Arrhythmogenic potential of drugs

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Common Study Protocol for Observational Database Studies

WP5 – Analytic Database Studies

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Authors (Partner)	Gianluca Trifiro' (EMC), Giampiero Mazzaglia (F-SIMG)			
Responsible Author	Gianluca Trifiro'		**Email**	g.trifiro@erasmusmc.nl
	Partner	EMC	**Phone**	+31 (0)10 7044128

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Definitions

Partners of the Artimo Consortium are referred to herein according to the following codes:

- **EMC:** Erasmus Universitair Medisch Centrum Rotterdam
- **FIMIM:** Fundació IMIM
- **LSHTM:** London School of Hygiene and Tropical Medicine
- **UNIBO:** Alma Mater Studiorum-Università di Bologna
- **UNI-HB:** Universitaet Bremen
- **UoNEW:** University of Newcastle
- **UB2:** Université Victor Segalen Bordeaux2
- **FSM-MCL:** Fondazione Salvatore Maugeri Clinica del Lavoro e Della Riabilitazione
- **CHARITE:** Charite - Universitaetsmedizin Berlin
- **UNIVR:** Universita Degli Studi di Verona
- **SGHMS:** St. George's Hospital Medical School
- **AZ:** AstraZeneca AB
- **PHARMO:** PHARMO Coöperatie U.A
- **F-SIMG:** Fondazione Scientifica SIMG-ONLUS
- **AUH-AS:** Aarhus Universitetshospital, Aarhus Sygehus
- **AMC:** Academisch Medisch Centrum bij de Universiteit van Amsterdam
- **DSRU:** Drug Safety Research Trust

Abbreviations

The following abbreviations are used in this report:

- **AIFA –** Italian Drug Agency
- **ATC** – Anatomical therapeutic chemical classification system
- **BMI** – Body Mass Index
- **COPD** – Chronic Obstructive Pulmonary Disease
- **DDD** – Defined Daily Dose
- **EU –** European
- **GP** – general practitioner
- **ICD-9-CM** – International Classification of Disease, 9th rev., Clinical Modification
- **ICD-10-GM** – International Classification of Disease, 10th rev., German Modification
- **ICPC** – International Classification of Primary Care
- **IPCI** – Integrated Primary Care Information Project
- **IV** - Intravenous
- **AMI** – Acute Myocardial Infarction
- **OR** – Odds ratio
- **OTC** – over-the-counter medication
- **RX** – prescription
- **SCD –** Sudden Cardiac Death
- **SUD** – Sudden Unexpected Death
- **UK** – United Kingdom
- **VA –** Ventricular Arrhythmia
- **VF** – Ventricular Fibrillation
- **VT –** Ventricular Tachycardia
- **WHO** – World Health Organization

1. Background

Cardiac ventricular arrhythmia as a side effect of anti-arrhythmic and non-antiarrhythmic drugs has become a major pharmacological safety concern for the pharmaceutical industry and the health regulatory authorities[1,2]. Among drug-induced arrhythmias, Torsade de Pointes (TdP) is by far the most important and worrisome.

In recent years, a number of blockbuster antipsychotic, antihistaminic, gastrointestinal and anti-infective drugs (e.g. thioridazine, astemizole, cisapride, grepafloxacin)[3] have been withdrawn from the market because of reports of TdP and sudden unexpected death or sudden cardiac death (SUD or SCD), and several others were restricted in use (e.g. terfenadine, haloperidol, sertindole). This has resulted in health concerns for patients as well as billions of dollars of lost revenues for the pharmaceutical industry[4]. The relative rarity of drug-induced TdP in non-antiarrhythmic drugs[5] and our imperfect prediction of risk for a given individual, make this a particularly vexing problem for clinicians.

Although various studies have been conducted to assess the postmarketing risk of QTc prolongation, TdP[1,5,6], ventricular fibrillation[7] and sudden death[8,9,10] with non-arrhythmic drugs, it is difficult to compare these studies since they differ in population composition (age, gender), methodology (such as in- and exclusion criteria), case definitions and type of drug exposure information. Moreover these studies are usually done in a specific region or country which restricts heterogeneity in exposure resulting in lack of power to look at the entire range of drugs.

The overall objective of the ARITMO project is to analyse the ventricular arrhythmogenic potential of individual drugs belonging to the following classes (> 400 compounds): antipsychotics (ATC - Anatomical Therapeutic Chemical classification: N05A), anti-infectives (antibacterials (J01), antimycotics (J02), antivirals (J05), and antiprotozoals (P01)) and H1-antihistamines (R06).

This safety issue will be explored using different data sources and from different perspectives. In this deliverable, we describe the protocol for the observational database studies targeted to estimate rates and relative risks for the outcomes of interest associated with the use of antipsychotics, anti-infectives and H1-antihistamines using electronic data from seven European (EU) healthcare databases.

The total size of the study population in the project will be around 27 million from five EU countries (Italy, Netherlands, UK, Denmark and Germany). Rough estimations show that around 5% of persons are treated with antipsychotic drugs each year, 30% with anti-infectives and 10% with antihistamines in the underlying populations of the participating databases. In light of these figures, the scale of assessment of the arrhytmogenic potential for the drugs of interest is unprecedented.

Some of the information that is reported in this deliverable has been retrieved from the deliverable 6.1 "Internal Report Draft Study Protocol for Observational Studies" from the Safety of non-steroidal anti-inflammatory drugs – SOS project. This deliverable was created by the Uni-HB.

2. Study Objectives

The aim of observational database study is to investigate the pro-arrhitmic risk associated to the medications belonging to the following classes: anti-infectives, antihistamines and antipsychotics.

In detail, the primary objective is to estimate the rates and relative risks of (a) symptomatic QT prolongation, (b) Torsade de Pointes (TdP), (c) ventricular arrhythmia (VA) and (d) sudden unexpected death (SUD)/sudden cardiac death (SCD) associated with the most frequently prescribed individual anti-infectives, antihistamines and antipsychotics. To estimate the comparative risks of the study drugs, different comparators will be selected for each drug class of interest.

Due to overlapping aim, sharing of data concerning case patients (i.e. patients with diagnosis of TdP registered in the databases) with WP4 (i.e. cohort studies) will be taken into account.

Secondary objectives of the study are:

- to explore the effect of dose and duration of use and route of administration on the association between study outcomes and drugs of interest;

- to identify demographic and clinical predictors for the specific drug-induced arrhythmias

- to describe the prescribing pattern of the study drugs in different databases (see protocol for drug utilization study – Annex I)

3. Methods

3.1. Study Design

Preliminary analyses using data from the participating databases showed that symptomatic QT prolongation and Torsade de Pointes (TdP) may not be properly investigated using these data sources due to either missing information (i.e. ECG for confirmation of symptomatic QT prolongation) or limited number of potential cases (i.e. TdP), as reported in the Appendix II. For this reason, the possibility to include in the cohort studies (WP4) all the patients with a diagnosis of symptomatic QT prolongation or TdP registered in the databases is currently under evaluation. This inclusion would first require a case validation and subsequently for all the validated cases the request of additional information would be explored (i.e. blood collection for genotyping). For each of the other two outcomes (ventricular arrhythmia (VA) and sudden cardiac death (SCD)/sudden unexpected death (SUD)), matched, nested case control studies will be conducted separately to assess the rates and the relative risk associated with anti-infectives, antihistamines and antipsychotics. As regard the anti-infectives, different case control subsets will be created for each drug subgroup (i.e. antibiotics, antivirals, antimycotics and antiprotozoals). For each drug class, matched case control studies will be nested in new user inception cohorts.

Overall, 12 case controls studies will be performed.

Except for the definition of the comparators and potential confounders (i.e. confounding by indication) the same study design will be used for all the studies.

With respect to anti-infectives, the possibility to conduct a sensitivity analysis using the case-cross-over design will be explored.

3.2. Data Sources

The data sources for the observational database studies are represented by seven European healthcare databases. The combination of multiple databases from different countries had the advantage to provide a large sample size of the study population and heteregoneous drug prescribing pattern. The terminologies and coding system to register both events and drugs differ among various databases, as shown in Table 1. For this reason, terminology mapping has been already performed to provide every database owners with homogeneous information for the data extraction about events and drugs. This task has been described in the Deliverable 5.1 that was created by UB2 in collaboration with EMC.

The characteristics of the databases are described more in detail below.

3.2.1. IPCI Database

Database description

In 1992 the Integrated Primary Care Information Project (IPCI) was started by the Department of Medical Informatics of the Erasmus University Medical School. 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. GPs receive a minimal reimbursement for their data and completely control usage of their data, through the Steering Committee and are permitted to withdraw data for specific studies. Collaborating practices are located throughout the Netherlands and the collaborating GPs are comparable to other GPs in the country according to age and gender.

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. Turnover occurs as patients move and transfer to new practices. The records of 'transferred out' patients remain in the database and are available for retrospective studies with the appropriate time periods.

The system complies with European Union guidelines on the use of medical data for medical research and has been validated for pharmaco-epidemiological research. Approval for this study will be obtained from the 'Raad van Toezicht' an IPCI specific ethical review board.

Database updates and data time lag

The database is updated continuously, every 3 months a data draw down is made for research purposes.

Data subsets and variables

The database contains identification information (age, sex, patient identification, GP registration information), notes, prescriptions, physician-linked indications for therapy, physical findings, and laboratory values (e.g. potassium, creatinine).

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 dispensed, dosage regimens, strength and indication are entered into the computer. The National Database of Drugs, maintained by the Royal Dutch Association for the Advancement of Pharmacy, enables the coding of prescriptions, according to the Anatomical Therapeutic Chemical (ATC) classification scheme recommended by the WHO.

Limitations of the database

Limitations of the databases are that a lot of information is available in narratives, especially information from specialists and symptoms. Also specialist medications are not complete if the GP does not enter them. It is known, however, that this proportion is minor.

3.2.2. PHARMO Database

Database description

The PHARMO medical record linkage system is a population-based patient-centric data tracking system that includes high quality and complete information of patient demographics, drug dispensings, hospital morbidity, clinical laboratory, and date of death of 3.2 million community-dwelling inhabitants of 65 municipal areas in the Netherlands. The drug dispensings originate from out-patient-pharmacies. This core dispensing database is linked on a patient level with different databases, among which the hospital morbidity data The Dutch National Medical Register (LMR). This register comprises all hospital admissions in the Netherlands, i.e., admissions for more than 24 hrs and admissions for less than 24 hours for which a bed is required. Only hospital admissions for the out-patient-pharmacy patients are collected in the PHARMO database. Clinical laboratory tests are available for a subset of the out-patient-pharmacy patients in a completely computerized format. Dates of death are available from the Central Bureau of Genealogy (CBG). The CBG is the Dutch information and documentation centre for genealogy, family history and related sciences. Data are collected since October 1994 and include mortality. The CBG returns date of death for the out-patient-pharmacy patients. The linkage method used for individuals of the separate databases is probabilistic.

Database updates and data time lag

The out-patient-pharmacy database is updated every month with a time lag of 1 month and covers the period 1998-2009. Hospital admission data are collected on a yearly basis and every new complete year is available in July. Clinical laboratory are linked to the PHARMO databases on a yearly basis and available in July. Date of death returned from the CBG have a lag time of 2 years and are available in July.

Data subsets and variables

The PHARMO-LMR database contains the following information:

- **Socio-demographic data:**
  Unique anonymous person identification number
  Gender
  Birthdate (yyyymmdd)
  Last known ZIP-code
  Date first contact
  Date last contact
  Reason last contact
  Date of death

- **Outpatient dispensing drug data:**
  Unique person identification number
  Unique pharmacy identification number
  Type prescriber (GP, specialist)
  ATC
  Molecule name
  Dispensed quantity (number of units)
  Type of unit (fluid, tablets etc.)
  Dispensation date
  DDD (number of DDD in one unit)
  Duration of dispensing
  Number of units to take each day (free text in Dutch)
  Strength of one unit

- **Hospital data:**
  Unique person identification number
  Unique hospital identification number
  Main diagnoses are coded in ICD9-CM
  Main diagnostic/surgical procedure
  Side diagnoses
  Dates of hospital admission and discharge
  Type of care (day/clinical)

Limitations of the database

- Date of first entry, last entry in the population might be subject to misclassification.
- Linkage is high sensitive and specific but does not exclude a small percentage of linkages as misclassified
- CBG data have a lag time of 2 years compared to 1 year or less for the other sources of data.

Clinical lab tests are only available for a subset of the PHARMO database

3.2.3. Aarhus University Hospital

Database description

The regional Registry of Patients comprises data on all discharges from hospitals in the northern and central region of Jutland in Denmark. This region accounts for around 30% of the Danish population (~1.8M) and the population is entirely covered by a system of electronically linkable databases. The registry includes information on all in-patients in the region, emergency room visits, outpatient visits and selected in-hospital treatments. Data are available in the period 1994-2009.

As a part of tax-funded healthcare the Danish National Health Service reimburses part of the patient expenditure on a wide range of prescribed drugs. These prescriptions dispensed at pharmacies in the northern and central region of Jutland in Denmark have been stored since 1996 in a prescription database. The database is maintained by the Department of Clinical Epidemiology, Aarhus University Hospital.

The regional Registry of Causes of Death comprises data from all death certificates in the region including information on events that led to death and autopsy findings. Before 2007 the information from the certificate was interpreted and coded by the National Health Service (ICD10 code) with one underlying cause of death and up to three additional immediate causes. From 2007 and onwards, data have been collected electronically and entered directly by the physician who completed the certificate.

Database updates and data time lag

The prescription database and the patient registry are updated yearly. The Registry of Causes of Death is updated until 2008. Variables available in the databases are described below.

