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Quantitative Safety & Epidemiology

Non-Interventional Study Protocol

NVA237A2401T

Title	Multinational, multi-database drug utilization study of inhaled NVA237 in Europe
Protocol version identifier	v02
Date of last version of protocol	05 September 2014
EU PAS register number	ENCEPP/SDPP/4845
Active substance	Glycopyrronium bromide (NVA237)
	(R03BB06)
Medicinal product	Seebri® Breezhaler® / Tovanor® Breezhaler® / Enurev® Breezhaler®
Product reference	NVA237
Procedure number	Seebri Breezhaler: EMEA/H/C/0002430
	Tovanor Breezhaler: EMEA/H/C/0002690
	Enurev Breezhaler: EMEA/H/C0002691

Marketing authorization holder(s)	Novartis Europharm Limited Wimblehurst Road Horsham West Sussex RH12 5AB United Kingdom
Joint PASS	No
Research questions and objectives	In the context of the NVA237 marketing authorization application (and it's multiple marketing authorization applications), the Committee for Medicinal Products for human use (CHMP) recommended conditions for marketing authorization and product information and suggested to conduct a post-authorization drug utilization study. The objectives of this study are to estimate the subpopulation with cardiovascular co-morbidity and to identify patients groups with missing information in the Risk Management Plan.
Country (-ies) of study	UK, Denmark, Italy, The Netherlands, Spain
Author	[redacted], MD, PhD [redacted] The Netherlands Tel: [redacted]

QPPV or delegate | Signature | Date

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NI Protocol Template Version 31-Jan-2013

Marketing authorization holder(s)

Marketing authorization holder(s)	Novartis Europharm Ltd
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2 List of abbreviations

ADM	Administrative
(A)MI	**(**Acute) myocardial infarction
ATC	anatomical therapeutic chemical classification system
BNF	British National Formulary
CHMP	Committee for Medicinal Products for human use
CI	confidence interval
COPD	chronic obstructive pulmonary disease
DUS	drug utilization study
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GOLD	Global Initiative for chronic obstructive Lung Disease
GP	general practitioner
GPP	Good pharmaco-epidemiology practice
HF	heart failure
HSD	Health Search CSD Longitudinal Patient Database
ICD-9	international classification of disease, 9th rev
ICD-10	international classification of disease, 10th rev
ICPC	international classification of primary care
ICS	inhaled corticosteroid
IPCI	Integrated Primary Care Information Project
LABA	long acting β2 agonist
LAMA	long acting antimuscarinic antagonist
LTRA	Leukotriene receptor antagonist
MR	Medical Records
NOS	Nothing specified

OTC	Over-the-counter
PASS	Post authorization safety study
PDE	Phosphodiesterase
PSUR	Periodic Safety Update Report
RRE	Remote research environment
SAC	Scientific Advisory Committee
SABA	short acting β2 agonist
SAMA	Short Acting Muscuranic Agent
SD	Standard deviation
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SmPC	Summary of Product Characteristics
TIA	Transient ischemic attack
THIN	The Health Information Network
UMLS	Unified Medical Language System
WHO	World Health Organisation

3 Responsible parties

Table 3-1 Main responsible parties

Role	Person
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Role	Person
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4 Abstract

Title	Multinational, multi-database drug utilization study of inhaled NVA237 in Europe Study number: CNVA237A2401T
Version and Date	v02, 05 September 2014
Name and affiliation of main author	[redacted], MD, PhD, [redacted]
Rationale and background	NVA237 is a long-acting muscarinic antagonist (LAMA) which was approved in EU in September 2012 as maintenance bronchodilator treatment to relieve symptoms of chronic obstructive pulmonary disease (COPD). In the past, use of inhaled LAMA has been associated with an increased risk of anticholinergic effects, such as acute urinary retention and glaucoma. More recently, use of LAMA has been associated with an increased risk of cardiovascular and cerebrovascular events. In view of this knowledge, the current labeling of NVA237 recommends caution when used in patients with a medical history of glaucoma and urinary retention, as well as caution in patients with a medical history of cardiovascular disease. As NVA237 is predominantly cleared by the kidney, caution is needed when administered to patients with severe renal impairment or end-stage renal disease. Finally, as patients with a medical history of cardiovascular disease were excluded from the phase II - phase III clinical trials, NVA237 should be used with caution in these patients groups. The missing information in the Risk Management Plan (RMP) includes the use of NVA237 in patients with unstable ischemic heart disease, arrhythmia and long QT-syndrome, use in patients with liver impairment, use in pregnancy and lactation, long-term use in COPD beyond 1 year, off-label use in adults with asthma without COPD and in the pediatric population; and safety and efficacy of alternative dosing regimens. Therefore, upon approval of NVA237, the Committee for Medicinal Products for Human Use (CHMP) requested Novartis, the marketing authorization holder of inhaled NVA237, to conduct a post-authorization drug utilization study (DUS) to estimate the subpopulation with cardiovascular comorbidity and to identify patient groups with missing information in the risk management plan.
Research question and objectives	To estimate the subpopulation with cardiovascular co-morbidity and to identify patient groups with missing information in the RMP.
Study design	An exploratory, descriptive study will be conducted on new user cohorts of NVA237 using multi-national, multi-databases from five European electronic health care databases from the Netherlands, Italy, United Kingdom (UK), Denmark and Spain to describe characteristics of patients newly initiating NVA237. Patient characteristics will be described at the time of index date (= date of first NVA237 prescription during study period). The study will be initiated after the date of first drug launch in any of the five selected countries.

Population	All patients registered in the respective electronic health care databases (see below- 'Data sources') with a minimum of 1 year of valid database history and with at least one prescription of inhaled NVA237.
Variables	Demographics (age, gender), indication of use, prescribed daily dosage, concomitant use of other respiratory drugs, concomitant use of drugs with anticholinergic properties, underlying co-morbidities (renal impairment, narrow angle glaucoma, urinary retention or symptomatic bladder outflow obstruction, cardiovascular and cerebrovascular disease and liver disease), lifestyle factors, COPD characteristics (duration and COPD severity).
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 Aarhus (Denmark) and the Health Search CSD Longitudinal Patient Database (HSD) from Italy.
Study size	The actual sample size for the study will be determined by the market uptake of NVA237 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 at least 3000 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 November 2012 End of data collection: 01 November 2015 Interim report 1: 25 October 2013 Interim report 2: November 2014 Interim report 3: November 2015 Registration in the EU PAS register: 26 September 2013 Final report of study results: November 2016

5 Amendments and updates

Table 5-1 Study protocol amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	17 June 2013	4 Abstract	The abstract has been updated clarifying the study size, the rationale and background and the primary/secondary objectives of this study.	Based on PRAC comments
2	17 June 2013	7 Rationale and background	This section has been updated clarifying that this DUS will be conducted to estimate the subpopulation of NVA237 users with cardiovascular co-morbidity and to identify patient groups with missing information in the risk management plan.	Based on PRAC comments
3	17 June 2013	8 Research question and objectives	The objectives have been updated. The primary objective of this study is to determine the proportion of patients using NVA237 who also have cardio/cerebrovascular comorbidities and to identify patient groups with missing information in the risk management plan.	Based on PRAC comments
4	17 June 2013	9.2.2 Study period	Study period has been clarified stating that 3000 patients will be included within 3 years after launch (= November 2015).	Based on PRAC comments

Number	Date	Section of study protocol	Amendment or update	Reason
5	17 June 2013	9.3.7 Underlying comorbidity	This section has been updated. Arrhythmia is one of the comorbidities of interest and encompasses: atrial fibrillation/flutter, malignant ventricular arrhythmia (ventricular tachycardia, ventricular fibrillation and “Torsade de pointes”), long QT syndrome and AV block.	Based on PRAC comments
6	17 June 2013	9.4 Data sources	Details on the methods for collection of hospitalization data have been added.	Based on PRAC comments
7	17 June 2013	9.5 Study Size	The sample size of 3000 patients, to be enrolled within 3 years after launch, has been clarified. This session now also contains information on population coverage of the individual databases and the projected market uptake of NVA237.	Based on PRAC comments
8	17 June 2013	9.6 Data management	This section has been updated with information on the methods that will be used to pool the data of the different databases.	Based on PRAC comments
9	17 June 2013	Annex 2 – Indication of use and co-morbidity definition	The codes for the co-morbidities for “cardiovascular diseases” presented in Annex 2 have been expanded to also include “ischemic heart disease”	Based on PRAC comments
10	05 September 2014	8.2 Secondary objective	Now also includes COPD disease severity measured by proxy or by pulmonary function	To provide better insight into COPD severity in patients initiating NVA237

Number	Date	Section of study protocol	Amendment or update	Reason
11	05 September 2014	9.3.3 Indication of use for inhaled NVA237	In case NVA237 is prescribed for other reasons than COPD or asthma, the respective disease codes, around the prescribing of NVA237 will be provided	Internal request by Novartis
12	05 September 2014	9.3.7 Underlying co-morbidities	Cardiac arrhythmia as comorbidity has been updated and now also includes supraventricular tachycardia, sick sinus syndrome and premature depolarization	Based on SAC comment
13	05 September 2014	9.3.7 Underlying co-morbidities	BPH has been added as comorbidity	Based on SAC comment
14	05 September 2014	Annex 4 - Indication of use and co-morbidity definition	Disease codes have been updated	Based on continuous review of disease codes
15	05 September 2014	Annex 3 - Exposure and concomitant medication definition	Drug codes have been updated	Based on continuous review of disease codes
16	05 September 2014	9.5 Study size	Clarification and justification of study sample size; clarification of discontinuation rule based on accrued no. of patients and duration of follow-up	Justification of sample size based on previous response already submitted to PRAC in 2013, but details not yet in protocol; discontinuation rule based on patient counts identified during current preparation of second yearly interim report
17	05 September 2014	Not applicable	Transcription of the entire protocol into the Novartis protocol template for non-interventional PASS	To follow Novartis-internal guidelines

6 Milestones

Table 6-1 Study milestones

Milestone	Planned date
Start of data collection	Upon launch of Seebri® Breezhaler® (November 2012)
End of data collection	Maximum 3 years after launch of NVA237
Study progress reports	Yearly progress reports – first report planned at 1 year after launch of NVA237
Interim reports	Yearly - first report planned at 1 year after launch of NVA237
Registration in the EU PAS register	Following PRAC endorsement
Final report of study results	Maximum 1 year after study completion (= end of data collection)

7 Rationale and background

According to GOLD (Global initiative of lung disease), COPD is a common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients. Chronic obstructive pulmonary disease (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 β_2 agonists, anticholinergics (AC), methylxanthines and phosphodiesterase – 4 inhibitors, used alone or in combination.

