WP2 Framework for pharmacoepidemiological studies
WG3 Drug utilisation data

DRUG CONSUMPTION DATABASES IN EUROPE

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TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

PREFACE

This report shows the results of one of the goals set by the PROTECT project: to build up an inventory on national drug consumption databases across Europe. The interest behind this inventory is to collect information on sources of drug utilisation data across Europe from a researcher's point of view, trying to include aspects such as drug providers, national healthcare organisation, and characteristics more specific to the databases. The information has been collected in a structured manner to facilitate its handling for research purposes such as the degree of comparability between the databases. This report includes information on non-commercial and commercial drug consumption data providers, and on international network groups working in drug utilisation research. The report is organised into 6 chapters.

Chapter 1 offers an overview of the current status of sources of information on drug exposure and the objectives of the document.

Chapter 2 describes the methodology to get the information to develop the inventory. A section "General methods"explains the first steps taken to gather general information on drug consumption databases, from governmental agencies in charge of pricing and reimbursement of medicines, to different international groups working on drug utilisation research. Information is available for the out- and inpatient healthcare setting.

Chapter 3 gives the results of the search.It is divided into 3 subsections: background data, outpatient drug utilisation resources and inpatient drug utilisation resources.

Chapter 4 is entirely dedicated to describing how the validity of national drug consumption data is assessed.

Chapter 5 discusses the findings in light of what has already been done in this field and the stated objectives.

Chapter 6 deal with the conclusions.

Hopefully, all this information will be of interest not only for drug utilisation research but also in general pharmacoepidemiological research.

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LIST OF ABBREVIATIONS

AB, Antibiotics
ABC Calc, Antibiotic Consumption Calculator
ACE-inhibitors, Angiotensin-converting enzym inhibitors
ADEs, Adverse Drug Events
ADQ, Average Daily Quantity
AEMPS, Spanish Agency for Medicines and Health Products
AFMPS, Belgian Federal Agency for Medicines and Health Products
AG, Board of Health of Lichtenstein
AGES, Austrian Agency for Health and Food Safety
AIFA, The Italian Drug Agency
ALIMS, Agency for Medicines and medical devices of Serbia
AMI, Acute Myocardial Infarction
ANM, (Romanian) National Medicines Agency
ANSM, French Agency for the Safety and Health Products
ARITMO, Arrhytmogenic potential of drugs
ARPAC, Antibiotic Resistance Prevention and Control
ATC, AnatomicTherapeutic Chemical-Classification System
BfArM, German Federal Institution for Drugs and Medical Devices
BIFAP, Spanish General Practice Research Pharmacoepidemiologic database
BMG, Austrian Federal Ministry of Health
BNF, British National Formulary
CAGR, Compound Annual Growth Rate
CEPS, (French) Committee of Health Products Economics
CIMA, Spanish online pharmaceutical information centre database
CNAM-TS, The French National Insurance for Salaried Employees
CNC, Cross National Comparison of Drug Utilisation Research
CNHIM, (French) National Hospital Centre on Medicines Information
CPN, Central Pharmaceutical Number
CSD, Cegedim Strategic Data
CU, Counting Units
D-AE, Drug-adverse event
DID, Number of DDDs per 1,000 inhabitants per day
DDD, Defined Daily Dose
DILI, Drug-induced liver injury
DIMDI, German Institute of Medical Documentation and Information
DKMA, Danish Medicines Agency
DLO,(Russian) Supplementary Medicines Provision
DoHC, (Irish) Department of Health and Children
DU, Drug Utilisation
DRUID, Driving under the influence of Drugs, Alcohol and Medicines
DURQUIM, Drug Utilisation Research Quality Indicator Meeting
EACPT, European Association of Clinical Pharmacology and Therapeutics
EAHP, European Association of Hospital Pharmacists
EC, European Commission
EEA/EFTA, European Economic Area/European Free Trade Association

EFPIA, European Federation of Pharmaceutical Industries and Associations
EMA, European Medicines Agency
eMC, Electronic Medicines Compendium
ENCePP, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EOF, (Greek) National Organisation for Medicines
ePACT, Electronic Prescribing Analyses and Cost database
EPAS, Permanent Sample of Salaried Employees, insured by the French CNAMTS
EPhMRA, European Pharmaceutical Market Research Association
EPIB-AM, Permanent Sample of French Insured Citizens
ERASME, The French National Insurance for Salaried Employees database
ESAC, European Surveillance of Antimicrobial Consumption
ESC, European Society of Cardiology
ESCMID, European Society of Clinical Microbiology and Infectious Diseases
ESEMeD, European Study of the Epidemiology of Mental Disorders
ESGAP, European Study Group on Antibiotic Policy
ESGARS, European Study Group on Antibiotic Resistance Surveillance
ESGEM, European Study Group on Epidemiological Markers
ESGNI, European Study Group on Nosocomial Infections
EU, European Union
EUDRAPharm, European Union Drug Regulating Authorities Pharmaceutical Database
EUPHIN, European Union Public Health Information Network
EUROASPIRE, European Action on Secondary and Primary Prevention by Intervention to Reduce Events
EuroDURG, European Drug Utilisation Research Group
EUROMEDSTAT, European Medicines Statistics
FEDRA, (Spanish) Electronic transmission on suspected adverse reactions with human use medicines
FICF, Foundation Catalan Institute of Pharmacology (Spain)
FP6, Sixth Framework Programme for Research and Technological Development
FP7, Seventh Framework Programme for Research and Technological Development
G-BA, German Federal Joint Committee
GIP, Drug Information System of the Dutch Health Insurance Board
GKV, German Statutory Health Insurance
GP, General Practitioner
GPRD, The General Practice Research Database. Currently CPRD: Clinical Practice Research Database
HALMED, (Croatian) Agency for medicinal products and medical devices
HAPPY AUDIT, Health Alliance for Prudent, Yield and Use of Antimicrobial Drugs in the treatment of respiratory tract infections
HBV, (Austrian) Federation of Austrian health Insurance
HMUD, Scottish Hospital Medicines Utilisation Database
HSD, (Italian)Health Search Database Project
HSE, (Irish) Health Service Executive
HOM, Hospital-only-medicines
HOPE, European Hospital and Healthcare Association
HSE, (Irish) Health Services Executive of the Corporate Pharmaceutical Unit

ICU, Intensive Care Unit
IMI-JU, Innovative Medicines Initiative - Joint Undertaking
IMS, Intercontinental Marketing Services (currently, IMS Health)
INFARMED, (Portuguese) National Authority of Medicines and Health
INSERM, French National Institute for Medical Research
ISPE, International Society of Pharmacoepidemiology
ISPOR, International Society of Pharmacoeconomics and Outcomes Research
LA-SER, Research and Development Company founded in 2004, based in Paris (France)
LHA, Local Health Authority
LMU, Ludwig-Maximilians University, Munich (Germany)
M, Pharmaceutical Manufacturers
MEMO, Medicines Monitoring Unit at the University of Dundee (UK)
MHRA, (British) Medicines and Healthcare Products Regulatory Agency
MIDAS, Multinational Integrated Multianalysis System
MIMS, (Irish) Monthly Index of Medical Specialties
MMG, Italian General Practitioner List
MSA, French National Insurance Scheme for employees working in the rural sector
NCBI, National Centre for Biotechnology Information
NDCDB, National Drug Consumption Databases
NeLM, British National electronic Library on Medicines
NHS, United Kingdom National Health System
NIC, Net Ingredient Cost
NMUU, The Scottish National Medicines Utilisation Unit
NorPD, The Norwegian Prescritption Database
NorPEN, The Nordic Pharmacoepidemiological Network
NWIS, NHS Wales Informatics Services
OECD, Organisation for Economic Co-operation and Development
OTC, Over-the-counter medicines
OsMED, Italian Observatory of Drug Utilisation
PDD, Prescribed Daily Dose
PEI, Paul-Ehrlich Institute
POM, Prescription-only medicines
PGRx, Pharmacoepidemiologic General Research eXtension group (by LA-SER)
PHIS, Pharmaceutical Health Information System
PIL, Patient's Information Leaflet
PK, (Austrian) Pricing Committee of the Ministry of Health
PPRI, Pharmaceutical Pricing and Reimbursement Information System
PPS, Point Prevalence Survey
Pre-W, Pre-Wholesalers
PROTECT, Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium
RCT, Randomised Clinical Trials
ReFI, Italian Pharmaceutical Catalogue
RIZIV, Belgian National Health Insurance Institute
RSI, French National Insurance Scheme for the self-employees
SFK, Dutch Foundation for Pharmaceutical Statistics

SMCA, (Lithuanian) State Medicines Control Agency
SIETES, Spanish electronic information system database on pharmacoepidemiology
SIG-DUR, Special Interest Group on Drug Utilisation Research
SPA, Scottish Prescription Analyses
SPC, Summary of Product Characteristics
TEDDY, Task-force in Europe for Drug Development for the Young
TUPP, The Users Perspective Project
UNCAM, (French) National Union of Health Insurance Organisations
UK, United Kingdom
UKMi, British National Health System pharmacy medicines information service
USA, United States of America
UU, University of Utrecht (The Netherlands)
VAT, Value Added Tax
W, Wholesalers
WG, Working Group
WHO, World Health Organization
WiDO, The Research Institute of the AOK –German Health Insurance Company-
WP, Work Package
ZVA, (Latvian) State of Medicines Agency

EXECUTIVE SUMMARY

Different initiatives have arisen in Europe to gather information on drug utilisation (DU) for the last 20 years. Knowledge of the quantitative and qualitative patterns of drug use is a key element for the rational use of medicines, the rational assessment of the risk-benefit ratio and for decision-making on risk minimising actions for medicines.

In DU studies, information on prevalence, incidence, indication and duration of a treatment can be derived from different sources. First of all, there are data stemming from the different stages in the distribution chain of medicines: (i) dispensation with or without prescription, (ii) adquisition of medicines by hospital and community pharmacies or other outlets, straight from pharmaceutical manufacturers (M) or through wholesalers (W), and (iii) reimbursement data. These data may be collected by governmental agencies or stored on pharmacies' databases or those of insurance companies. These sources of data are known as non-commercial drug data providers. In addition, data mining companies conduct market surveys to sell the data stored in their databases. These sources of data are known as commercial data providers. In this report only IMS Health is mentioned as a commercial data provider. Secondly, there are sources of data on drug exposure obtained from the prescriptions registered on clinical databases. Thirdly, the current ingestion of medicines may be collected through interviews to patients. Finally, there are pharmacoepidemiological studies from which the utilisation rate for a class of drugs can be derived.

The databases cover large proportions of the population, the data are readily available and easy to access. However, these databases were initially created with an administrative purpose hampering their use in research. Not all variables regarded as potential confounders may be collected. Another problem is the inexistence of a standard method to evaluate the validity and accuracy of the data collected by these databases. Finally, the information is only registered for those individuals that reach the healthcare system, excluding a segment of the population.

The objective of the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) project is to address the limitations of methods currently used in pharmacovigilance and pharmacoepidemiology, and to strengthen the monitoring of the benefit-risk assessment of medicines in Europe. The project is organised into seven workpackages (WP). The overall objective of WP2 "Framework for Pharmacoepidemiological Studies" is to develop, test and disseminate methodological standards for the design, conduct and analysis of pharmacoepidemiological studies. WP2 is organised into three working groups (WG). WG3 is in charge of reviewing and compiling knowledge about European sources of data on DU in the out- and inpatient healthcare sector. The project follows the recommendations from the World Health Organization (WHO) on the

adoption of the Anatomical Therapeutic Chemical classification (ATC) of drugs and the measurement of drug exposure in Defined Daily Doses (DDDs).The PROTECT project includes the following Adverse Drug Events (ADEs): calcium channel blockers (C08)- malignancies; antiepileptics (N03A)- suicide; benzodiazepine derivatives (N05BA, N05CD) - hip fracture; antidepressants (N06A, N06CA) - hip fracture; beta-2-adrenergics (R03AC, R03AK) - acute myocardial infarction (AMI); macrolides (J01FA) and amoxicillin-clavulanic acid (J01CR02) - drug-induced liver injury (DILI).

To find out information on nationwide drug consumption databases we developed a search strategy that allowed for getting different sources of data on drug consumption considered of interest for DU studies: data providers, pricing and reimbursement agencies, information on marketed active substances, healthcare systems and reimbursement decisions adopted in each European country, and international DU working groups. As this is an ongoing study, we first limited the inventory to those European countries with a high population density, tradition in DU research and participation in the PROTECT project. For later versions we tried to include all European countries. First of all, we conducted a specific website search of global European institutions to country-specific governmental websites. Then, we searched bibliographic databases to find articles published by international WG followed by a Google search, and finally we conducted interviews with experts in the field of DU. For each of the national drug consumption databases, the following information is provided: data provider, website, source of drug consumption, setting, population coverage, accessibility, drug codification, unit of measurement, drug-based information, prescriber and pharmacy information, potential confounders of a drug exposure, language of the database, record period and record linkage.

For the inpatient sector, the search strategy was slightly different. First of all, we reviewed the main available information on hospital DU for the drugs selected by the PROTECT using a website and a bibliographic database search. Then, because of the importance of antibacterial consumption in the inpatient sector, which is linked to the emergence and selection of antibiotic-resistant bacteria, a specific literature review was conducted to establish the availabilty of inpatient macrolides and amoxicillin-clavulanic acid consumption data.

An area of special interest was to determine the validity of the nationwide drug consumption data. Considering the bibliography available on the validity of drug consumption data and on the validity of automated databases in research, we developed a questionnaire including most of the items considered of relevance when measuring drug exposure. The key items referred to the definition of in- and outpatient drug consumption, population coverage, drug- and patient-based information, and database validity. However, these key items are also factors used to interpret the results obtained when comparing drug consumption across countries and/or over time.

This complex methodology yielded a list of comprehensive and more specific institutional European websites and international networks on DU studies (Table 3). From them, we derived what we term background data: list of national medicines agencies (Table 4), healthcare systems (Appendix 7.3), pricing and reimbursement agencies (Table 5), pharmaceutical data sources by country (Table 6) and international networks and WGs in pharmacoepidemiology (Section 3.2.6). For each of the international WGs, the following information was collected: website, definition, objectives, record period, country-participants, funding and publications. These international networks have been divided into those offering general information: general research groups, and specific research groups, i.e. those studying either specific diseases or groups of drugs of interest for the PROTECT project.

Information on national drug consumption databases in Europe is provided for Belgium, Bulgaria, Croatia, The Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Norway, Poland, Portugal, Russia, Slovenia, Spain, Sweden, Switzerland, The Netherlands and The United Kingdom. Few countries can provide data on the inpatient sector at a national level. From the bibliographic database search in the inpatient sector, the majority of articles were set in the oupatient setting and expressed drug consumption as a percentage of the active substance. Questionnaires were received from Belgium, Croatia, The Czech Republic, Denmark, France, Hungary, Iceland, Ireland, Italy, Norway, Poland, Portugal, Slovenia, Spain, Sweden, and The Netherlands.

The PROTECT inventory provides information on 21 European working groups and 31 nationwide drug consumption databases. For Bulgaria, Croatia, Denmark, Estonia, Finland, France, Hungary, Latvia, Italy, Norway, Portugal and Sweden, inpatient drug consumption is available. As expected, the Nordic countries and The Netherlands with their long tradition in DU research, are the ones to provide drug consumption data online which is free to download. For the rest of the countries, information should be applied for. Finland requires 1-1.5 years of notice before divulging such information. Russia and Switzerland do not hold nationwide drug consumption databases.

The interest in compiling such information has evolved in the last 25 years from the EuroMedicines project that developed a drug directory for 14 European countries, to the EUROMEDSTAT project, the Cross National Comparison (CNC) project, the EuroDURG-ISPE (European drug utilisation group and International Society of Pharmacoepidemiology) collaboration and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Several specific international WGs have also been established to deal with a specific disease or a group of drugs that indirectly involve DU research.

Generally speaking, there is a scarcity of nationwide hospital drug consumption information, mainly attributed to the high heterogeneity in the

management of medicines at a hospital level. In addition, when studying drug consumption in inpatient settings, the recommendations from the World Health Organization (WHO) for adjusting drug consumption to clinical activity are barely followed. In contrast to this lack of information on inpatient DU from non-commercial data providers, in 2008, IMS Health started the Hospital Audit Prescription Index which collects information on drugs dispensed from hospital pharmacies to the patient, containing more clinical information.