Patient register:

- Patient ID: unique person identification number used for record linkage
- Sex
- Birth date
- Date of admission, date of discharge and date of outpatient visit
- Main or Secondary diagnoses (ICD10)
- Procedures/surgery/treatment code

Prescription:

- Patient ID: unique person identification number used for record linkage
- ATC code of the drug
- Varenr (Unique code used to identify each box of each drug)

- Prescription Date
- Quantity: number of prescribed boxes
- DDD, commercial name, coverage of the box

The Registry of Causes of Death:

- Patient ID: unique person identification number used for record linkage
- ICD10 code underlying cause
- ICD10 codes immediate causes
- Date of death
- Manner of death (natural, suicide, accident etc.)
- Place of death

Limitations of the database

QT intervals are not available in the Patient Registry, but needs to be retrieved from medical charts. However, congenital long QT and acquired long QT are coded (ICD10 I472E, I4772F)

Data on TdP, ventricular fibrillation, syncope and sudden cardiac death (ICD10: I461) are available in the Patient Registry and Cause of death Registry. The validity of the diagnoses are unknown, but can be validated from medical charts. The prescription database does not contain information on any over-the-counter (OTC) medication. However, the database contains complete information on any prescriptions on antinfecivtes, ati-histamines or antipsychotics. In the prescription database there is no information on the prescribed dose or the indication for prescribing.

3.2.4. BIPS Database

Database description

The BIPS database consists of claims data from four German statutory health insurance (SHI) providers. It covers about 14 million insurants throughout Germany who have at any time between 2004 and 2006 been enrolled in one of the four SHIs. The database population represents approximately 17% of the German population of 82 million inhabitants.

Membership in an SHI is compulsory in Germany for employees with an annual income up to approximately 47.000 €. Subjects with higher incomes can choose private health insurance providers instead of an SHI and are probably underrepresented in SHIs. However, some of these higher-income subjects are voluntary members of SHIs, most often because SHIs provide free health insurance for unemployed family members (children and spouse) whereas in private health insurance plans all family members have to be paid for. About 70 million people (85% of the German population) are SHI members, including children and insurants who are retired or unemployed and about five million voluntary members.

Three of the four SHIs contributing to the database are so called 'Ersatzkassen' which are more likely to insure people of middle to higher socio-economic status. The database also includes

data from one 'Allgemeine Ortskrankenkasse', an SHI which has traditionally insurants of lower socio-economic status. Two large SHIs contributing to the database together insure more than 13 million subjects all over Germany. We therefore expect the data to be adequately representative with respect to age, sex, and region of residence.

Since German SHIs pay the costs for ambulatory physician visits, hospital stays and prescription drugs for their enrolled members, information on these health services are contained in the database.

An advantage of data from German SHIs is the stability of their membership which makes long term follow-up studies feasible. In the BIPS database membership is stable in about 75% of all subjects from 2004 to 2006. However, insurants leaving a specific SHI and entering one of the other three participating SHIs cannot be identified as the same individual (synonym error).

Database updates and data time lag

The initial database of about 14.3 million subjects covers the years 2004 until 2006. Database updates are requested from the SHIs on an annual basis. The data for the preceding year will be available to the SHIs about nine months later. Data transfer from the SHIs takes about three months. Data cleaning and preparation for analysis will take another two months. Data transfer for the year 2007 has been delayed due to delays in permission for data transfer. We expect that data for 2007 and 2008 will be available in March 2010.

Data subsets and variables

The SHI database contains the following information:

- **Socio-demographic data:**
  Unique person identification number: allows longitudinal analysis and linkage between the subsets
  Family identification number: identifies members of a family who are insured together
  Year of birth
  Sex
  Region of residence
  Nationality
  Indicators for social status
  Dates of insurance coverage (entry and exit)
  Reasons for end of coverage (including death)

- **Hospital data:**
  Unique person identification number
  Unique hospital identification number
  Hospital diagnoses are coded in ICD-10-GM (at least 4 digits). Diagnosis at admission, main diagnosis at discharge, and a variable number of accessory diagnoses are available
  Dates of hospital admission and discharge

Reason for admission
Reason for discharge (including death)
Diagnostic and surgical procedures (OPS Codes)

- **Outpatient prescription drug data:**
  Unique person identification number
  Unique pharmacy identification number
  Unique physician identification number: allows identification of speciality of prescribing physician
  PZN (Pharmazentralnummer): a pharmaceutical reference identification number
  Prescribed quantity (number of packages)
  Prescription date
  Dispensation date

A central pharmaceutical reference database with all PZN on the German market has been built up by BIPS. It contains information on generic name, brand, manufacturer, packaging size, strength, defined daily dose (DDD), pharmaceutical formulation, and ATC code. Information from the central pharmaceutical reference database is linked to the SHI database via the PZN.

- **Outpatient medical treatment data:**
  Unique person identification number
  Unique physician identification number: allows identification of specialty of consulted physician
  Ambulatory diagnoses are coded in ICD-10-GM (at least 4 digits). These diagnoses are not linked to a definite date, but refer to a quarter, as physicians' claims are collected quarterly.
  Diagnostic certainty: coded as certain, suspected, excluded, status post
  Dates of treatment / visits
  Types of treatment / diagnostic procedures with exact date (EBM codes, developed for payment of physicians for the outpatient treatment of German SHI patients)

Limitations of the database

- Exact date of birth is not known, only birthyear available.
- Database contains no information on hospital or OTC medication.
- Only prescribed quantity, not prescribed dose available for medication data.
- Exact date for outpatient diagnoses is not known, only quarter available, however ambulatory diagnostic or therapeutic procedures (EBM codes) come with exact date.
- No laboratory values are contained in the database, but ordering of lab values is contained with exact date.
- The diagnostic certainty is missing for some ambulatory diagnoses, mostly 2004.
- No information on diagnoses, treatments, and prescriptions for occupational accidents and during rehabilitation is available as they are insured by a different carrier.

3.2.5. THIN Database

The Health Improvement Network (THIN) is a database of primary care medical records from the United Kingdom. General practitioners are trained to record 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.

Currently, the database has 2.7 million active patients registered. Recently a validation study was conducted and concluded that "THIN data that are collected outside of the General Practice Research Database (GPRD) appear as valid as the data collected as part of the GPRD."

Database updates and data time lag:
In this project the version of the database containing updated data until the end 2009 will be use through licence from the Department of Medical Informatics from Erasmus University Medical Center.

Data subset and variables:

Data recorded in THIN include demographics, details from general practitioners' visits such as medical diagnoses and prescriptions written by the general practitioners, diagnoses from specialist referrals and hospital admissions, some results of laboratory tests, some lifestyle characteristics and other measurements as taken in the practice. Within the database, diagnoses are recorded using READ codes. Prospective data collection for THIN began in September 2002, with electronic medical records that date back to 1985. In addition, practices may retrospectively enter significant medical events into the electronic medical record.

Limitations of the database:

Limitations of the databases are that a lot of information is available in narratives, especially information from specialists and symptoms. Also specialist medications are not complete if the GP does not enter them. It is known, however, that this proportion is minor.

3.2.6. Health Search Database/CSD Longitudinal Patient (HSD)

The Health Search/Longitudinal Patients Database (HSD) is a longitudinal observational database that is representative of the general Italian population. It was established in 1998 by the Italian College of General Practitioners. The HSD contains data from computer-based patient records from a select group of GPs (covering a total of 1.5 million patients) located throughout Italy who voluntarily agreed to collect data for the database and attend specified training courses. Turnover occurs as patients move and transfer to new practices. The records of 'transferred out' patients remain in the database and are available for retrospective studies with the appropriate time periods. The HSD complies with European Union, guidelines on the use of medical data for research. The HSD has been the data source for a number of peer-reviewed publications on the prevalence of disease conditions, drug safety and prescription patterns in Italian primary care. Approval for use of data is obtained from the Italian College of Primary Care Physicians. Data are in house, no ethical approval needed.

Data subset and variables:
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, free text patients diary, hospital admission, and death. All diagnoses are coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Drug names are coded according to the ATC classification system. 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. At the time in which this study will initiate, 650 GPs homogenously distributed across all Italian areas, covering a patient population of around million patients, reached the standard quality criteria.

Database updates and data time lag:
The database is updated continuously, every 6 months a data draw down is made for research purposes.

Limitations of the database:
The main limitation is the difficulty to provide additional information from GPs since in such a case an ethical approval from all the local health authorities of the respective GP practice is needed.
Medication not reimbursed from the NHS are incomplete, as well as those prescribed by the specialists. Symptoms and diagnostic instrumental results are in free text form and are not necessarily complete.

3.2.7. Emilia Romagna regional Database (ERD)

Database description

In the Emilia Romagna regional database, data are obtained from the electronic healthcare databases of the Emilia Romagna region. Emilia Romagna is one of the largest Italian regions with about 4.5 million inhabitants, about 8% of the population of Italy. This population is entirely covered by a system of electronically linkable databases containing information on health services reimbursable by the National Health Service, including outpatient prescription of drugs free of charge.

The Emilia Romagna regional database has a full population coverage (i.e. the population covered is not selected by any criteria) and the available information is related to drug prescriptions for the period 2003 – June 2010 and to hospital admissions for the period 1997 – June 2010.

Database updates and data time lag:

The Emilia Romagna Regional database is updated monthly.

Data subsets and variables:

The Emilia Romagna regional database contains the following information:

- **Patient register:**
  - Patient ID: unique person identification number used for record linkage
  - Sex
  - Birth date
  - Death date

- **Prescription:** Contains all outpatients prescriptions of drugs reimbursable by the NHS
  - Patient ID: unique person identification number used for record linkage
  - ATC code of the drug
  - AIC (Marketing Authorization): Unique code, released by AIFA (Italian Drug Agency), used to identify each box of each drug in commerce
  - Prescription Date
  - Quantity: number of prescribed boxes

Using the AIC code it is possible to link drug prescriptions to a drug register which contains information on the commercial name of the drug, the quantity of active principle of the drug contained in one box, defined daily doses (DDDs) of the active principle, and the estimated coverage of one box.

- **Hospitalization:** Contains all reimbursed hospitalisations occurring in the public and private hospitals in Emilia Romagna
  - Patient ID: unique person identification number used for record linkage
  - ICD-9-CM codes for diagnoses: there are 6 fields (one for the main diagnosis and 5 for the secondary diagnoses) containing ICD-9 codes
  - Diagnostic procedures/surgery code: there are 5 to 15 fields (each field corresponds to a different procedure)
  - Hospitalization Date: date of hospital admission
  - Discharge Date: date of discharge from the hospital
  - Procedures Date: there are 5 to 15 fields containing the date of the associated procedures

Limitations of the database:

- The database does not contain information on non-reimbursed medications (antihistamines are reimbursed only in case of severe forms of allergy) and on drugs

dispensed directly from hospital pharmacies to outpatients (about 9% of antipsychotic prescriptions are not recorded in the database of reimbursed prescriptions).

- The inspection of clinical charts for validation would require many difficult steps (but a few previous experiences exist: e.g. the ongoing study on biphosphonates funded by AIFA).

Table 1. Overview of databases and characteristics relevant for the study *(at 20/09/2010)*

Characteristics	**IPCI** (NL)	**PHARMO** (NL)	**THIN** (UK)	**HSD** (ITA)	**Emilia Romagna Regional DB** (ITA)	**Aarhus DB** (DK)	**BIPS** (Germany)
Type of database	GP	Record linkage	GP	GP	Claims	Claims	Claims
Total Population	1 million	2.4 million	2.6 million	1.2 million	4 millions	1.6 million	17 million
Coding system for drug	ATC	ATC	BNF	ATC	ATC	ATC	ATC
Coding system for event	ICPC	ICD9-CM	READ	ICD9-CM	ICD9-CM	ICD10	ICD10-GM
Presence of free text	Yes	No	Yes	Yes	No	No	No

3.3. Study period

The available follow-up years vary across databases and are currently comprised between 1st January 1996 and 30th June 2010, as summarized in Table 2. The lag time for the update of data also vary across databases. All the databases will contribute data from the earliest data to the latest data possible at the time of extraction. As the interest of the project is greater for the recently marketed drugs, all the efforts will be put to have from all the databases the most recent data before the data extraction.

Table 2. Availability of follow-up years in different healthcare databases *(at 20/09/2010)*

	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
IPCI															
PHARMO															
THIN															
HSD															
ERD															

BIPS															
AARHUS															

3.4. Cohort Definition

3.4.1. Inclusion Criteria

Cohort members have to fulfil all of the following inclusion criteria:

- At least one study drug prescription/dispensing during the study period.
- At least 12 months of continuous enrolment before initial prescription/dispensing of a study drug (as defined in Annex III). This period is required to characterize the subject in relation to previous occurrence of study outcomes or previous exposure to study drugs. Patients with ventricular arrhythmias registered within the year prior the study entry will be identified and analysed in a specific sub-group analysis.
- For each drug class, no use of any drug belonging to that class (as defined in Annex III) for six months before initial prescription/dispensing. This wash-out period is required to avoid selection of prevalent users and potential depletion of suceptibles.

No exclusion criteria or age restrictions will be considered.

Additionally, an external reference from the general population in any databases will be selected to calculate the age and gender specific background rate for the study outcomes. This external reference however will not be included in the case control studies.

3.4.2. Cohort Entry

Cohort entry for each of the 12 studies is defined as the date of the first study drug prescription during the study period:

- when the subject had no prescription of a study drug (as defined in Annex III) for six months before this date
- and was continuously enrolled for at least 12 months before this date

Re-entry after cohort exit is not possible.

3.4.3. Cohort Exit

Cohort exit is defined for each of the 12 studies separately as the first of the following dates:

- End of study period, i.e. December 31, 2009 (or database-specific last data update).
- Occurrence of respective study outcome as defined below.
- Transfer out of database / end of registration / end of membership / instituzionalization. (defined on the basis of pharmacy data (PHARMO, BIPS, Aarhus and ERD) or GP registration (THIN, IPCI, HSD)).

- Hospital staying longer than three months (i.e. three months gap without any contact with general practitioner or any dispensing in pharmacy registry).
- Death.