Use of inhaled LAMA has been associated with an increased risk of anticholinergic effects such as glaucoma and urinary retention (Afonso et al 2011, Verhamme et al 2008). More recently, the use of LAMA has been associated with an increased risk of cardiovascular and cerebrovascular events but the data are conflicting. (Dong Yaa-Hui 2012, Jara et al 2007, Lee et al 2008, Michele et al 2010, Singh et al 2011, Singh et al 2008, Verhamme et al 2012, Jara et al 2012)

NVA237 is a synthetic, quaternary ammonium, anticholinergic (antimuscarinic) agent that acts through competitive antagonism of acetylcholine at the muscarinic receptors: Seebri® Breezhaler® (along with the Multiple Marketing Authorizations Enurev® Breezhaler® and Tovanor® Breezhaler®) is the Novartis brand name for this long-acting muscarinic antagonist (LAMA). NVA237 is a dry powder formulation, developed as a once-daily inhalation treatment for patients with COPD. NVA237 is indicated as maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD.

The Summary of Product Characteristics (SmPC) of NVA237 specifies that it should be used with caution in patients with a medical history of urinary retention and narrow angle glaucoma as these conditions could aggravate upon concomitant use of drugs with anticholinergic effects. As NVA237 is predominantly cleared by the kidney, caution is needed when administered to patients with severe renal impairment or end-stage renal disease. Finally, as patients with a medical history of cardiovascular disease were excluded from the phase II - phase III clinical trials, NVA237 should be used with caution in these patients groups. The missing information in the Risk Management Plan (RMP) includes use of NVA237 in patients with unstable ischemic heart disease, arrhythmia and long QT-syndrome, use in patients with liver impairment, use in pregnancy and lactation, long-term use in COPD beyond 1 year, off-label use in adults with asthma without COPD and in the pediatric population; and safety and efficacy of alternative dosing regimens.

Therefore, in the context of the NVA237 marketing authorization application and the multiple marketing authorization applications for Tovanor® Breezhaler® and the Enurev® Breezhaler®, the Committee for Medicinal Products for Human Use (CHMP) requested Novartis to conduct a drug utilization study (DUS) to estimate the subpopulation with cardiovascular co-morbidity and to identify patients groups with missing information in the RMP.

This DUS will allow us to check whether NVA237 is prescribed according to the current labelling.

8 Research question and objectives

In this post-authorization DUS, we will estimate the subpopulation with cardiovascular co-morbidity and will identify patients groups with missing information in the RMP.

8.1 Main objectives

1. To determine the proportion of patients using NVA237 who also have the following cardiovascular or cerebrovascular comorbidities:
    - cardiovascular diseases: unstable ischemic heart disease, heart failure, myocardial infarction, cardiac arrhythmia (atrial flutter/fibrillation, malignant ventricular arrhythmia (ventricular tachycardia, ventricular fibrillation and “Torsade de pointes”), long QT syndrome and atrioventricular (AV) block)
    - cerebrovascular diseases: hemorrhagic or ischemic stroke, transient ischemic attack [TIA]
2. To determine the proportion of patients using NVA237 who have the missing information in the RMP or high risk treatment conditions:

    2a) To determine the proportion of patients using NVA237 with the history of the following conditions:

    - Unstable ischemic heart disease, cardiac arrhythmia and long QT-syndrome
    - Urinary retention or symptomatic bladder outflow obstruction

- Narrow angle glaucoma
- Renal impairment
- Liver disease
- Pregnancy or breast feeding

2b) To determine the proportion of patients using NVA who do not meet the criteria specified in the NVA237 label ('off-label use'): NVA237 has been registered for use in patients with COPD, older than 18 years of age. Use of NVA237 in patients younger than 18 years or in patients without a diagnosis of COPD will thus be considered as *"off-label"* use. Use of NVA237 in patients with a diagnosis of both COPD and asthma will not be considered as being off-label.

2c) To determine the proportion of new initiators of NVA237 with an uninterrupted use for more than one year.

8.2 Secondary objectives

- Demographics (age and gender)
- COPD duration (from diagnosis of COPD until first prescription of NVA237)
- COPD exacerbation (need of oral corticosteroids and/or hospitalization for COPD) in 1 year prior to first prescription of NVA237)
- COPD disease severity
- Smoking status at time of first prescription of NVA237
- Prescribed dosage/posology
- Concomitant use of other respiratory drugs
- Concomitant use of other anticholinergic drugs

9 Research methods

9.1 Study design

An exploratory, descriptive study will be conducted on new user cohorts of NVA237 using multi-national, multi-databases from five health care databases from various European countries, namely the Netherlands, Italy, the UK, Denmark and Spain.

From these databases, a new user cohort of NVA237 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 Netherland, 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 – Data sources.

From these databases, we will first select a population of patients with at least 1 year of valid database history.

The study population will comprise of all patients who newly initiated therapy with NVA237 in the databases. Initiation of therapy will be defined as a first prescription or dispensing of NVA237 preceded by at least 1 year of NVA237 free valid database history. The date of the first prescription of NVA237 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 2012) up to a maximum of 3 years following this first launch (December 2015). 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 3000 patients initiating NVA237 overall (including all databases) within 3 years of drug launch. Based on the NVA237 market uptake, it is assumed that by November 2015 latest, a minimum of 3000 new NVA237 users with at least 1 year of follow-up will be included (see also this protocol, section 9.5 - Study size).

Planned dates for launch of NVA237 in the five countries are as follows:

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

Countries	Actual launch date
Denmark	November 2012
Italy	April 2013
Netherlands	February 2013
Spain	April 2013
United Kingdom	November 2012

9.2.3 In- and exclusion criteria

Patients with a first prescription or dispensing of NVA237 preceded by at least 1 year of NVA237-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 NVA237 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

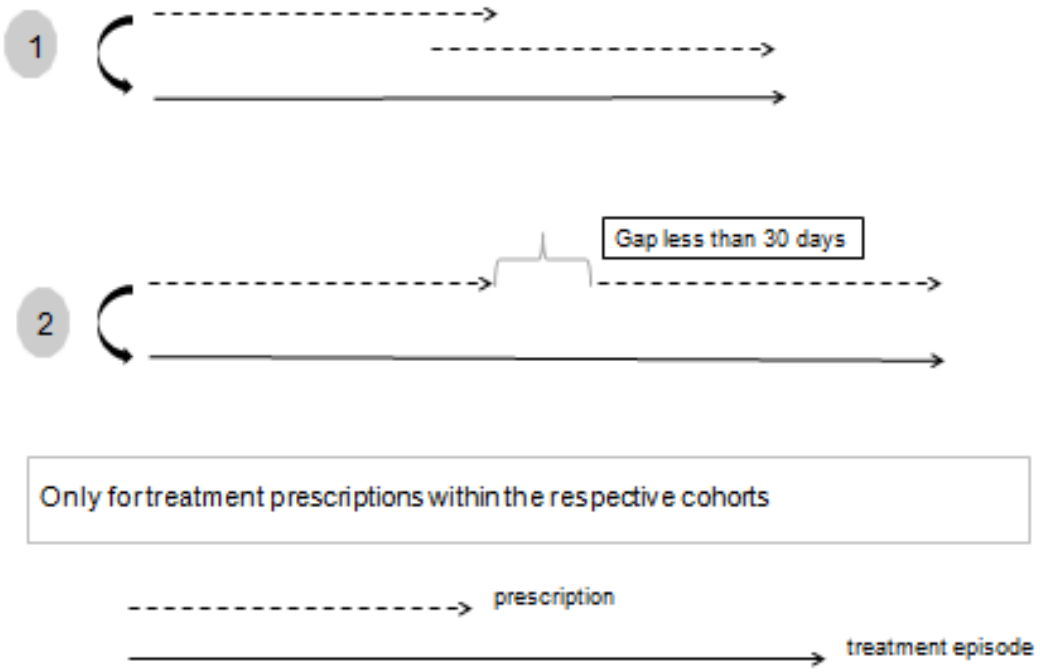
9.3.1 NVA exposure and duration of use

Patients prescribed NVA237 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 – 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 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) in Figure 9-1).

Figure 9-1 Creation of treatment episode for NVA237



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

From this study cohort, all NVA237 patients with uninterrupted use of more than 365 days will be identified and the proportion among the total of patients initiating NVA237 will be described.

9.3.2 Demography, life style factors and COPD characteristics at time of first prescription

- For all patients, information on gender and age (at time of first prescription of NVA237) 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.
- Duration of COPD (from date of diagnosis of COPD until date of first prescription)
- Number of COPD exacerbations requiring hospitalization 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 4 – 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 4 - 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 for inhaled NVA237

For each patient initiating treatment with NVA237, the indication of use will be assessed. Indication of use will be defined either as:

- COPD
- COPD and asthma
- 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 4 – 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 NVA237 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 NVA237 contains 55 micrograms of NVA237 equivalent to 44 micrograms of glycopyrronium. The recommended dose is the inhalation of the content of one capsule once daily using the Breezhaler® inhaler.

Although it is expected that patients use NVA237 once daily, for this study, we will register the frequency of use as following based on the patient specific dosing regimen (if available):

- Once daily
- Every other day

- Twice daily
- 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 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 – Exposure and concomitant medication definition). The following types of bronchodilating and anti-inflammatory drugs will be considered as respiratory drugs:

- Short acting muscarinic agents (SAMAs)
- LAMAs (excluding NVA237)
- Single-ingredient SABA
- Single-ingredient LABA
- Inhaled corticosteroids (ICS)
- Xanthines
- Fixed combination therapy (LABA + inhaled corticosteroids, anticholinergic agents + SABA)
- Oral $ß_2$-agonists
- Leukotriene receptor antagonists (LTRAs)
- Systemic corticosteroids
- Oral phosphodiesterase- 4 (PDE-4) inhibitors
- Fixed combination therapy of LABA+LAMA

9.3.6 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 – Exposure and concomitant medication definition). The following types of drugs will be considered as anticholinergic drugs:

- Antipsychotic drugs
- Tricyclic and tetracyclic antidepressant agents
- Disopyramide
- Antispasmodics

- Antiparkinsonian agents
- Cholinesterase inhibitors
- Atropine
- H1-antihistamines
- Anticholinergics for treatment of overactive bladder in patients with bladder outlet obstruction

9.3.7 Underlying co-morbidities

Underlying co-morbidities will be assessed during the complete database history prior to the index date (start of first prescription of NVA237). Underlying comorbidity will be identified via an automated search on disease specific codes (see Annex 4 – Indication of use and co-morbidity definition).

Co-morbidities of interest are the following:

- Chronic kidney disease (with relevant stages)
- Narrow angle glaucoma
- Urinary retention or symptomatic bladder outflow obstruction
- Benign prostatic hyperplasia (BPH)
- Cardiovascular disease (unstable ischemic heart disease, heart failure, myocardial infarction, cardiac arrhythmia (atrial flutter/fibrillation, malignant ventricular arrhythmia (ventricular tachycardia, ventricular fibrillation and "Torsade de pointes"), long QT syndrome and atrioventricular (AV) block, supraventricular tachycardia, sick sinus syndrome and premature depolarization).
- Cerebrovascular disease (hemorrhagic or ischemic stroke, transient ischemic attack [TIA])
- Hepatic impairment (e.g. hepatic failure, cirrhosis)

9.3.8 Pregnancy or breast-feeding at initiation of NVA237

Information on pregnancy or breast feeding at initiation of NVA237 will only be provided for those databases (THIN and IPCI) that capture this information via specific codes or free text search. Pregnancy will be determined at or during 9 months prior index date. Lactation will be determined at or during 12 months prior to index date. Codes for pregnancy and/or breast feeding are described under Annex 5 – Pregnancy and breastfeeding.