The evaluation of validity of drug consumption data is important to determine the comparability of the results in patterns of drug use across different countries or over time. Three European databases collect dispensed medicines which best assess drug exposure, as they include over-the-counter (OTC) drugs. Eleven databases collect reimbursed data, and six prescription data. The rest of the databases collect information on sales from wholesalers (W). The population coverage of most of these databases reaches 100% of the resident people. ATC/DDD methodology has been adopted by all these databases, including the British electronic prescribing analyses and cost (ePACT)database which collects information according to the British National Formulary (BNF) and measures drug consumption with Average Daily Quantities (ADQs). The ePACT database provides ATC codes and DDDs upon request. Most of the databases update retrospectively the ATC codes and DDD according to the WHO guidelines released every year. The problem with the ATC/DDD methodology has already been pointed out. First of all, the lack of an ATC code or the non assignation of a DDD to some of the marketed drugs. In this case, the strategy adopted for each of the databases varied considerably. Secondly, there is the fact that the DDD does not correspond to the prescribed daily dose (PDD), and that there are no DDDs assigned to children.

The questionnaire allowed us to evaluate the different degrees of ascertainment of those variables considered potential confounders of drug exposure. Very few databases provide the age and gender of the patient, though some provide information on the prescriber and the community pharmacy where the patient purchased the drug. However, some databases allow the development of a record linkage system.

The PROTECT inventory is a comprehensive and structured source of information on drug consumption data that should promote the correct interpretation of the results of a DU study. In addition, a brief summary of the data provided by IMS Health is available. For academic researchers PROTECT offers a basis for future collaborations while giving regulatory agencies and pharmaceutical companies the possibility of supporting post-marketing and safety studies. Such an inventory would not have been possible without the previous initiatives that compiled this information and knowledge.

1. INTRODUCTION

1.1 BACKGROUND

Before marketing, the safety and efficacy of drugs are usually evaluated using randomised clinical trials (RCT). Although a clinical trial is the most reliable design for causal inference, it is usually conducted in populations and conditions which are different from those of usual clinical practice (1). In particular, patients exposed to new medicines in usual clinical practice differ from those in clinical trials in terms of age, indication for use, dose, dosage patterns, duration of use, concomitant medications and comorbidities. In addition, pre-approval drug trials are usually done in highly qualified study centres with experienced investigators (2). All these factors may alter the benefit-risk ratio of the drug of interest which may differ as soon as the drug becomes available on the market (3).

The economic development in the 1950s led governments to establish a public health system. An increasing number of medicines became available on the market due to a growing economic development. The pharmaceutical industry and more universal access to health care transformed the pharmaceutical market. Soon, monitoring drug consumption was important not only from an economic perspective (health expenditure in terms of drug costs, and a high competition between pharmaceuticalindustries), but also from a health perspective (assessment of the risk-benefit ratio of a drug). In 1957, Intercontinental Marketing Services (currently known as IMS Health) published its first audit on pharmaceutical sales inthe West German market (4).

Pharmaceutical expenditure is the result of the quantity of drugs dispensed multiplied by their price. During the 1990s, pharmaceutical expenditure became the target of health-care cost-containment efforts.Although several factors influence pharmaceutical expenditure, the availability of drug consumption data became a central issue for policy decisions about a country's pharmaceutical expenditure (5).Quantitative data on drug consumption is available from national databases, maintained by governmental agencies or health insurance companies, and from commercial data providers. These for-profit-companies conduct market surveys to sell the data at an aggregated level to third parties (6).

Besides storingquantitative data on drug use collected in non-commercial and commercial databases, its validity needs to be assessed if used for research.In the context of the PROTECT project, validity of drug consumption data includes validity in terms of drug-exposure measurement and validity in terms of potential biases introduced in a DU study by the way the information is collected.

1.2. RATIONALE

The establishment of automated databases monitoring drug use is the result of an increasing number of electronically registered patient-health care encounters and an advance in new technologies. In DU studies, information on prevalence, incidence, indication and duration of a treatment can be derived from different sources:

- Distribution data: dispensed medicines (with or without prescription), purchasing of medicines by hospital/community pharmacies or other outlets, prescribed and dispensed or reimbursed medicines data. It usually stems from governmental agencies, pharmacies' databases, and insurance companies. These sources are generally known as non-commercial DU data providers. Another source of drug consumption data are market surveys (6).
- Prescribed medicines data from clinical databases. Medical audits allow the collection of the individual extent and profile of drug use on a continuing basis and it may be correlated with healthcare utilisation data (6).
- Information on actual ingestion of medicines through interviews to patients (6).
- Pharmacoepidemiological studies from which the utilisation rate for a class of drugs can be obtained (6).

Apart from the interest in knowing the characteristics of the data providers, it is also of interest to know whether the information, in each country, is available for the outpatient and inpatient sector.

Furthermore, the PROTECT project proposed collecting drug consumption data for medicinal substances for hospital or specialist use, which neither national drug consumption databases, nor commercial data providers held. However, when the project started and the drug-adverse event (D-AE) pairs were selected, none of the groups of selected medicines belonged to this category. See Appendix 7.1 for a detailed list of medicines included in the PROTECT project and Appendix 7.2 for the pairs D-AE, included in this project.

When the interest is on studying drug exposure in inpatient settings at a national level, the task becomes more complex. Hospital pharmaceutical expenditure represents roughly 15% of the total pharmaceutical expenditure (7). In addition, there are two key factors which make the collection of inpatient drug exposure data at a national level difficult: the distribution chain of medicines in hospitals and the availability of a hospital pharmacy.

Only macrolides (J01FA) and amoxicillin-clavulanate (J01CR02) consumption will be studied in the inpatient setting for the PROTECT project. Antibacterials for systemic use in hospital settings are relevant because there is a close relationship between the emergence of microorganisms resistance, and the use and misuse of antibiotics (8). The costs of antibiotics in hospitals have also grown from 10% to over 15%. The misuse and increasing costs underlies the development of institutional clinical guidelines to influence their prescription (9).

Historically, drug consumption databases were created with an administrative purpose in mind: to record drug use in the outpatient setting so they could get a refund. Thus, the units of measurement were in financial terms. Back in 1969, the WHO Drug Consumption Group was created, shifting the attention of drug consumption onto other healthcare research fields (10). In research, these databases offer several advantages: they cover large sizes of the population; the data is already available and it is easy to access. This represents lower costs and less time spent on getting results (11-13).

These databases also have their downsides. First of all, data were initially collected for purposes different to that of the current research question (14). Not all variables regarded as potential confounders of the association under study (e.g. drug exposure-adverse event) may be collected (15). Secondly, there is no standardised method to evaluate the validity and accuracy of data collected by these databases, nor a standard set of rules on how to collect the data (11-13). Finally, the information is only registered for those individuals that use the health services.

Independently of whether the automated databases collect information on outpatient or inpatient drug consumption, their validity needs to be assessed. The validity of an automated database measuring drug exposure is best determined by comparing with medical records at an individual patient level (16) or conducting surveys with interviews and home inventory with patients (17). However, there is no consensus on which is the best gold standard (18).

1.3. OBJECTIVES

The aim of the PROTECT project is to address the limitations of methods currently used in pharmacovigilance and pharmacoepidemiology and to strengthen the monitoring of the benefit-risk assessment of medicines in Europe.

PROTECT is organised into seven WPs. The overall objective of WP2, Framework for Pharmacoepidemiological Studies is to develop, test and disseminate methodological standards for the design, and to conduct and analyse the pharmacoepidemiological studies. The specific objective of this WP2 is to study five pairs of selected D-AE and to develop new methods to enhance the detection of ADEs. WP2 is organised into 3 WGs.

1.3.1. GENERAL OBJECTIVE

WG3 is in charge of reviewing and compiling knowledge about European sources of data on DU in the outpatient and inpatient health care sector.

This document is intended to be an updated list of drug consumption data sources in Europe with details on the available information that may have an influence on the patterns of medicines usage. It aims to revise and complete the information already available from similar initiatives conducted previously, and to facilitate access to drug consumption data.These databases may be used to detect public health problems related to the safety of medicines .

1.3.2. SPECIFIC OBJECTIVES

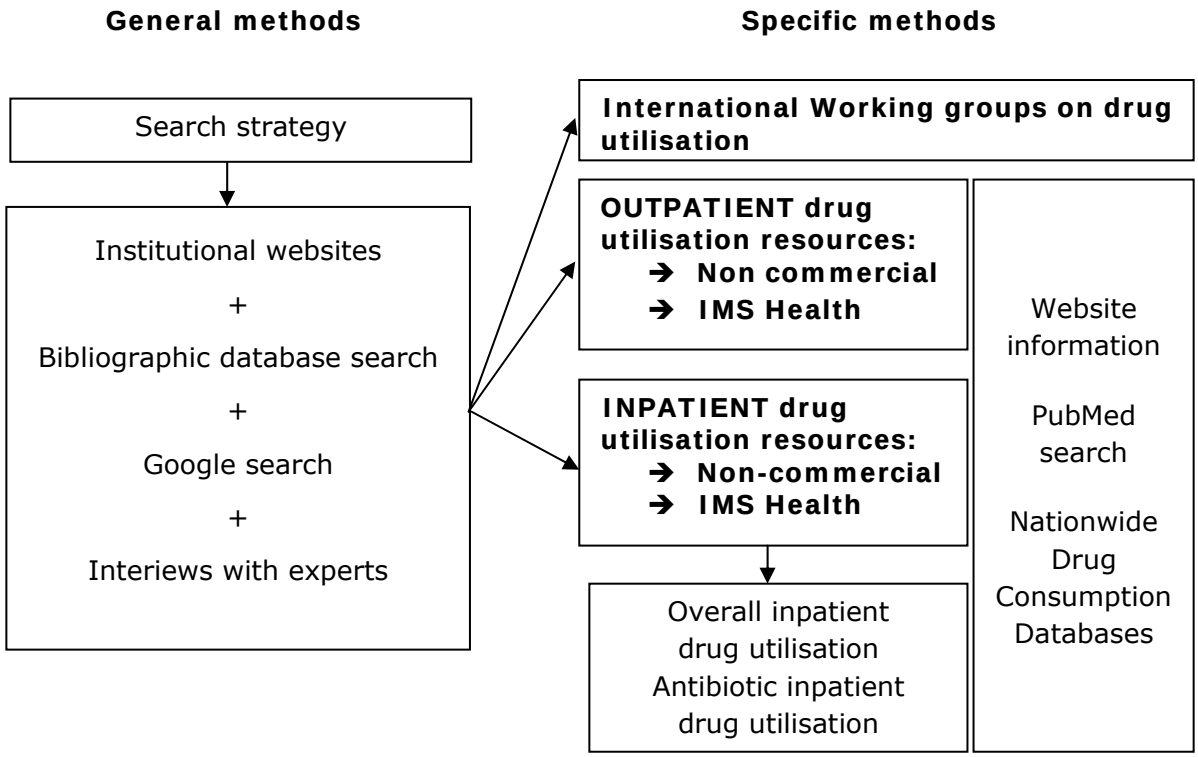
- List the non-commercial providers of drug consumption data in Europe.
- Describe the main characteristics of the market data collected internationally by IMS Health.
- Provide an updated list of national drug consumption databases in Europe.
- Describe the main characteristics and accessibility of these nationwide drug consumption databases.
- Outline the validity and degree of comparability of drug consumption data.

– Explore the availability of inpatient drug consumption at national level in Europe.

2. METHODOLOGY

Figure 1 shows the steps taken in searching fordrug consumption data information.

Figure 1. Summary of methodology



2.2. GENERAL METHODS

We list the national medicines agencies, national pricing and reimbursement agencies, and international WGs on DU to eventually obtain information on the nationwide drug consumption databases. In addition, we provide a brief summary of the national healthcare systems.

The search was conducted in a hierarchical manner, from global European institutions down to the country level. Once the national data source on drug consumption was identified and accessibility established, we looked for the appropriate contact person to obtain drug data and additional information for DU research studies.

2.2.1. SEARCH STRATEGY

First, we consulted the European Union and the European Medicines Agency (EMA) (www.ema.eu) websites. The goal was to find institutions, networks, and research projects related to DU in Europe. Secondly, we sought information regarding national health system policies and national competent authorities that regulate licensing, pricing and reimbursement of drugs in European countries. We thought that these national authorities might be directly involved in collecting drug consumption data. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) website (www.ispor.org) provides an overview of specific country health systems and reimbursement processes. Thirdly, we conducted a bibliographic database search. The goal was to find articles published by European or international –with European collaboration- groups, working on pharmacoepidemiology and/or DU research, to check whether they had any databases on drug consumption or whether they had articles or reports published with information on drug consumption data.

We conducted the search on PubMed and SIETES (Spanish electronic information system database on pharmacoepidemiology). PubMed http://www.ncbi.nlm.nih.gov/pubmed (last accessed 11/2013) is a database maintained by the National Centre for Biotechnology Information (NCBI), at the United States National Library of Medicine. It provides access to MEDLINE and other web sites and is linked to the other NCBI molecular biology resources, life science journals, and e-books. SIETES (www.sietes.org, last accessed 11/2013) is an electronic drug information system in Spanish maintained by the Foundation of the Catalan Institute of Pharmacology. The database includes critical reviews of selected articles. The keywords were "pharmacoepidemiology", "drug utilisation", "international cooperation", "databases", and "Europe". We excluded WGs studying a single medical condition and/or those focusing on drugs of no interest to the PROTECT project. Fourthly, we conducted a Google search using the same keywords as in the electronic bibliographic search. Moreover, we searched by author's surname. Fifthly, from each website we found, we cross-linked it with other websites. Finally, we interviewed experts in the field of DU research; including EuroDURG, contacts (Table 1).

Table 1.EuroDURG Group: National groups and contact persons

Country	Contact Person	e-mail
ARMENIA	Dr. Irina Kazaryan Head Department of Pharmacy National Institute of Health 49/4 Komitas Avenue Yerevan 0052 Republic of Armenia	d-pharm@nih.sci.am durg@mail.ru ikazaryan@yahoo.com
BELGIUM	Monique Elseviers University of Antwerp Campus drie Eiken Universiteitsplein 1 B-2610 Wilrijk Belgium	monique.elsevier@ua.ac.be
CROATIA	Vera Vlahović-Palčevski Unit for Clinical Pharmacology University Hospital Rijeka Kresimirova 42 51000 Rijeka Croatia	vvlahovic@inet.hr
CZECH REPUBLIC	Petr Dvorak Vsenory 448 25231 Czech Republic	Pdvorak448@volny.cz
GERMANY	Sebastian Harder (co-chair Katrin Jahnsen) Clinical Pharmacology Johann Wolfgang Goethe University Frankfurt am Main Theodor Stern Kai 7 60590 Frankfurt Germany www.gaa-arzneiforschung.de	harder@em.uni-frankfurt.de
HUNGARY	Gyongyver Soos Department of Clinical Pharmacy University of Szeged, Faculty of Pharmacy Szikra utka 8 Szeged H 6725 Hungary	soos@pharm.u-szeged.hu
ITALY	Domenico Motola Department of Pharmacology University of Bologna Via Irnerio, 48 I 40126 Bologna Italy	domenico.motola@unibo.it
NORWAY	Randi Selmer National Institute of Public Health Mailbox 4404 Nydalen 0403 Oslo Norway	Randi.Selmer@fhi.no
RUSSIA	Svetlana Ratchina, MD, PhD Smolensk State Medical Academy Department of Clinical Pharmacology, Assistant Professor Institute of Antimicrobial Chemotherapy, Senior Research Fellow 28 Krupskaya str, PO Box 5 Smolensk 214019 Russian Federation	svetlana.ratchina@antibiotic.ru
SWEDEN	Björn Wettermark The Swedish Society for Pharmacoepidemiology Läkemedelscentrum Stockholms láns landsting Box 17533 SE-118 91 Stockholm Sweden	bjorn.wettermark@sll.se
UNITED	Steve Chapman	s.r.chapman@mema.keele.ac.uk

Country	Contact Person	e-mail
KINGDOM and IRELAND	Department of Medicines Management University of Keele Stafffordshire ST5 5BG Keele	

2.2.2. INCLUSION CRITERIA

Setting: Countries included in the inventory

Initially, the countries to be included were limited according to the following criteria: member states of the European Economic Area (EEA)(see Table 2 for a list of the EEA countries) with a population over 30 million inhabitants (France, Germany, Italy, Spain, Poland and United Kingdom) or, by country of origin of participants in the PROTECT project with available clinical databases such as Denmark, France, Germany, The Netherlands, Spain and United Kingdom or, by countries known to have a long tradition in collecting drug consumption data and/or with on-line accessible drug consumption data such as Denmark, Sweden, Norway, Finland and The Netherlands.Table 2. Economic European Area countries

Countries contacted			
Countries in alphabetical order (Total population –inhabitants- in 2013)			
Country	**Total population (inhabitants) in 2013**	**Country**	**Total population (inhabitants) in 2013**
Austria	8,451,860	Latvia	2,023,825
Belarus	9,463,800	Liechtenstein	36,838
Belgium	11,161,642	Lithuania	2,971,905
Bosnia and Herzegovina	3,835,645[P]	Luxembourg	537,039
Bulgaria	7,284,552	Malta	421,364
Croatia	4,262,140	Netherlands	16,779,575
Cyprus	865,878	Norway	5,051,275
Czech Republic	10,516,125	Poland	38,533,299
Denmark	5,602628	Portugal	10,487,289
Estonia	1,324,814	Romania	20,057,458
Finland	5,426,674	Russia[a]	142,946,800
France	65,633194[p]	Serbia	7,241,295[b]
Germany	80,523,746[P]	Slovakia	5,410,836
Greece	11,062,508	Slovenia	2,058,821
Hungary	9,908,798	Spain	46,704,308
Iceland	321,857	Sweden	9,555,893
Ireland	4,591,087	Switzerland	8,039,060
Italy	59,685,227[P]	United Kingdom	63,730,107[p]
		Ukraine[c]	45,600,000

Source: www.epp.eurostat.ec.europa.eu (accessed on11/2013). [b]www.worldpopulationreview.com
[b]Data for year 2012 [c]http://database.ukrcensus.gov.ua/PXWEB2007/popul_eng.htm[P]Provisional.