3.5. Case Definition

Only the first occurrence of ventricular arrhythmia and the occurrence of sudden unexpected death (SUD)/sudden cardiac death (SCD), as defined below, will be considered as primary outcomes for the observational database studies. Patients with ventricular arrhythmias registered within the year prior the study entry will be identified and analysed in a specific sub-group analysis. Recurrent ventricular arrhythmia (VA) after the first occurrence during the study period will not be examined. The index date is defined as the date of first diagnosis of VA or the date of SUD/SCD during the study period.

Both VT and SUD/SCD will be ascertianed in each database by applying coding algorithms already used in database studies.[11-13] Subsequently, all the potential cases (if not possible, a random sample of ≥ 200 cases) will be validated through independent manual revision of medical records or chart review by an endpoint adjudication committee including two experts per database blinded towards the drug exposure. In case of disagreement, a third expert will arbitrate. The outcomes symptomatic QT prolongation and TdP will be identified using both diagnostic codes and key words for the search within free text, as selected in terminology mapping activities (see Deliverable 5.1). After their validation, the possibility to include those cases in the cohort studies (WP4) will be explored.

The protocols for the validation of all the outcomes are currently under development.

Based on different predefined level of certainty and availability of relevant information all the potential cases will be judged by the endpoint adjudication committee as: a) definite; b) possible; and c) non-assessable. The non-assessable cases will not be included in the analyses.

The definition of the study outcomes is reported below.

3.5.1. Symptomatic QT prolongation

Prolongation of heart rate corrected QT (QTc) interval from a 12-lead electrocardiogram (ECG). Cut-off points for prolongation are >450 milliseconds (ms) (430-450 ms=borderline) in men and >470 ms in females (450-470 ms=borderline) in presence of clinical symptomatology (syncope is the main clinical correlate). Bazett formula (QTc=QT/RR0.5) is most often used for heart rate correction.

3.5.2. Torsade de Pointes (TdP)

Torsade de pointes, literally twisting of points, is a 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.

3.5.3. Ventricular arrhythmia (VA)

Ventricular arrhythmia includes both ventricular tachycardia (VT) and fibrillation (VF).

VT is a sequence of three or more beats in a row, with wide QRS complex (QRS ≥120 ms) at a ventricular rate exceeding 100 beats/min. If the rhythm lasts more than 30 seconds or requires termination earlier due to haemodynamic instability, it is known as a sustained ventricular tachycardia. If the fast rhythm self-terminates within 30 seconds, it is considered a non-sustained ventricular tachycardia.

It can evolve to VF that is a rapid, chaotic, non-repetitive waveform usually preceded by rapid VT and in which there is uncoordinated contraction of the cardiac muscle of the ventricles. VF is clinically associated with loss of effective blood circulation and, if not immediately treated, leads to death.

Th risk of VT and VF will be also examined separately, if possible.

3.5.4. Sudden cardiac death (SCD)/Sudden unexpected death (SUD)

SUD: unwitnessed, unexpected death of someone with abrupt loss of consciousness within one hour of the onset of acute symptoms with an unknown cause.

SCD: Natural death due to cardiac causes, heralded by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present, but the time and the mode of death are unexpected.

3.6. Selection of Controls

For each case, up to 10 controls are selected using incidence density sampling from the new user cohort within each database. Controls will be matched to each case by date of birth (±2 years), gender, database and calendar time.

Controls will be assigned the same index date of the respective case.

3.7. Exposure Definition

Overall, the arrhytmogenic potential of three drug classes will be investigated within the ARITMO project: a) anti-infectives; b) antihistamines; and c) antipsychotics. Among anti-infectives four main subgroups will be analysed separately: a) antibacterials; b) antivirals; c) antimycotics; and d) antiprotozoals (if enough exposure is available in the data sources, as assessed in the drug utilization study – Annex I). The rates and relative risks of the study outcomes will be separately calculated for each individual medication (ATC V level) within each drug class, as listed in Annex III.

Special categories will be defined for concomitant use of more than one study drug belonging to the same drug class. The distinction between patients switching from one study drug to another and patients using concurrently more than one drug, and the resulting definition of concomitant use, will be based on results (e.g pattern analyses) from the drug utilization study.

We will obtaine data on the exposure to the study drug from prescription/dispensing files from each database and we will estimate the length of treatment on the basis of the prescribed/dispensed number of units and the dosing regimen or, if not available, the Defined Daily Dosage (DDD). In particular, the duration of each prescription/dispensing will be calculated by dividing the total number of units per prescription/dispensing by the prescribed daily number of units (i.e. IPCI, THIN, PHARMO) or the indication-specific DDD (i.e. HSD, BIPS, ERD, Aarhus). In the paragraph 3.7.1, more detailed information about the estimation of duration of use is reported.

In the case control analyses, exposure will be classified based on the drug being used and timing relative to the event, as follows:

- Current: if the drug prescription duration covered the index date or ended at most 30 days before (i.e. carry-over period)
- Recent: if the drug prescription duration ended between 30 and 180 days before the index date
- Past: if the exposure period ended more than 180 days before the index date

A 30 days carry-over period is considered to take into account the pharmacokinetic characteristics of the drugs and patients' compliance to the therapy. Sensitivity analyses will be performed in which 15 days or no carry-over period will be considered for the risk window for current users.

To estimate the comparative risk through the case control analyses, different reference categories (i.e. comparators) will be selected for each drug class, as listed below:

- Antibacterials: current use of amoxicillin [14]
- Antivirals: current use of aciclovir
- Antimycotics: current use of terbinafine
- Antiprotozoals: current use of metronidazole
- Antihistamines: current use of cetirizine
- Antipsychotics: current use of levomepromazine

A number of issues concerning the exposure to the different drug classes of interest have been taken into account for the definition of the reference categories (see Table 3).

In general, the selection of the comparators is in line with previous observational database studies. If none of the previous publications have explored the risk of arhhytmogenic potential for some of the drug classes (or have considered non-use as comparator), we selected as comparator the drugs which have never (or rarely) been associated to QT prolongation (Annex VI) among those with the largest exposure in the participating databases.

We decided not to select non-use or past use of the study drugs as potential comparator due to potential confounding by indication (see Table 3). As regard the study drugs, the assumption that non-users/past users carry the same baseline risk of the current users may not be satisfied.

Each of the above mentioned drug classes will be considered as potential conforunder when studying the risk for the other drug classes of interest.

Table 3. Issues concerning the exposure to the different drug classes of interest

Drug class	Type of exposure	Confounding by indication	Seasonality	Other remarks
Antipsychotics	Multiple indications of various natures and with specific dosing regimens, varying with different age groups. Both acute and chronic exposures are possible	Possible, due to unhealthy life-style (i.e. smoking, alcohol abuse) and burden of co-morbidities	No	Drug intoxication is an important risk factor for arrhythmias
Antihistamines	Intermittent use; Indications for in-hospital use may differ	Possible, as asthma and COPD may be related to increase risk of arrhythmia while there is no evidence about the effect of allergy	Yes, strong seasonality; matching on calendar time is necessary	Some antihistamines formulations (i.e. topical) are available as OTCs, thus exposure misclassification is possible. For this reason, topical formulations have not been selected among the study drugs
Anti-infectives				
Antibiotics	Mostly acute exposure but in some cases also cyclic and chronic exposure is possible (i.e. COPD and acne that are diseases pertaining specific age groups); Preventive use is also possible.	Possible, particularly in case of use in immunocompromised persons. In general, infections seem to be a risk factor for arrhythmias	Yes, use is particularly high in winter season; Matching on calendar time is necessary.	Persons with inherited QT prolongation are at higher risk during infection
Antivirals	Both acute and chronic exposures are possible	Possible, particularly in case of use in immunocompromised persons	Yes, use of anti-infleunza medications is high in winter season	Vaccines will not be considered. Not all DBs have information on anti-HIV medications
Antimycotics	Different indications for oral and intravenous (IV) use. IV use occurs mainly in hospital	Possible, particularly in case of use in immunocompromised persons	Yes	In-hospital use of antimycotics may not be assessed by most of databases even if the proarrhitmic risk of IV formulations would be of particular interest
Antiprotozoals	Preventive use is mainly captured in the DBs as these drugs are indicated for the treatment of infections that are not present in EU (i.e. malaria)	Possible, but limited evidence is available	Possible	Very low use is expected in the DBs

Among current users of the most frequently prescribed medications we will explore also the effect of: a) peak dose; b) duration of use; and c) route of administration.

For this reason, different exposure variables will be constructed as reported in the following paragraphs:

- Duration of continuous use (see 3.7.1)
- Dose (see 3.7.2)
- Route of administration (see 3.7.3)

3.7.1. Duration of Continuous Use

Duration of continuous use is defined as the sum of the durations of consecutive prescriptions. The duration of a prescription will be defined below. A grace period for the definition of consecutive prescriptions will be determined in the drug utilization study.

For sensitivity analyses the length of the grace period used in the definition of consecutive prescriptions will be varied.

Duration of a prescription/dispensing

The actual duration of each single prescription/dispensing will be used where contained in the database (i.e. THIN, PHARMO, IPCI).

For all other databases the duration of a prescription will be estimated as the length of the prescription interval. The duration of the ultimate prescription will be estimated as duration of the penultimate prescription interval, i.e. the time between the penultimate and ultimate prescription1 before the index date2, if both prescriptions are consecutive as defined above. If prescriptions are not consecutive or in case of single prescriptions, the defined daily dose (DDD) will be used to estimate the duration of a prescription as (strength*package size)/DDD (see table 1). That is, the best information available will be used for each database.

For sensitivity analyses, the prescription interval will also be estimated using not only the time between the penultimate and ultimate prescription before the respective date, but using the full period of consecutive use before the respective date, e.g. (pen)ultimate prescription interval = (time of ultimate prescription before index date - time of the first of the consecutive prescriptions)/(number of consecutive prescriptions before index date -1). Additionally, the duration of the prescription interval will also be estimated for databases containing the duration of a prescription and the duration of a prescription estimated by the DDD will be determined for

1 The choice whether to use dispensation date or prescription date depends on the databases. BIPS, Aarhus, ERD and PHARMO databases will use the dispensation date, all other databases the prescription date.

2 Taking into account that package size * strength might differ between the ultimate and penultimate prescription, e.g. $\text{duration}_{\text{ultimate}} = \text{duration}_{\text{penultimate}} * (\text{strength}_{\text{ultimate}} * \text{size}_{\text{ultimate}}) / (\text{strength}_{\text{penultimate}} * \text{size}_{\text{penultimate}})$.

all databases. Results based on the known duration of a prescription will be compared to results based on estimated duration (using only the last interval and using the full period of consecutive use) of the prescription interval and the duration estimated by the DDD.

Table 4. Overview of the different methods to estimate the duration of a prescription interval

available information	**method 1: use best information available**	**method 2: prescription interval, if possible**	**method 2a: prescription interval, if possible**	**method 3: use DDD**
duration of a prescription	known duration of prescription	estimated duration of prescription interval (estimated using only last interval)	estimated duration of prescription interval (estimated using full period of consecutive use)	(strength*package size)/DDD
no duration of prescription, > 1 consecutive prescription	estimated duration of prescription interval (estimated using only last interval)	estimated duration of prescription interval (estimated using only last interval)	estimated duration of prescription interval (estimated using full period of consecutive use)	(strength*package size)/DDD
no duration of prescription, only 1 (consecutive) prescription	(strength*package size)/DDD	-	-	(strength*package size)/DDD

Despite an acute effect is expected for the study drugs that may induce QT prolongation and related arrhythmias, the duration of use will be further investigated in this project. For this reason the duration of use for current users of the most frequently prescribed medications will be classified in the following categories:

- Very short= ≤7 days;
- Short= 7-29 days;
- Medium= 30-179 days;
- Long= ≥180 days.

Reference for duration of use comparisons is medium duration.

3.7.2. Dose

The prescribed daily dose will be used where contained in the database (i.e. IPCI, PHARMO, THIN, HSD).

For all the other databases the average daily dose will be estimated in the case of more than one consecutive prescription by strength, package size, and duration of prescription interval (i.e. time between the penultimate and ultimate prescription before index date) as (strength x

package size) / duration of prescription interval. If prescriptions are not consecutive or in case of single prescriptions, the defined daily dose (DDD) will be used (see table 2).

For sensitivity analyses, the prescription interval and based on that the average daily dose, will also be estimated using not only the time between the penultimate and ultimate prescription before the index date, but using full period of consecutive use, i.e prescription interval = (time of ultimate prescription before index date - time of the first of the consecutive prescriptions)/(number of consecutive prescriptions before the index date -1). Additionally, the average daily dose will also be estimated for databases containing the prescribed daily dose and the DDD will be determined for all databases. Dosage results based on prescribed daily dose will be compared to results based on estimated daily dose (estimated using only the last interval and estimated using the full period of consecutive use) and DDD within the same database for validation purposes.

Table 5. Overview of different methods to estimate dose

Available information	**method 1: use best information available**	**method 2: estimated average daily dose, if possible**	**method 2a: estimated average daily dose, if possible**	**method 3: DDD**
prescribed daily dose	prescribed daily dose	estimated average daily dose (estimated using only last interval)	estimated average daily dose (estimated using full period of consecutive prescriptions)	DDD
no prescribed daily dose, > 1 consecutive prescription	estimated average daily dose	estimated average daily dose (estimated using only last interval)	estimated average daily dose (estimated using full period of consecutive prescriptions)	DDD
no prescribed daily dose, only 1 (consecutive) prescription	DDD	-	-	DDD

Dose will be categorized as follows:

- low: < 0.5 DDD
- normal: 0.5 – 0.99 DDD
- high: 1.0 – 2 DDD
- very high: > 2 DDD

Reference for dose comparisons is low dosage. For each study drug, in the drug utilization study the median and mean dosage as well as the range of different dosages used in clinical practice will be calculated. Based on this information the above mentioned dose categorization may be revised.