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 NVA237. All of the participating databases are part of the EU-ADR alliance, a stable collaboration framework for running drug safety studies in a federated manner, especially when the participation of several electronic health care record databases is required.

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.(Cazzola et al 2011, Ehrenstein et al 2010, Garcia-Gil Mdel et al, 2011, Lewis et al 2007, Vlug et al 1999)

The databases will be THIN (UK), HSD (Italy), IPCI (NL), the Aarhus University Prescription Database (DK) and SIDIAP (Spain). Table 3 provides an overview of key elements of these databases. The total number of persons in the source population will be around 12 million.

Table 9-2 Overview of databases

Country	**NL**	**UK**	**DK**	**Italy**	**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
Date death	Yes	Yes	Yes	Yes	Yes
Cause of death	Yes	Yes	Yes	No	No
Updates	Bi-annually	Database releases 3 times a year	Yearly (April)	Bi-annually: (30/06 and 31/12)	Yearly (31/12). Pharmacy/dispensing data quarterly
Prescriptions					
Outpatient Rx	Yes (specialist incomplete)	Yes (specialist incomplete)	Yes	Yes (specialist incomplete)	Yes (specialist incomplete)
Coding of drugs	ATC	BNF/Multilex code	ATC	ATC	ATC
Dosing regimen	Yes	Yes	No	Yes (incomplete)	Yes
Outcomes					
Hospitalisations	Yes	Yes	Yes	Yes	Yes
Outpatient diagnoses	Yes	Yes	No	Yes	Yes

Country	NL	UK	DK	Italy	Spain
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 4 - 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 2008).

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

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

9.4.2 HSD - CSD Longitudinal Patient Database

The Italian arm of the study will use the Health Search CSD Longitudinal Patient Database (HSD), a longitudinal observational database that is representative of the Italian general population. It was established in 1998 by the Italian College of General Practitioners.(Filippi et al 2005) The HSD contains data from computer-based patient records from a selected group

of GPs covering a total of 1.5 million patients) located throughout Italy. These GPs voluntarily agreed to collect data for the database and attend specified training courses. The database includes information on the age, gender, and identification of the patient, and GP registration information, which is linked to prescription information, clinical events and diagnoses, hospital admission, and causes of death. All diagnoses are coded according to ICD-9-CM. Drug names are coded according to the ATC classification system (WHO 2008). To be included in the study, GPs must have provided data for at least 1 year and meet standard quality criteria pertaining to: levels of coding, prevalence of well-known diseases, and mortality rates. (Cricelli et al 2003) The HSD complies with EU, guidelines on the use of medical data for research. The HSD has been used as data source for a number of peer-reviewed publications on the prevalence of disease conditions, drug safety and prescription patterns in Italian primary care.(Cazzola et al 2011) Approval for use of data is obtained from the Italian College of General Practitioners. Dose must be inferred from the strength, assuming a once daily administration for NVA237 and according to the dosing regimens of the respective Summary of Product Characteristics for the other drugs.

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.

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 NVA237 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. Only GPs who meet quality control standards can participate in the SIDIAP database. Encoding personal and clinic identifiers ensures the confidentiality of the information in the SIDIAP Database. Recent reports have shown the SIDIAP data to be useful for epidemiological research (Garcia-Gil Mdel et al 2011).

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

9.5 Study size

The study size of this drug utilization study will consist of the sum of new initiators of NVA237 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 3000 patients initiating NVA237 overall (including all databases) within 3 years of drug launch.

The proposed sample size of 3000 is sufficient to describe the use of NVA237 in patients with different cardiovascular or other co-morbidities (including missing information) based on background prevalence data from the literature. The table below shows the estimated exact 95% Clopper-Pearson-CIs for a sample size of 3000:

Table 9-3 Estimated two sided 95% confidence intervals per co-morbidity (N=3000)

Co-morbidity	Background prevalence (%)*	Estimated 95% CI
Ischemic heart disease	8.4	7.43 - 9.45
Myocardial infarction	4.8	4.06 - 5.63
Cerebrovascular disease	4.2	3.51 - 4.98
Heart failure	7.2	6.30 - 8.18
Cardiac arrhythmia	7.2	6.30 - 8.18
Atrial fibrillation	13.0	11.82 - 14.26
QT_C prolongation	13.4	12.20 - 14.67
Chronic renal failure	6.3	5.46 - 7.23
Chronic liver disease	5.0	4.25 - 5.84
Glaucoma	5.3	4.53 - 6.16
Diabetes	12.2	11.05 - 13.42

Source: *Conservative estimates of background prevalence were used: Suruki et al (2009), Feary et al (2010), Schneider et al (2010), Cazzola et al (2012), Divo et al (2012), García-Olmos et al (2013).

The numbers presented below in Table 9-4 represent estimates of population coverage by individual database:

Table 9-4 Population coverage (40+ years of age) by individual database

Database	Population coverage in overall country population (%)*	Population ≥40 years (%)*	Population coverage: ≥40 years (%)	Multiplicator
THIN-UK	6.0	49.8	3.0	0.030 (= 0.060 x 0.498)
HSD–Italy	3.0-5.0	56.2	1.7	0.017 (= 0.030 x 0.562)
SIDIAP–Spain**	12.8	51.2	6.6	0.066 (= 0.128 x 0.512)
Aarhus–Denmark	30.0	51.2	15.3	0.153 (= 0.300 x 0.512)

Database	Population coverage in overall country population (%)*	Population ≥40 years (%)*	Population coverage: ≥40 years (%)	Multiplicator
IPCI–Netherlands	12.0	52.0	6.2	0.062 (= 0.120 x 0.520)

*2012 Eurostat population estimates

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

The table below shows market-uptake estimates for the five countries (UK, Italy, Spain, the Netherlands and Denmark) included in the study. The numbers represent the estimated number of patients by year (2013-2015) who will be prescribed NVA237. The estimates include those patients who will be newly prescribed NVA237 in the corresponding year plus the ones continuing therapy (i.e. the ones who were prescribed the drug in the previous year already and continuing in the new calendar year). Annual estimates do not include those patients who discontinued therapy or died.

Table 9-5 Estimated number of patients prescribed NVA237 in the countries of interest 2013-2015

Country	2013	2014	2015
UK	7,847	40,455	53,347
Italy	34,491	177,819	234,485
Spain	24,281	125,183	165,076
Denmark	2,520	13,123	17,479
Netherlands	6,342	14,303	18,861
Total	**75,481**	**370,883**	**489,248**

The actual study size will be affected by the market uptake of NVA237 in the countries of interest. Based on the projected market uptake of NVA237 and the coverage of the databases of the total (country specific) population, the following predictions can be made about the number of NVA237 users within the different databases by end of 2014 (assuming that the final analysis will mostly include data up to the end of 2014):

Table 9-6 Individual database estimates of NVA237-treated patients for the year 2014

	Country estimate for 2014	Multiplicator	Individual database estimate of Seebri® treated patients by 2014
UK	40,455	0.030	1,214
Italy	177,819	0.017	3,023
Spain	125,183	0.066	8,262
Denmark	13,123	0.153	2,008
Netherlands	14,303	0.062	887
Total	**370,882**	**NA**	**15,393**

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

The total estimate across all databases would sum up to 15,393 patients. Based on these estimates, we are confident that we will be able to accrue the proposed sample size of at least 3000 patients in the NVA237 treatment cohort within 3 years.

The number of patients accrued in the study will be assessed yearly when preparing the annual progress and interim reports. The study will be discontinued when the number of patients with at least 1 year of follow-up, as described in the yearly report, exceeds 3000 (follow-up required to address main objective 2c).

9.6 Data management

Data from the five different databases will be pooled after local extraction, validation and data-cleaning. Clearly, it is not possible to use one single data extraction algorithm for all the databases. They use different coding schemes (e.g. ICD9-CM and ICD10, ICPC, READ) and their content comes from different data sources (e.g., general practitioners' records, hospital discharge diagnoses, and death registries). To reconcile differences across terminologies, we will build a shared semantic foundation 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 comorbidity data. The sequential steps of this process are shortly described below:

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 comorbidity are described in Annex 4 - Indication of use and co-morbidity definition.

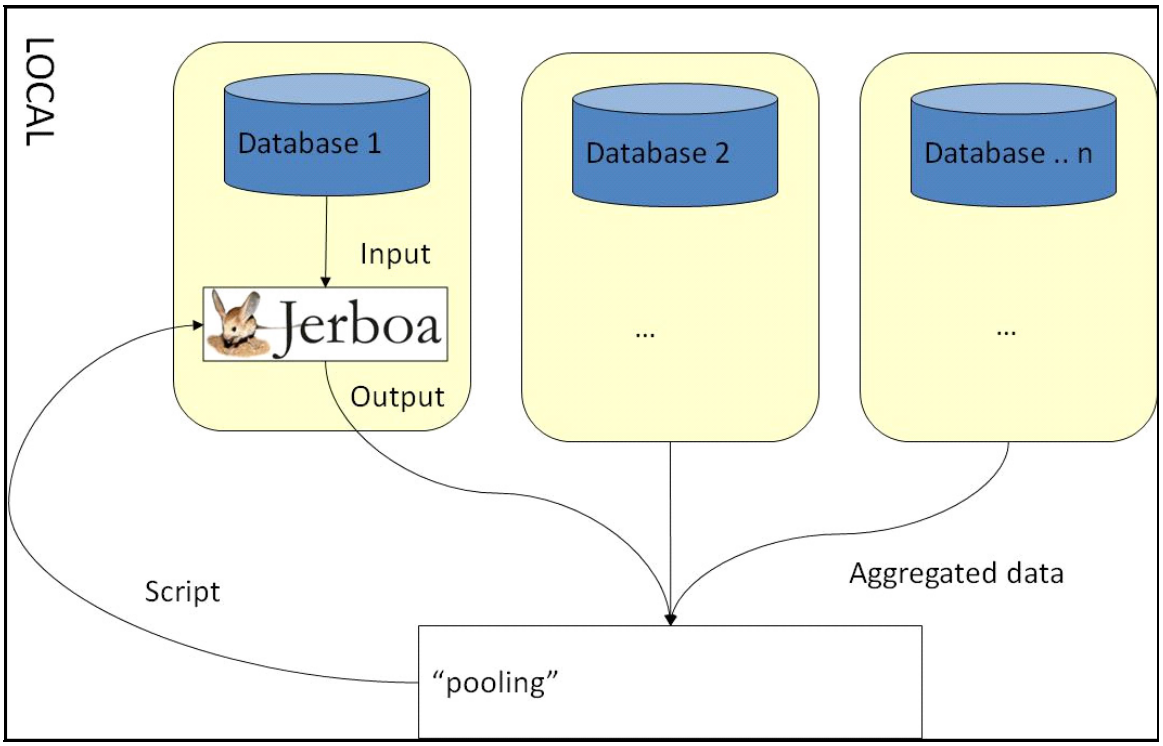
2. Definition of data extraction algorithm

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.