In a second phase, we tried to include as many countries as possible, covering first the European continent. We invited the following countries: Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, The Czech Republic, Cyprus, Estonia, Finland, Greece, Hungary, Iceland, Ireland, Latvia, Lithuania, Luxembourg,

Malta, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Sweitzerland and Ukraine.

Groups of medicines included in the PROTECT project

The groups of medicines of interest were defined by the ATC codes (19) and were calcium channel blockers, antibacterials, antiepileptic drugs, benzodiazepines, antidepressants, and inhaled beta2-agonists. For the inpatient, the focus was mainly on antibiotics; specifically macrolides and amoxicillin-clavulanate.

Language criterion

There was no language restriction. For those languages that none of the authors knew, the Google translator was used as a customised tool.

Accessibility criterion

Web sites free of charge and that did not require a registration/password were browsed for information on drug consumption data.

Quality of the websites

This was measured depending on the availability of current and complete information and their independence from commercial sponsorship.

The information of interest for each WG was website, definition of the group, objectives, working period, participating countries, and information on the group activities from their websites or publications, source of funding, and publications.

2.3. SPECIFIC METHODS FOR OUTPATIENT DRUG UTILISATION RESOURCES

2.3.1. NON-COMMERCIAL DATA PROVIDERS

See the above general methods. Information on the following characteristics was gathered for all nationwide drug consumption databases: data provider, website, source of drug consumption, setting, population coverage, accessibility, drug codification unit of measurement of drug consumption, drug-based information, prescriber and pharmacy information, potential confounders: age, gender, indication for use, co-morbidities, co-treatment, language of the database, record period and record linkage. We also provide references as in reports or published articles that used these databases in pharmacoepidemiological studies or that described their characteristics.

2.3.2. COMMERCIAL DATA PROVIDERS

IMS health is the only commercial source of drug consumption data being used for the PROTECT project (permission given for specific analyses and prospective publication).

Interviews with experts provided information on two other market research companies. One company collecting information on drug consumption data in Germany was Pharmafakt (www.pharmafakt.de , last accessed on 8/2013). ThisGerman company sells reimbursement drug consumption data to the pharmaceutical industry.The other company, operating in more than 60 countries, is Cegedim Strategic Data (CSD), part of the Cegedim group (http://www.cegedim.com/Pages/default.aspx, last accessed on 8/2013).

No contact was established with these companies.

2.4. SPECIFIC METHODS FOR INPATIENT DRUG UTILISATION RESOURCES

2.4.1. NON-COMMERCIAL DATA PROVIDERS

First of all, we reviewed the main available information on hospital DU for the drugs selected by PROTECT. Then, because of the importance of antibacterials in the inpatient sector, a specific literature review was conducted to establish the availability of inpatient antibacterial consumption data in the selected PROTECT European countries.

2.4.1.1. HOSPITAL DRUG UTILISATION (GENERAL OVERVIEW)

There were three potential sources of information on DU studies in hospital settings: general information available on the web, public nationwide databases and electronic bibliographic databases.

General Website Information

We extracted general information on hospital medicines management from the Pharmaceutical Health Information System website (http://whocc.goeg.at/Publications/Articles, last accessed on 8/2013).

Using links from this website index, three other websites with general information were identified: the European Association of Hospital Pharmacists website, www.eahp.eu (last accessed on 8/2013), the European Hospital and Healthcare Association website, www.hope.be (last accessed on 8/2013) and the Organisation for Economic Cooperation and Development (OECD) website, http://www.oecd.org (last accessed on 8/2013).

National Public Databases

Information on the type of drug consumption data and the healthcare sector covered by the different nationwide databases was already available from the search in the outpatient sector. In addition, we explored whether the National Medicines Agencies websites had published reports on inpatient drug consumption.

Bibliographic database search

We searched on PubMed. This search was not a systematic review of hospital medicines consumption but rather a broad overview of the number of DU studies conducted in a hospital setting, for the selected PROTECTS drugs. The search terms were "hospital drug utilisation"," calcium channel blockers", "antiepileptic drugs", "beta2-agonists", "antidepressants" and "benzodiazepines" Each of the medicine groups was combined with "hospital drug utilisation", using the Boolean logic AND.

The titles retrieved in the search were included if they had been published in 1980 or thereafter, and were set in any kind of European hospital. Inpatient or hospital drug consumption for this review meant nursing homes, psychiatric clinics, or any other institution categorised as a long-term care unit. It excluded drug

consumption referred to prescription of medicines to outpatients by specialists or prescription of hospital-only-medicines to outpatients.

According to the WHO, there are four different categories of DU studies: studies covering the patterns of use, quality of use, determinants of use, and outcome of use (20). Only articles related to patterns of drug use, regardless of indication, were included. All units and methods of measurement of drug consumption were valid for the review. We highlighted those abstracts classifying medicines according to the ATC codification and/or quantifying drug use in DDDs. Active pharmaceutical ingredients classified in ATC level 5 for the selected PROTECT drugs were considered drugs of interest. We included any type of study design. Any article published in a language understood by any of the group members was included: English, Spanish or any other Romanic languages, and Swedish.

2.4.1.2. ANTIMICROBIAL (J01FA, J01CR02) DRUG UTILISATION IN HOSPITALS

It aimed to determine the availability and nature of information in the public domain on hospital consumption of macrolides and amoxicillin-clavulanate in Europe between 2000 and 2010. The search was conducted on the Internet and on PubMed. If of interest, please contact Pili Ferrer to get further information (pf@icf.uab.cat).

2.4.2. COMMERCIAL DATA PROVIDERS

Because the only commercial data provider studied in this report is IMS Health, the information provided for outpatient resources is also valid for inpatient resources, unless otherwise stated.

3. RESULTS

From the general methods section we retrieved a list of websites and other sources of information. This list of websites has been classified according to the website search strategy (Table 3).

The information obtained from the whole search strategy has been organised into two categories of data sources. The first category is termed background data and it covers information provided by comprehensive institutional websites and specific national websites. This background data offers information on the national health systems, medicines regulatory agencies, drugs marketed in each of the countries, information on the pharmaceuticals licensed in each country and international research WGs. The second category is termed national drug consumption databases.

For the inpatient sector we present a brief summary of the search.

At the end of this section readers can find a summary with all potential sources of medicines consumption data for the out- and inpatient healthcare settings (see Tables 7-11).

Table 3. Comprehensive and more specific institutional European websites, and international networks websites

GENERAL INSTITUTIONAL EUROPEAN WEBSITES	www.europa.eu	Official website of the European Union.
	www.ema.europa.eu	European Medicines Agency.
	www.who.int	World Health Organization.
	www.oecd.org	Organization for Economic Cooperation and Development.
MORE SPECIFIC INSTITUTIONAL WEBSITES Information on drug data providers, pricing and reimbursement agencies and national medicines agencies	www.ispor.org	International Society for Pharmacoeconomics and Outcomes Research.
	www.eudrapharm.eu	It provides, among other, information on all medicinal products approved by the European Union.
	www.euro.who.int/observatory	The European Observatory on Health Care Systems and Policies.
	whocc.goeg.at	WHO Collaborating Centre for Pharmaceutical and Reimbursement Policies and the Austrian Ministry Of Health.
	www.eahp.eu	European Association of Hospital Pharmacists.
	www.hope.be	European Hospital and healthcare Association.
	www.bridgetodata.org	Online listing of more than 140 databases from 21 countries.
WEBSITES OF INTERNATIONAL NETWORKS ON MEDICINES UTILISATION STUDIES	www.encepp.eu	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance.
	www.pharmacoepi.org/eurodurg	European Drug Utilisation Research Group.
	http://ec.europa.eu/eahc/projects/database.html?prjno=2003133	Statistics on Medicines in Europe.
	www.pharmacoepi.org	International Society of Pharmacoepidemiology with a special group interested in DU Research and Cross-National Comparisons in DU.
	www.nhv.se/norpen	Nordic network on pharmacoepidemiological research.
	www.piperskagroup.com	They are involved in reimbursement, formulary listing and/or enhancing the rational use of drugs in their countries.

See specific tables for specific drug utilisation networks.
All websites were last accessed on 8/2013

3.2. BACKGROUND DATA

3.2.1. DATA PROVIDERS OF AUTHORISED MEDICINAL PRODUCTS

Table 4. List of national medicines agencies

Country	National medicines agencies	Website
Austria	Agentur für Gesundheit und Ernährungssicherheit (AGES) Austrian Agency for Health and Food Safety	www.ages.at
Belarus	республиканский центр экспертиз и испытания в здравоохранении Centre for Expertise and Testing in Health Care State Enterprise	www.rceth.by
Belgium	Agence Fédérale des Médicaments et des Produits de Santé -AFMPS Federal Agency for Medicines and Health Products	www.fagg-afmps.be
Bosnia-Herzegovina	Agencija za lijekove i medicinska sredstva Bosne i Hercegovine Agency for Medicinal Product and Devices of Bosnia-Herzegovina	http://www.almbih.gov.ba/
Bulgaria	ИЗПЪЛНИТ НА АГЕНЦИЯ ПО ЛЕКАРСТВАТА Bulgarian Drug Agency	www.bda.bg
Croatia	Agencija za lijekove i medicinske proizvode: HALMED Agency for Medicinal products and Medical devices	www.almp.hr/
Cyprus	ΦΑΡΜΑΚΕΥΤΙΚΕΣΥΠΗΡΕΣΙΕΣ Ministry of Health of the Republic of Cyprus. Pharmaceutical Services	www.moh.gov.cy/phs
The Czech Republic	Státní ústav pro kontrolu léčiv State Institute for Drug Control	www.sukl.cz
Denmark	Lægemiddelstyrelsen Danish Health and Medicines Authority	www.laegemiddelstyrelsen.dk
Estonia	Ravimiamet State Agency of Medicines	www.sam.ee
Finland	Lääkealan turvallisuus- ja kehittämiskeskus Finnish Medicines Agency	www.fimea.fi
France	Agence nationale de sécurité du médicament et des produits de santé (ANSM) National Agency for the Safety of Medicines and Healthcare Products	www.ansm.sante.fr
Germany	Bundesinstitut für Arzneimittel und Medizinprodukte – BfArM Federal Insitute for Drugs and Medical Device	http://www.bfarm.de/DE/Home/home_node.html
Greece	Εθνικός Οργανισμός Φαρμάκων - ΕΟΦ National Organisationfor Medicines -EOF	www.eof.gr
Hungary	Országos Gyógyszerészeti Intézet Föigazgatóság Directorate General of National Institute of Pharmacy	www.ogyi.hu
Iceland	Lyfjastofnun Icelandic Medicines Agency	www.lyfjastofnun.is www.imca.is
Ireland	Irish Medicines Board	www.imb.ie
Italy	Agenzia Italiana del Farmaco - AIFA The Italian Medicines Agency	www.agenziafarmaco.gov.it

Country	National medicines agencies	Website
Latvia	Zāļu valsts aģentūra (ZVA) State Agency Medicines	www.vza.gov.lv
Liechtenstein	Amt für Gesundheit (AG) Board of Health	http://www.llv.li/amtsstellen/llv-ag-heilmittel-2.htm
Lithuania	Valstybinė vaistu kontrolės tarnyba Prie Lietuvos Respublikos Sveikatos Apsaugos Ministerijos The State Medicines Control Agency	www.vvkt.lt
Luxembourg	Ministère de la Santé, Direction de la Santé, Division de la Pharmacie et des Médicaments Ministry of Health, Directorate of Health, Division of Pharmacy and Medicines	www.ms.etat.lu/fr/
Malta	Awtorità dwar il-Mediċini Medicines Authority	www.medicinesauthority.gov.mt
The Netherlands	College ter Beoordeling van Geneesmiddelen Medicines Evaluation Board	www.cbg-meb.nl
Norway	Statens legemiddelverk Norwegian Medicines Agency	www.legemiddelverket.no
Poland	Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products	www.urpl.gov.pl
Portugal	INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde, I.P. The National Authority of Medicines and Health Products (INFARMED, I.P.)	www.infarmed.pt
Romania	Agentia Nationala a Medicamentului şi a Dispozitivelor Medicale- ANM National Agency for Medicines and Medical Devices	www.anm.ro
Serbia	Агенција за лекове и медицинска средства Србије (АЛИМС) Agency for Medicines and Medical Devices Agency of Serbia (ALIMS)	www.alims.gov.rs
Slovakia	Štátny ústav pre kontrolu liečiv State Institute for Drug Control	www.sukl.sk
Slovenia	Javna agencija Republike Slovenije za zdravila in medicinske pripomočke Agency for medicinal products and medical devices of the Republic of Slovenia	www.jazmp.si
Spain	Agencia Española de Medicamentos y Productos Sanitarios-AEMPS Spanish Agency for Medicines and Medical Devices	www.aemps.gob.es
Sweden	Läkemedelsverket Medical Products Agency	www.lakemedelsverket.se
Sweitzwerland	Swissmedic Swiss Agency for therapeutic products	http://www.swissmedic.ch
The United Kingdom	Medicines and Healthcare products Regulatory Agency - MHRA	www.mhra.gov.uk
Ukraine	Державна адміністрація України з лікарських засобів State administration of Ukraine on medicinal products	http://diklz.gov.ua/

Sources: Eudrapharm website (http://www.eudrapharm.eu/eudrapharm/welcome.do?selectedStaticLocale.languageCode=en) and the list of globally identified websites of Medicines Regulatory (http://www.who.int/medicines/areas/quality_safety/regulation_legislation/ListMRAWebsites.pdf). Last accessed on 8/2013.

3.2.2. HEALTH CARE SYSTEMS

European countries have a variety of approaches to the organisation of health systems and are diverse in terms of language, history, and wealth. Knowledge of the different health systems gives us important information about financing and access of the population to health.

Appendix 7.3 shows the main characteristics of each country health system.It describes the health care provider, population coverage, and the model of health care financing.

3.2.3. PRICING AND REIMBURSEMENT AGENCIES

All websites updated on 8/2013.