3.7.3. Route of administration

We included in the study only those medications that are administered systemically to the patients. On the contrary, medications that are generally used as topical formulations (i.e.eye drops, ear drops, epicutaneous, inhalational drugs) were excluded. This exclusion would prevent exposure misclassification for some drug classes (i.e. some topical formulations of antihistamines are available as over the counter and therefore would not be captured in the healthcare databases participating in the project).

It will be investigated the effect of route of administration by creating the following categories for each drug class:

- Enteral formulations (i.e. oral, sublingual adminsitration)
- Parenteral formulations (i.e. intravenous, intra-arterial administration)

Some medications have both enteral and parenteral formulation. The information about the route of administration is available for some databases. For those databases in which this information is missing, the specific drug code identification (i.e. CODIFA in Italy) will be used to distinguish between enteral and parenteral formulations.

It is anticipated that the parenteral use of some study drugs may not be captured in most of the databases (i.e. parenteral formulations of antimycotics and antibacterials are administered in hospital).

3.8. Covariates

As covariates of interest, we will consider all the potential risk factors of the study outcomes. As there is a common pathway leading from torsade de pointes to sudden cardiac death we do not distinguish the risk factors for individual study outcomes. Apart from the risk factors of arrhytmias, we will identify also the main indications for use of the different study drugs.
Different covariates will be considered according to the the drug classes of interest.
As source of information for the initial identification of the potential risk factors, we used medical textbooks and recent scientific publications (i.e. review and observational studies)[1,15-20] that examined the risk of drug-induced QT prolongation, ventricular arrhythmia and sudden cardiac death using data from healthcare databases.
The preliminary list of covariates has been revised and updated by the cardiologists and database owners participating in the project. The final list includes demographic and clinical covariates (together with the criteria for their assessment), stratified by drug class (Annex IV).
Diagnostic codes, laboratory findings and use of specific medications will be considered, as needed, for the identification of co-morbidities and indications for use. As regard the diagnostic codes for those covariates, the terminology mapping has been already performed for all the covariates (see **deliverable 5.1**). In addition, also the key words in different languages (English, Italian and Dutch) for the free text search have been identified. The free text search is only possible in IPCI, HSD and THIN.

As the databases contain different types of information and level of detail, individual strategies will be applied to gather the best information possible for each database. Benchmarking of

crude incidence rates for different co-morbidities/indications for use across databases will be conducted to identify any issue in the assessment of these covariates.

In addition to co-morbidities and indications for use, we will consider as covariates:

- the concomitant use of drugs that have a potential for pharmacokinetic interaction with the study drugs via inhibition of isoenzymes of cytrocrome P450 (Annex V)
- the concomitant use of drugs with arrhytmogenic potential (Annex VI)

The potentially interacting drugs have been identified using the information reported in the website of the Division of Clinical Pharmacology of Indiana University (http://medicine.iupui.edu/clinpharm/ddis/).[21] Only the drugs that may inhibit the isoenzymes of cytrocrome P450 involved in the metabolism of any of the study drugs have been included in the list. Based on the degree of the inhibition, these drugs have been classified as strong, moderate or weak inhibitors.

The drugs with arrhytmogenic potential have been identified using the information reported in the website of ArizonaCERT | Center for Education and Research on Therapeutics (http://www.azcert.org/medical-pros/drug-lists/bycategory.cfm). Arizona CERT is a program of the Critical Path Institute in collaboration with The University of Arizona College of Pharmacy.

Drugs with a definite, possible and conditional risk of TdP have been listed, separately.

The presence of co-morbidities and indications for use will be identified at the cohort entry to characterize users of different drugs (see protocol for drug utilization studies – Annex I) and at the index date (i.e. date of diagnosis of the outcome) for the case control analysis. The concomitant use of drugs will be assessed within 90 days respectively prior to the cohort entry and the index date for the case control analysis.

4. Primary Statistical Analyses

4.1. Main Analysis

The main objective of the study is to estimate the rates and the relative risks of ventricular arrhythmias and SCD/SUD associated with the use of individual anti-infectives (antibacterials, antivirals, antimycotics and antiprotozoals), antipsychotics and antihistamines in order to rank them by arrhytmogenic potential. The inclusion of symptomatic QT prolongation and TdP as outcomes for the observational database studies is still under discussion.

First, the crude incidence rate [together with 95% Confidence Interval (CI)] for each study outcome will be separately calculated for each drug class and individual medication dividing the number of events occurring during the exposure to the study drug(s) by the total number of person-years of exposure.

In addition, age and gender crude incidence rates will be assessed also in an external reference group from general population in order to estimate the background incidence rate for study ouctomes.

Subsequently, to determine the comparative risks for VA and SCD/SUD, case controls will be conducted separately within each inception cohort of new users of the study drug classes. By

means of conditional logistic regression analyses, odds ratios (ORs) together with 95% CI will be calculated for each individual study drugs as compared to corresponding reference category.

All analyses will first be performed for each database separately and the heterogeneity between databases will be examined.

To account for the heterogeneity between databases as well as for the matching on database and index date, a mixed model will be used for the combined analysis.

A datawarehouse will be put in place for the ARITMO project. Datawarehouse is based on distributed data network principle: work up data locally and share aggregated/pooled data.

In detail, aggregated demographic, clinical and prescription data from the seven databases in five countries (Denmark, Italy, Netherlands, UK and Germany) will be pooled through a distributed network approach by generation of common input data followed by local aggregation through custom-built software, Jerboa© (Annex VII), which was developed within the EU-ADR project - ICT-215847 (http://www.euadr-project.org/). The EU-ADR Consortium members agreed to share this software.

This software queries locally patient-level data in the different databases, which are later aggregated, de-identified and sent in encrypted format to a central repository for evaluation and further analysis.

4.2. Sub-Analyses

4.2.1. Effect of Dosage

The objective of these sub-analyses is to determine the effect of dosage of individual study drugs on the risk of VA and SCD/SUD. In these analyses the risk associated with different dosages of the same drug or drug group will be compared as well as the risk of individual study drugs with reference within each dose category.

Sensitivity analyses will be conducted based on different methods of dose estimation (see above).

Moreover, for each drug class and individual medication we will test a linear trend across the dose strata, including in the model dose as a categorical variable.

For some drug classes, the dose varies substantially based on the indication of use (i.e. antipsychotics for the treatment of schizophrenia vs dementia and related disorders). This aspect should be taken into account when exploring the dose effect of antipsychotics.

4.2.2. Effect of Duration of Use

The objective of these sub-analyses is to determine the effect of the length of treatment with the study drugs on the risk of VA and SCD/SUD. In these analyses the risk associated with different durations of use of the same drug or drug group will be compared.

Sensitivity analyses will be conducted based on different methods of duration of use estimation (see above).

Moreover, we will test a linear trend across the duration of use strata, including in the model duration of use as a categorical variable.

4.2.3. Effect of Prior Use

The objective of these sub-analyses is to determine the risks for recent and past use of study drugs. In these analyses the risk associated with different types of use status within the same drug or drug group will be compared.

4.2.4. Effect of Co-Medication

The objective of these sub-analyses is to determine the modifying effect of frequently used and potentially harmful concomitant medications on the risk of VA and SCD/SUD associated to the study drugs. Co-medications taken into account are:

a) Drugs potentially inhibiting the isoenzime of cytocrome P450 involved in the metabolism of the study drugs as specified in Annex V. As the metabolism varies substantially across the study drugs, the list of concomitant medications will be different for each drug class.

b) Drugs that may prolong QT interval as specified in Annex VI. For each drug class, all the medications other than those belonging to that specific class will be taken into account.

In these analyses the odds ratio (OR) of the co-medication as well as the OR of the interaction between co-medication and individual study drugs will be examined. Additionally, a stratified analysis will be performed.

4.2.5. Effect of Co-Morbidity

The objective of these sub-analyses is to determine the modifying effect of specific co-morbidities on the risk of VA and SCD/SUD. Co-morbidities taken into account are prior cardiovascular diseases and presence of cancer as specified in Annex IV. In addition, patients with ventricular arrhythmias registered within one year prior the study entry will be identified and also analysed in a specific sub-analysis.

Cancer patients are an important group for the exposures to some drug classes (i.e. antibacterials and antimycotics) under investigation. However, problems could be expected wfor the case validation because persons are hospitalized for long periods of time and it may be difficult to identify the exact cause of death of these patients. Moreover, chemotherapy may be a strong confounder of the association between study drugs and outcomes.

In these analyses the OR of the co-morbidity as well as the OR of the interaction between co-morbidity and individual study drugs will be examined. Additionally, a stratified analysis will be performed.

4.2.6. Effect of Indication for use

The objective of these sub-analyses is to determine the modifying effect of specific indication for use on the risk of VA and SCD/SUD associated to the study drugs. Indications for use taken into account for each drug class are listed in Annex IV. These categories may be further revised based on the findings from the drug utilization study.

In these analyses the OR of the indication for use as well as the OR of the interaction between indication for use and individual study drugs will be examined. Additionally, a stratified analysis will be performed.

4.2.7. Examination of Drug Subgroup Effects

The objective of these sub-analyses is to determine whether the risks of study outcomes is increased in specific study drugs that are grouped together based on:

a. hERG-encoded potassium channel inhibiting capacity

b. Affinity to other biological targets that are identified on the basis of the findings from *in silico* simulation within WP7

c. Chemical characteristics (i.e. phenothiazines, butyrophenones, benzamides, and atypicals among antipsychotics; macrolides, cephalosporins, fluorochinolones, tetraciclines, aminoglycoside, and sulfonamides among antibacterials).

These sub-analyses will allow for testing biological hypotheses.

In these analyses OR will be calculated for each drug subgroup using the same comparator as in the main analysis. Moreover, the linear trend will be tested for a) and b).

4.2.8. Examination of Age and Sex Effects

The objective of these sub-analyses is to determine whether there is an interaction between age and sex and VA and SCD/SUD risk associated with the use of study drugs.

In these analyses the ORs of the two-way interactions between individual study drugs and age or sex will be examined. Additionally a stratified analysis will be performed.

4.3. Selection of confounders

A stepwise approach for confounder selection will be applied:

1. Covariates specified in the a priori list (see Annex IV) will be considered as potential confounders.
2. Univariate analyses will be performed for each potential confounder and outcome through conditional logistic regression. If the potential confounder is univariately associated with the outcome *(p <0.10)*, it will be kept as potential confounder for further steps in the model building process. Else, it will not be further considered.

3. As confounders, we will retain all the covariates that are significantly associated with the study outcome and change the crude risk estimate for current use of the study drugs for more than 10% [22].

4.4. Sensitivity Analyses

A number of sensitivity analyses will be performed to evaluate the robustness of the results and investigate the effect of potential biases and exposure and outcome misclassification:

- To explore the potential effect of outcome misclassification, we will perform a sensitivity analysis in which only the cases judged as definite will be included.
- To explore the potential effect of exposure misclassification, in some sensitivity analyses we will vary the risk window for current users removing the 30 days carry-over period or considering only 15 days period.
- The risk of ventricualar rhythmia is extremely high in the period following the occurrence of acute myocardial infarction (AMI). For this reason, we will perform a sensitivity analysis by excluding all the patients with a diagnosis of AMI recorded within one week prior to the index date
- Different categorizations for dose and duration of continuous use, and use status, will be applied and the results will be compared.
- As regard the anti-infectives, the possibility to conduct a sensitivity analysis using the case cross over design will be explored.

5. Quality assurance

The study will be conducted according to the guidelines for Good Pharmacoepidemiology Practice (GPP). Quality assurance guidelines has been produced by WP 1 (EMC) in the deliverable D1.1 "Report on Quality Assurance Guidelines and Procedures".

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 (i.e. SAS, SPSS, FoxPro, Stata) will be used for statistical analysis.

6. Ethical, Data Privacy, and Legal Issues

Ethical, data privacy, and legal issues have been addressed in detail by WP1 (EMC) in the deliverable D.1.2 "Report on Ethical Framework and Procedures in the Project".

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 for 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.

According to the European Commission directive 95/46/EC, processing of personal data is legitimate for scientific purposes if adequate safeguards are provided and followed. All member states have implemented this directive into their own national data protection legislation. All of the databases used in this study are currently already used for pharmacoepidemiological 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.

To observe these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate anonimized data with less information (e.g. no exact dates) that will be pooled across databases.

The observational database studies that will be conducted within the ARITMO project will be approved by each appropriate Scientific and Ethical Advisory Board.

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ANNEXES

Annex I – Protocol for drug utilization studies

A1.1 Background

In this Annex the design of the drug utilization study within the context of the ARITMO project is described. Some of the information reported is retrieved from the SOS project [FP7-HEALTH-223495], in which a similar protocol for drug utilization studies using data from healthcare databases was developed by EMC. SOS members agreed to share this protocol. There are several objectives for the drug utilazion studies in the ARITMO project:

1. Patterns of antipsychotics, antihistamines and anti-infectives use will be analyzed, in terms of prevalence, incidence, volume and dose of use. Also user profiles will be analysed.

2. Additionally, we will study how the definition of "wash-out period" and the calculation of duration of use affect cohort size, distribution of exposure across types of drugs and duration categories, respectively. This information will be used to formulate the proper exposure status in the observational studies.

Finally, together with information on the rates and relative risk for the study outcomes associated to the drugs of interest, estimated data on the prevalence of use for antipsychotics, antihistamines and anti-infectives will allow for the assessment of the potential public health impact of the study findings.

A1.2 Study Objective

The aim of this study is to describe the utilization of antipsychotics, antihistamines and anti-infectives on three levels:

- ***Population level***

(a) Prevalence and incidence of use during the study period by age groups, gender, and calendar time

(b) Drug consumption (number of Rx, DDD/1000 inhabitants day) by age, gender and calendar time

- ***Person level***

(a) Volume of drug use per user (number of Rx, duration of exposure) by age, gender

(b) Switch patterns by age, gender

(c) Gaps between consecutive prescriptions

- ***Prescription level***

(a) Patient determinants at each prescription and channelling

(b) Daily dose per prescription (Rx) by age, gender, type of observed drug, and calendar time.