3. Event data extraction and pooling

Subsequently, each database extracts data using a common data model, i.e. standardized patient, drug, and comorbidity 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 9-2 Model for data sharing and elaboration (obtained from www.EU-ADR-project.org)



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% CI will be calculated either based on the normal distribution (in case of large numbers) or either 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.

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.

For this 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) (WHO 2008) and according to the ENCePP code of conduct (EMA 2013).

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 NVA237 exposure is less of a concern as these drugs are prescribed according to a fixed dose, namely once daily.

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.

Comorbidity 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), which hinders the conduct of long term follow-up studies. For this study, as we want to assess off-label use of NVA237, 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) [redacted]. 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.

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).

Members of the scientific advisory committee are the following:

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

Dr [redacted], USA

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well-being of patients participating in non-interventional studies are protected (consistent with the principles that have their origin in the Declaration of Helsinki) and that the study data are credible and responsibly reported.

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 (Vandenbroucke, 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' (European Medicines Agency 2013).

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). All adverse events/reactions should be summarized 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.

13 References (available upon request)

Afonso AS, Verhamme KM, Stricker BH, et al. 2011. Inhaled anticholinergic drugs and risk of acute urinary retention. *BJU Int,* 107**,** 1265-72.

Bateman ED, Hurd SS, Barnes PJ, et al. 2008. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J,* 31**,** 143-78.

Bigger JT, Jr. 1983. Definition of benign versus malignant ventricular arrhythmias: targets for treatment. *Am J Cardiol,* 52**,** 47C-54C.

Camm AJ, Kirchhof P, Lip GY, et al. 2010. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J,* 31**,** 2369-429.

Casson, RJ, Chidlow G, Wood JP, et al. 2012. Definition of glaucoma: clinical and experimental concepts. *Clin Experiment Ophthalmol,* 40**,** 341-9.

Cazzola M, Puxeddu E, Bettoncelli G, et al. 2011. The prevalence of asthma and COPD in Italy: a practice-based study. *Respir Med,* 105**,** 386-91.

Cazzola M, Calzetta L, Bettoncelli G, et al (2012) Cardiovascular disease in asthma and COPD: a population-based retrospective cross-sectional study. Respir Med; 106(2):249-56.

Cricelli C, Mazzaglia G, Samani F, et al. 2003. Prevalence estimates for chronic diseases in Italy: exploring the differences between self-report and primary care databases. *J Public Health Med,* 25**,** 254-7.

Curkendall SM, Lanes S, De Luise C, et al. 2006. Chronic obstructive pulmonary disease severity and cardiovascular outcomes. *Eur J Epidemiol,* 21**,** 803-13.

Dickstein K, Cohen-Solal A, Filippatos G, et al. 2008. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J,* 29**,** 2388-442.

Divo M, Cote C, de Torres JP, et al (2012) Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med; 186(2):155-61.

Dong Yaa-Hui LH-H, Shau Wen-Yi, Wu Yun-Chun, Chang Chia-Hsuin, Lai Mei-Shu 2012. Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease; systematic review and mixed treatment comparison meta-analysis of randomised controlled trials. *Thorax*.

Easton JD, Saver J L, Albers GW, et al. 2009. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke,* 40**,** 2276-93.

Ehrenstein V., Antonsen S. & Pedersen L. 2010. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. *Clin Epidemiol,* 2**,** 273-9.

Eisner MD, Trupin L, Katz PP, et al. 2005. Development and validation of a survey-based COPD severity score. *Chest,* 127**,** 1890-7.

EMA 2005. GUIDELINE ON THE EVALUATION OF THE PHARMACOKINETICS OF MEDICINAL PRODUCTS IN PATIENTS WITH IMPAIRED HEPATIC FUNCTION**,** 1-10.

EMA 2013. The ENCePP Code of Conduct – revision 3/EMA/929209/2011.

Feary JR, Rodrigues LC, Smith CJ, et al (2010) Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care. Thorax; 65:956-62.

Filippi A., Vanuzzo D., Bignamini AA, et al. 2005. The database of Italian general practitioners allows a reliable determination of the prevalence of myocardial infarction. *Ital Heart J,* 6**,** 311-4.

Fox K, Garcia MA, Ardissino D, et al. 2006. Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. *Eur Heart J,* 27**,** 1341-81.

Garcia-Gil Mdel M., Hermosilla E, Prieto-Alhambra D, et al. 2011. Construction and validation of a scoring system for the selection of high-quality data in a Spanish population primary care database (SIDIAP). *Inform Prim Care,* 19**,** 135-45.

García-Olmos L, Alberquilla A, Ayala V, et al (2013) Comorbidity in patients with chronic obstructive pulmonary disease in family practice: a cross sectional study. BMC Fam Pract; 14:11 (Internet) Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3556139/pdf/1471-2296-14-11.pdf> (Accessed 04 September 2014).

GOLD 2011. Global Strategy for Diagnosis, Management, and Prevention of COPD.

GOLD 2011. Global Strategy for Diagnosis, Management, and Prevention of COPD.

Goldstein LB, Bushnell CD, Adams RJ, et al. 2011. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke,* 42**,** 517-84.

Halbert RJ, Natoli JL, Gano A, et al. 2006. Global burden of COPD: systematic review and meta-analysis. *Eur Respir J,* 28**,** 523-32.

ISPE 2008. Guidelines for good pharmacoepidemiology practices (GPP). *Pharmacoepidemiol Drug Saf,* 17**,** 200-8.

Jara M, Lanes SF, Wentworth C, 3rd, et al. 2007. Comparative safety of long-acting inhaled bronchodilators: a cohort study using the UK THIN primary care database. *Drug Saf,* 30**,** 1151-60.

Jara M, Wentworth C, 3rd & Lanes, S. 2012. A new user cohort study comparing the safety of long-acting inhaled bronchodilators in COPD. *BMJ Open,* 2.

Juliao AA, Plata M, Kazzazi A, et al. 2012. American Urological Association and European Association of Urology guidelines in the management of benign prostatic hypertrophy: revisited. Curr Opin Urol, 22(1):34-9

Lee TA, Pickard AS, Au DH, et al. 2008. Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. *Ann Intern Med,* 149**,** 380-90.

Levey AS & Coresh J. 2012. Chronic kidney disease. *Lancet,* 379**,** 165-80.

Levey AS, Stevens LA, Schmid CH, et al. 2009. A new equation to estimate glomerular filtration rate. *Ann Intern Med,* 150**,** 604-12.

Lewis JD, Schinnar R, Bilker WB, et al. 2007. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiol Drug Saf,* 16**,** 393-401.

Michele TM, Pinheiro S & Iyasu S 2010. The Safety of Tiotropium - The FDA's Conclusions. *N Engl J Med,* 363**,** 1097-1099.

Pauwels RA, Buist AS, Calverley PM, et al. 2001. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med,* 163**,** 1256-76.

Schneider C, Bothner U, Jick SS, et al (2010) Chronic obstructive pulmonary disease and the risk of cardiovascular diseases. Eur J Epidemiol; 25(4):253-60.

Singh S., Loke Y. K., Enright P. L., et al. 2011. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials. *BMJ,* 342**,** d3215.

Singh S., Loke Y. K. & Furberg CD. 2008. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Jama,* 300**,** 1439-50.

Soriano JB, Maier WC, Visick G, et al. 2001. Validation of general practitioner-diagnosed COPD in the UK General Practice Research Database. *Eur J Epidemiol,* 17**,** 1075-80.

Suruki RY, Sampson TJ, Muellerova H, et al (2009) Examination of corrected QT intervals among participants with COPD in NHANES III. Am J Respir Crit Care Med; 179:A4529 [abstract] (Internet) Available from: <http://www.atsjournals.org/doi/pdf/10.1164/ajrccm-conference.2009.179.1_MeetingAbstracts.A4529> (Accessed 04 September 2014).

Thygesen K, Alpert JS, Jaffe AS, et al. 2012. Third universal definition of myocardial infarction. *Eur Heart J,* 33**,** 2551-2567.

Verhamme KM, Afonso AS, Van Noord C, et al. 2012. Tiotropium Handihaler and the risk of cardio- or cerebrovascular events and mortality in patients with COPD. *Pulm Pharmacol Ther,* 25**,** 19-26.

Verhamme KM, Sturkenboom MC, Stricker BH, et al. 2008. Drug-induced urinary retention: incidence, management and prevention. *Drug Saf,* 31**,** 373-88.

Vlug AE, Van Der Lei J, Mosseveld BM, et al. 1999. Postmarketing surveillance based on electronic patient records: the IPCI project. *Methods Inf Med,* 38**,** 339-44.

Voordouw AC, Sturkenboom MC, Dieleman JP, et al. 2004. Annual revaccination against influenza and mortality risk in community-dwelling elderly persons. *JAMA,* 292**,** 2089-95.

WHO Expert Committtee (2008). The selection and use of essential medicines. *World Health Organ Tech Rep Ser***,** backcover, vii-174.

Zipes DP, Camm AJ, Borggrefe M, et al 2006. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). *J Am Coll Cardiol,* 48**,** e247-346.

Annex 1 – List of stand-alone documents

None.