Table 5. Pricing and reimbursement agencies

Country	Pricing agency	Reimbursement agency
Austria	Bundesministerium für Gesundheit(BMG). The Austrian Federal Ministry of Health. It has the overall responsibility for pricing, marketing and reimbursement.For pricing it is assisted by Preiskommission (PK).Furthermore there is a price notification agreement in place between the Federal Chamber of Labour (Bundesarbeiterkammer) and the Federal Chamber of Commerce (Wirtschaftskammer). For drugs seeking reimbursement:Federal Ministry of Health. Pricing Committee (PK). For OTCs and products not seeking reimbursement, the manufacturer notifies the BMG of ex-factory price. www.bmg.gv.at	The BMG is the overall responsible for the reimbursement assisted by the Hauptverband der Österreichischen Sozialversicherungsträger (HBV) (Federation of Austrian Social Insurance) www.sozialversicherung.at http://www.hauptverband.at(MainAssociation of Austrian Social Security Organisations). The HBV in turn relies on the recommendation of the Pharmaceutical Evaluation Board (Helmittel-Evaluierungskommission, HEK). An independent drug commission (Unabhängige Heilmittel-Kommission, UHK) within the Ministry of Health is charged with monitoring the HBV and HEK. The UHK is the manufacturers side and has the power to vet but not overrule reimbursement decisions taken.
Belgium	SPF Economie, PME, Classes moyennes et Energie. Service des Prix Federal Minister of Economic Affairs. Price Services. FOD Economie, KMO, Middenstand en Energie. Prijzendienst. www.economie.fgov.be/fr/consommateurs/Prix_reglementes/	Institute National d'Assurance Maladie- Invalidité. Commission de Remboursement des Médicaments. Rijksinstituut voor ziekte- en invaliditeitsverzekering. Commissie Tegemoetkoming Geneesmiddelen. www.riziv.fgov.be
Bulgaria	Министерство на здравеопето Ministry of Health There is a Pricing Commission,a Pricing Transparency Commission and a	Национална здравноосигурителна каса. National Health Insurance Fund This is the health insurer that reimburses the medicines. The

Country	Pricing agency	Reimbursement agency
	Positive List Commisssion that support and implement the pricing and reimbursement policy of the government. www.mh.government.bg	reimbursement policy is the responsability of the Ministry of Health. http://www.nhif.bg/
Croatia	Hrvatski zavod za zdravstveno osiruranje Croatia Health Insure Fund http://www.hzzo-net.hr/	Hrvatski zavod za zdravstveno osiruranje Croatia Health Insure Fund http://www.hzzo-net.hr/
Cyprus	ΥπουργείοΥγείας Ministry of Health (following the recomendation of Price Control Committe) http://www.moh.gov.cy	ΥπουργείοΥγείας Ministry of Health The Department of Pharmaceutical Service www.gov.moh.cy
Czech Republic	Státní ústav pro kontrolu léčiv (SÚKL). State Institute for Drug Control www.sukl.cz	Státní ústav pro kontrolu léčiv (SÚKL). State Institute for Drug Control. http://www.sukl.eu/sukl/reimbursement-of-costs-for-advice-provision
Denmark	Indenrigs-og Sundhedsministeriet The Ministry of Interior and Health www.im.dk	Lægemiddelstyrelsen The Danish Medicines Agency www.laegemiddelstyrelsen.dk
Estonia	Raviviamet www.sam.ee	
Finland	Sosiali –ja Terveysministeriö. Lääkkeiden hintalautakunta Ministry of Social Affairs and Health. Pharmaceutical Pricing Board www.stm.fi/stm/neuvottelukunnat/hila/etusivu	Kansaneläkelaitos Social Insurance Institution www.kela.fi
France	Comité d'Economie de Produits de Santé (CEPS) Economic Committee of Health Products www.sante.gouv.fr/comite-economique-des-produits-de-sante-ceps.html	Commission d'Evaluation des Médicaments. . Ministère des Affaires sociales et de la Santé Ministery of Social Affairs and Health www.sante.gouv.fr Union Nationale des Caisses d'Assurance Maladie (UNCAM) National Union of Health Insurance Funds. www.ameli.fr
Germany	Bundesministerium für Gesundheit Federal Ministry of Health www.bmg.bund.de Manufacturers are free to set the price for the first year of a new pharmaceutical product. Gemeinsamer Bundesausschuss (G-BA) Federal Joint Committee. www.g-ba.de	Gemeinsamer Bundesausschuss (G-BA) Federal Joint Committee. www.g-ba.de Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen Institute for Quality and Efficiency in Health Care www.iqwig.de Die Verbände der gesetzlichen Krankenkassen (GKV) The associations of Statutory Health Insurance http://www.g-k-v.de/gkv/

Country	Pricing agency	Reimbursement agency
Greece	Υπουργείο Ανάπτυξης Γενική Γραμματεία Εμπορίου Διεύθυνση Εσωτερικής των τιμών βιομηχανικών προϊόντων και φαρμάκων.Ministry of Development www.ypoian.gr/General Secretariat of Internal Commerce Directorate of pricing industrial products and medicines. www.gge.gr	Υπουργός Υγείας και Κοινωνικής Αλληλεγγύης ΔιεύθυνσηΦαρμάκωνκαιΦαρμακείων Ministry of Health and Social Solidarity Directorate of Medicines and Pharmacies. www.moh.gov.gr/Social Security Funds(based on a recovery price). www.ika.gr(the largest in Greece).
Hungary	Országos Egészségbiztosítási Pénztar The National Health Insurance Fund Administration www.oep.hu	Országos Egészségbiztosítási Pénztar The National Health Insurance Fund Administration www.oep.hu
Iceland	Pricing and Reimbursement Committee Ministry of Welfare http://eng.velferdarraduneyti.is/agencies/nr/33953	Pricing and Reimbursement Committee Ministry of Welfare http://eng.velferdarraduneyti.is/agencies/nr/33953
Ireland	The Department of Health www.dohc.ie The Health Services Executive (HSE). Corporate Pharmaceutical Unit. www.hse.ie	The Department of Health ww.dohc.ie The Health Services Executive (HSE). Corporate Pharmaceutical Unit. www.hse.ie
Italy	Agenzia Italiana del Farmaco (AIFA).Comitato Prezzi e Rimborso. Italian Medicines Agency. Pricing and Reimbursement Committee. www.agenziafarmaco.it	Agenzia Italiana del Farmaco (AIFA). Comitato Prezzi e Rimborso. Italian Medicines Agency. Pricing and Reimbursement Committee. www.agenziafarmaco.it
Latvia	Nacionālais Veselības Dienests National Health Service http://www.vmnvd.gov.lv/lv (established 1st November 2011)	Nacionālais Veselības Dienests National Health Service http://www.vmnvd.gov.lv/lv (established 1st November 2011)
Lithuania	The Ministry of Health http://www.sam.lt/go.php/lit/IMG/4	Ministry of Health The Pharmaceuticals Reimbursement Committee (representatives of the Ministry of Health, the State Medicines Control Agency, and the National Health Insurance Fund)
The Netherlands	Ministerie van Volksgezondheid, Welzijn en Sport Ministry of Health, Welfare and Sport www.rijksoverheid.nl/onderwerpen/geneesmiddelen	Ministerie van Volksgezondheid, Welzijn en Sport Ministry of Health, Welfare and Sport www.rijksoverheid.nl/onderwerpen/geneesmiddelen College voor Zorgverzekeringen Health Care Insurance Board www.cvz.nl
Norway	Statens Legemiddelverk Norwegian Medicines Agency www.legemiddelverket.no	Statens Legemiddelverk Norwegian Medicines Agency www.legemiddelverket.no Helse-og omsorgsdepartementet

Country	Pricing agency	Reimbursement agency
		Ministry of Health and Care Services www.regjeringen.no
Poland	Ministerstwo Zdrowia. Zespół zarządzający narkotyków. Ministry ofHealth. The Drug Management Team. Free pricing for OTC drugs (determined by the manufacturer). www.mz.gov.pl/ They determine the pricing of amedicine	Ministry of Health. www.mz.gov.pl It also determines the level of reimbursement of a medicine. Narodowy Fundusz Zdrowia (NFZ) National Health Fund. www.nfz.gov.pl/new/
Portugal	Direcção Geral das Actividades Económicas Directorate General of Economic Activities www.dgae.min-economia.pt	Ministerio da Saúde Ministry of Health www.min-saude.pt INFARMED. Autoridade Nacional do Medicamento e Produtos de Saúde, I.P. National Authority of Medicines and Health Products, IP www.infarmed.pt/portal/page/portal/INFARMED
Romania	The Ministry of Health www.ms.gov.ro/	The Ministry of Health, www.ms.gov.ro/ Casa Nationala de Asigurari de Sanatate The National Insure Fund www.cnas.ro
Russian Federation[a]	Ministry of Health and Social Development Roszdravnadzor. The Federal Service on Surveillance in Healthcare and Social Development It is the subordinate executive authority of the Ministry of Healthand Social development of the Russian Federation. Division of registration of medicaments and medical equipment http://www.roszdravnadzor.ru	Ministry of Health and Social Development Federal Mandatory Health Insurance It covers only 16 milion people, with more than half of them opting to receive cash. Dopolnitel'noe Lekarstvennoe Obespechenie (DLO) The Supplementary Medicines Provision It provides free subsidized pharmaceuticals
Slovakia	Ministerstvo zdravotníctva The Ministry of Health www.health.gov.sk	Ministerstvo zdravotníctva The Ministry of Health www.health.gov.sk
Slovenia	Agency for medicinal products and medical devices, a department of the Ministry of Health. www.mz.gov.si	The Health Insure Institute www.zzzs.si
Spain	Ministerio de Sanidad , Servicios Sociales e Igualdad Dirección General de Farmacia y Productos Sanitarios. Ministry of Health,Social Services and Equality Directorate of Pharmacy and Health Products. www.msc.es/profesionales/farmacia/organizacion.htm	Ministerio de Sanidad,Servicios Sociales e Igualdad. Dirección General de Farmacia y Productos Sanitarios. Ministry of Health and Social Services and Equality Directorate of Pharmacy and Health Products. www.msc.es/profesionales/farmacia/organizacion.htm
Sweden	Tandvård-och Läkemedelsförmånsverket Dental and Pharmaceutical Benefits Agency www.tlv.se	Tandvård-och Läkemedelsförmånsverket Dental and Pharmaceutical Benefits Agency www.tlv.se

Country	Pricing agency	Reimbursement agency
The United Kingdom	National Health Service (NHS) www.nhs.uk Department of Health www.dh.gov.uk	National Health Service (NHS) www.nhs.uk Department of Health www.dh.gov.uk

Source: http://uk.practicallaw.com/4-501-0563

3.2.4. PHARMACEUTICAL INFORMATION

Table 6 lists websites with general pharmaceutical information (trade names, prices, specific dates a drug has been marketed or withdrawn, and approved indications).All websites accessed on 9/2013.

Table 6. Pharmaceutical data sources by country

Country	Source of pharmaceutical information	Information provided	Website
Austria	Online search of pharmaceutical specialties	Summary of product characteristics (SPC) and patient's information leaflet (PIL)	https://aspregister.basg.gv.at
	Erstattungskodex (EKO). Reimbursement code	Reimbursement status of the drug: green, red or yellow. Updated monthly.	http://www.oertl.at/ek/
Belarus	National Center for Expertise and Testing in Health Carehttp://www.rceth.by/	Register of medicinal products of the Republic of Belarus	http://www.rceth.by/Refbank/default.aspx
Belgium	Association Pharmaceutique Belge	Internal list with all the prices of medical specialties online	www.apbtarif.be (No free access)
	Centre Belge d'Information Pharmaceutique Belgisch Centrum voor Farmacotherapeuhsche Informatie	Repertoire of medicines with comments on them	www.bcfi.be
	Agence Fédérale des Médicaments et des Produits de Santé - AFMPS Federal Agency for Medicines and Health Products	Database with all medicines authorized at national level (Belgium and Luxembourg) and by the European commission	http://www.fagg-afmps.be/fr/items-HOME/Bases_de_donnees/
Bulgaria	ИзпълнитНА АГЕНЦИЯПОЛЕКАРСТВАТА Bulgarian drug Agency	Medicines with a marketing authorization in Bulgaria. The drugs authorized through the centralized procedure are not included in this Register. Information given: composition, dosage, package, and manufacturer	http://www.bda.bg/images/stories/documents/register/Mp.htm

Country	Source of pharmaceutical information	Information provided	Website
Croatia	Agencija za lijekove i medicinske proizvode: HALMED Agency for medicinal products and medical devices of Croatia	Information about medications that are given authorization for a medicinal product in the Republic of Croatia.	http://www.almp.hr/?ln=hr&w=lijekovi
Czech Republic	Státní ústav pro kontrolu léčiv (SÚKL). State Institute for Drug Control. *Medicinal Products Database.*	Information about medicinal products in the Czech market.	http://www.sukl.eu/modules/medication/search.php
Denmark	Laegemiddelstyrelsen. Danish Medicines Agency	Prices of medicines, and other information on the different pharmaceutical products (summary of product characteristics, package leaflet). Lists with information about medicinal products updated daily.	http://laegemiddelstyrelsen.dk/ www.produktresume.dk
	Dansk laegemiddelinformationInformation on medicines	Information on medicinal products for both the patients and health care professionals.	www.medicin.dk
Estonia	Ravimiamet. State Agency of Medicines	Information on medicinal products authroised for use in Estonia. Basic data for products will be presented in tabular format with links to the more detailed data, summary of product characteristics and package insert.	http://193.40.10.165/register/register.php?keel=eng&inim_vet=inim
Finland	Lääkealan turvallisuus- ja kehittämiskeskus Finnish Medicines Agency	Free search service on information on medicinal products, summary of product characteristics, patient leaflets.	http://www.fimea.fi/medicines/fimeaweb
France	Dictionnaire Vidal	Information on drugs for healthcare professionals and patients.	http://www.vidal.fr/les-produits-professionnels/dictionnaire-vidal (No free access)
	Centre National Hospitalier d'Information sur le Médicament (CNHIM)	A database for Health care professionals has been developed with information on all drugs available in France.	http://www.cnhim.org/ http://www.theriaque.org (No free access)
	Agence Nationale du Securité du Médicament. French French National Medicines Agency	ECODEX database with information on all drugs marketed in France.	http://agence-prd.ansm.sante.fr/php/ecodex/index.php
Germany	Rote list	Information on drugs for pharmacists and medical doctors.	http://www.rote-liste.de(No free access)
	Summary of Product Characteristics in	Information on drugs for medical doctors and	www.fachinfo.de (No free access)

Country	Source of pharmaceutical information	Information provided	Website
	Germany.Fachinfo	pharmacists.	
	Fachinformationsverzeichnis Deutschland Federal and State governments portal for drug information (in collaboration with the Ministry of Health	Information on medicinal products. Sections of this information are public and can be accessed by the public. It contains administrative data (Authorisation of medicinal products, SPC and PIL).	http://www.pharmnet-bund.de/dynamic/de/am-info-system/index.html
Greece	National Organization for Medicines	Register of medicines of Greece	http://www.eof.gr/web/guest/search
Iceland	Icelandic Medicines Agency	Information of all drugs marketed in Iceland	http://serlyfjaskra.is/
Ireland	Irish Medicines Board	Human Medicines Listing with information on SPC, PIL and Product Assessment Reports.	http://www.imb.ie/EN/Medicines/HumanMedicines/HumanMedicinesListing.aspx
	Irish Pharmaceutical Healthcare Association	SPC and PIL information.	www.medicines.ie
Italy	Elsevier editorial	Information on drugs marketed in Italy. The information is available online and as a book.	www.prontuario.it (No free access)
	Repertorio Farmaceutico Italiano (ReFI)	Online database containing information (partly from ReFI) regarding drugs for pharmacists and other healthcare professions.	www.codifa.it (No free access)
		Book: L'Informatori farmaceutico (updated yearly).	No online
	Italian Medicines Agency	It is a database containing all medicines commercialised in Italy, either reimbursed by the NHS (class A-H) or paid by the patient (class C, OTC), price and delivery system.	https://farmaci.agenziafarmaco.gov.it/aifa/servlet/HomeDispatcher
	Farmadati Italia	It collaborates with AIFA in mantaining the drugs database.	www.farmadati.it (No free access)
Latvia	State Agency of Medicines in Latvia	Containing information regarding a total of medicines authorised in the national, mutual recognition, decentralised, centralised procedures, as well as parallel imported medicines. This issue contains trade names of medicines, pharmaceutical forms, international nonproprietary names (INN) of actives substances, strength/concentration, pharmacotherapeutic group, Anatomical Therapeutic Chemical (ATC) classification code, authorisation number, issuance procedure and marketing authorisation holders.	http://www.zva.gov.lv//?id=377&sa=377&top=112
Lithuania	The State Medicines Control Agency (SMCA)	Information of all medicines registered in Lithuania	http://extranet.vvkt.lt/paieska/

Country	Source of pharmaceutical information	Information provided	Website
Luxembourg	Ministère de la Santé.Division de la Pharmacie et des Medicaments. Ministry of health. Pharmacies and drug division Agence Fédérale des Médicaments et des Produits de Santé - AFMPS Federal Agency for Medicines and Health Products	Database with all medicines authorized at national level (Luxembourg and Belgium) and by the European commission	http://www.fagg-afmps.be/fr/items-HOME/Bases_de_donnees/
	Caisse nationale de santé The Luxembourg National Health Fund	List of marketeddrugs. Pricing list.	http://www.cns.lu/prestataires/?m=55-41-28&p=248
Malta	Medicines Authority	A list of medicinal products which are licensed by the Medicines Authority to be placed on the market in Malta. Through the Malta Medicines List, you may: (i)find whether a medicine is authorised to be placed on the market in Malta or not; (ii) find different products containing the same active ingredient/s; (iii) find different formulations of the same product or of an active ingredient; (iv) know whether a product is classified as Prescription only Medicine (PoM) or Over the Counter Medicine.	http://www.maltamedicineslist.com/
The Netherlands	College ter Beoordeling van Geneesmiddelen Medicines Evaluation Board	Database on information about all drugs marketed in The Netherlands	http://www.cbg-meb.nl/CBG/nl/humane-geneesmiddelen/geneesmiddeleninformatiebank/default.htm
Norway	Statens legemiddelverk Norweigian Medicine Agency	Approved and marketed pharmaceuticals sold in Norwegian pharmacies	http://www.legemiddelverket.no/English/Database_approved_and_marketed_pharmaceuticals/Sider/default.aspx
Poland	The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products	Only reimbursement products	http://leki.urpl.gov.pl/index.php
Portugal	Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.	Prontuário Terapêutico (for drugs dispensed in the community). Formulário Hospitalar de Medicamentos (FHNM). Both available online.	http://www.infarmed.pt/prontuario/index.php http://www.infarmed.pt/formulario/index.html
		INFARMED database: Access to information on all drugs marketed in Portugal	http://www.infarmed.pt/infomed/inicio.php
Romania	Agentia Nationala a Medicamentului şi a Dispozitivelor Medicale- ANM Natioanal Agency for Medicines and	Database of drugs authorized in Romania	http://193.169.156.200/app/nom1/anm_list.asp

