02 Pyridostigmine
  N07AA03 Distigmine
  N07AA30 Ambenonium
  N07AA51 Neostigmine, combinations

Atropine
A03BA01 Atropine

- H1-antihistamines
  R06AA Aminoalkyl ethers
  R06AA01 Bromazine
  R06AA02 Diphenhydramine
  R06AA04 Clemastine
  R06AA06 Chlorphenoxamine
  R06AA07 Diphenylpyraline
  R06AA08 Carbinoxamine
  R06AA09 Doxylamine
  R06AA52 Diphenhydramine, combinations
  R06AA54 Clemastine, combinations
  R06AA56 Chlorphenoxamine, combinations
  R06AA57 Diphenylpyraline, combinations
  R06AA59 Doxylamine, combinations
  R06AB Substituted alkylamines
  R06AB01 Brompheniramine
  R06AB02 Dexchlorpheniramine
  R06AB03 Dimetindene
  R06AB04 Chlorphenamine
  R06AB05 Pheniramine
  R06AB06 Dexbrompheniramine
  R06AB07 Talastine
  R06AB51 Brompheniramine, combinations
  R06AB52 Dexchlorpheniramine, combinations
  R06AB54 Chlorphenamine, combinations
  R06AB56 Dexbrompheniramine, combinations
  R06AC Substituted ethylene diamines
  R06AC01 Mepyramine
  R06AC02 Histapyrrodine
  R06AC03 Chloropyramine
  R06AC04 Tripelennamine
  R06AC05 Methapyrilene
  R06AC06 Thonzylamine
  R06AC52 Histapyrrodine, combinations
  R06AC53 Chloropyramine, combinations
  R06AD Phenothiazine derivatives
  R06AD01 Alimemazine
  R06AD02 Promethazine
  R06AD03 Thiethylperazine
  R06AD04 Methdilazine

R06AD05 Hydroxyethylpromethazine
R06AD06 Thiazinam
R06AD07 Mequitazine
R06AD08 Oxomemazine
R06AD09 Isothipendyl
R06AD52 Promethazine, combinations
R06AD55 Hydroxyethylpromethazine, combinations
R06AE Piperazine derivatives
R06AE01 Buclizine
R06AE03 Cyclizine
R06AE04 Chlorcyclizine
R06AE05 Meclozine
R06AE06 Oxatomide
R06AE07 Cetirizine
R06AE09 Levocetirizine
R06AE51 Buclizine, combinations
R06AE53 Cyclizine, combinations
R06AE55 Meclozine, combinations
R06AK Combinations of antihistamines
R06AX Other antihistamines for systemic use
R06AX01 Bamipine
R06AX02 Cyproheptadine
R06AX03 Thenalidine
R06AX04 Phenindamine
R06AX05 Antazoline
R06AX07 Triprolidine
R06AX08 Pyrrobutamine
R06AX09 Azatadine
R06AX11 Astemizole
R06AX12 Terfenadine
R06AX13 Loratadine
R06AX15 Mebhydrolin
R06AX16 Deptropine
R06AX17 Ketotifen
R06AX18 Acrivastine
R06AX19 Azelastine
R06AX21 Tritoqualine
R06AX22 Ebastine
R06AX23 Pimethixene
R06AX24 Epinastine

R06AX25 Mizolastine
R06AX26 Fexofenadine
R06AX27 Desloratadine
R06AX28 Rupatadine
R06AX29 Bilastine
R06AX53 Thenalidine, combinations
R06AX58 Pyrrobutamine, combinations

- Anticholinergics for treatment of overactive bladder
  G04BD Urinary antispasmodics
  G04BD01 Emepronium
  G04BD02 Flavoxate
  G04BD03 Meladrazine
  G04BD04 Oxybutynin
  G04BD05 Terodiline
  G04BD06 Propiverine
  G04BD07 Tolterodine
  G04BD08 Solifenacin
  G04BD09 Trospium
  G04BD10 Darifenacin
  G04BD11 Fesoterodine