Annex 2 – ENCePP checklist for study protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

London, 25 July 2011
Doc.Ref. EMEA/540136/2009

ENCePP Checklist for Study Protocols (Revision 1)

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

The purpose of the Checklist developed by ENCePP is to stimulate consideration of important epidemiological principles when designing a pharmacoepidemiological or pharmacovigilance study and writing a study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. ENCePP welcomes innovative designs and new methods of research. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology (http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideofMethStaENCePPGuid.pdf) 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)	☒	☐	☐	17-18
1.1.2 The objectives of the study?	☒	☐	☐	18-19
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)	☒	☐	☐	19-20
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?	☒	☐	☐	19-20
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	20
2.2.2 Age and sex?	☐	☒	☐	
2.2.3 Country of origin?	☒	☐	☐	19-20
2.2.4 Disease/indication?	☒	☐	☐	17-18
2.2.5 Co-morbidity?	☒	☐	☐	25

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☒	☐	☐	20

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	18-19
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	19
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?	☒	☐	☐	30-32
3.5 Is statistical power calculated?	☐	☐	☒	

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)	☒	☐	☐	21-22
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?	☒	☐	☐	22-25

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☒	☐	☐	21-22
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.)	☒	☐	☐	22-25
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	Annex 4;73-108
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)	☒	☐	☐	Annex 3;48-72
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	32-33

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)	☒	☐	☐	21-22
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)	☒	☐	☐	21-22
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	21-22
5.4 Is exposure classified based on biological mechanism of action?	☒	☐	☐	21-22

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☐	☐	☒	
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?	☒	☐	☐	34-35
7.1.2 Information biases?	☒	☐	☐	34-35
(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?	☒	☐	☐	34-35

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?	☒	☐	☐	33
8.3 Are descriptive analyses included?	☒	☐	☐	33
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)	☒	☐	☐	32-33
9.2 Are methods of quality assurance described?	☒	☐	☐	34
9.3 Does the protocol describe quality issues related to the data source(s)?	☒	☐	☐	25-30
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	30-32
9.5 Does the protocol specify timelines for				
9.5.1 Study start?	☒	☐	☐	17
9.5.2 Study progress? (e.g. end of data collection, other milestones)	☒	☐	☐	17
9.5.3 Study completion?	☒	☐	☐	17
9.5.4 Reporting? (i.e. interim reports, final study report)	☒	☐	☐	17
9.6 Does the protocol include a section to document	☒	☐	☐	14

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
future amendments and deviations?				
9.7 Are communication methods to disseminate results described?	☒	☐	☐	36
9.8 Is there a system in place for independent review of study results?	☒	☐	☐	35

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

Comments:

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

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

Date: 05 September 2014

Signature: _____

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

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

Annex 3 – Exposure and concomitant medication definition

NVA237

	ATC code	Multilex id code
NVA237	R03BB06	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

Single-ingredient short-acting β2 agonists

R03AC02 Salbutamol

R03AC03 Terbutaline

R03AC04 Fenoterol

Long-acting β2 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 (adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics)

R03AK01 Epinephrine and other drugs for obstructive airway diseases

R03AK02 Isoprenaline and other drugs for obstructive airway diseases

R03AK04 Salbutamol and sodium cromoglycate

R03AK05 Reproterol and sodium cromoglycate R03AK06 Salmeterol and fluticasone

R03AK07 Formoterol and budesonide

R03AK08 Formoterol and beclomethasone

R03AK09 Formoterol and momethasone

R03AK10 Vilanterol and fluticasone furoate

R03AK11 Formoterol and fluticasone

Fixed combinationtherapy (adrenergics in combination with anticholinergics)

R03AL01 Fenoterol and ipratropium bromide

R03AL02 Salbutamol and ipratropium bromide

R03AL03 Vilanterol and umeclidinium bromide

R03AL04 Indacaterol+glycopyrronium bromide

Oral ß2-agonists

R03CC02 Salbutamol

R03CC03 Terbutaline

R03CC04 Fenoterol

R03CC05 Hexoprenaline

R03CC06 Isoetarine

R03CC07 Pirbuterol

R03CC08 Procaterol

R03CC09 Tretoquinol

R03CC10 Carbuterol

R03CC11 Tulobuterol

R03CC12 Bambuterol

R03CC13 Clenbuterol

R03CC14 Reproterol

R03CC53 Terbutaline, combinations

QR03CC90 Clenbuterol, combinations

Leukotriene receptor antagonists (LTRA)

R03DC01 Zafirlukast

R03DC02 Pranlukast

R03DC03 Montelukast

R03DC04 Ibudilast

Concomitant use of drugs with anticholinergic action

Antipsychotic drugs

N05AA Phenothiazines with aliphatic side-chain

N05AA01 Chlorpromazine

N05AA02 Levomepromazine

N05AA03 Promazine

N05AA04 Acepromazine

N05AA05 Trifluprom azine

N05AA06 Cyamemazine

N05AA07 Chlorproethazine

N05AB Phenothiazines with piperazine structure

N05AB01 Dixyrazine

N05AB02 Fluphenazine

N05AB03 Perphenazine

N05AB04 Prochlorperazine

N05AB05 Thiopropazate

N05AB06 Trifluoperazine

N05AB07 Acetophenazine

N05AB08 Thioproperazine

N05AB09 Butaperazine

N05AB10 Perazine

N05AC Phenothiazines with piperidine structure

N05AC01 Periciazine

N05AC02 Thioridazine

N05AC03 Mesoridazine

N05AC04 Pipotiazine

N05AD Butyrophenone derivatives

N05AD01 Haloperidol

N05AD02 Trifluperidol

N05AD03 Melperone

N05AD04 Moperone

N05AD05 Pipamperone

N05AD06 Bromperidol

N05AD07 Benperidol

N05AD08 Droperidol

N05AD09 Fluanisone

QN05AD90 Azaperone

N05AE Indole derivatives

N05AE01 Oxypertine

N05AE02 Molindone

N05AE03 Sertindole

N05AE04 Ziprasidone

N05AF Thioxanthene derivative

N05AF01 Flupentixol

N05AF02 Clopenthixol

N05AF03 Chlorprothixene

N05AF04 Thiothixene

N05AF05 Zuclopenthixol

N05AG Diphenylbutylpiperidine derivatives

N05AG01 Fluspirilene

N05AG02 Pimozide

N05AG03 Penfluridol

N05AH Diazepines, oxazepines, thiazepines and oxepines

N05AH01 Loxapine

N05AH02 Clozapine

N05AH03 Olanzapine

N05AH04 Quetiapine

N05AH05 Asenapine

N05AH06 Clotiapine

QN05AK Neuroleptics, in tardive dyskinesia

N05AL Benzamides

N05AL01 Sulpiride

N05AL02 Sultopride

N05AL03 Tiapride

N05AL04 Remoxipride

N05AL05 Amisulpride

N05AL06 Veralipride

N05AL07 Levosulpiride

N05AN Lithium

N05AN01 Lithium

N05AX Other antipsychotics

N05AX07 Prothipendyl

N05AX08 Risperidone

N05AX10 Mosapramine

N05AX11 Zotepine

N05AX12 Aripiprazole

N05AX13 Paliperidone

N05AX14 Iloperidone

QN05AX90 Amperozide

Tricyclic and tetracyclic antidepressant agents

N06AA Non-selective monoamine reuptake inhibitors

N06AA01 Desipramine

N06AA02 Imipramine

N06AA03 Imipramine oxide

N06AA04 Clomipramine

N06AA05 Opipramol

N06AA06 Trimipramine

N06AA07 Lofepramine

N06AA08 Dibenzepin

N06AA09 Amitriptyline

N06AA10 Nortriptyline

N06AA11 Protriptyline

N06AA12 Doxepin

N06AA13 Iprindole

N06AA14 Melitracen

N06AA15 Butriptyline

N06AA16 Dosulepin

N06AA17 Amoxapine

N06AA18 Dimetacrine

N06AA19 Amineptine

N06AA21 Maprotiline

N06AA23 Quinupramine

N06AX Other antidepressants

N06AX01 Oxitriptan

N06AX02 Tryptophan

N06AX03 Mianserin

N06AX04 Nomifensine

N06AX05 Trazodone

N06AX06 Nefazodone

N06AX07 Minaprine

N06AX08 Bifemelane

N06AX09 Viloxazine

N06AX10 Oxaflozane

N06AX11 Mirtazapine

N06AX12 Bupropion

N06AX13 Medifoxamine

N06AX14 Tianeptine

N06AX15 Pivagabine

N06AX16 Venlafaxine

N06AX17 Milnacipran

N06AX18 Reboxetine

N06AX19 Gepirone

N06AX21 Duloxetine

N06AX22 Agomelatine

N06AX23 Desvenlafaxine

N06AX24 Vilazodone

N06AX25 Hyperici herba

N06AX90 Selegiline

Disopyramide

C01BA03 Disopyramide

Antispasmodics

A03AA Synthetic anticholinergics, esters with tertiary amino group

A03AA01 Oxyphencyclimine

A03AA03 Camylofin

A03AA04 Mebeverine

A03AA05 Trimebutine

A03AA06 Rociverine

A03AA07 Dicycloverine

A03AA08 Dihexyverine

A03AA09 Difemerine

A03AA30 Piperidolate

A03AB Synthetic anticholinergics, quaternary ammonium compounds

A03AB01 Benzilone

A03AB02 Glycopyrronium

A03AB03 Oxyphenonium

A03AB04 Penthienate

A03AB05 Propantheline

A03AB06 Otilonium bromide

A03AB07 Methantheline

A03AB08 Tridihexethyl

A03AB09 Isopropamide

A03AB10 Hexocyclium

A03AB11 Poldine

A03AB12 Mepenzolate

A03AB13 Bevonium

A03AB14 Pipenzolate

A03AB15 Diphemanil

A03AB16 (2-benzhydryloxyethyl) diethyl-methylammonium iodide

A03AB17 Tiemonium iodide

A03AB18 Prifinium bromide

A03AB19 Timepidium bromide

A03AB21 Fenpiverinium

A03AB53 Oxyphenonium, combinations

QA03AB90 Benzetimide

QA03AB92 Carbachol

QA03AB93 Neostigmin

Anti-Parkinson drugs

N04A Anticholinergic agents

N04AA Tertiary amines

N04AA01 Trihexyphenidyl

N04AA02 Biperiden

N04AA03 Metixene

N04AA04 Procyclidine

N04AA05 Profenamine

N04AA08 Dexetimide

N04AA09 Phenglutarimide

N04AA10 Mazaticol

N04AA11 Bornaprine

N04AA12 Tropatepine

N04AB Ethers chemically close to antihistamines

N04AB01 Etanautine

N04AB02 Orphenadrine (chloride)