Country	Source of pharmaceutical information	Information provided	Website
	Medical Devices		
Serbia	Агенција за лекове и медицинска средства Србије (АЛИМС) Agency for Medicines and Medical Devices Agency of Serbia (ALIMS)	Database of marketed drugs	http://www.alims.gov.rs/ciril/lekovi/pretrazivanje-humanih-lekova/
Slovakia	Štátny ústav pre kontrolu liečiv National Competent Authority	Database of registered drugs	http://www.sukl.sk/sk/databazy-a-servis/databazy/vyhladavanie-v-databaze-registrovanych-liekov?page_id=242
Slovenia	The Health Insurance Institute of Slovenia(http://www.zzzs.si/indexeng.html)	Database of marketed drugs	http://www.cbz.si/cbz/bazazdr2.nsf/Search/$searchForm?SearchView
Spain	Consejo General de Colegios Oficiales de Farmacéuticos. General Council of the Official Pharmaceutical Professional Association	Catálogo de Especialidades Farmacéuticas. Edited reference drug information book.	No online information.
		Database with information about drugs by region (summary of product characteristics, patient leaflet, patient counseling)	https://botplusweb.portalfarma.com/(No free access).
	Agencia Española de medicamentos y productos sanitarios (AEMPS). Spanish Agency of medicines and health products	CIMA database. Centro de información online de Medicamentos de la AEMPS. Information on all drugs marketed in Spain	https://sinaem4.agemed.es/consaem/fichasTecnicas.do?metodo=detalleForm&version=new
Sweden	FASS	Information on drugs marketed in Sweden for the general public (PIL) and health care professionals (SPC).	www.fass.se
	Läkemedelsverket Swedish Medical Products Agency	Basic information on a medicinal product .	http://www.lakemedelsverket.se/malgrupp/Halso---sjukvard/Sok-lakemedelsfakta/
Sweitzerland	Swissmedic (Swiss Agency for therapeutic products)	Database of authorized drugs	http://www.swissmedicinfo.ch/default.aspx
The United Kingdom	The electronic Medicines Compendium (eMC)	Information about the UK licensed medicines (SPC and PIL).	http://www.medicines.org.uk/emc/
	NHS Business Services Authority, NHS Prescription Services	NHS Electronic Drug Tariff (for England and Wales). Information on prices of drugs for GPs, pharmacy contractors and appliance contractors. Updated monthly.	http://www.ppa.org.uk/edt/May_2011/mindex.htm
	British Medical Association and the Royal Pharmaceutical Society	Information about the clinical use of medicines.	www.bnf.org (No free access, except for UK residents and residents of low-and middle-income countries listed on the web).

Country	Source of pharmaceutical information	Information provided	Website
	National electronic Library for Medicines (NeLM). Content provided by NHS pharmacy medicines information service (UKMi)	Medicines information portal in the NHS. It includes news, evidence-based reviews on drugs and drug therapy and health promotion material.	www.nelm.nhs.uk

All websites listed have free access unless otherwise stated.

3.2.5.OTHER DATABASES WITH PHARMACEUTICAL INFORMATION

Database	Website	General overview
Common European Drug Database	http://cedd.oep.hu/drugs.tib?s=drug-art&f=ceddart1&id=l8xakdcq3osro9bz&portallang=en (pilot website)	It is an initiative of the National Health Insurance Fund Administration of Hungary. It makes available updated price information of medications. Currently it compares the prices of Austria, Czech Republic, Finland, Hungary, Ireland, Lithuania, Norway, Poland, Slovenia, and Slovakia

3.2.6. INTERNATIONAL NETWORKS AND WORKING GROUPS IN PHARMACOEPIDEMIOLOGY

Several public and private networks and working groups have been established to promote the research on DU through a collaborative international initiative with a variety of objectives.

The groups have been divided into those offering general information on DU research, general research groups; and, on those groups studying either specific diseases or a group of drugs of interest for the PROTECT project, the specific research groups.

All websites and information accessed on 9/2013.

3.2.6.1 GENERAL RESEARCH GROUPS

We provide up to a maximum of three publications, the most recent ones, for each of the international WGs.

3.2.6.1.1 ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance)

Web	www.encepp.eu
Definition	Project led by the EMA since 2006 to convey available expertise and research experience in the fields of Pharmacoepidemiology and Pharmacovigilance, comprising research and medical-care centres, healthcare databases, electronic registries and existing networks.
Objectives	To strengthen post-authorisation monitoring of medicinal products in Europe.
Working period	2006-ongoing
Participants	European countries
Information	The project has been developed in several phases. Currently it holds the ENCePP database of research resources, which encloses the inventory of research institutions and the registry of European data sources, and it is complemented with an e-register of studies. This database is publicly available.
Funding	European Medicines Agency
Publications	ENCePP Code of conduct ENCePP checklist for study protocols

3.2.6.1.2 EuroDURG (European Drug Utilisation Research Group)

Web	www.pharmacoepi.org/eurodurg
Definition	EuroDURG aims at improving DU through cross-national DU studies based on the ATC/DDD methodology. Recently, the organisation merged with the International Society of Pharmacoepidemiology (ISPE) and it now constitutes the European chapter of ISPE's special interest group for Drug Utilisation research (ISPE-SIG's DUR). It collaborates with the WHO Regional Office for Europe, and the European Association of Clinical Pharmacology and Therapeutics (EACPT). It is a platform for discussing medical, social, economic, ethnic, and ethical questions of determinants and effects of drug utilisation in Europe.
Objectives	Encourage communication and cooperation between scientists in several disciplines interested in DU and pharmacoepidemiology. Work towards the adoption of standards for international and national DU

	research methodology to measure regional variations in DU across Europe and to account for it. Maximise the potential of the information available on DU for improving patient care. Cooperate with international and national drug regulatory authorities, health insurance agencies, the pharmaceutical industry, academic departments, and professional bodies in furthering DU research and its applications. Promote the incorporation of DU research and its applications in educational programmes.
Working period	1993-ongoing
Participants	15 national groups (2013):Armenia, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Germany, Greece, Hungary, Iceland, Israel, Italy, Norway, Portugal, Serbia, Spain, Russia, Sweden, UK.
Information	Membership is open to European residents or collective legally constituted national research WGs. Meetings jointly held with ISPE every year. It participates in several scientific projects: International ATC browser, CNC of DU which are also participated by other institutions and groups.
Funding	Through ISPE
Publications	EuroDurg bulletins (Bulletin Nº1 in April 2007-Bulletin Nº23 in January 2013). Bergman U. The history of the Drug Utilisation Research Group in Europe. Pharmacoepidemiol Drug Saf 2006;15:95-98.

3.2.6.1.3. CNC (Cross-National Comparison of Drug Utilisation Research)

Web	**http://www.pharmacoepi.org/eurodurg/workgr/cross_national.cfm**
Definition	In collaboration with ISPE's SIG-DUR, and EuroDURG it gathers worldwide information on national DU monitoring systems and DU data for antibacterials, proton pump inhibitors, statins and clopidogrel.
Objectives	Stimulate worldwide use of WHO indicators of rational drug use and cross-national monitoring DU programmes for specific drugs. Record of DU in cross-national epidemiological disease registers. To enhance comparability of data on drug exposure on international databases.
Working period	2008-ongoing.
Participants	24 countries
Information	Information on DU monitoring and expenditure in each of the participant countries collected by a questionnaire, sent out to national contact persons in countries all over the world. All participant countries work out the comparison of proton pumb inhibitors and H2-antihistaminics, in ambulatory care, with and without prescriptions or whether the prescription is issued by a family doctor or specialist.
Funding	Through ISPE and EuroDURG.
Publications	Structured poster session presented at ISPE Conference in Copenhagen August 16-21, 2008. EuroDURG bulletin Nº22, January 2012.http://www.pharmacoepi.org/eurodurg/bulletins/previssues.cfm Gillström A, Wettermark B. Literature Review. Cross-national comparison of DU activities. EuroDURG/ISPE meeting 2011, Ambères (Belgium). Available at:http://www.pharmacoepi.org/eurodurg/workgr/index.cfm

3.2.6.1.4. DURQUIM (Drug Utilisation Research Quality Indicator Meeting)

Web	**https://pharmacoepi.org/eurodurg/durquim.cfm**

Definition	In collaboration with WHO, develop a list of indicators to be taken into account when evaluating the prescribing quality.
Objectives	Analyse the patterns of drug use and to implement strategies for improving the prescribing and use of drugs. Provide the framework for constructing prescribing quality indicators.
Working period	2004-ongoing
Participants	19 European countries, US, Canada and Australia
Information	A meeting held in Belgium, regarding the potential and pitfalls in measuring prescribing quality using indicators derived from national drug consumption databases. The meeting focussed on 4 issues: a taxonomy of prescribing quality indicators, types of available data sources for working with indicators, the validity of the indicators, and the possible (in)appropriate uses of prescribing quality indicators.
Funding	WHO, EuroDURG, RIZIV (Belgian National Health Insurance Institute)
Publications	Hoven JL, Haaijer-Ruskamp FM, Vander Stichele RH. Indicators of prescribing quality in drug utilisation research: report of a European meeting (DURQUIM, 13-15 May 2004). Eur J Clin Pharmacol 2005; 60(11):831-834. Avorn J. An American Reflection on DURQUIM. Power point presentation http://www.pharmacoepi.org/EURODURG/AmericanReflectionDURQUIM.PDF Wettermark B, Bergman U. Kvalitetsindikatorer för läkemedel –nya europeiska rekommendationer. Läkartidningen 2006;306(45):3469-72.

3.2.6.1.5. EUROMEDSTAT (European Medicines Statistics)

Web	**http://ec.europa.eu/eahc/projects/database.html?prjno=2003133** (last updated 2007)
Definition	It is a report expalining the web-based European drug database designed to establish an inventory of DU data sources and a survey of available DU data, assess data reliability and comparability among countries, develop recommendations for data management (collection, validation, and comparison), and develop a set of indicators for monitoring price, expenditure, and utilisation of medicines in the EU.
Objectives	They developed a set of indicators, to be integrated in the EU Public Health Information network (EUPHIN) for monitoring price, expenditure and utilisation of medicinal products, and to facilitate comparisons under a public health perspective. Build a European database of licensed medicines.
Working period	2002-2003 (meetings until 2007). Project finalised.
Participants	A collaboration of academics and government agencies from most EU Member States, representatives of the WHO and the Council of Europe.
Information	Licensed medicines, price, statistics on the number of licensed medicines per country and utilisation and expenditure of medicines according to the ATC/ DDD guidelines. Search for a specific active ingredient or trade name, number of active ingredients and trade names for a specific ATC group and selected countries, and number of active ingredients mutually available and exclusively available.Utilisation and expenditure data for one selected country (time course for one country) or for more selected countries (comparison across countries). Information on medicines withdrawn from the market for safety reasons. Usage of ATC codes in the European countries.
Funding	European Commission (Directorate General of Health and Consumer Protection)
Publications	http://ijphjournal.it/article/view/5945/5688 http://ijphjournal.it/article/view/5947

3.2.6.1.6. ISPE'S SIG-DUR (International Society of Pharmaco Epidemiology's Special Interest Group on Drug Utilisation/Health Service Research)

Web	**www.pharmacoepi.org**
Definition	The SIG-DUR was created in 2006 as a result of a convergence between EuroDURG and ISPE.
Objectives	Create a global forum for discussion and cooperation between DU researchers.
Working period	2006-ongoing
Participants	Euro DURG members and other regional chapters (Australia, Canada, USA).
Information	Website with a collection of national drug dictionaries, linked to the ATC and DDD. Information from a contact person on each working subgroup. Project working subgroups: (i) ATC/DDD browser, (ii) prescribing quality indicators, (iii) cross-national comparisons, (iv)relationship with the health insurers, and (v) methods for testing interventions.
Funding	ISPE
Publications	The newsletter SCRIBE is released twice a year. The Pharmacoepidemiology and Drug Safety journal is the official journal of the ISPE.

3.2.6.1.7. NorPEN (The Nordic Pharmacoepidemiological Network)

Web	**www.nhv.se/norpen**
Definition	Network for knowledge exchange, research and research training to document, facilitate and promote Nordic pharmacoepidemiological research initiatives.
Objectives	Increase quality of research and methodological development. Create an interactive forum for PhD-students and supervisors. Assist researchers in (i) initiating and designing new studies, (ii) improving quality, and (iii) avoiding common pitfalls and duplication of efforts.
Working period	2009-ongoing
Participants	Denmark, Finland, Iceland, Norway and Sweden.
Information	They focus on rare exposures and rare events, prescribing quality indicators, reproductive health, medicine use in children, and mental health. It aims to create an interactive forum for PhD students and supervisors within several pharmacoepidemiological research areas. Information about the meetings and the research groups is available on the webpage.
Funding	Norden NordFosk, a Nordic research board operating under the Nordic Council of Ministers provides funding for Nordic research cooperation.
Publications	Wettermark B, Zoëga H, Furu K, Korhonen M et al. The Nordic prescription databases as a resource for pharmacoepidemiological research-a literature review. Pharmacoepidemiol Drug Saf 2013;22:691-699. Furu K, Wettermark B, Andersen M, Martikainen J, Almarsdottir AB, Sørensen HT. The Nordic Countries as a Cohort for Pharmacoepidemiological Research. Basic Clin Pharmacol Toxicol 2009;106:86-94. Power point presentation of NorPen by Helle Kieler. Centre for Pharmacoepidemiology. Karolinska Institutet. Sweden .

3.2.6.1.8. PIPERSKA Group

Web	**www.piperskagroup.com**
Definition	Group of leading professionals actively involved in reimbursement, formulary listing, and/or enhancing the rational use of drugs in their countries that meet to debate ways of maintaining the ideals underlying socially-funded and equal

	health services across Europe alongside the growing demands of the 21st century.
Objectives	Ensure robust systems are in place in Europe to enhance the rational use of drugs, including new expensive drugs, to improve health.
Working period	2008-ongoing
Participants	Initially 33 leading healthcare professionals drawn from 9 EU countries.
Information	Workshops: intended for healthcare professionals involved in decision making about the funding of new drugs and/or managing their introduction in Europe.
Funding	No external funding.
Publications	http://www.piperska.org/resources/publications

3.2.6.2. DRUG RESEARCH GROUPS WITH FOCUS ON SPECIFIC DRUGS/DISEASES

3.2.6.2.1 Arrhytmogenic potential of drugs (ARITMO)

Web	http://www.aritmo-project.org/
Definition	To analyse the arrhythmic potential ofantipsychotics**,** anti-infectives (antibacterials, antimycotics and antivirals) and H1-antihistamines.
Objectives	Use existing data and generate a wealth of new data through field, database and in silico studies. From the literature and a variety of databases information on the risk of QTc prolongation, torsade de pointes, ventricular fibrillation and sudden death will be obtained and analysed at a pre-clinical, clinical and postmarketing level. An international prospective case-control surveillance network will run in UK, Germany, Italy and Netherlands and will collect data on risk factors as well as blood samples for candidate gene analyses. Assess both the associations with specific drugs as well as the interaction with genetic factors. All information generated will be integrated in order to provide lists that will allow ranking the arrhythmic potential of antihistaminics, antipsychotics and antiinfective drugs by selected parameters.
Working period	January 1, 2010 -June 30, 2013
Participants	17 partners (listed in the website).
Information	It's been divided into 9 WP: scientific coordination, project management, pharmaovigilance, analystic field studies, analytic database studies, review of existing preclinical and clinical data, molecular, ECG, genetic aspects, evidence integration and Dissemination. They presented a symposium with the final results in this year 29th ICPE in Montreal, Canada.
Funding	The Health Area of the European Comission under the 7thFramework Programme.
Publications	http://www.aritmo-project.org/?q=content/publications

3.2.6.2.2 DRUID (Driving Under the Influence of Drugs, Alcohol and Medicines)

Web	http://www.druid-project.eu/cln_031/nn_107548/Druid/EN/about-DRUID/about-DRUID-node.html?__nnn=true
Definition	Part of the project is to gather information about the consumption of drugs with a central nervous system (side)-effect in the general (non-hospitalised) population in various European countries. The majority of the participants are members of the Forum of European Road Safety Research Institutes.