The secondary objective is to study the effects of the length of "the wash-out period", defined as the pre-specified period in which no study drugs should be used before cohort entry to identify incident users only, on the rate and type of new users.

A1.3 Study Design

This drug utilization study is a descriptive, retrospective study.

A1.4 Source data

The underlying population will consist of all eligible persons retrieved from the databases as mentioned in the main protocol **(see Paragraph 3.2)**.

A1.5 Study period

The available follow-up years vary across databases and are currently comprised between 1st January 1996 and 31st December 2009. The lag time for the update of data also vary across databases. All the databases will contribute data from the earliest data to the latest data possible at the time of extraction **(see Paragraph 3.3)**.

A1.6 Study population

The study population will comprise all persons in the source population who are registered with the databases during the study period and have at least one year of valid data **(see Paragraph 3.4)**.

A1.7 Follow-up period

The patients start contributing to the study at the latest of the following dates:

- 12 month of continuous registration in the database with up to standard quality data (as usually defined in specific database).
- Start of study period

The follow-up ends at the earliest of the following dates

- End of study period, i.e. December 31, 2009.
- Transfer out of database / end of registration / end of membership / interruption of registration or membership / last data collection of the database.
- Death.

A1.8 Data collection

The following data need to be prepared by the database owners into a common data input model (similar to safety studies). These will be the input variables and files for Jerboa, the software tool which was previously developed in EU-ADR (*FP7*-ICT-2007-215847) and which will be adapted to ARITMO to extract, prepare and aggregate data from a common data input model and subsequently to calculate the proposed drug use parameters in a systematic and uniform approach **(see Annex VII for current description of Jerboa)**.

A1.8.1 Population file

For the source population the following data will be extracted:

- Patient ID: same as in other files
- Eligibility date: date of patient entry into the database with up to standard information (NOTE: the one year run in period does not need to applied by database owner, will be done automatically by Jerboa, Annex VII)
- Exit date: date patient ends his follow-up (transfer out of database / end of registration / end of membership / interruption of registration or membership/ Death) or last data collection date of the database
- Date of birth
- Gender

A1.8.2 Drug file: antipsychotics, antihistamines and anti-infectives

The following information on antipsychotics (ATC: N05A), anti-infectives (antibacterials [J01], antimycotics [J02], antivirals [J05], and anti-protozoals [P01) and H1-antihistamines (ATC: R06) will be retrieved from the databases (**see Annex III for the complete list of drugs**), according to the different outcome measures **(see Paragraph A1.9)**:

- Patient ID
- ATC code (7 characters; 5th level)
- Date of prescription or dispensing (whichever is more reliable if both are available)
- Route of administration (OS=oral; P=parenteral; INHAL: inhalation; REC: rectal; TOP: topical or local)
- Total quantity of active principle in each prescription
- DDD-value (based on WHO criteria; 2010 version)
- Formulation (G: grams; MG: milligrams; ML: millilitres; U: tablets, vials, suppository, etc.)
- Number of Units per prescription (means the number of tablets, capsule, vials, suppositories, etc. contained in each prescription)
- Strength per Unit (means the quantity of active principle per Unit)
- Number of prescribed Units per day (if available)
- Total number of DDD in each prescription/dispensing
- Duration_1 (based on the formula: Total quantity of active principle/[Strength per Unit* Number of prescribed Units per day]); if available
- Duration_2 (based on the assumption that a person takes one DDD per day: Total quantity of active principle/DDD-value); all databases
- Coded indication (i.e. the disease/symptom for which the drug is prescribed/dispensed)
- Date of coded indication (i.e. not necessarily it correspond to the date of prescription)
- Type of coding (ICD9; ICD10; ICPC; READ; FREE TEXT)

If two or more prescriptions are issued on the same date, these will be entered as separate rows as well.

Data on drugs should cover the period from eligibility (patient registered and database up to quality/standard) and thus includes also all drugs during the one year run in period.

A1.8.3 Event file

Several covariates will be retrieved to describe the characteristics of the study drug users **(see Annex IV)** and need to be extracted locally and prepared for the common input model. The dataset that needs to be prepared for each of these conditions comprises the following variables:

- Patient ID
- Date of diagnosis of the event (repeatedly over time: i.e. each occurrence if acute disease, or once at date of first registration for chronic disease)
- Type of event (for names see Jerboa names as specified in the Jerboa event extraction instructions for the observational studies)
- Code of the event (if available)
- Type of coding (ICD9; ICD10; ICPC; READ; FT: free text; LAB: lab value; D: drug)

Data on events should cover the period from eligibility (patient registered and database up to quality/standard) and thus includes all events during the one year run in period, plus recurrent events.

A1.9 Outcome measures

A1.9.1 Population level

A1.9.1.1 Prevalence of antipsychotics, antihistamines and anti-infectives use

Prevalence of use, overall and by type of observed drug, will be measured as the number of individuals receiving at least one drug prescription in a specific time-window, divided by the number of person-time (months, years) of all individuals alive and registered in the database in the corresponding time-window.

Table A1.1.1: Prevalence of antipsychotics, antihistamines and anti-infectives use parameters

Indicator	Time-window	Measure	Numerator	Denominator	Output Jerboa
Prevalence of specific drug use	PT (month, year)	Number/ 1,000 PT	Number of individuals having at least one day of exposure to specific drug during an observed time window	Total PT in the observed time window	Prevalence of use per drug (ATC 5th level) by calendar month and calendar year stratified by age and gender

Prevalence of chemical/therapeutic/ pharmacological subgroup use	PT (month, year)	Number/ 1,000 PT	Number of individuals having at least one day of exposure to specific chemical/therapeutic/ pharmacological subgroup during an observed time window	Total PT in the observed time window	Prevalence of use per drug (ATC 4th level) by calendar month and calendar year stratified by age and gender
Prevalence of therapeutic/ pharmacological subgroup use	PT (month, year)	Number/ 1,000 PT	Number of individuals having at least one day of exposure to specific therapeutic/ pharmacological subgroup during an observed month	Total PT in the observed time window	Prevalence of use per drug (ATC 3rd level) by calendar month and calendar year stratified by age and gender
Prevalence of therapeutic subgroup use	PT (month, year)	Number/ 1,000 PT	Number of individuals having at least one day of exposure to specific therapeutic subgroup during an observed month	Total PT in the observed time window	Prevalence of use per drug (ATC 2nd level) by calendar month and calendar year stratified by age and gender

PT: person-time

The output files of Jerboa that will be shared will comprise the numerator, denominator and outcome measures by different ATC levels, age, gender and calendar month/year. These datasheets will be sent from the local sites to the data warehouse in Rotterdam.

A1.9.1.2 New users and incidence of antipsychotics, antihistamines and anti-infectives use

A 'new' user is defined as a patient receiving the first prescription for antipsychotics/antihistamines/anti-infectives during the study period without having any prescription in a specific "wash-out period" preceding the onset of the study period. Patients can re-enter if during the follow-up period they would stop and have a long enough wash-out to re-enter again.
The length of the required wash-out period can vary and this will influence the size and composition of a new user cohort. This will be investigated in two runs using a 6 and 12 month period as wash out period.

Incidence of use will be calculated as the number of 'new' users in a defined time-window divided by the number of person-time (months, years) for antipsychotics, antihistamines and anti-infectives naïve persons at start of the time-window.

Table A1.1.2: Incidence of antipsychotics, antihistamines and anti-infectives use parameters

Indicator	Time-window	Measure	Numerator	Denominator	Output Jerboa

Incidence of specific drug use	PT (month, year)	Number/ 1,000 PT	Number of new users in that time window (with a certain naïve period: 6 months and 12 months)	Total PT in the observed time window (censoring not necessary)	Incidence of use per drug (ATC 5th level) by calendar month and calendar year stratified by age and gender
Incidence of chemical/therapeutic/ pharmacological subgroup use	PT (month, year)	Number/ 1,000 PT	Number of new users in that time window (with a certain naïve period: 6 months and 12 months)	Total PT in the observed time window (censoring not necessary)	Incidence of use per drug (ATC 4th level) by calendar month and calendar year stratified by age and gender
Incidence of therapeutic/ pharmacological subgroup use	PT (month, year)	Number/ 1,000 PT	Number of new users in that time window (with a certain naïve period: 6 months and 12 months)	Total PT in the observed time window (censoring not necessary)	Incidence of use per drug (ATC 3rd level) by calendar month and calendar year stratified by age and gender
Incidence of therapeutic subgroup use	PT (month, year)	Number/ 1,000 PT	Number of new users in that time window (with a certain naïve period: 6 months and 12 months)	Total PT in the observed time window (censoring not necessary)	Incidence of use per drug (ATC 2nd level) by calendar month and calendar year stratified by age and gender

PT: person-time

The output files of Jerboa that will be shared will comprise the numerator, denominator and outcome measures by different ATC levels, calendar month/year, age and gender per data-naïve period. These datasheets will be sent from the local sites to the data warehouse.

A1.9.1.3 Drug consumption of antipsychotics, antihistamines and anti-infectives use

The consumption of antipsychotics, antihistamines and anti-infectives use will be expressed by the number of Rx and the DDD/1,000 inhabitants/day. The DDD/1,000 inhabitants/day will be calculated by using the following formula:

$$\frac{\text{Total number of DDD being prescribed}}{\text{Total active population X defined time-window / 1,000}}$$

The total number of DDD prescribed corresponds to the total amount of active principle divided by the DDD of the corresponding molecule as defined by the WHO (Available at: http://www.whocc.no/atc_ddd_index/. Accessed 17/09/2010).

Table A1.1.3: Volume of antipsychotics, antihistamines and anti-infectives use parameters

Indicator	Time-window	Measure	Numerator	Denominator	Output Jerboa
Number of antipsychotics, antihistamines and anti-infectives prescriptions	PT (month, year)	Number/ 1,000 PT	Number of Rx	Total PT in the observed time window	Sum of Rx per drug (ATC 5th level) by calendar month and calendar year stratified by age and gender
DDD/1,000 inhabitants day for antipsychotics, antihistamines and anti-infectives	PT (month, year)	DDD/1,000 inhabitants day	Total number of DDD being prescribed	Total active population X defined time-window divided by 1,000	DDD/1,000 inhabitants day per drug (ATC 5th level) by calendar year stratified by age and gender (for each method of duration calculation)

PT: person-time

The Jerboa output file that will be sent to the coordinating centre will comprise the numerator, denominator and outcome measures by ATC code and calendar month/year and age, gender.

A1.9.2 Person level use analyses

For each individual patient, from the drug file **(See Paragraph A7.8.2)**, we will calculate several parameters to estimate duration and consumption as well as switching over the study period. The Jerboa output file will be at the level of an individual patient and comprise the following variables:

- Patient ID
- ATC code (5th level) for index antipsychotics, antihistamines and anti-infectives, date of cohort entry (i.e. date of first drug Rx after the specific naïve period of 6 and 12 months in the different runs), age at cohort entry, gender, days of follow-up after index Rx;
- sum drug Rx during follow-up, duration of exposure during follow-up, number of different antipsychotics, antihistamines and anti-infectives during follow-up;
- sum drug Rx one year after cohort entry, duration of exposure one year after cohort entry, number of different antipsychotics, antihistamines and anti-infectives one year after cohort entry;
- ATC code of first switch

These data will be produced locally and sent to the data warehouse.

A1.9.2.1 Volume of antipsychotics, antihistamines and anti-infectives use per user

The following parameters will be calculated per patient from the date of cohort entry until the end of the follow-up (or one year after cohort entry):

Table A1.2.1: Parameters to estimate volume of antipsychotics, antihistamines and anti-infectives use per patient

Indicator	Time-window	Measure	Numerator	Denominator	Output Jerboa
Number of prescription with antipsychotics, antihistamines and anti-infectives per patient	Follow-up	Mean (median) number/ 1,000 PY	Number of Rx	Total PY per patient	Sum of Rx per drug (ATC 5th level) during follow-up, stratified by age and gender
Duration of exposure with antipsychotics, antihistamines and anti-infectives per patient	Follow-up	Mean (median) exposure/1,000 PY	PT of exposure	Total f PY per patient	Sum of person days of drug exposure (ATC 5th level) during follow-up, stratified by age and gender
Number of prescription with antipsychotics, antihistamines and anti-infectives per patient 1st year after study cohort entry	1st year of follow-up	Mean (median) number/ 1,000 PY	Number of Rx	One PY per patient	Sum of Rx per drug (ATC 5th level) 1st year after study cohort entry, stratified by age and gender
Duration of exposure with antipsychotics, antihistamines and anti-infectives per patient 1st year after study cohort entry	1st year of follow-up	Mean (median) exposure/1,000 PY	PT of exposure	One PY per patient	Sum of person days of drug exposure (ATC 5th level) 1st year after study cohort entry stratified by age and gender

PY: person-year; PT: person-time

A1.9.2.2 Switch between antipsychotics, antihistamines and anti-infectives use

In order to study switches, we will calculate for each drug class the number of different 5th level antipsychotics, antihistamines and anti-infectives that the patients are using after cohort entry and during the first year after cohort entry. In addition we will identify the first switch, described as the first antipsychotics/antihistamines/anti-infectives being prescribed during follow-up after the initial index drug. All these analyses will be conducted for each drug class, separately.

These parameters will be added as output variables in the Jerboa output as specified under A1.9.2.

A1.9.2.3 Gaps between antipsychotics, antihistamines and anti-infectives prescriptions

In order to estimate the gap length between subsequent prescriptions, starting from the date of cohort entry, we will estimate for each prescription dispensed/prescribed during the study period the time since the end of the previous prescription (may extend the wash-out period) and the time until the next prescription. The time (days) from the end of the last drug prescription and the mean time (days) until the next one will be calculated per patient. Patients with only one prescription in follow-up will get a missing value.

The estimations on the gap between two similar drugs within each observed category will be used to substantiate the definition of continuous periods use, i.e. the allowed grace period between two consecutive prescriptions.