N04AC Ethers of tropine or tropine derivatives

N04AC01 Benzatropine

N04AC30 Etybenzatropine

Choline-esterase inhibitors

N07AA Anticholinesterases

N07AA01 Neostigmine

N07AA02 Pyridostigmine

N07AA03 Distigmine

N07AA30 Ambenonium

N07AA51 Neostigmine, combinations

Atropine

A03BA01 Atropine

H1-antihistamines

R06AA Aminoalkyl ethers

R06AA01 Bromazine

R06AA02 Diphenhydramine

R06AA04 Clemastine

R06AA06 Chlorphenoxamine

R06AA07 Diphenylpyraline

R06AA08 Carbinoxamine

R06AA09 Doxylamine

R06AA52 Diphenhydramine, combinations

R06AA54 Clemastine, combinations

R06AA56 Chlorphenoxamine, combinations

R06AA57 Diphenylpyraline, combinations

R06AA59 Doxylamine, combinations

R06AB Substituted alkylamines

R06AB01 Brompheniramine

R06AB02 Dexchlorpheniramine

R06AB03 Dimetindene

R06AB04 Chlorphenamine

R06AB05 Pheniramine

R06AB06 Dexbrompheniramine

R06AB07 Talastine

R06AB51 Brompheniramine, combinations

R06AB52 Dexchlorpheniramine, combinations

R06AB54 Chlorphenamine, combinations

R06AB56 Dexbrompheniramine, combinations

R06AC Substituted ethylene diamines

R06AC01 Mepyramine

R06AC02 Histapyrrodine

R06AC03 Chloropyramine

R06AC04 Tripelennamine

R06AC05 Methapyrilene

R06AC06 Thonzylamine

R06AC52 Histapyrrodine, combinations

R06AC53 Chloropyramine, combinations

R06AD Phenothiazine derivatives

R06AD01 Alimemazine

R06AD02 Promethazine

R06AD03 Thiethylperazine

R06AD04 Methdilazine

R06AD05 Hydroxyethylpromethazine

R06AD06 Thiazinam

R06AD07 Mequitazine

R06AD08 Oxomemazine

R06AD09 Isothipendyl

R06AD52 Promethazine, combinations

R06AD55 Hydroxyethylpromethazine, combinations

R06AE Piperazine derivatives

R06AE01 Buclizine

R06AE03 Cyclizine

R06AE04 Chlorcyclizine

R06AE05 Meclozine

R06AE06 Oxatomide

R06AE07 Cetirizine

R06AE09 Levocetirizine

R06AE51 Buclizine, combinations

R06AE53 Cyclizine, combinations

R06AE55 Meclozine, combinations

R06AK Combinations of antihistamines

R06AX Other antihistamines for systemic use

R06AX01 Bamipine

R06AX02 Cyproheptadine

R06AX03 Thenalidine

R06AX04 Phenindamine

R06AX05 Antazoline

R06AX07 Triprolidine

R06AX08 Pyrrobutamine

R06AX09 Azatadine

R06AX11 Astemizole

R06AX12 Terfenadine

R06AX13 Loratadine

R06AX15 Mebhydrolin

R06AX16 Deptropine

R06AX17 Ketotifen

R06AX18 Acrivastine

R06AX19 Azelastine

R06AX21 Tritoqualine

R06AX22 Ebastine

R06AX23 Pimethixene

R06AX24 Epinastine

R06AX25 Mizolastine

R06AX26 Fexofenadine

R06AX27 Desloratadine

R06AX28 Rupatadine

R06AX29 Bilastine

R06AX53 Thenalidine, combinations

R06AX58 Pyrrobutamine, combinations

Anticholinergics for treatment of overactive bladder

G04BD Urinary antispasmodics

G04BD01 Emepronium

G04BD02 Flavoxate

G04BD03 Meladrazine

G04BD04 Oxybutynin

G04BD05 Terodiline

G04BD06 Propiverine

G04BD07 Tolterodine

G04BD08 Solifenacin

G04BD09 Trospium

G04BD10 Darifenacin

G04BD11 Fesoterodine

Antibiotics (if given for the treatment of lower respiratory tract infections = acute bronchitis, pneumonia)(J01)

J01AA Tetracyclines (J01A)

J01AA01 Demeclocycline

J01AA02 Doxycycline

J01AA03 Chlortetracycline

J01AA04 Lymecycline

J01AA05 Metacycline

J01AA06 Oxytetracycline

J01AA07 Tetracycline

J01AA08 Minocycline

J01AA09 Rolitetracycline

J01AA10 Penimepicycline

J01AA11 Clomocycline

J01AA12 Tigecycline

J01AA20 Combinations of tetracyclines

J01AA53 Chlortetracycline, combinations

J01AA56 Oxytetracycline, combinations

J01B Amphenicols (J01B)

J01BA

J01BA01 Chloramphenicol

J01BA02 Thiamphenicol

J01BA52 Thiamphenicol, combinations

J01BA90 Florfenicol

J01BA99 Amphenicols, combinations

J01C Beta-lactam antibacterials, penicillins (J01C)

J01CA Penicillins with extended spectrum

J01CA01 Ampicillin

J01CA02 Pivampicillin

J01CA03 Carbenicillin

J01CA04 Amoxicillin

J01CA05 Carindacillin

J01CA06 Bacampicillin

J01CA07 Epicillin

J01CA08 Pivmecillinam

J01CA09 Azlocillin

J01CA10 Mezlocillin

J01CA11 Mecillinam

J01CA12 Piperacillin

J01CA13 Ticarcillin

J01CA14 Metampicillin

J01CA15 Talampicillin

J01CA16 Sulbenicillin

J01CA17 Temocillin

J01CA18 Hetacillin

J01CA19 Aspoxicillin

J01CA20 Combinations

J01CA51 Ampicillin, combinations

J01CE Beta-lactamase-sensitive penicillin

J01CE01 Benzylpenicillin

J01CE02 Phenoxymethylpenicillin

J01CE03 Propicillin

J01CE04 Azidocillin

J01CE05 Pheneticillin

J01CE06 Penamecillin

J01CE07 Clometocillin

J01CE08 Benzathine benzylpenicillin

J01CE09 Procaine benzylpenicillin

J01CE10 Benzathine phenoxymethylpenicillin

J01CE30 Combinations

J01CE90 Penethamate hydroiodide

J01CE91 Benethamine penicillin

J01CF Beta-lactamase-resistant penicillins

J01CF01 Dicloxacillin

J01CF02 Cloxacillin

J01CF03 Methicillin

J01CF04 Oxacillin

J01CF05 Flucloxacillin

J01CF06 Nafcillin

J01CG Beta-lactamase inhibitors

J01CG01 Sulbactam

J01CG02 Tazobactam

J01CR Combinations of penicillins, including beta-lactamase inhibitors

J01CR01 Ampicillin and enzyme inhibitor

J01CR02 Amoxicillin and enzyme inhibitor

J01CR03 Ticarcillin and enzyme inhibitor

J01CR04 Sultamicillin

J01CR05 Piperacillin and enzyme inhibitor

J01CR50 Combinations of penicillins

J01D Other beta-lactam antibacterials (J01D)

J01DB First-generation cephalosporins

J01DB01 Cefalexin

J01DB02 Cefaloridine

J01DB03 Cefalotin

J01DB04 Cefazolin

J01DB05 Cefadroxil

J01DB06 Cefazedone

J01DB07 Cefatrizine

J01DB08 Cefapirin

J01DB09 Cefradine

J01DB10 Cefacetrile

J01DB11 Cefroxadine

J01DB12 Ceftezole

J01DC Second-generation cephalosporins

J01DC01 Cefoxitin

J01DC02 Cefuroxime

J01DC03 Cefamandole

J01DC04 Cefaclor

J01DC05 Cefotetan

J01DC06 Cefonicide

J01DC07 Cefotiam

J01DC08 Loracarbef

J01DC09 Cefmetazole

J01DC10 Cefprozil

J01DC11 Ceforanide

J01DC12 Cefminox

J01DC13 Cefbuperazone

J01DC14 Flomoxef

J01DD Third-generation cephalosporins

J01DD01 Cefotaxime

J01DD02 Ceftazidime

J01DD03 Cefsulodin

J01DD04 Ceftriaxone

J01DD05 Cefmenoxime

J01DD06 Latamoxef

J01DD07 Ceftizoxime

J01DD08 Cefixime

J01DD09 Cefodizime

J01DD10 Cefetamet

J01DD11 Cefpiramide

J01DD12 Cefoperazone

J01DD13 Cefpodoxime

J01DD14 Ceftibuten

J01DD15 Cefdinir

J01DD16 Cefditoren

J01DD17 Cefcapene

J01DD54 Ceftriaxone, combinations

J01DD62 Cefoperazone, combinations

J01DD90 Ceftiofur

J01DD91 Cefovecin

J01DE Fourth-generation cephalosporins

J01DE01 Cefepime

J01DE02 Cefpirome

J01DE03 Cefozopran

J01DE90 Cefquinome

J01DF Monobactams

J01DF01 Aztreonam

J01DF02 Carumonam

J01DH Carbapenems

J01DH02 Meropenem

J01DH03 Ertapenem

J01DH04 Doripenem

J01DH05 Biapenem

J01DH51 Imipenem and enzyme inhibitor

J01DH55 Panipenem and betamipron

J01DI Other cephalosporins and penems

J01DI01 Ceftobiprole medocaril

J01DI02 Ceftaroline fosamil

J01DI03 Faropenem

J01E Sulfonamides and trimethoprim (J01E)

J01EA Trimethoprim and derivatives

J01EA01 Trimethoprim

J01EA02 Brodimoprim

J01EA03 Iclaprim

J01EB Short-acting sulfonamides

J01EB01 Sulfaisodimidine

J01EB02 Sulfamethizole

J01EB03 Sulfadimidine

J01EB04 Sulfapyridine

J01EB05 Sulfafurazole

J01EB06 Sulfanilamide

J01EB07 Sulfathiazole

J01EB08 Sulfathiourea

J01EB20 Combinations

J01EC Intermediate-acting sulfonamides

J01EC01 Sulfamethoxazole

J01EC02 Sulfadiazine

J01EC03 Sulfamoxole

J01EC20 Combinations

J01ED Long-acting sulfonamides

J01ED01 Sulfadimethoxine

J01ED02 Sulfalene

J01ED03 Sulfametomidine

J01ED04 Sulfametoxydiazine

J01ED05 Sulfamethoxypyridazine

J01ED06 Sulfaperin

J01ED07 Sulfamerazine

J01ED08 Sulfaphenazole

J01ED09 Sulfamazon

J01ED20 Combinations

J01EE Combinations of sulfonamides and trimethoprim, including derivatives

J01EE01 Sulfamethoxazole and trimethoprim

J01EE02 Sulfadiazine and trimethoprim

J01EE03 Sulfametrole and trimethoprim

J01EE04 Sulfamoxole and trimethoprim

J01EE05 Sulfadimidine and trimethoprim

J01EE06 Sulfadiazine and tetroxoprim

J01EE07 Sulfamerazine and trimethoprim

J01EQ Sulfonamides

J01EQ01 Sulfapyrazole

J01EQ02 Sulfamethizole

J01EQ03 Sulfadimidine

J01EQ04 Sulfapyridine

J01EQ05 Sulfafurazole

J01EQ06 Sulfanilamide

J01EQ07 Sulfathiazole

J01EQ08 Sulfaphenazole

J01EQ09 Sulfadimethoxine

J01EQ10 Sulfadiazine

J01EQ11 Sulfamethoxazole

J01EQ12 Sulfachlorpyridazine

J01EQ13 Sulfadoxine

J01EQ14 Sulfatroxazol

J01EQ15 Sulfamethoxypyridazine

J01EQ16 Sulfazuinoxaline

J01EQ17 Sulfamerazine

J01EQ18 Sulfamonomethoxine

J01EQ19 Sulfalene

J01EQ21 Sulfacetamide

J01EQ30 Combinations of sulfonamides

J01EQ59 Sulfadimethoxine, combinations

J01EW Combinations of sulfonamides and trimethoprim, including derivatives

J01EW03 Sulfadimidine and trimethoprim

J01EW09 Sulfadimethoxine and trimethoprim

J01EW10 Sulfadiazine and trimethoprim

J01EW11 Sulfamethoxazole and trimethoprime

J01EW12 Sulfachlorpyridazine and trimethoprim

J01EW13 Sulfadoxine and trimethoprim

J01EW14 Sulfatroxazol and trimethoprim

J01EW15 Sulfamethoxypyridazine and trimethoprim

J01EW16 Sulfaquinoxaline and trimethoprim

J01EW17 Sulfamonomethoxine and trimethoprim

J01EW18 Sulfamerazine and trimethoprim

J01EW30 Combinations of sulfonamides and trimethoprim

J01F Macrolides, lincosamides and streptogramins (J01F)