Objectives	Give scientific support to the EU transport policy through recommendations and measures to combat impaired driving.
Working period	2006-2011
Participants	19 countries
Information	Published data Data provided by national agencies, public health institutes, insurance companies, community pharmacies, ministries of health (2000-2005). Information is not publicly available. Coverage population: 100% for 6 countries. Outpatient healthcare setting.
Funding	6th Framework Programme
Publications	Gjerde H, Christophersen AS, Normann PT, Assum T, Oiestad EL, Mørland J. Norwegian roadside survey of alcohol and drug use by drivers (2008-2011). Traffic Inj Prev 2013;14:443-52 Ravera S, Monteiro SP, de Gier JJ, Gómez-Talegón T, Álverez FJ, the DRUID Project WP4 Partners. A European approach to categorising medicines for fitness to drive: Outcomes of the DRUID project. Br J Clin Pharmacol 2012. Published ahead online. DOI: 10.1111/j. 1365-2125.2012.04279.x Final report (01.08.2012): .http://www.druid-project.eu/cln_031/nn_112414/Druid/EN/deliverales-list/deliverables-list-node.html?__nnn=true

3.2.6.2.3 EU-PoMME (European User's Perspectives on Mood Modifying Medicines)

Web	**No website.**
Definition	Previously known as TUPP,The Users Perspective Project (http://www.pharmacoepi.org/eurodurg/workgr/tupp/index.htm) Website currently withdrawn
Objectives	To frame a protocol for pan-European research on the user's perspective on mood modifying medicines.
Working period	1997- finalised/group dissolved?
Participants	11 countries
Information	Sample patient interview. There is currently no other source of information for this group or what they have done except the publications cited here.
Funding	?
Publications	Stevenson F, Knudsen P. Discourses of agency and the search for the authentic self: The case of mood-modifying medicines. Soc Sci Med 2008;66:170-181 Stevenson F. Images of nature in relation to mood modifying medicines: a user perspective. Health (London) 2004 8:241. Knudsen P, Hansen EH, Eskildsen K. Leading ordinary lives: a qualitative study of younger women's perceived functions of antidepressants. Pharm World Sci 2003;25:162-167.

3.2.6.2.4 ARPAC (Antibiotic Resistance Prevention and Control)

Web	**http://www.abdn.ac.uk/arpac/index.htm** (not updated)
Definition	The project"Development of Strategies for Control and Prevention of Antibiotic Resistance in European Hospitals" , aims to lay the foundations for a better understanding of the emergence and epidemiology of antibiotic resistance and to evaluate and harmonise strategies for prevention and control of antibiotic resistant pathogens in European hospitals.

Objectives	Identify antibiotic policies and prescription patterns associated with lower resistance rates. Identify infection control policies associated with low incidence rates of "Alert organisms" i.e. transmissible antibiotic-resistant strains. Make recommendations on which specific measures, such as antibiotic policies and infection control policies, lead to low rates of antibiotic resistance.
Working period	January 1, 2002 – June 2005
Participants	The project was run by four study groups belonging to the European Society of Clinical Microbiology & Infectious Diseases (ESCMID). Individual study groups were responsible for specific areas of the project and were represented on the project steering committee. Study groups: European Study Group on Antibiotic Resistance Surveillance (ESGARS) European Study Group on Antibiotic Policies (ESGAP) European Study Group on Nosocomial Infections (ESGNI) European Study Group on Epidemiological Markers (ESGEM)
Information	139 hospitals from 30 European countries provided antibiotic consumption data for 2001 in DDD/100 bed-days.
Funding	European Commission (Quality of Life thematic programme of the 5th Framework for Research and Development).
Publications	Bruce J et al. Antibiotic stewardship and consumption: findings from a pan-European hospital study. JAC 2009;64:853-60. MacKenzie FM, Gould IM, Bruce J, Mollison J, Monnet DL, et al. The role of microbiology and pharmacy departments in the stewardship of antibiotic prescribing in European hospitals. J Hosp Infec 2007:73-81. MacKenzie FM, Bruce J, Struelens MJ, Goossens H, Mollison J, Gould IM, ARPAC Steering Group. Antimicrobial drug use and infection control practices associated with methicillin-resistant *Staphylococcus aureus* in European Hospitals. Clin Microbiol Infec 2007;13:269-276.

3.2.6.2.5 ARPEC (Antibiotic Resistance Prevention and Control in European Children)

Web	**www.arpecproject.eu**
Definition	It is an initiative of the European Society of Pediatric Infectious Diseases. It includes existing paediatric infectious diseases networks.
Objectives	Improve the quality of antibiotic prescribing for children in Europe. Reduce the prevalence of antimicrobial resistance in bacterial infections in children.
Working period	2010-ongoing.
Participants	17 European countries.
Information	The project will use established methodologies from ESAC and EARSS and existing community prescribing databases to develop a prospective surveillance system to monitor rates of antibiotic prescribing and resistance in European children. It collects information on in- and outpatient healthcare setting.
Funding	Co-funded by the European Commission DG Sanco through the Executive Agency for Health and Consumers (EAHC).
Publications	Versporten A, Sharland M, Bielicki J, Drapier N, Vankerckhoven V, Goossens H; ARPEC Project Group Members.The antibiotic resientence and prescribing in European Children project: a neonataland pediatric antimicrobial web-based point prevalence survay in 73 hospital worlwide. Pediatr Infect Dis J. 2013;32:e242-53. Henderson KL, Muller-Pebody B, Johnson AP, Goossens H, Sharland M; ARPEC Group. First set-up meeting for Antibiotic Resistence and Prescribing in European Children (ARPEC) Euro Surveill. 2009;14(45).

	http://www.eurosurveillance.org/images/dynamic/EE/V14N45/art19404.pdf

3.2.6.2.6 ESGAP (European Study Group on Antibiotic Policy)

Web	**https://www.escmid.org/research_projects/study_groups/esgap/**
Definition	ESGAP is a research group within the ESCMID that aims to play a significant role in Europe in formulating and promulgating strategies to improve antimicrobial prescribing policies and practices and so improve patient care and prevent or reduce the development of antimicrobial resistance.
Objectives	To increase communication between member countries by linking different networks and providing a forum for all those involved in antimicrobial stewardship. To promote an awareness of anti-microbial misuse. To provide an opportunity for training in the appropriate use of antimicrobials through workshops and courses in collaboration with other ESCMID Study Groups or other organisations. To provide the evidence base for a better understanding of the factors involved in anti-microbial misuse and to inform the strategies to meet the mission statement by: facilitating the collection and establishing thecomparability of antibiotic prescribing data within the EU, identifyingproblems of antimicrobial resistance related to antimicrobial use and providing tools that will enable the implementation and monitoring of prescribing policies and practices.
Working period	1998-ongoing.
Participants	9 ARPAC partners.
Information	ABC Calc is a computer tool used to measure hospital antibiotic consumption as number of DDD per 100 bed-days.
Funding	ESCMID economically supports all study groups under specific circumstances.
Publications	http://www.escmid.org/research_projects/study_groups/esgap/presentations_publications/ Dyar OJ,Howard P,Nathwani D,Pulcini C;ESGAP(the ESCMID [European Society of Clinical Microbiology, Infectious Diseases] Study Group for Antibiotic Policies). Knowledge, attitudes, and belifs of French medical students about antibiotic prescribing and resistence. Med Mal Infect. 2013; 43:423-430.

3.2.6.2.7 ESAC (European Surveillance of Antimicrobial ConsumptionNet)

Web	Currently known as ESAC-Net http://www.ecdc.europa.eu/en/activities/surveillance/esac-net/Pages/index.aspx
Definition	European project to collect data on the use of systemic antimicrobials
Objectives	Collect comprehensive out-and inpatient antimicrobial consumption. Provide timely information on antimicrobial consumption. European database will be used to develop (i) health indicators of antimicrobial use and (ii) evidence-based guidelines, and (iii) educational tools to manage the risk of infections and antimicrobial resistance. Give regular feed-back to the relevant authorities of the participating countries. Deepen the knowledge of antibiotic consumption by focusing on specific consumption groups and/or patterns in collaboration with those countries where the appropriate data are available.
Working period	2001-ongoing The European Commission funded the European Surveillance of Antimicrobial Consumption (ESAC) project coordinated by the University of Antwerp, Belgium, from 2001 to 2007. By May 2007, the ESAC project was funded by the European Centre for Disease Prevention and Control (ECDC). In july 2011

	survillance of consumption was integrated into the ECDC and the network became the European Survillance Sytem and the network became The European Survillance of Antimicrobial Consumption Network (ESAC-Net).
Participants	34 countries: 27 Member States, 3 EEA/EFTA and 3 candidate countries (Croatia, Former Yugoslavian Republic of Macedonia and Turkey). Each country has its own national network of experts.
Information	Publicly accessible interactive database with consumption for years up to 20, expressed in DID. The information gathered by country varies and specific results for all participating countries are available on the country sheets of the year concerned. Hospital-care data collected for individual hospitals with a linkage to the Disease Related Groups. Ambulatory-care databroken down by age and sex, specific prescriber groups, high consumer groups and by specific indications (in collaboration with existing networks of sentinel practices). Nursing homes with detailed information on the frequency, indications, characteristics and seasonal variations of antibiotic prescriptions, as well as on the institutional determinants of antibiotic use. Additionally, the effects of socio-economic determinants on antimicrobial consumption of European countries will be explored, and regional variation within a particular country will be studied using econometric models.
Funding	DG Sanco until 2006. ECDC from 2007.
Publications	List of publications at: http://www.esac.ua.ac.be/main.aspx?c=*ESAC2&n=50032 http://www.ecdc.europa.eu/en/activities/surveillance/ESAC-Net/publications/Pages/documents.aspx

3.2.6.2.8 ESEMeD (European Study of the Epidemiology of Mental Disorders)

Web	**No website**
Definition	European Study of the Epidemiology of Mental Disorders.
Objectives	To collect data using a cross-sectional survey, on prevalence, risk factors, health-related quality of life and use of services associated with common mental disorders
Working period	MHEDEA-ESEMeD 2000
Participants	Belgium, France, Germany, Italy, the Netherlands and Spain
Information	Epidemiology of mental diseases. Data of use of any psychotropic drug (including antidepressants, ansiolytics, hypnotics, antipsychotics, or mood stabilizers) from 2001-2003.
Funding	European Commission, national and regional health authorities, Glaxo Smithkline.
Publications	Nicoli M, Nieto I, GasquetI, Kovess V, Lépine JP. [Prevalence and risk factors for suicide ideation, plans and attempts in the French general population: result from ESEMeD study]. Encephale 2012;38:296-303. Almansa J. Measurement and description of underlying dimensions of co morbid mental disorders using Factor Mixture Models: results of the ESEMeD project. Psychiatric Research 2011;20:116-133. Demyttenaere K. Clinical factors influencing the prescription of antidepressants and benzodiazepines: Results from the European study of the epidemiology of mental disorders (ESEMeD). J Affect Disorders 2008;110:84-93.

3.2.6.2.9 The AMSP (Arzneimittelsicherheit in der Psychiatrie, Drug Safety in Psychiatry)

Web	**http://www.amsp.de/doku.php?id=start**
Definition	The AMSP drug safety program assesses severe adverse reactions to all marketed psychotropic drug in the naturalistic setting of routine clinical treatment of psychiatric inpatients.
Objectives	To improve the safety of psychiatry treatment
Working period	1993 - ongoing
Participants	Austria, Germany and Switzerland.
Information	The programme records severe adverse drug reactions in patients from a large age range who are hospitalised in psychiatric setting. It also records the prescriptions of drugs and personal data such as age, sex and diagnosis. The association between adverse event and the medication is done through an expert consensus committee. 60 psychiatric hospitals in Germany, Austria and the German-speaking part of Switzerland are involved.
Funding	By pharmaceutical companies, by government and by individual members.
Publications	See:http://www.amsp.de/doku.php?id=publikum:literatur

3.2.6.2.10 EUROASPIRE (European Action on Secondary and Primary Prevention by Intervention to Reduce Events)

Web	**Link to Euro Heart Survey Programme from the European Society of Cardiology http://www.escardio.org/guidelines-surveys/ehs/Pages/welcome.aspx**
Definition	EUROASPIRE (EA) is a European survey conducted within the Euro Heart Survey on Prevention Programme to describe current clinical practice in relation to secondary prevention of coronary heart disease. Three surveys have been completedin 1995-6, 2001 and 2008.
Objectives	To determine whether the major risk factors for coronary heart disease are recorded in patient medical records. To measure the modifiable risk factors and describe their current management following hospitalization. To determine whether first degree blood relatives have been screened.
Working period	1994-ongoing
Participants	15 European partners in EA I and II: Belgium, Czech Republic, Finland,France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Poland, Slovenia, Spain, Sweden and United Kingdom. Twenty-three countries involved in EA III: Bulgaria, Croatia, Cyprus, Latvia, Lithuania, Romania, Russia, and Turkey.
Information	In- hospital drug consumption data on antiplatelets, beta-blockers, ACE-inhibitors, calcium-chanel blockers, lipid-lowering drugs and anticoagulants was collected for the period 2006-2007 (EUROASPIRE III). During 2013, they have prepared to conduct EUROASPÎRE IV which aims at studying whether coronary heart disease guidelines are followed.
Funding	European Society of Cardiology.
Publications	Kotseva K, Wood D, De Backer G, De Bacquer D,(on behalf of the EUROASPIRE III Study Group). Use and effects of cardiac rehabilitation in patients with coronary heart disease: results from the EUROASPIRE III survey. Eur J Prev Cardiol 2013;20:817-826. Cooney MT, Kotseva K, Dudina A, De Bacquer G, Wood D, Graham I.Determinants of risk factor control in coronary patients: a follow-up of EUROASPIRE I. Eur J Prevent Cardiol 2013;20:686-691. Prugger C, Keil U et al. Blood pressure control and knowledge of target blood pressure in coronary patients across Europe: results from the EUROASPIRE III

	survey. J Hypertens 2011;29:1641-8.

3.2.6.2.11 HAPPY AUDIT (Health Alliance for Prudent Prescribing, Yield and Use of Antimicrobial Drugs in the treatment of respiratory tract infections)

Web	**http://www.happyaudit.org/**
Definition	In collaboration with Odense University (Denmark).
Objectives	It aims to strengthen the surveillance of respiratory tract infections in primary health care (and the use of antimicrobials to treat these conditions) in Europe through development of intervention programmes targeting general practitioners (GPs), parents of young children and healthy adults.
Working period	2007-2010.
Participants	12 countries.
Information	Report of the results is available online. According to the APO (*Audit Project Odense*): auditing a GP Sample of GP Out-hospital.
Funding	6thFP
Publications	Final report: http://www.happyaudit.org/files/pub/4398.pdf Jørgensen LC,Friis Christensen S,Cordoba Currea G,Llor C, Bjerrum L.Antibiotic prescribing in patients with acute rhinosinusitis is not in agreement with European recommendations.Scand J Prim Health Care 2013;31:101-5. Bjerrum et al. Health Alliance for Prudent Prescribing, Yield and Use of Antimicrobial Drugs in the Treatment of Respiratory Tract Infections (HAPPY AUDIT)- impact of a non-randomised multifaceted intervention programme. BMC Family Practice 2011, 12:52.

3.2.6.2.12 GRIP (Global Research in Paediatrics)

Web	http://www.grip-network.org/index.php/cms/en/home
Definition	GRiP aims to stimulate and facilitate the development and safe use of medicine in children.
Objectives	Buld an integrated research infrastructure for epidemiologic and post licensure paediatric studies. Identify healthcare databases comprising paediatrics data, identifying available databases of Spontaneus Adverse Event Reports. Produce recommendations on governance and ethical issues. Map terminologies and harmone data. Define methods for signal detection. Define a common methodology for drug and vaccine utilisation studies, disease incidence and prevalence studies, drug and vaccine safety assessment. Develope comparative effectiveness methodology. Produce proof of concept studies. Develope training modules on pharmacoepidemiology. Develope recommendations for the role of pharmacoepidemiology in paediatrics drug development and the testing of medicines in children.
Working period	January 2011 and expected to last until 31 December 2015.
Participants	21 partner institutions from Europe, North America and Japan as well the WHO.
Information	The GRiP Network is currently producing scientific papers and studies, organising events, building education programmes in paediatric pharmacology, and working to promote and diffuse the cultural and methodological changes needed to improve the results of paediatric research worldwide. GRIP publishes regular newsletters to bring an up to date with the progress of the GRiP Project, whose main objective isdeveloping researchandknowledgein Paediatric Pharmacology. The last newsletter September 2013 (http://www.gripnetwork.org/index.php/cms/en/newsletter_03#top)
Funding	The GRiP Project is funded by the European Union Seventh Framework

	Programme (FP7/2007-2013) under grant agreement n° 261060.
Publications	Salunke S, Giacoia G, Tuleu C. The STEP (Safety and Toxicity of Excipients for Paediatrics) database. Part 1-A need assessment study. Int J Pharm 2012; 435:101-111. Hoppu K, Anabwani G, Garcia-Bournissen F, Gazarian M, Kearns GL, Nakamura H, Peterson RG, Ranganathan S, de Wildt SN. The status of paediatric medicines initiatives around the world – chat has happened ant what has not? Eur J Clin Pharmacol 2012; 68:1-10.