A1.9.3 Prescription level analyses

A1.9.3.1 Patient determinants at each prescription and channelling

The determinants of antipsychotics, antihistamines and anti-infectives use will be assessed for the most frequently drugs (ATC 7; 5th level) included in **Annex III**. These determinants are different among the drug classes of interest (as listed in **Annex IV).** Such list is part of the general list of confounders in ARITMO and is synchronised with the other WPs. The date of each prescription will be used as the index date aimed to characterise patients.

A1.9.3.2 Daily dose per prescription

Starting from the drug file, daily dose for each drug will be calculated where available by multiplying the Strength per Unit with Number of prescribed Units per day. Such information will be stratified by age, gender, type of observed drug, and calendar time.

A1.10 Analyses of study drug use

All data analyses will be done locally by Jerboa, query output will be shared centrally in the datawarehouse in Rotterdam for further analyses. Antipsychotics, antihistamines and anti-infectives use will be described at population and person level and compared between databases and countries.

Characteristics of drug users will be described and compared between individual medication by database and by country. An important aspect will be to describe channelling (i.e. a form of allocation bias, where drugs with similar therapeutic indications are prescribed to groups of patients with prognostic differences) in different countries by product and to see whether channelling has changed over calendar time.

Chi-square test for categorical variables and Student's t-test for continuous variables, with a significance level of $P < 0.05$, will be used for assessing the differences among use of various drug types compared to the reference exposure, which will be represented by the most widely used drug in participating countries, within each therapeutic group.

Annex II – Frequency of outcomes in different databases^ – preliminary analyses

Outcome	BIPS (Germany)	SIMG (ITA)	Emilia Romagna regional DB (ITA)	IPCI (NL)	PHARMO (NL)	Aarhus (DK)
Study Years	2004-2008	2005-2009	2003-2009	1996-2009	1998-2008	2000-2007
Symptomatic QT prolongation*	Not available at this moment	N=313 QT prolong (252 from free text)	N=53,406 (syncope) N=716 (QT prolong.) No ECG	N=5,061 QT prolong (3,638 pts) Validation required	N=19,618 (syncope) N=418 (QT prolong.) No ECG	N=35,950 ECG data may be retrieved ad hoc
TdP	Not available	N=35 Validation required	Not available	N=57 Validation required	Not available	Not available
Ventricular arrhythmia**	N=33,300	N=983 To be revised	N=38,813	N=9,277	N=7,342	N=4,628 (185 with resuscitation)
SCD/SUD***	Death registry will be soon available	N=301	Not available	N=1,800 Based on Priori'criteria	Not available	N=748

In this table the preliminary number of patients with the unvalidated study outcomes per database is reported.
^ THIN database could not be explored for this preliminary analysis
** QT prolongation and non vaso-vagal syncope in primary discharge diagnoses or medical records using codes*
*** This outcome include both tachycardia and fibrillation*
**** most of the database requires much more time to ascertain this outcome and for this reason data for the preliminary analysis were available only for few databases*

Annex III – List of drugs that will be investigated in the ARITMO project

ANTIBIOTICS AND ANTIMYCOBACTERIALS	
A02	**DRUGS FOR ACID RELATED DISORDERS**
A02B	**DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)**
A02BD	**COMBINATIONS FOR ERADICATION OF HELICOBACTER PYLORI**
A02BD01	OMEPRAZOLE, AMOXICILLIN AND METRONIDAZOLE
A02BD02	LANSOPRAZOLE, TETRACYCLIN AND METRONIDAZOLE
A02BD03	LANSOPRAZOLE, AMOXICILLIN AND METRONIDAZOLE
A02BD04	PANTOPRAZOLE, AMOXICILLIN AND CLARITHROMYCIN
A02BD05	OMEPRAZOLE, AMOXICILLIN AND CLARITHROMYCIN
A02BD06	ESOMEPRAZOLE, AMOXICILLIN AND CLARITHROMYCIN
A02BD07	LANSOPRAZOLE AMOXICILLIN AND CLARITHROMYCIN
A07	**ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS**
A07A	**INTESTINAL ANTIINFECTIVES**
A07AA	**ANTIBIOTICS**
A07AA01	NEOMYCIN
A07AA03	NATAMYCIN
A07AA04	STREPTOMYCIN
A07AA05	POLYMYXIN B
A07AA06	PAROMOMYCIN
A07AA08	KANAMYCIN
A07AA09	VANCOMYCIN
A07AA10	COLISTIN
A07AA11	RIFAXIMIN
A07AA51	NEOMYCIN, COMBINATIONS
A07AA54	STREPTOMYCIN, COMBINATIONS
A07AB	**SULFONAMIDES**
A07AB02	PHTHALYLSULFATHIAZOLE
A07AB03	SULFAGUANIDINE
A07AB04	SUCCINYLSULFATHIAZOLE
G01	**GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS**
G01AA	**ANTIBIOTICS**
G01AA02	NATAMYCIN
G01AA04	CANDICIDIN
G01AA05	CHLORAMPHENICOL
G01AA06	HACHIMYCIN
G01AA07	OXYTETRACYCLNE
G01AA08	CARFECILLIN
G01AA09	MEPARTRICIN
G01AA10	CLINDAMICIN

G01AA11	PENTAMYCIN
J01A	**TETRACYCLINES**
J01AA	**Tetracyclines**
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
J01AA56	oxytetracycline, combinations
J01B	**AMPHENICOLS**
J01BA	**Amphenicols**
J01BA01	chloramphenicol
J01BA02	thiamphenicol
J01BA52	thiamphenicol, combinations
J01C	**BETA-LACTAM ANTIBACTERIALS, PENICILLINS**
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
J01CA20	combinations
J01CA51	ampicillin, combinations
J01CE	**Beta-lactamase sensitive penicillins**

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
J01CF	**Beta-lactamase resistant penicillins**
J01CF01	dicloxacillin
J01CF02	cloxacillin
J01CF03	meticillin
J01CF04	oxacillin
J01CF05	flucloxacillin
J01CG	**Beta-lactamase inhibitors**
J01CG01	sulbactam
J01CG02	tazobactam
J01CR	**Combinations of penicillins, incl. 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**
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
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
J01DD54	ceftriaxone, combinations
J01DD62	cefoperazone, combinations
J01DE	**Fourth-generation cephalosporins**
J01DE01	cefepime
J01DE02	cefpirome
J01DF	**Monobactams**
J01DF01	aztreonam
J01DH	**Carbapenems**
J01DH02	meropenem
J01DH03	ertapenem
J01DH04	doripenem
J01DH51	imipenem and enzyme inhibitor
J01DH55	panipenem and betamipron
J01DI	**Other cephalosporins**
J01DI01	ceftobiprole medocaril
J01E	**SULFONAMIDES AND TRIMETHOPRIM**
J01EA	**Trimethoprim and derivatives**
J01EA01	trimethoprim
J01EA02	brodimoprim
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	sulfamazone
J01ED20	combinations
J01EE	**Combinations of sulfonamides and trimethoprim, incl. 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
J01F	**MACROLIDES, LINCOSAMIDES AND STREPTOGRAMINS**
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
J01FF	**Lincosamides**
J01FF01	clindamycin
J01FF02	lincomycin
J01FG	**Streptogramins**
J01FG01	pristinamycin
J01FG02	quinupristin/dalfopristin
J01G	**AMINOGLYCOSIDE ANTIBACTERIALS**
J01GA	**Streptomycins**
J01GA01	streptomycin
J01GA02	streptoduocin
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
J01M	**QUINOLONE ANTIBACTERIALS**
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
J01MB	**Other quinolones**
J01MB01	rosoxacin
J01MB02	nalidixic acid
J01MB03	piromidic acid
J01MB04	pipemidic acid
J01MB05	oxolinic acid
J01MB06	cinoxacin
J01MB07	flumequine
J01R	**COMBINATIONS OF ANTIBACTERIALS**
J01RA	**Combinations of antibacterials**
J01RA01	penicillins, combinations with other antibacterials
J01RA02	sulfonamides, combinations with other antibacterials (excl. trimethoprim)
J01RA03	cefuroxime, combinations with other antibacterials
J01RA04	spiramycin, combinations with other antibacterials
J01X	**OTHER ANTIBACTERIALS**
J01XA	**Glycopeptide antibacterials**
J01XA01	vancomycin
J01XA02	teicoplanin
J01XA03	telavancin
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
J01XX	**Other antibacterials**
J01XX01	fosfomycin
J01XX02	xibornol
J01XX03	clofoctol
J01XX04	spectinomycin
J01XX05	methenamine
J01XX06	mandelic acid
J01XX07	nitroxoline
J01XX08	linezolid
J01XX09	daptomycin
J04A	**DRUGS FOR TREATMENT OF TUBERCULOSIS**
J04AA	**Aminosalicylic acid and derivatives**

J04AA01	aminosalicylic acid
J04AA02	sodium aminosalicylate
J04AA03	calcium aminosalicylate
J04AB	**Antibiotics**
J04AB01	cycloserine
J04AB02	rifampicin
J04AB03	rifamycin
J04AB04	rifabutin
J04AB05	rifapentine
J04AB30	capreomycin
J04AC	**Hydrazides**
J04AC01	isoniazid
J04AC51	isoniazid, combinations
J04AD	**Thiocarbamide derivatives**
J04AD01	protionamide
J04AD02	tiocarlide
J04AD03	ethionamide
J04AK	**Other drugs for treatment of tuberculosis**
J04AK01	pyrazinamide
J04AK02	ethambutol
J04AK03	terizidone
J04AK04	morinamide
J04AM	**Combinations of drugs for treatment of tuberculosis**
J04AM01	streptomycin and isoniazid
J04AM02	rifampicin and isoniazid
J04AM03	ethambutol and isoniazid
J04AM04	thioacetazone and isoniazid
J04AM05	rifampicin, pyrazinamide and isoniazid
J04AM06	rifampicin, pyrazinamide, ethambutol and isoniazid
J04B	**DRUGS FOR TREATMENT OF LEPRA**
J04BA	**Drugs for treatment of lepra**
J04BA01	clofazimine
J04BA02	dapsone
J04BA03	aldesulfone sodium
R02A	**THROAT PREPARATIONS**
R02AB	**Antibiotics ***
R02AB01	NEOMYCIN
R02AB02	TYROTHRICIN
R02AB03	FUSAFUNGINE
R02AB04	BACITRACIN
R02AB30	GRAMICIDIN

ANTIVIRALS

J05A	**DIRECT ACTING ANTIVIRALS**

J05AA	**Thiosemicarbazones**
J05AA01	metisazone
J05AB	**Nucleosides and nucleotides excl. reverse transcriptase inhibitors**
J05AB01	aciclovir
J05AB02	idoxuridine
J05AB03	vidarabine
J05AB04	ribavirin
J05AB06	ganciclovir
J05AB09	famciclovir
J05AB11	valaciclovir
J05AB12	cidofovir
J05AB13	penciclovir
J05AB14	valganciclovir
J05AB15	brivudine
J05AC	**Cyclic amines**
J05AC02	rimantadine
J05AC03	tromantadine
J05AD	**Phosphonic acid derivatives**
J05AD01	foscarnet
J05AD02	fosfonet
J05AE	**Protease inhibitors**
J05AE01	saquinavir
J05AE02	indinavir
J05AE03	ritonavir
J05AE04	nelfinavir
J05AE05	amprenavir
J05AE06	lopinavir
J05AE07	fosamprenavir
J05AE08	atazanavir
J05AE09	tipranavir
J05AE10	darunavir
J05AF	**Nucleoside and nucleotide reverse transcriptase inhibitors**
J05AF01	zidovudine
J05AF02	didanosine
J05AF03	zalcitabine
J05AF04	stavudine
J05AF05	lamivudine
J05AF06	abacavir
J05AF07	tenofovir disoproxil
J05AF08	adefovir dipivoxil
J05AF09	emtricitabine
J05AF10	entecavir
J05AF11	telbivudine
J05AF12	clevudine
J05AG	**Non-nucleoside reverse transcriptase inhibitors**

J05AG01	nevirapine
J05AG02	delavirdine
J05AG03	efavirenz
J05AG04	etravirine
J05AH	**Neuraminidase inhibitors**
J05AH01	zanamivir
J05AH02	oseltamivir
J05AR	**Antivirals for treatment of HIV infections, combinations**
J05AR01	zidovudine and lamivudine
J05AR02	lamivudine and abacavir
J05AR03	tenofovir disoproxil and emtricitabine
J05AR04	zidovudine, lamivudine and abacavir
J05AR05	zidovudine, lamivudine and nevirapine
J05AR06	emtricitabine, tenofovir disoproxil and efavirenz
J05AX	**Other antivirals**
J05AX01	moroxydine
J05AX02	lysozyme
J05AX05	inosine pranobex
J05AX06	pleconaril
J05AX07	enfuvirtide
J05AX08	raltegravir
J05AX09	maraviroc
N04BB01	Amantadine*

**Amantadine is mainly used for the treatment of Parkinson's disease. However, it was included in the list based on the recent warning about its proarrhytmic risk when used as antivirals. This safety warning was issue by the US agency "Center for Disease Control and Prevention"*

ANTIMYCOTICS

A07AA02	NYSTATIN
A07AC	**IMIDAZOLES DERIVATES**
A07AC01	MICONAZOLE
D01	**ANTIFUNGALS FOR DERMATOLOGICAL USE**
D01B	**ANTIFUNGALS FOR SYSTEMIC USE**
D01BA01	GRISEOFULVIN
D01BA02	TERBINAFINE
G01AF	**IMIDAZOLE DERIVATES**
G01AF02	CLOTRIMAZOLE
G01AF04	MICONAZOLE
G01AF05	ECONAZOLE
G01AF06	ORNIDAZOLE
G01AF07	ISOCONAZOLE
G01AF08	TIOCONAZOLE
G01AF11	KETOCONAZOLE
G01AF12	FENTICONAZOLE