J01FA Macrolides

J01FA01 Erythromycin

J01FA02 Spiramycin

J01FA03 Midecamycin

J01FA05 Oleandomycin

J01FA06 Roxithromycin

J01FA07 Josamycin

J01FA08 Troleandomycin

J01FA09 Clarithromycin

J01FA10 Azithromycin

J01FA11 Miocamycin

J01FA12 Rokitamycin

J01FA13 Dirithromycin

J01FA14 Flurithromycin

J01FA15 Telithromycin

J01FA90 Tylosin

J01FA91 Tilmicosin

J01FA92 Tylvalosin

J01FA93 Kitasamycin

J01FA94 Tulathromycin

J01FA95 Gamithromycin

J01FA96 Tildipirosin

J01FF Lincosamides

J01FF01 Clindamycin

J01FF02 Lincomycin

J01FF52 Lincomycin, combinations

J01FG Streptogramins

J01FG01 Pristinamycin

J01FG02 Quinupristin/dalfopristin

J01FG90 Virginiamycin

J01G Aminoglycoside antibacterials (J01G)

J01GA Streptomycins

J01GA01 Streptomycin

J01GA02 Streptoduocin

J01GA90 Dihydrostreptomycin

J01GB Other aminoglycosides

J01GB01 Tobramycin

J01GB03 Gentamicin

J01GB04 Kanamycin

J01GB05 Neomycin

J01GB06 Amikacin

J01GB07 Netilmicin

J01GB08 Sisomicin

J01GB09 Dibekacin

J01GB10 Ribostamycin

J01GB11 Isepamicin

J01GB12 Arbekacin

J01GB13 Bekanamycin

J01GB90 Apramycin

J01GB91 Framycetin

J01M Quinolone antibacterials (J01M)

J01MA Fluoroquinolones

J01MA01 Ofloxacin

J01MA02 Ciprofloxacin

J01MA03 Pefloxacin

J01MA04 Enoxacin

J01MA05 Temafloxacin

J01MA06 Norfloxacin

J01MA07 Lomefloxacin

J01MA08 Fleroxacin

J01MA09 Sparfloxacin

J01MA10 Rufloxacin

J01MA11 Grepafloxacin

J01MA12 Levofloxacin

J01MA13 Trovafloxacin

J01MA14 Moxifloxacin

J01MA15 Gemifloxacin

J01MA16 Gatifloxacin

J01MA17 Prulifloxacin

J01MA18 Pazufloxacin

J01MA19 Garenoxacin

J01MA21 Sitafloxacin

J01MA90 Enrofloxacin

J01MA92 Danofloxacin

J01MA93 Marbofloxacin

J01MA94 Difloxacin

J01MA95 Orbifloxacin

J01MA96 Ibafloxacin

J01MA97 Pradofloxacin

J01MB Other quinolones

J01MB01 Rosoxacin

J01MB02 Nalidixic acid

J01MB03 Piromidic acid

J01MB04 Pipemidic acid

J01MB05 Oxolinic acid

J01MB06 Cinoxacin

J01MB07 Flumequine

J01MQ Quinoxalines

J01MQ01 Olaquindox

J01R Combinations of antibacterials (J01R)

J01RA Combinations of antibacterials

J01RA01 Penicillins, combinations with other antibacterials

J01RA02 Sulfonamides, combinations with other antibacterials (excluding trimethoprim)

J01RA03 Cefuroxime, combinations with other antibacterials

J01RA04 Spiramycin, combinations with other antibacterials

J01RA90 Tetracyclines, combinations with other antibacterials

J01RA91 Macrolides, combinations with other antibacterials

J01RA92 Amphenicols, combinations with other antibacterials

J01RA94 Lincosamides, combinations with other antibacterials

J01RA95 Polymyxins, combinations with other antibacterials

J01RA96 Quinolones, combinations with other antibacterials

J01RA97 Aminoglycosides, combinations with other antibacterials

J01RV Combinations of antibacterials and other substances

J01RV01 Antibacterials and corticosteroids

J01X Other antibacterials (J01X)

J01XA Glycopeptide antibacterials

J01XA01 Vancomycin

J01XA02 Teicoplanin

J01XA03 Telavancin

J01XA04 Dalbavancin

J01XA05 Oritavancin

J01XB Polymyxins

J01XB01 Colistin

J01XB02 Polymyxin B

J01XC Steroid antibacterials

J01XC01 Fusidic acid

J01XD Imidazole derivatives

J01XD01 Metronidazole

J01XD02 Tinidazole

J01XD03 Ornidazole

J01XE Nitrofuran derivatives

J01XE01 Nitrofurantoin

J01XE02 Nifurtoinol

QJ01XE90 Furazolidine

QJ01XQ Pleuromutilins

QJ01XQ01 Tiamulin

QJ01XQ02 Valnemulin

J01XX Other antibacterials

J01XX01 Fosfomycin

J01XX02 Xibornol

J01XX03 Clofoctol

J01XX04 Spectinomycin

J01XX05 Methenamine

J01XX06 Mandelic acid

J01XX07 Nitroxoline

J01XX08 Linezolid

J01XX09 Daptomycin

J01XX10 Bacitracin

QJ01XX55 Methenamine, combinations

QJ01XX93 Furaltadone

QJ01XX95 Novobiocin

Annex 4 – 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.

Annex 4.1 Definition of 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 comorbidities contribute to the overall severity in individual patients. A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production and/or a history of exposure to risk factors for the disease. Spirometry is required to make the diagnosis in this clinical context; the presence of a postbronchodilator FEV1/FVC < 0.70 confirms the presence of persistent airflow limitation and thus of COPD (GOLD 2011). In this DUS, we are interested in the indication of use of NVA237. 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 the outcomes of COPD.

Terms	ICD10	ICD9CM	Read Codes	ICPC
Chronic obstructive pulmonary disease, unspecified	J44.9			R95
Chronic airway obstruction		496.*		
Obstructive chronic bronchitis		491.2*	H312z00	
Chronic obstructive lung disease			H3...00	
Chronic obstructive airways disease			H3...11 H3z..00	
Other chronic obstructive pulmonary disease	J44			
Other specified chronic obstructive pulmonary disease	J44.8		Hyu31 H3z..11	
Chronic obstruct pulmonary dis with acute lower respiratory infection			H3y0.00	
Chronic obstructive pulmonary disease with acute exacerbation,	J44.1		H3y1.00	

unspecified				
Chronic obstructive pulmonary disease monitoring			66YB.00 66YB000 66YB100 66YD.00	
Mild chronic obstructive pulmonary disease			H36..00	
Moderate chronic obstructive pulmonary disease			H37..00	
Severe chronic obstructive pulmonary disease			H38..00	
Very severe chronic obstructive pulmonary disease			H39..00	
End stage chronic obstructive airways disease			H3A..00	
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 Chronic obstructive pulmonary disease does not disturb sleep			66Yg.00 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	
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 for the three different exposure cohorts on the basis of spirometry data or on the basis of a severity classification if spirometry is not available.

- If spirometry is available:

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

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

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

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

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

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

In addition, in accordance with the updated GOLD guidelines (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.

Since the COPD Assessment Test (CAT) is not performed routinely in clinical practice, and since a CAT score < 10 occurs only in the setting of screening programs in general

populations, all patients will be considered as COPD GOLD B or D patients: COPD GOLD B if FEV1 > 50% AND a history of ≤ 1 exacerbation in the previous year; COPD GOLD D if FEV1 ≤ 50% OR a history of ≥ 2 exacerbations in the previous year.

- If spirometry is not available:

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

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

Annex 4.2 Definition of Asthma

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

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

Terms	ICD10	ICD9CM	Read Codes	ICPC
Asthma	J45*	493.*	H33..	R96
Asthma, unspecified	J45.9	493.90	H33z	
Nonallergic asthma Intrinsic asthma	J45.1	493.1	H331z 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 Emergency admission, asthma			663y.00 8H2P.00	
Status asthmaticus	J46	493.91		
Extrinsic asthma with status asthmaticus		493.01		
Intrinsic asthma NOS		493.10		
Intrinsic asthma with status asthmaticus		493.11		
chronic obstructive asthma		493.2		
Other forms of asthma		493.8		
Asthma severity Mild asthma Moderate asthma Severe asthma			663V.00 663V100 663V200 663V300	
Asthma management Asthma monitoring Asthma monitoring due Asthma management plan given Change in asthma management plan Step up change in asthma management plan Step down change in asthma man Asthma annual review			661M100 661N100 663..11 66YE.00 663U.00 66Y5.00 66Y9.00 66YA.00 66YJ.00	

Asthma follow-up Asthma monitoring by nurse Asthma monitoring by doctor Patient has a written asthma personal action plan Asthma clinical management plan			66YK.00 66YQ.00 66YR.00 8CMA000 8CR0.00	
History of asthma Resolved asthma			14B4.00 2126200	
Induced asthma			173A.00 173c.00 173d.00 1780.00 1781.00 1782.00 1783.00 1784.00 1785.00 1786.00 1787.00 1788.00 1789.00 178A.00 178B.00	
Asthma and exercise			663e.00 663e000 663e100 663f.00 663w.00 663x.00	
Asthma currently dormant Asthma currently active			663h.00 663j.00	

Asthma treatment compliance satisfactory Asthma treatment compliance unsatisfactory			663n.00 663p.00	
Asthma disturbing sleep Asthma causing night waking Asthma disturbs sleep weekly Asthma disturbs sleep frequently Asthma not disturbing sleep Asthma never disturbs sleep Asthma night-time symptoms Asthma causes night time symptoms Asthma causes symptoms most nights Asthma never causes night symptoms			663N.00 663N000 663N100 663N200 663O.00 663O000 66YP.00 66Yq.00 66Yr.00 66Ys.00	
Asthma limits activities 1 to 2 times per month Asthma limits activities 1 to 2 times per week Asthma limits activities most days Asthma not limiting activities			663P000 663P100 663P200 663Q.00	
Asthma causes night symptoms 1 to 2 times per month Asthma never causes daytime symptoms Asthma causes daytime symptoms 1 to 2 times per month Asthma causes daytime symptoms 1 to 2 times per week Asthma causes daytime symptoms			663r.00 663s.00 663t.00 663u.00 663v.00	
Asthma prophylactic medication used			663W.00	

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

Annex 4.3 Definition of lower respiratory tract infection (eventname=LRTI)

Lower respiratory tract infection consists of both pneumonia and (acute) bronchitis

The following concepts of disease have been mapped through the Unified Medical Language System (UMLS) for lower respiratory tract infection.

Terms	**ICD10**	**ICD9CM**	**Read Codes**	**ICPC**
Pneumonia, unspecified	J18.9		X100E	R81
Bacterial pneumonia, unspecified	J15.9	482.9	X100H H22z.	
Viral pneumonia	J12.9	480 480.9	XE0YG H20z.	
Acute bronchitis Acute tracheo-bronchitis	J20 J20.9	466 466.0	H06.. XE0Xr H060z H0605	R78

Annex 4.4 Ischemic heart disease

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

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

Definition of Angina Pectoris

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

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

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

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

Terms	ICD10	ICD9CM	Read Codes	ICPC
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..	