3.2.6.2.13 TEDDY (Task-force in Europe for Drug Development for the Young)

Web	**http://www.teddyoung.org** (last update 2010)
Definition	TEDDY aims to promote the availability of safe and effective medicines for children in Europe by integrating existing expertises and good practices, as well as stimulating further developments.
Objectives	Establish a rationale for the safe and efficacious use of medicines in children. Identify unmet needs for the development and use of medicinal products and orphan drugs in children. Develop, validate and harmonise pre-clinical and clinical methods for assessing the safety and efficacy of current and new drugs in children. Explore, validate, and consolidate the existing data sources containing information on medicines used by children before setting up a harmonised, integrated and reliable European database (or system of databases) to provide an information centre service. Increase awareness and contribute to the debate on the ethical issues arising from paediatric drug research. To bring together industries and other relevant stakeholders to encourage the development of new drugs, optimise paediatric formulations and provide labelling recommendations for current drugs. To build critical mass capacity by means of training and education activities, the dissemination of information and the development of guidelines.
Working period	2005-2010.
Participants	19 partners from 11 countries.
Information	Reports, publications, conferences on the webpage. Link to national regulatory bodies under "useful links". There is a European Paediatric Medicines Database with multiple search functions by ATC, active substance, tradename, marketing authorisation holder, national availability, main pathology. The results from the search offers the marketing authorisation holder, the country where the active substance is available, what kind of paediatric studies have been conducted and the main safety concerns.
Funding	Funded under the Sixth EU Framework Programme for Research and Technological Development (FP6).
Publications	Mellado Peña MJ, Piñeiro Pérez R, Medina Claros AF, Ceci A. Use, implementation and impact of the TEDDY network in Europe.Farm Hosp 2012;36:109-10. Altavilla A, Manfredi C, Baiardi P et al. Impact of the new european paediatric regulatory framework on ethics committees: overview and perspectives. Acta Paediatrica 2012; 101:e27-e32. Sen EF, Verhamme KMC, et al. Assessment of Pediatric asthma drug use in three European countries; a TEDDY study. European Journal of Pediatrics 2011;170:81-92.

3.3 OUTPATIENT DRUG UTILISATION RESOURCES

3.3.6 NON-COMMERCIAL DATA PROVIDERS

3.3.6.2 NATIONAL DRUG CONSUMPTION DATABASES IN EUROPE

3.3.6.2.1 Belgium

Pharmanet database	
Organisation	Institut national d'assurance maladie-invalidité (INAMI). National Institute for Health and Disability Insurance.
Web	www.riziv.fgov.be (Flemish). www.inami.be (French).
Source	Prescribed and reimbursed drugs, including magistral formulations, sterile insulin syringes and other medical devices, medical foods and since Jan 2011 active bandages, analgesics and contraceptives for young people reimbursed under special circumstances.
Setting	Outpatient. General practitioners, doctors under specialist training, specialists in internal medicine, cardiology, pneumology, gastroenterology, rheumatology, paediatrics, dermatology, gynecology and other specialists, and dentists.
Population coverage	>90%
Accessibility	Outpatient data collected by pharmacies, pharmaceutical invoice offices, and by the health insurers, which send data to the INAMI. Contact: marc.defalleur@fgov.inami.be Requested data should be accompanied with a full protocol (objectives, the scientific or social rationale, methodology and the way data will be disseminated), principal investigator's name, and people with access to the data, address where data will be analysed, source of funding and the heading under which the use of the data may be classified. A special committee will evaluate the feasibility of the project. After acceptance, a contract will be signed between INAMI and the investigator. There is a fee for the data requested.
Drug codification	ATC (through linkage to another database).
Data	**Drug-based data:** Reimbursement category, CNK code, (unique identification number for each packaging of a drug in Belgium), codification for magistral preparations, pharmaceutical form of the magistral preparation, number of packages/modules dispensed, amount of the insurance contribution, reduction in the insurance contribution, reduced insurance contribution, reference to the authorisation to reimburse magistral preparations and prescription drugs for which the direct settlement system is authorised, the dispensing unit for magistral preparations, lump sums for cystic fibrosis, indication that the drug is prescribed under its international non-proprietary name. **Patient-based data:** permanent identification number of the beneficiary, gender, year of birth, national statistical institute code of the patient address, reference data of the SIS-card, beneficiary codes, amount of the copayment.**Dispenser-based data:**identification of the invoice office, pharmacy number, prescription date (still optional), dispensing date, invoicing year and month.**Prescriber-based data:** identification of the prescriber.
Record period	Since 1996
Language	French and Flemish Analytical report on the contents of Pharmanet is available in English.
Record linkage	Yes, with INAMI's other databases ATC/DDD, reimbursable prescription drugs file, healthcare provider file, pharmacy/invoice office/health insurer file and the "population" file.
References	http://inami.fgov.be/drug/fr/statistics-scientific-information/pharmanet/introduction/pdf/analyticalreport_eng.pdf

	Fraeyman J, Verbelen M, Hens N, Van Hal G, De Loof H, Beutels P.Evolutions in Both Co-Payment and Generic Market Share for Common Medication in the Belgian Reference Pricing System.Appl Health Econ Health Policy. 2013;11:543-552. Fraeyman J, Van Hal G, Godman B, Beutels P.The potential influence of various initiatives to improve rational prescribing for proton pump inhibitors and statins in Belgium. Expert Rev Pharmacoecon Outcomes Res. 2013;13:141-51.

3.3.6.2.2 Bulgaria

Organisation	Bulgarian Drug Agency
Web	www.bda.bg
Source	Sales from wholesalers (more than 150 distributors in Bulgaria) every January for the previous year.
Setting	Out- and Inpatient.
Population coverage	100%
Accessibility	Request to the Agency. Medicines Use Control Department maria.popova@bda.bg
Drug codification	ATC code as in the marketing authorisation.
Data	Trade name, INN, pharmaceutical form and strength, ATC code, legal status, number of packages sold to hospitals, pharmacy stores and other outlets. The data is collected at the end of January each year.
Record period	Since 2009.
Language	Bulgarian and English.
Record linkage	No.
References	In the Bulgarian version of the website there is a report on the number of prescriptions consumed during 2009 in Bulgaria by ATC level 1 and 2. Guenka P, Manova M, Stoimenova S, Savova A, Peikov P. Cardiovascular medicines prescribing in Bulgaria. Comptes Rendus de l'Académie Bulgare des Sciences 2011;64:285-292. Ivanova AD, Petrova GI. Changes in the prescribing habits of insulin in Bulgaria. Arh Pharm 2007;57:192-203.

3.3.6.2.3 Croatia

Organisation	Croatian Drug Agency
Web	http://www.almp.hr/?ln=en
Source	Sales from wholesalers
Setting	Out- and Inpatient.
Population coverage	100%
Accessibility	Request to the Agency Contact person: viola.macolic@halmed.hr
Drug codification	ATC code
Data	Information about sales for the out- and inpatient healthcare sectors. It includes quantity of drug sold, package size, number of packages dispensed, strength, dose form, ATC code updated in the beginning of the year, DDD/1000 inhabitants/day (DID)
Record period	Since 2004
Language	Croatian and English
Record linkage	No.
Other	There is the database of the Croatian Health Insurance Fund with information

databases	on reimbursed medicines: http://www.hzzo-net.hr/
References	On the website, there are annual reports on drug consumption in Croatia http://www.almp.hr/?ln=en&w=publikacije&d=potrosnja_lijekova (only in croatian). Tomić S, Filipović Sucić A, Plazonić A, Truban Zulj R, Macolić Sarinić V, Cudina B, Ilić Martinac A. Regulating medicines in Croatia: five-year experience of Agency for Medicinal Products and Medical Devices. Croat Med J. 2010;51:104-12. Vlahović-Palcevski V, Francetić I, Palcevski G, Rosovic-Bazijanac V. Utilization of antimicrobials in Rijeka (Croatia). Pharmacoepidemiol Drug Saf. 2004;13:105-10.

3.3.6.2.4 The Czech Republic

Organisation	The State Institue for Drug Control.
Web	www.sukl.cz
Source	Sales from wholesalers from 2006 up to now. Since 2011, dispensed medicines also available.
Setting	Outpatient.
Population coverage	100%
Accessibility	Application to the Information and Press Department infs@sukl.cz
Drug codification	ATC
Data	Information about sales includingpackage size, mumber of packages, strenght, dosage form, etcSales of OTC from wholesalers dispensing OTC with limits. Indication for use: Only for increased reimbursement from health insurance (International Classification of Diseases). For not assigned ATC/DDD, they use number of packages as units sold and the SUKL identification number assigned to all drugs.
Record period	Since 2006 sales from wholesalers. Dispensed medicines since 2011.
Language	Czech and English.
Record linkage	No
References	On the website reports of the activity of the Czech Medicines Agency provide information on the database http://www.sukl.eu/sukl/publication-activities (accessed on 10/2013) Al Warafi A, Vlček J. Analyses of the consumption of sedatives and hypnotics drugs in Yemen and Czech Republic. Ceska Slov Farm. 2013;62:149-53. Kořístková B, Grundmann M. Consumption of antiepileptics in 1993-2004 using various methods. Čes. Slov. Farm 2006; 55:18-23.

3.3.6.2.5 Denmark

The Danish Registry of Medicinal Products Statistics.	
Organisation	Sundhedsstyrelsen (Danish Health and Medicines Authority).
Web	http://sundhedsstyrelsen.dk/en/about-us The Danish Registry of Medicinal Products Statistics http://www.ssi.dk/English/HealthdataandICT/Health%20data/Registries/Register%20of%20Medicinal%20Products%20Statistics.aspx
Source	For primary health sector: Dispensed medicines (prescribed or not prescribed) from community pharmacies, dispensing doctors, shops selling liberalised drugs and The Danish State Serum Institute (only vaccines, immune sera and immunoglobulines). Supplies to nursing homes, abuse centres and other similar institutions included. For hospital sector: sales of medicines by ward codes.
Setting	Out- and inpatient.

Population coverage	100%
Accessibility	Free online (http://www.medstat.dk/): aggregated data. Further data is only available through Statistics Denmark to authorised Danish research institutions or foreign researchers affiliated to an authorised Danish research institution (stapost@dkma.dk).
Drug codification	ATC
Data	Statistics can be downloaded by groups of medicines, ATC code or product name. Results are presented in DDD, DID, number of users, number of users/1000 inhabitants, turnover (including VAT value added tax, and other prescription charges), and number of packages, number of packages eligible for reimbursement and paid reimbursement. It can be downloaded by region, age and gender.**Other information:** date, time and place of sale; sales number; code for the sale (e.g. OTC), number of the person reporting the sale, person receiving the medicinal product, prescriber's code (which corresponds to doctor's practice; doctor's registration number only for specific drugs), type of reimbursement and authority involved, number of packets, de-selection of generic substitution, reiteration number (number of times the product has been sold on prescription), number of prescribed product, number of dispensed product; unique patient identification (ID) number or if a child without ID number, the age; sales price, and price on which the reimbursement is calculated, date of pricing of sale of medicinal products, payment from patient, regional and municipality reimbursements, reimbursement entitled to the patient, dose for ordination. There is the possibility to report indication for use in free-text on the prescriptions. However, it is not yet available for research.
Record period	From 2005 available online. The registry began in January 1995, data for outpatient available since 1996.In-hospital data available since 1997. Since 2001 new outlets selling OTC medicines report their sales to the register.
Language	Danish and English
Record linkage	Yes Health registers, demographic data (residence, migration, death, family), socioeconomic data (education, occupation, employment status, income) through Statistics Denmark (www.dst.dk). There exists the possibility of linking up with researchers' own register with the Register of medicines from Denmark.
References	Johansen AN, Stenzhorn AA, Rosenzweig M, Thirstrup S, Gazerani P. Prescribing patterns and safety monitoring of duloxetine using the Danish Register of Medicinal Product Statistics as a source. Scand J Public Health. 2013;41:866-873. Hallas J, Christensen R, Andersen M, Søren F, Bjerrum L. Long term use of drugs affecting the renin-angiotensin system and the risk of cancer: a population-based case-control study. Brit J Clin Pharmacol 2012;7481:180-8.

Danish National Database of Reimbursed Prescriptions (DNRP)	
Organisation	Department of Clinical Epidemiology at Aarhus University Hospital
Web	http://kea.au.dk/en/research/thedanishnationaldatabaseofreimbursedprescriptions/
Source	Reimbursed prescriptions
Setting	Outpatient (community pharmacies and hospital-based outpatient pharmacies).
Population coverage	All Danish population including residents of long-term care institutions.
Accessibility	Researchers from all over Denmark after approval from the Danish Data Protection Agency have been obtained. Application to the data provider with a 3-page protocol to the corresponding

	board member of the region that the researcher works in.
Drug codification	ATC
Data	**Patient details:** personal identification number, birth year, age at dispensing date, gender, municipal and region of residence. **Dispensing details:** product code (Nordic article number), encoding name, form, strength and pack size, trade name, number of packets or units, pharmaceutical form, DDD, dispensing date, generic substitution done at pharmacy (if any), retail price, price forming basis of reimbursement calculation. **Prescriber details:** practice code. **Pharmacy details:** unique pharmacy identifier
Record period	Since 2004, prescription data collected by the Danish Regions have been stored in a database mantained by the Computer Science Corporation (CSC), an IT-consulting firm. Since March 2011, a contract between Danish Regions and Aarhus University approved the use of the data for research.
Language	Danish and English
Record linkage	Yes. Other Danish registries through the unique personal identification number.
References	Johannesdottir SA, Horváth-Puhó E, Ehrenstein V, Schmidt M, Pedersen L, Sorensen HT. Existing data sources for clinical epidemiology: The Danish National Database of Reimbursed Prescriptions. Clin Epidemiol 2012;4:303-13.

3.3.6.2.6 Estonia

	EHIF database	SAM database
Organisation	Estonian Health Insurance Fund	State Agency of Medicines
Web	http://www.haigekassa.ee/	www.sam.ee/en
Source	Reimbursed drugs.	Sales from wholesalers
Setting	Outpatient.	Out- and Inpatient
Population coverage	95%	100%
Accessibility	Application to infor@haigekassa.ee	Application to info@raviamet.ee
Drug codification	ATC	ATC
Data	Information including manual, electronic and electronic prescription in the pharmacy not collected by the patients, indication for drug use (ICD-10), date prescribed (for electronic prescriptions), date dispensed, quantity od drug, package size, number of packages dispensed, dose, strenght, dosage form, prescriber information (name and speciality), ATC code (update March 1st) , DDDs for combination products, patient related information (unique idetification number, age and gender)	All the wholesalers report their drug sales data to the State Agency of Medicines 4 times a year.Information about sales includingATC code (update March 1st),ingredients, trade name, pharmaceutical form, strength, package size and the manufacturer, DDD, DID, monetary value.
Record period	In 2002 is published the first report	Mid-1990s
Language	Estonian and English.	Estonian and English
Record linkage	No	No
References	On the website, reports of the activity of Estonian Health Insurance Fund provide information on the database. http://www.haigekassa.ee/uploads/userfiles/EHK_aastaraamat2012_eng.pdf (accessed on 10/2013) Lass J, Odlind V, Irs A, Lutsar I. Antibiotic	On the website there are annual reports of drug consumption data http://www.sam.ee/en/statistics-medicines (accessed 10/2013) Lõivukene K, Maaroos HI, Kolk H, Kull I, Labotkin K, Mikelsaar

	prescription preferences in paediatric outpatient setting in Estonia and Sweden. Springerplus 2013;21;2:124.	M. Prevalence of antibiotic resistance of Helicobacter pylori isolates in Estonia during 1995-2000 in comparison to the consumption of antibiotics used in treatment regimens. Clin Microbiol Infect. 2002;8:598-603.