G01AF13	AZANIDAZOLE
G01AF14	PROPENIDAZOLE
G01AF15	BUTCONAZOLE
G01AF16	OMOCONAZOLE
G01AF17	OXICONAZOLE
G01AF18	FLUTRIMAZOLE
G01AF20	COMBINATIONS OF IMIDAZOLE DERIVATES
G01AG02	TERCONAZOLE
G04CX03	Mepartricin
J02A	**ANTIMYCOTICS FOR SYSTEMIC USE**
J02AA	**Antibiotics**
J02AA01	amphotericin B
J02AA02	hachimycin
J02AB	**Imidazole derivatives**
J02AB01	miconazole
J02AB02	ketoconazole
J02AC	**Triazole derivatives**
J02AC01	fluconazole
J02AC02	itraconazole
J02AC03	voriconazole
J02AC04	posaconazole
J02AX	**Other antimycotics for systemic use**
J02AX01	flucytosine
J02AX04	caspofungin
J02AX05	micafungin
J02AX06	anidulafungin

ANTIPROTOZOALS

P01A	**AGENTS AGAINST AMOEBIASIS AND OTHER PROTOZOAL DISEASES**
P01AA	**Hydroxyquinoline derivatives**
P01AA01	Broxyquinoline
P01AA02	Clioquinol
P01AA04	Chlorquinaldol
P01AA05	Tilbroquinol
P01AA52	Clioquinol, combinations
P01AB	**NITROIMIDAZOLE DERIVATES**
P01AB01	METRONIDAZOLE
P01AB02	TINIDAZOLE
P01AB03	ORNIDAZOLE
P01AB04	AZANIDAZOLE
P01AB05	PROPENIDAZOLE
P01AB06	NIMORAZOLE
P01AB07	SECNIDAZOLE
P01AC	**Dichloroacetamide derivatives**
P01AC01	Diloxanide

P01AC02	Clefamide
P01AC03	Etofamide
P01AC04	Teclozan
P01AR	**Arsenic compounds**
P01AR01	Arsthinol
P01AR02	Difetarsone
P01AR03	Glycobiarsol
P01AR53	Glycobiarsol, combinations
P01AX	**Other agents against amoebiasis and other protozoal diseases**
P01AX01	Chiniofon
P01AX02	Emetine
P01AX04	Phanquinone
P01AX05	Mepacrine
P01AX06	Atovaquone
P01AX07	Trimetrexate
P01AX08	Tenonitrozole
P01AX09	Dihydroemetine
P01AX10	Fumagillin
P01AX11	Nitazoxanide
P01AX52	Emetine, combinations
P01B	**ANTIMALARIALS**
P01B	**ANTIMALARIALS**
P01BA	**Aminoquinolines**
P01BA01	Chloroquine
P01BA02	Hydroxychloroquine
P01BA03	Primaquine
P01BA06	Amodiaquine
P01BB	**Biguanides**
P01BB01	Proguanil
P01BB02	Cycloguanil embonate
P01BB51	Proguanil, combinations
P01BC	**Methanolquinolines**
P01BC01	Quinine
P01BC02	Mefloquine
P01BD	**Diaminopyrimidines**
P01BD01	Pyrimethamine
P01BD51	Pyrimethamine, combinations
P01BE	**Artemisinin and derivatives**
P01BE01	Artemisinin
P01BE02	Artemether
P01BE03	Artesunate
P01BE04	Artemotil
P01BE05	Artenimol
P01BE52	Artemether, combinations
P01BX	**Other antimalarials**

P01BX01	Halofantrine
P01C	**AGENTS AGAINST LEISHMANIASIS AND TRYPANOSOMIASIS**
P01CA	**Nitroimidazole derivatives**
P01CA02	Benznidazole
P01CB	**Antimony compounds**
P01CB01	Meglumine antimonate
P01CB02	Sodium stibogluconate
P01CC	**Nitrofuran derivatives**
P01CC01	Nifurtimox
P01CC02	Nitrofural
P01CD	**Arsenic compounds**
P01CD01	Melarsoprol
P01CD02	Acetarsol
P01CX	**Other agents against leishmaniasis and trypanosomiasis**
P01CX01	Pentamidine isethionate
P01CX02	Suramin sodium
P01CX03	Eflornithine

ANTIHISTAMINES FOR SYSTEMIC USE

D04AA	**ANTIHISTAMINES FOR TOPICAL USE***
D04AA01	thonzylamine
D04AA02	mepyramine
D04AA03	thenalidine
D04AA04	tripelennamine
D04AA09	chloropyramine
D04AA10	promethazine
D04AA12	tolpropamine
D04AA13	dimetindene
D04AA14	clemastine
D04AA15	bamipine
D04AA22	isothipendyl
D04AA32	diphenhydramine
D04AA33	diphenhydramine methylbromide
D04AA34	chlorphenoxamine
R06A	**ANTIHISTAMINES FOR SYSTEMIC USE**
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
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
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
R06AX53	thenalidine, combinations
R06AX58	pyrrobutamine, combinations

ANTIPSYCHOTICS

N05AA	**Phenothiazines with aliphatic side-chain**
N05AA01	chlorpromazine
N05AA02	levomepromazine
N05AA03	promazine
N05AA04	acepromazine
N05AA05	triflupromazine
N05AA06	cyamemazine
N05AA07	chlorproethazine
N05AB	**Phenothiazines with piperazine structure**
N05AB01	dixyrazine
N05AB02	fluphenazine
N05AB03	perphenazine
N05AB04	prochlorperazine

N05AB05	thiopropazate
N05AB06	trifluoperazine
N05AB07	acetophenazine
N05AB08	thioproperazine
N05AB09	butaperazine
N05AB10	perazine
N05AC	**Phenothiazines with piperidine structure**
N05AC01	periciazine
N05AC02	thioridazine
N05AC03	mesoridazine
N05AC04	pipotiazine
N05AD	**Butyrophenone derivatives**
N05AD01	haloperidol
N05AD02	trifluperidol
N05AD03	melperone
N05AD04	moperone
N05AD05	pipamperone
N05AD06	bromperidol
N05AD07	benperidol
N05AD08	droperidol
N05AD09	fluanisone
N05AE	**Indole derivatives**
N05AE01	oxypertine
N05AE02	molindone
N05AE03	sertindole
N05AE04	ziprasidone
N05AF	**Thioxanthene derivatives**
N05AF01	flupentixol
N05AF02	clopenthixol
N05AF03	chlorprothixene
N05AF04	tiotixene
N05AF05	zuclopenthixol
N05AG	**Diphenylbutylpiperidine derivatives**
N05AG01	fluspirilene
N05AG02	pimozide
N05AG03	penfluridol
N05AH	**Diazepines, oxazepines and thiazepines**
N05AH01	loxapine
N05AH02	clozapine
N05AH03	olanzapine
N05AH04	quetiapine
N05AH05	asenapine
N05AH06/N05AX09	clotiapine*
N05AL	**Benzamides**
N05AL01	sulpiride

N05AL02	sultopride
N05AL03	tiapride
N05AL04	remoxipride
N05AL05	amisulpride
N05AL06	veralipride
N05AL07	levosulpiride
N05AX	**Other antipsychotics**
N05AX07	prothipendyl
N05AX08	risperidone
N05AX10	mosapramine
N05AX11	zotepine
N05AX12	aripiprazole
N05AX13	paliperidone

**The ATC code for this drug was changed at the beginning of the year 2010*

Annex IV – Covariates of interest

AB = Antibiotics
AV = Antivirals
AP = Antipsychotics
AM = Antimycotics
A-Pr = Antiprotozoals
AH = Anti-histamines

Covariate	Assessment	AB	AM	AV	A-Pr	AP	AH
Demographics							
Age	Date of birth	X	X	X	X	X	X
Gender	Gender	X	X	X	X	X	X
Country of residence	Database	X	X	X	X	X	X
Frequency of attendance to physician	N. of contacts in the in GP database and number of hospitalization in the year prior index date	X	X	X	X	X	X
Cardiovascular Diseases							
History of Coronary Heart Disease	Disease codes OR use of vasodilators (ATC: C01D)	X	X	X	X	X	X
Subarachnoid haemorrhage	Disease codes	X	X	X	X	X	X
History of other Cerebrovascular Events	Disease codes	X	X	X	X	X	X
Hypertension	Disease codes OR use of anti-hypertensive medications*: ACE inhibitors (ATC:C09A, C09B), AT II antagonists(C09C, C09D), Beta blockers(C07), Calcium antagonists - (C08) and other hypertensive drugs (C02A-K, C02N) OR blood pressure measurements**	X	X	X	X	X	X
Conduction disorders	Disease codes	X	X	X	X	X	X
Atrial flutter/fibrillation	Disease codes	X	X	X	X	X	X
Other cardiac arrhythmias	Disease codes	X	X	X	X	X	X
Peripheral arterial disease	Disease codes	X	X	X	X	X	X
Heart Failure	Disease codes	X	X	X	X	X	X

Covariate	Assessment	AB	AM	AV	A-Pr	AP	AH
Valve disorders	Disease codes	X	X	X	X	X	X
Cardiomyopathies	Disease codes (*including both dilated and hypertrophic cardiomyopathies)*	X	X	X	X	X	X
ARVC/ARVD	Disease codes	X	X	X	X	X	X
Congenital heart disease	Disease codes	X	X	X	X	X	X
Pacemaker/defibrillator	Disease codes	X	X	X	X	X	X
Metabolic diseases							
Lipid metabolism disorder	Disease codes OR use of lipid lowering drugs (ATC: C10*)	X	X	X	X	X	X
Diabetes mellitus	Disease codes OR use of hypoglycemic drugs (ATC:A10*)	X	X	X	X	X	X
Obesity	Disease codes OR BMI ≥ 30 OR use of antiobesity drugs (ATC:A08*)	X	X	X	X	X	X
Hypokalemia	Disease codes OR lab value (≤3.5 mmol/L)	X	X	X	X	X	X
Hypocalcaemia	Disease codes OR lab value (≤ 1.1 mmol/L)	X	X	X	X	X	X
Hypomagnesiemia	Disease codes OR lab value (≤ 1.8 mmol/L)	X	X	X	X	X	X
Other diseases							
Acute and chronic renal failure	Disease codes	X	X	X	X	X	X
Chronic liver disease	Disease codes	X	X	X	X	X	X
Cancer (except for basal cell carcinomas)	Disease codes	X	X	X	X	X	X
Chronic obstructive pulmonary disease	Disease codes OR use of specific medications: (ATC:R03*)	X	X	X	X	X	X
Epilepsy	Disease codes OR use of specific medication [ATC: N03*, excluding valproic acid (N03AG01), carbamazepine (N03AF01), gabapentin (N03AX12) and pregabaline	X	X	X	X	X	X

Covariate	Assessment	AB	AM	AV	A-Pr	AP	AH
	(N03AX16)]						
Hypothyroidism	Disease codes OR use of specific medications: (ATC: H03A*, H03C*)	X	X	X	X	X	X
Hyperthyroidism	Disease codes OR use of specific medications: (ATC:H03B*)	X	X	X	X	X	X
Use of medication							
Concomitant use of medication inducing hypokaliemia	Use within three months prior index date. List of drugs *(incuding diuretics)* is available in the website: www.farmacovigilanza.org	X	X	X	X	X	X
Prior use of antiarrhythmia drugs	Any use (ATC=C01B*)	X	X	X	X	X	X
Concomitant use of QT prolonging drugs	Use within three months prior index date. See Annex VI.	X	X	X	X	X	X
N of drugs per ATC, as proxy of severity	Categories of number of drugs belonging to different ATC I level in the last year (to be defined)	X	X	X	X	X	X
Indication for use							
Schizophrenia	Disease codes					X	
Other psychoses	Disease codes					X	
Depression	Disease codes					X	
Bipolar disorder	Disease codes OR use of lithium (ATC: N05AN*)					X	
Anxiety	Disease codes					X	
Dementia	Disease codes OR use of anti-dementia drugs (ATC:N06D*)					X	
Substance abuse	Disease codes					X	
Urticaria	Disease codes						X
Allergic rhinitis	Disease codes						X
Allergic conjunctivitis	Disease codes						X

Covariate	Assessment	AB	AM	AV	A-Pr	AP	AH
Angioedema	Disease codes						X
Anaphylactic reactions	Disease codes						X
Bacterial Infections	Disease codes	X					
HIV	Disease codes			X			
Other viral Infections	Disease codes			X			
Fungal Infection	Disease codes		X				
Protozoal Infection	Disease codes				X		

Legend: ARVC=arrhytmogenic right ventricular cardiomiopathy; ARVD=arrhytmogenic right ventricular displasya

* These drugs will be considered proxy for hypertension even if may be prescribed for the treatment of other cardiovascular diasease as hypertension is more likely to be the main indication of use. Diuretics will be considered separately as these drugs may ne a risk factor for arrhythmia via induction of hypokalemia