Definition of Acute Myocardial Infarction (AMI)

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

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

Terms	ICD10	ICD9CM	Read Codes	ICPC
Cardiac infarction	I22*			
Cardiac infarction	I21*			
Acute myocardial infarction	I21*	410.*	G30z.	K75
Acute myocardial infarction, unspecified	I21.9	410.9		

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

Terms	ICD10	ICD9CM	Read Codes	ICPC
Acute myocardial infarction, of antero lateral wall		410.0	G300.	
Acute antero septal myocardial infarction			G3011	
Acute inferior myocardial infarction		410.4	G308.00	
Acute myocardial infarction, true posterior wall infarction		410.6		
True posterior myocardial infarction			G306.	
Acute myocardial infarction, of inferoposterior wall		410.3	G303.]	
Other specified anterior myocardial infarction			G301.]	
Acute transmural myocardial infarction of unspecified site	I21.3		Gyu34 G30X.00	
Acute transmural myocardial infarction of anterior wall	I21.0 I22.0			
Acute transmural myocardial infarction of inferior wall	I21.1 I21.19 I22.1			
Acute transmural myocardial infarction of other sites	I21.2 I21.29 I22.8			
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		

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

Annex 4.5 Cardiac arrhythmia

Cardiac arrhythmia as comorbidity 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 Society 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

Terms	ICD10	ICD9CM	Read Codes	ICPC
Atrial fibrillation		427.31	G5730	
Atrial fibrillation and flutter	I48	427.3	G573.	K78
Atrial fibrillation and flutter NOS			G573z	
Unspecified atrial fibrillation and atrial flutter	I48.9			
AF - Paroxysmal atrial fibrillation			G573200	K79.01
Chronic atrial fibrillation	I48.2			
Persistent atrial fibrillation	I48.1		G573500	
Permanent atrial fibrillation	I48.2		G573400	
Non-rheumatic atrial fibrillation			G573300	
ECG: atrial fibrillation			3272.	
H/O: atrial fibrillation			14AN.00	
Atrial fibrillation resolved			212R.00	
Atrial fibrillation monitoring			662S.00	
			6A9..00	
			8HTy.00	
			9hF1.00	
			9Os..	

Supraventricular tachycardia (SVT)

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

Terms	ICD10	ICD9CM	Read Codes	ICPC
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

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

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	K84.02
			G5610	
Atrioventricular and left bundle-branch block	I44			
Mobitz (type) II atrioventricular block		426.12	G5612	
Other second degree atrioventricular block		426.13		
ECG: complete atrioventricular block			3298.	
Partial atrioventricular block			G561.	
ECG: partial atrioventricular block			3294.	
ECG: partial atrioventricular block - 2:1			3295.	
ECG: partial atrioventricular block - 3:1			3296.	

Premature depolarization

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

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

Terms	ICD10	ICD9CM	Read codes	ICPC
Extrasystole	I49.4	427.6	G576z00	K80
	I49.40		G576011	
	I49.49			
Supraventricular extrasystole		427.61	G576100	K80.01
Ventricular extrasystole	I49.3		G576500	K80.02
			G576200	
Atrial premature depolarization	I49.1		G576300	
Junctional premature depolarization	I49.2		G576400	
[X]Other and unspecified premature depolarization			Gyu5Z00	
ECG: ectopic beats		427.6	326..00	
ECG: extrasystole			3262.00	
ECG: ventricular ectopics			3263.00	
ECG: atrial ectopics			3264.00	
ECG: ectopic beats NOS			326Z.00	
Ectopic beats			G576.00	
Premature beats			G576.11	
Ectopic beats unspecified			G576000	

Annex 4.6 Definition of Heart Failure

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

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

Terms	ICD10	ICD9CM	Read Codes	ICPC

Terms	ICD10	ICD9CM	Read Codes	ICPC
Heart failure	I50	428*	G58..	K77
Heart failure, unspecified	I50.9	428.9		
Congestive heart failure	I50.0	428.0	G580.00	
Congestive heart disease	I50.9			
Left ventricular failure	I50.1	428.1	G581.00	
Acute heart failure			G582.	
			G5800	
Admit heart failure emergency			8H2S.00	
Chronic congestive heart failure			G5801	
H/O: heart failure			14A6.00	
			14AM.00	
Hypertensive heart disease with (congestive) heart failure	I11.0	402.01	G21z011	
		402.91		
Hypertensive heart and renal disease with (congestive) heart failure	I13.0	402.11	G232.00	
Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	I13.2	404.01		
		404.91		
Heart failure confirmed			1O1..00	
Heart failure resolved			2126400	
Heart failure management			661M500	
			661N500	
New York Heart Association classification - class II			662g.00	
New York Heart Association classification - class III			662h.00	
New York Heart Association classification - class IV			662i.00	
New York Heart Assoc classification heart failure symptoms			ZRad.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
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	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Heart transplant failure and rejection			SP08400	
Heart failure as a complication of care			SP11111	

Annex 4.7 Cerebrovascular events

For this study, cerebrovascular events encompass stroke and TIA. The definitions of stroke and TIA and their respective disease codes are described below.

Definition of Stroke

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

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

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

Terms	ICD10	ICD9CM	Read Codes	ICPC
Stroke, not specified as hemorrhage or	I64			
Stroke NOS	I63.9			K90
Intracerebral haemorrhage		431	G61..	
Cerebrovascular accident (CVA)			G66..13	
Stroke and cerebrovascular accident unspecified			G66..00	
Stroke NOS			G66..12	
Sequelae of stroke, not specified as hemorrhage or infarction	I69.4		Gyu6C	
Brain stem stroke syndrome	G46.3		G663.	
Cerebellar stroke syndrome	G46.4		G664.	

Terms	ICD10	ICD9CM	Read Codes	ICPC
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 without residual deficits	Z86.73	V12.54		
Management/monitoring of stroke			661M700	
			661N700	
			662e.00	
			662e.11	
			662M.00	
			662M100	
			662M200	
			662o.00	
			9Om..00	
			9Om0.00	
			9Om1.00	
			9Om2.00	
			9Om3.00	
			9Om4.00	
Delivery of rehabilitation for stroke			7P24200	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Stroke referral			8HBJ.00	
			8HTQ.00	
			8IEC.00	
Seen in stroke clinic			9N0p.00	
Quality indicators stroke			9h2..00	
			9h21.00	
			9h22.00	
Sequelae of cerebral infarction		438.*	G683.00	
Sequelae of stroke, not specified as haemorrhage or infarction			G68X.00/Gyu6C00	
Cerebral infarction due unspecified occlusion/stenosis of pre-cerebral arteries		433.*	G6W..00/Gyu6300	
Cerebral infarction due to unspecified occlusion/stenosis of cerebral arteries		434.*	G6X..00/Gyu6G00	
[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.

Definition of 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			

Terms	ICD10	ICD9CM	Read Codes	ICPC
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

Annex 4.8 Definition of chronic kidney disease(Levey and Coresh 2012)

Chronic kidney disease is defined as either kidney damage or glomerular filtration rate <60 mL/min/1.73 m^2 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.

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	585.9	1Z1..	U99
	N18.9	583*	K05..13	
		585*		
		586*		
Hypertensive chronic kidney disease	I12	403		
Chronic kidney disease, Stage I		585.1	1Z10.00	
			1Z17.00	
			1Z18.00	
			1Z18.11	
			K051.00	
End stage renal disease		585.6	K050.00	
			K0D..00	
Chronic kidney disease, Stage 5		585.5	1Z14.00	
			1Z1K.00	
			1Z1K.11	
			1Z1L.00	
			1Z1L.11	
			K055.00	
Hypertensive chronic kidney disease, malignant		403.0		
Hypertensive heart and chronic kidney disease	I13	404		
Chronic kidney disease, stage 2 (mild)	N18.2	585.2	1Z11.00	
			1Z19.00	
			1Z19.11	
			1Z1A.00	
			1Z1A.11	
			K052.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Chronic kidney disease, stage 3 (moderate)	N18.3	585.3	1Z12.00	
			1Z15.00	
			1Z16.00	
			1Z1B.00	
			1Z1B.11	
			1Z1C.00	
			1Z1C.11	
			1Z1D.00	
			1Z1D.11	
			1Z1E.00	
			1Z1E.11	
			1Z1F.00	
			1Z1F.11	
			1Z1G.00	
			1Z1G.11	
			K053.00	
Chronic kidney disease, stage 4 (severe)	N18.4	585.4	1Z13.00	
			1Z1H.00	
			1Z1H.11	
			1Z1J.00	
			1Z1J.11	
			K054.00	
Hypertensive heart and chronic kidney disease, malignant		404.0		
		403.xx, 404.xx		
Renal failure	N17-N19.9	586	D215.00	
			D215000	
			K05..00	
			K05..12	
			K050.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			K06..00	
			K06..12	
Other chronic renal failure	N18.8		Kyu21	
Chronic kidney diseases monitoring/self-management			661M200	
			661N200	
			66i..00	
			6AA..00	
			9Ni9.00	
			9Ot..00	
			9Ot0.00	
			9Ot1.00	
			9Ot2.00	
			9Ot3.00	
			9Ot4.00	
Dialysis		V45.1	7L1..	
		V56.0	SP06B00	
		V56.8	Z1A..	
			Z91A.00	
			Z91A100	
			ZV45100	
			ZV56..	
			ZVu3G00	
CKD quality indicators			9hE..00	
			9hE0.00	
			9hE1.00	
Predicted stage chronic kidney			9Ot5.00	
Renal impairment			K060.00	
Impaired renal function			K060.11	
Acute-on-chronic renal failure			K0E..00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
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 0.993^Age 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.

Annex 4.9 Definition of bladder outlow obstruction/urinary retention

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

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	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Hesitancy			1A34.00	
Hesitancy of micturition			1A34.11	
BOO - Bladder outflow obstruction			K160.13	
Bladder outflow obstruction			K165200	

Annex 4.10 Definition of BPH (eventtype=BPH)

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

Terms	ICD10	ICD9CM	Read Codes	ICPC
Benign prostatic hypertrophy/ Benign prostatic hyperplasia	N40	600.0	XE0e6	Y85
			K20*	
Prostatic hyperplasia			K20z.	
			K200.	
Benign neoplasm of prostate			B7C2.00	

Annex 4.11 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	

Annex 4.12 Definition of 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	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			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	K74.3			

Terms	ICD10	ICD9CM	Read Codes	ICPC
cirrhosis	K74.4			
	K74.5			
History of hepatitis			141E.00	
			141F.00	
			2126700	
H/O: liver disease			14C5.00	
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	

Annex 5 Pregnancy and breastfeeding

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
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

Terms	Read Codes	ICPC
		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
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

Terms	Read Codes	ICPC
		W95
Establishing lactation	Z2B5400	
Promotion of lactation	Z2B5412	
Dietary advice for lactation	ZC2L.11	