** At least two measurements with systolic blood pressure values ≥ 140 mm/Hg or diastolic blood pressure ≥ 90 mm/Hg

Annex V – List of medications that may potentially interact with the study drugs

ISOENZYME	SUBSTRATES	ATC	INHIBITORS	ATC
CYP1A2	Clozapine	N05AH02	fluvoxamine*	N06AB08
	Olanzapine	N05AH03	ciprofloxacin*	S02AA15
	Haloperidol	N05AD01	cimetidine**	A02BA01
			amiodarone***	C01BD01
			fluoroquinolones***	J01MA
			interferon***	S01AD05
			methoxsalen***	D05BA02
			mibefradil***	C08CX01
CYP2B6	Efavirenz	J05AG03	thiotepa***	L01AC01
			ticlopidine***	B01AC05
CYP2C8	Amodiaquine	P01BA06	gemfibrozil*	C10AB04
			trimethoprim**	J01EA01
			glitazones***	A10BG
			montelukast***	R03DC03
CYP2C19	Chloramphenicol	S03AA08	lansoprazole***	A02BC03
	Nelfinavir	J05AE04	omeprazole***	A02BC01
	Proguanil	P01BB01	pantoprazole***	A02BC02
			rabeprazole***	A02BC04
			chloramphenicol***	S01AA01
			cimetidine***	A02BA01
			felbamate***	N03AX10
			fluoxetine***	N06AB03
			fluvoxamine***	N06AB08
			indomethacin***	C01EB03 M01AB01 M02AA23 S01BC01
			ketoconazole***	J02AB02
			modafinil***	N06BA07

			oxcarbazepine***	N03AF02
			probenicid***	M04AB01
			ticlopidine***	B01AC05
			topiramate***	N03AX11
CYP2D6	Promethazine	R06AD02	bupropion*	N06AX12
	Dexchlorpheniramine	R06AB02	cinacalcet*	H05BX01
	Chlorphenamine	R06AB04	fluoxetine*	N06AB03
	Chlorpromazine	N05AA01	paroxetine*	N06AB05
	Perphenazine	N05AB03	quinidine*	C01BA01
	Thioridazine	N05AC02	duloxetine**	N06AX21
	Haloperidol	N05AD01	sertraline**	N06AB06
	Zuclopenthixol	N05AF05	terbinafine**	D01AE15
	Risperidone	N05AX08	amiodarone***	C01BD01
	Aripiprazole	N05AX12	cimetidine***	A02BA01
			celecoxib***	L01XX33
			citalopram***	N06AB04
CYP3A4	Dexchlorpheniramine	R06AB02	indinavir*	J05AE02
	Chlorphenamine	R06AB04	nelfinavir*	J05AE04
	Astemizole	R06AX11	ritonavir*	J05AE03
	Terfenadine	R06AX12	clarithromycin*	J01FA09
	Haloperidol	N05AD01	itraconazole*	J02AC02
	Ziprasidone	N05AE04	ketoconazole*	J02AB02
	Pimozide	N05AG02	nefazodone*	N06AX06
	Quetiapine	N05AH04	saquinavir*	J05AE01
	Risperidone	N05AX08	telithromycin*	J01FA15
	Aripiprazole	N05AX12	aprepitant**	A04AD12
			erythromycin**	J01FA01 S01AA17 D10AF02 QJ51FA01
			fluconazole**	D01AC15
			verapamil**	C08DA01
			diltiazem**	C08DB01
			cimetidine***	A02BA01
			amiodarone***	C01BD01
			ciprofloxacin***	S02AA15
			delaviridine***	J05AG02

			fluvoxamine***	N06AB08
			gestodene***	G03AA10
			imatinib***	L01XE01
			mibefradil***	C08CX01
			mifepristone***	G03XB01
			norfloxacin***	J01MA06
			norfluoxetine***	N06AB03
			voriconazole***	J02AC03

* Strong inhibitors
**Moderate inhibitors
*** Weak inhibitors

Annex VI – List of medications that may prolong QT interval

Drugs with a risk of TdP	ATC
Amiodarone	C01BD01
Arsenic trioxide	L01XX27
Astemizole	R06AX11
Bepridil	C08EA02
Chloroquine	P01BA01
Chlorpromazine	N05AA01
Cisapride	A03FA02
Clarithromycin	J01FA09
Disopyramide	C01BA03
Dofetilide	C01BD04
Domperidone	A03FA03
Droperidol	N05AD08
Erythromycin	S01AA17
Halofantrine	P01BX01
Haloperidol	N05AD01
Ibutilide	C01BD05
Levomethadyl	N02AC
Mesoridazine	N05AC03
Methadone	N07BC02
Pentamidine	P01CX01
Pentamidine	P01CX01
Pimozide	N05AG02
Probucol	C10AX02
Procainamide	C01BA02
Quinidine	C01BA01
Sotalol	C07AA07
Sparfloxacin	J01MA09
Terfenadine	R06AX12
Thioridazine	N05AC02

Drugs with a possible risk of TdP **	ATC
Alfuzosin	G04CA01
Amantadine	N04BB01
Atazanavir	J05AE08
Azithromycin	S01AA26
Chloral hydrate	N05CC01
Clozapine	N05AH02
Dolasetron	A04AA04
Dronedarone	C01BD07
Escitalopram	N06AB10
Escitalopram	N06AB10
Felbamate	N03AX10
Flecainide	C01BC04
Foscarnet	J05AD01
Fosphenytoin	N03AB05
Gatifloxacin	S01AX21
Gemifloxacin	J01MA15
Granisetron	A04AA02
Indapamide	C03BA11
Isradipine	C08CA03
Lapatinib	L01XE07
Lapatinib	L01XE07
Levofloxacin	S01AX19
Lithium	N05AN01
Moexipril/HCTZ	C09AA13
Moxifloxacin	S01AX22
Nicardipine	C08CA04
Nilotinib	L01XE08
Octreotide	H01CB02
Ofloxacin	S01AX11
Ondansetron	A04AA01
Oxytocin	H01BB02

Paliperidone	N05AX13
Perflutren lipid microspheres	V08DA01
Quetiapine	N05AH04
Ranolazine	C01EB18
Risperidone	N05AX08
Roxithromycin	J01FA06
Sertindole	N05AE03
Sertindole	N05AE03
Sunitinib	L01XE04
Tacrolimus	L04AD02
Tamoxifen	L02BA01
Telithromycin	J01FA15
Tizanidine	M03BX02
Vardenafil	G04BE09
Venlafaxine	N06AX16
Voriconazole	J02AC03
Ziprasidone	N05AE04

Drugs with a <u>conditional</u> risk of TdP ***	**ATC**
Amitriptyline	N06AA09
Ciprofloxacin	S03AA07
Citalopram	N06AB04
Clomipramine	N06AA04
Desipramine	N06AA01
Diphenhydramine	R06AA02
Doxepin	N06AA12
Fluconazole	J02AC01
Fluoxetine	N06AB03
Fluoxetine	N06AB03
Galantamine	N06DA04
Imipramine	N06AA02
Itraconazole	J02AC02
Ketoconazole	J02AB02
Mexiletine	C01BB02
Nortriptyline	N06AA10
Paroxetine	N06AB05
Protriptyline	N06AA11
Ritonavir	J05AE03
Sertraline	N06AB06
Solifenacin	G04BD08
Trazodone	N06AX05
Trimethoprim-Sulfamethoxazole	J01EE01
Trimipramine	N06AA06

Some of the study drugs are included as well.

*Drugs that are generally accepted by the QTdrugs.org-Advisory Board to carry a risk of torsades de pointes.

**Drugs that prolong the QT interval and/or in some reports have been associated with torsades de pointes but at this time lack substantial evidence for causing torsades de pointes.

***Drugs that carry a risk of torsades de pointes and/or QT prolongation under certain conditions, such as patients with congenital long QT syndrome, drug overdose or co-administration of interacting drugs.

Annex VII – Description of the software Jerboa as developed in EU-ADR project

The basic version of the software Jeboa, as initially developed within the EU-ADr project, is presented below. For the ARITMO project wew tools will be subsequently implemented in this version. The new verion of Jerboa will be fully described in the deliverable WP5.3.

User Manual

EU-ADR internal document
Version 1.5
M.J. Schuemie

1. Starting Jerboa

Jerboa requires Java in order to run. You can download the latest version from:
http://www.java.com/getjava/
Double-click on the Jerboa Jar file to start Jerboa. Alternatively, you can start Jerboa from the command line using:
java –jar Jerboa.jar

Giving Jerboa more memory

By default, Java allows each program to use a maximum of 128MB of RAM. Especially for larger data sets, Jerboa will run faster if it can use more memory. To give Jerboa 1024MB of RAM, use the following command:
java –Xmx1024m –jar Jerboa.jar

Executing Jerboa from the command line interface

For advanced uers, it is also possible to run Jerboa with predefined settings from the command line. The command line parameters are specified in section 7.

2. Using Jerboa

After startup, Jerboa will display its main screen.

Working folder

Here you must specify a valid folder on the hard disc where Jerboa can write the final and intermediate results, as well as several temporary files.

Workflow

This shows the main workflow for processing the input data (specified in the section Input formats), using several processing steps (specified in the section Processing steps).
In the workflow panel, you can adjust the processing step parameters. You can save and load these parameters using the **Save workflow parameters** and **Load workflow parameters** options in the **File** menu.

Console

This will show output generated by Jerboa during processing.

Run

Executes the main workflow, and generates the aggregated data file.

Wrap it up

Open the dialog as shown on the right. When you press **Run** in this dialog, the selected aggregated data file will be compressed and encrypted using the public key embedded in Jerboa. The file can then be send to the central repository.

3. Input formats

Three tables serve as input:

- **Prescriptions:** Describes the prescriptions taken by patients.
- **Events:** Describes the events.
- **Patients:** Describes the patients included in the study.

All tables are in CSV (Comma Separated Values) format. The first row should contain the column headers. The order of the columns and rows is not important.
Tip: you can use the tool "Test Input Files" to test your input files!

Dates

All dates are formatted as follows:
YYYYMMDD
For example: the 4th of July, 2008, is formatted as:
20080704

Patient IDs

A patient ID is an alphanumeric string that uniquely identifies a patient. So patient IDs can be numbers (1, 2, 3, etc.) or combination of numbers and letters (a01, a02, b01, etc).

3.1 Table: Prescriptions

Fields:
Date The start date of the prescription.
PatientID Patient ID.
Duration The duration (in days) of the prescription.
ATC The ATC code corresponding to the medication.

3.2 Table: Events

Fields:
PatientID Patient ID.
Date Date of the event.
EventType Type of event. This fields is currently ignored by Jerboa.

3.3 Table: Patients

Fields:
PatientID Patient ID.
Birthdate Date of birth.
Gender Gender. Can be either **F** or **M**, for Female or Male respectively.
Startdate Date from which the patient is eligible to be included in the study. This is typically the date the patient is entered into the registration sytem.
Enddate Date after which the patient is no longer eligible for inclusion in the study.

4. Processing steps

The main workflow consists of the following steps:

4.1 Merge repeats

Prescriptions with the same ATC code where the start date of one prescription precedes the end date of the other prescription are merged into a single episode of drug use, starting at the start of the first prescription, and ending at the end of the last prescription.

4.2 Exposure coding

Episodes of drug use are divided into periods. The default labels are as follows:

- VS: very short exposure: 1-7 days
- S: short exposure: 8-30 days
- M: medium exposure: 31-180 days
- L: long exposure: 6-12 months

These labels can be altered in the workflow panel if needed.

4.3 Combine concomitant

Periods of concomitant drug use are labeled as separate episodes. In the result, there will be, by definition, no more overlapping episodes.

4.4 Code non-drug use

Using the inclusion and exclusion dates of the patients, Jerboa determine and mark those periods during which a patient is included in the study, but is not using any medication according the input files.

4.5 Cohort entry date calculation

Based on the startdate in the patient file, the date is calculated at which time the patient will enter the cohort. By default, this is 365 days after the startdate. An exception is small children. If

they are younger than the specified number of days (default = 365 days), the inclusion date for the cohort study is their date of birth.

4.6 Data merge

Here the prescription, patient and event data are merged. By default, patient age is classified into 10-year interval bins, but this can be altered in the workflow panel if needed.
An additional option during the data merge is to delete all patient data following the first recorded event of that patient.
Another option is to split up episodes further by years, so no episode will belong to two calendar years.

4.7 Aggregate data

The data is aggregated over all patients. Jerboa will generate three different tables, with differing levels of aggregation.
The first table will contain information on the level of drug combinations used. Each line will contain this information: combination of exposure codes and ATC codes, age range, gender, exposure time, number of events, number of persons
For example:
VS:C12AA34 + C:M12AA34, 16-30, male, 300, 10, 20
Also included: data for 'exposure to no drugs', i.e. the time patients were listed in the practice but did not use prescribed drugs.
The second table will contain information at the level of single ATC codes. The third table will contain only the information needed to calculate incidence rates.
The aggregated data file will contain all selected tables, and is extended with the workflow settings and the version of Jerboa used to create the file.
It is also possible to remove all lines from the aggregated data that are based on a small number of subjects. The minimum number of subjects can be specified in the field "Minimum number of subjects per row".

5. Analysis

Jerboa can perform several analyses based on the aggregated data. Currently, only two are implemented:

5.1 Incidence rate

Jerboa will calculate the incidence rate for the whole population, and stratify it based on age and gender.

5.2 Relative risks

The risk of an event during exposure to a particular drug is compared to the risk when not using that drug (i.e. all remaining patient time).

6. Tools

Jerboa offers tools for users. Currently, there is only one tool:

6.1 Test Input Files

This can be used to test whether the input files can be read by Jerboa. First select the working folder in the main window, then select 'Tools' and 'Test input files'. Here you can specifiy the names of the input files.
It is possible to disable the test of particular files (for instance when you know they are ok). Uncheck the box labelled "Test this file".
Click 'Run' to perform the test(s). When Jerboa encounters an error, it will show 'Error' for the particular file. To show the part of the input file containing the error, click on 'Show'. If everything is ok, Jerboa will generate some statistics in the main console that can be used to verify if the data is not only formatted correctly, but also contains the correct data.

7. Command line interface parameters

Example:
java –Xmx1024m –jar Jerboa.jar –folder /home/data/ –settings /home/data/jerboaSettingsStudy1.txt –aggregate -wrap
Parameters:
-folder *pathToFolder*
Specifies the working folder.
-patients *patientsFile*
Specifies the input file containing the patient information.
-prescriptions *prescriptionsFile*
Specifies the input file containing the prescription information.
-events *eventsFile*
Specifies the input file containing the event information.
-out *outputFile*
Specifies the name of the aggregated data file created by Jerboa. The default is "AggregatedData.txt".
-wrapout *wrapOutputFile*
Specifies the name of the compressed and encrypted filename created by Jerboa. The default is "Data.enc".
-settings *settingsFile*
Specifies the file containing the settings for the Jerboa workflow.
-aggregate
Instructs Jerboa to automatically start the aggregation workflow.
-wrap