3.3.6.2.7 Finland

	Prescription Register at The Social Insurance Institution of Finland (Kansaneläkelaitos, Kela)	Drug sales register
Organisation	The Social Insurance Institution of Finland.	Finnish Medicines Agency.
Web	http://www.kela.fi/web/en/research (link to drug statistics).	http://www.fimea.fi/frontpage
Source	All reimbursed prescriptions.	Sales from wholesalers.
Setting	Outpatient. Excluded public nursing homes and hospitals.	Out (99%)- and inpatient (1%).
Population coverage	100%	100%.
Accessibility	Application to data provider: Kela research department tutkimus@kela.fi	Application to data provider communications@fimea.fi
Drug codification	ATC	ATC
Data	Medicine: Nordic Commodity Number (trade name, pharmaceutical form, strength, pack size, DDDs/package, marketing authorisation holder, ATC code); number of packs received; price; reimbursement; coded indication in the case of special reimbursement; dosage and indication as written by the doctor-only kept for approximately 1.5 years-; date of prescribing and date of dispensing. Patient: unique identification number (age, sex, place of residence, disease entitling to special reimbursement). Prescriber: Sickness insurance code (specialty, working place according to the latest survey). Dispenser: Unique Identification code (area, date of dispensing). *NO DATA*: OTC medicines, non-reimbursed medicines, inexpensive medicines until 31/12/2005, in-patient care, purchases under deduction limit or compensated by the employer, purchased abroad.	Data aggregated. Consumption expressed in DDD/1000 inhabitants/day. No data on age and gender.
Record period	Since 1994. Up to 2006 there are only registered reimbursed medicines for patients exceeding copayment of 10euros for normal refund or 5 euros for special refund.	Since 1987
Language	Suomi, Swedish, English	Suomi, Swedish, English
Record	Yes.	No

linkage	Hospital discharge register, Cancer register, Causes of death register, Longitudinal database of population censuses with data on socioeconomic variables, Population information system.	
References	http://www.fimea.fi/download/22707_SLT_2011_net.pdf Autti-Rämö I, Sourander A, Seppänen J, Martikainen E. Use of antidepressants among 0-26 year olds in Finland during 1997-2007. Eur J Psych 2011;25:154-162.	Kronholm E, Markkula J, Virta LJ. What is behind the seeming cessation of the increase in sleep medicine consumption in Finland during the last years?. J Public Healt Res 2012;1:*e23* Zahl P-H, De Leo D, Ekeberg Ø, Hjelmeland H, Dieserud G. The relationship between sales of SSRI, TCA and suicide rates in the Nordic countries. BMC Psychiatry 2010,10:62.

3.3.6.2.8 France

	ANSM database	ERASME database
Organisation	Agence Nationale de Sécurité du médicament et des produits de santé (ANSM) National Agency of Medicines and Health Products Safety	Caisse Nationale d'Assurance Maladie des Travailleurs Salariés (CNAMTS) National Insurance Fund for salaried employees.
Web	www.ansm.sante.fr	http://www.ameli.fr/index.php
Source	Sales of medicines from pharmaceutical companies turnovers.	Prescribed drugs dispensed by community pharmacies and reimbursed by the CNAMTS.
Setting	Out- and inpatient.	Outpatient
Accessibility	Application to data providercommunication@ansm.sante.fr	Application to data provider through their contact formulary. http://www.ameli.fr/l-assurance-maladie/formulaire-de-contact.php
Population coverage	100%	87%
Drug codification	ATC (all levels, except for those medicines with a single trademark that grouped at ATC level 4).	ATC
Data	Units of measurement: DDD, DDD/1000 inhabitants/year (DIY), DDD/100 admissions in in-patient, sales of packages. Drug information: Package size, strength, form of dosage.	**Patients**: Identification number, registration date, date of transfer, date of birth, address, gender, marital status. **Prescriber**: prescriber identification number, speciality, age, gender, year of graduation, year started work, geographical location of workplace, consultations performed, prescription performed, acts performed. **Pharmacy claims**: pharmacy identification number. **Drug information:** ATC, date dispensed, date prescribed, number of boxes delivered, unique identification number for every pharmaceutical form (national pharmaceutical form code), drug name, amount claimed. **Death information**: date of death. **Clinical Laboratory Data**: date of prescription, date of results, code of the

		exam (specific nomenclature). **Other medical acts**: date of prescription, date of purchase, date of reimbursment, code.
Record period	Reports available since 1993.	Since 2001
Language	French	French
Record linkage	No	Yes. SNIIRAM linked to PMSI (national hospital discharge database): anonymysed medical information of patients from all French health insurances. It collects information from the local health insurance offices (individual data). **Patient data:** age, date of birth, gender, region, date of death, full reimbursement for low income earners. **Outpatient data**: primary care and specialists consultations, reimbursed medicines, medical procedures, biological tests, medical devices, healthcare from other health care professionals. **Hospitalisation data** from all French publc and private hospitals: discharcge diagnoses (ICD-10 codes, principal, related, associated), medical procedures (specific code), date of discharge and length of stay, diagnosis-related groups, ambulatory visits in hospital, medicines and medical devices included in a specific list of costly and most necessary products. Access to SMIIRAM data is limited to the 3 last years + current year. http://www.piperska.org/sites/default/files/Day_3_Fagot.pdf (accessed on 10/2013).
References	Moulin G,Cavalie P,Pellanne I,Chevance A,Laval A,Millemann Y,Colin P,Chauvin CA. Comparison of antimicrobial usage in human and veterinary medicine in France from 1999 to 2005. J Antimicrob Chemother 2008; 62: 617-625. Analyse des ventes de médicaments aux officines et aux hôpitaux en France http://ansm.sante.fr/ANSM-media/Publications/Rapports-Syntheses-Medicaments#med (last accessed on 10/2013).	Orriols L, Foubert-Samier A, Gadegbeku B, Delorme B, Tricotel A, Philip P, Moore N, Lagarde E; CESIR Research Group. Prescription of antiepileptics and the risk of road traffic crash. J Clin Pharmacol. 2013;53:339-44. Bernard MA, Bénichou J et al. Use of health insurance claim patterns to identify patients using nonsteroidal anti-inflammatory drugs for rheumatoid arthritis. Pharmacoepidemiol Drug Safety 2012;21:573-83.
Other databases	There are two additional databases: The Régime Social des Indépendants (RSI) database: http://www.le-rsi.fr/ (covers 3.3 million individuals) and The Mutuelle Sociale Agricole (MSA) database: http://www.msa.fr/ (covers 3.6 million individuals), corresponding to the other 2 national insurance schemes, which contain similar information as ERASME database. The 3 databases cover 96% of the population in France.	

3.3.6.2.9 Germany

WidO database	
Organisation	Wissenschaftliches Institut der AOK (WIdO). The Research Institut of the Allgemeinen Ortskrankenkassen-AOK. (AOK is the General Medical Insurance Plan).

Web	http://wido.de/arzneiverordnungs-rep
Source	Reimbursed drugs.
Setting	Outpatient.
Population coverage	85%
Accessibility	Application to data provider: helmut.schroeder@wido.bv.aok.de valentina.coca@wido.bv.aok.de
Drug codification	ATC.
Data	Subject identification number assigned by the statutory health insurance, central pharmaceutical number, prescription number, date of prescription and date of delivery, amount prescribed, generic name, brand, packaging size, strength, DDD, pharmaceutical formulation, cost.
Record period	Since 1980, a report is published every year (no free access).
Language	German
Record linkage	Yes To other data files from statutory health insurance: socio-demographic variables, hospital and outpatient data.
Other databases	German Pharmacoepidemiological Database (GePaRD database). It includes records of 4 statutory health insurances covering approximately 17% of German population with information on prescriptions, developed by the University of Bremen.
References	Dörks M, Langner I, Dittmann U, Timmer A, Garbe E. Antidepressant drug use and off-label prescribing in children and adolescents in Germany: results from a large population-based cohort study. Eur Child Adolesc Psychiatry. 2013;22:511-8. Hamer HM, Dodel R, Strzelcyk A,et al. Prevalence, utilisation, and costs of antiepileptic drugs for epilepsy in Germany –a nationwide population-based study in children and adults. J Neurol 2012; 259:2376-84. Pigeot I, Ahrens W. Establishment of a pharmacoepidemiological database in Germany: methodological potential, scientific value and practical limitations. Pharmacoepidemiol Drug Saf. 2008; 17:215-223.

3.3.6.2.10 Hungary

Organisation	Directorate General of National Institute of Pharmacy.
Web	www.ogyi.hu
Source	Sales from wholesalers.
Setting	Out-and inpatient.
Population coverage	>90%
Accessibility	Application to data provider ogyi@ogyi.hu
Drug codification	ATC
Data	ATC code, quantity of drug dispensed, package size, date dispensed and number of packages dispensed, dose, strength and dosage form. For inpatient DU, number of beds, number of admissions and average length of stay is available.
Record period	Not available.
Language	Hungarian and English
Record linkage	No
Other databases	Hungarian National Health Fund Administration (HNHFA) provides dispensed medicines by all pharmacies with a contract with the National Health System. Information: patients age and gender, unique ID, dispensing pharmacy and prescribing doctor; dispensing date, ATC code, code of the medicines specific for trade name, pharmaceutical form, strength, and package size; number of packages, amount paid by the patient and amount reimbursed by the HNHFA.
References	Matuz M, Benkő R, Hajdú E, Viola R, Soós G. Evaluation of ambulatory

	antibiotic use in Hungary using drug-specific quality indicators. Orv Hetil. 2013;154:947-56. Balogh S, Papp R, Jozan P, CsaszarA. Continued improvement of cardiovascular mortality in Hungary –impact of increased cardio-metabolic prescriptions. BMC Public Health 2010;10. Doró P, Benkő R, Kosik E, Matuz M, Tóth K, Soós G. Utilisation of oral antihyperglycemic drugs over a 7-year period (1998-2004) in a Hungarian population and adherence to drug therapy. Eur J ClinPharmacol 2005; 61:893-7.

3.3.6.2.11 Iceland

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Organisation	Icelandic Medicines Agency	Directorate of Health (Landlæknir)
Web	http://www.lyfjastofnun.is http://www.imca.is/imca/	http://www.landlaeknir.is/english/
Source	Sales from wholesalers.	All dispensed prescription drugs. Reimbursed and non-reimbursed.
Setting	Out-and inpatient (they report data at the wholesale level, which includes the distribution of the medicines at both healthcare settings without distinguishing the destination)	Outpatient
Population coverage	99%	93%
Accessibility	Free.	Application to data provider through a contact formulary: http://www.landlaeknir.is/um-embaettid/abendingar/
Drug codification	ATC	ATC
Data	Available free online [http://www.lyfjastofnun.is/Tolfraedi/ http://www.imca.is/imca/statistics/nr/235]: ATC code (updated yearly in January), DDD, DID, retail price. For inpatient DU, number of beds and average length of stay is available.	**Dispensed drugs**:ATC code, DDD, number of package, prescribed dose (free text), date of prescription, dispensing date. **Patient:** unique identifier, age, sex, place of residence. **Prescriber:**unique identifier, age, gender, profession, speciality. **Pharmacy:** unique identifier, location.
Record period	2000?	January 1, 2003
Language	Icelandic and English	Icelandic and English
Record linkage	No	Yes, National registries like cancer registry, mortality registry
References	Asmundsdottir LR, Erlendsdottir H, Gottfredsson M. Nationwide study of candidemia, antifungal use, and antifungal drug resistance in Iceland, 2000 to 2011. J Clin Microbiol. 2013;51:841-8 Tómasson K, Tómasson H, Zoëga T, Sigfússon E, Helgáson T. Epidemiology of psychotropic medication use: comparison of sales, prescriptions, and survey data in Iceland. Nord J Psychyatry 2007;61:475-8	Reports: http://www.landlaeknir.is/servlet/file/store93/item2847/4473.pdf Linnet K,Halldórsson M,Thengilsdóttir G,Einarsson ÓB,Jónsson K, Almarsdóttir AB. Primary non-adherence to prescribed medication in general practice: lack of influence of moderate increases in patient copayment. Fam Pract 2013;30:69-75.

3.3.6.2.12 Ireland

The Irish Health Service Executive-Primary Care Reimbursement Services (HSE-PCRS) national

primary care prescribing database	
Organisation	Department of Health and Children and administered through The Health Service Executive (HSE)
Web	http://www.hse.ie/eng/staff/PCRS/
Source	Prescriptions dispensed by pharmacists and reimbursed by the GMS scheme
Setting	Outpatient.
Population coverage	37%: This database covers only the population eligible for the General Medical Scheme. It depends on the people's income for those <70 years and free for all ≥70 years. The scheme over represents females, socio-economically deprived and elderly people.
Accessibility	Application to data provider: pcrs@hse.ie
Drug codification	ATC.
Data	Provides details on monthly dispensed medications for each individual within the sheme. Including prescriber information, brand name, ATC code, DDD, strengh, quantity, method and unit of administration, ingredient cost, pharmacist dispensing fees per item dispensed. Drugs are categorised into four classes: unbranded generic, branded generic, proprietary drug with a generic equivalent and proprietary drug with no generic equivalent. Gender, age group and health board region is also recorded. No information on diagnosis.
Record period	1990
Language	English
Record linkage	Yes To other Irish databases like The National Cancer Registry and other smaller hospital datasets.
References	On the website there are reports about primary care reimbursement service: http://www.hse.ie/eng/staff/PCRS/PCRS_Publications Grimes T, Fitzsimons M, Galvin M, Delaney T. Relative accuracy and availability of an Irish National Database of dispensed medication as a source of medication history information: observational study and retrospective record analysis. J Clin Pharm Ther 2013;38:219-24. Zaharan NL, Williams D, Bennett K. Prescribing of antidiabetic therapies in Ireland: 10-year trends 2003-2012. Ir J Med Sci. 2013. Epub ahead: DOI: 11845-013-1011-1.

3.3.6.2.13 Italy

OsMed database	
Organisation	Agenzia Italiana del Farmaco. Osservatorio Nazionale sull'impiego dei medicinali (OsMed). The Italian Medicines Agency. The Medicines Utilisation Monitoring Centre.
Web	http://www.agenziafarmaco.gov.it/it/content/consumi-e-spesa-farmaceutica-e-attivit%C3%A0-hta
Source	Dispensed medicines (reimbursed and non-reimbursed) by public and private pharmacies. Two sources of data: All Prescribed and dispensed medicines covered by the National Health System (it excludes direct and "per conto" distribution and medicines dispensed at the time of discharge) and dispensed medicines (with or without prescription) purchased privately by the patient. The data is provided by the regional databases through Assofarm (Association of Public Pharmacies)and FEDERFARMA (Association of the Private Pharmacies with an agreement with the Italian Health System), and by IMS Health, respectively. In addition, there is a central databank that collects information on the tracebility of medicines, which allows to follow a medicines package sold alongside the chain distribution up to the final user (community pharmacies, hospital, primary healthcare centres, etc) within the Public Health System.
Population coverage	100%

Setting	Out-and inpatient
Accessibility	Application to data provider farmaciline@aifa.gov.it
Drug codes	ATC (all levels)
Data	Full account of the medicine dispensed, date of purchase, patient identification code(age and sex)and prescriber's code. Number of people who have received at least one prescription, turnover, DDD. Indicators of drug consumption published every year by OsMED: DID, DDD average cost, DDD per user (DDD/Ut): average number of days of treatment per user (Total DDD consumption/Total number of people who have received one prescription),compound annual growth rate (CAGR),prevalence of use: Proportion of individuals who have been prescribed one drug over all potential users,gross cost,net cost, Cost/capita.
Record period	Reports are available on the web from 2000 onwards.
Language	Italian and English.
Record linkage	Yes (at regional level). No, for the OsMed database. Demographic data on patients (sex, date of birth, place of residence) and on physicians (sex, age, place of residence and year of graduation) is available on other databases which can be linked through patient and physician keys present in the prescription.
References	L'uso dei farmaci in Italia – Rapporto Osmed 2012.http://www.agenziafarmaco.gov.it/sites/default/files/Rapporto_OsMed_2012.pdf [Italian] Onder G, Bonassi S, Abbatecola AM, Folino-Gallo P, Lapi F, Marchionni N, Pani L, Pecorelli S, Sancarlo D, Scuteri A, Trifirò G, Vitale C, Zuccaro SM, Bernabei R, Fini M; the GeriatricsWorking Group of theItalianMedicines Agency (AIFA). High Prevalence of Poor Quality Drug Prescribing in OlderIndividuals: A Nationwide Report From the Italian Medicines Agency (AIFA).J Gerontol A Biol Sci Med Sci 2013; doi:10.1093/gerona/glt118. Piovani D, Clavenna A, Cartabia M, Bonati M.The regional profile of antibiotic prescriptions in Italian outpatient children. Eur J Clin Pharmacol 2012; 68:997-1005.

3.3.6.1.14 Latvia

Organisation	State Agency of Medicines of Latvia.
Web	http://www.vza.gov.lv/index.php?id=305&sa=305&top=298
Source	Sales of medicines from wholesalers.
Setting	Out-and inpatient alltogether (not separated databases).
Population coverage	100%
Accessibility	Application to data provider info@zva.gov.lv
Drug codification	ATC
Data	Medicinal product ID, number of packages sold, package price, consumer group to which the medicinal product is sold (defined by law): inpatient sector, medical treatment institution included in a specific register for these institutions, community pharmacies, and doctor's practices.
Record period	Since 2003 (on the website).
Language	Latvian and English
Record linkage	No
Other databases	National Health Service (Nacionālaisveselībasdienests).(21)
References	Statistics on medicines consumption 2012. State Agency of Medicines 2013. Prepared by E. Gailīte, A Seilis and A Zaķe. http://www.zva.gov.lv/doc_upl/Zalu_paterina_statistika_2012-20130604.pdf Vrublevska K, Jekabons K, Rugaja Z, Zile I et al. Antidepressant prescription

	and dispensing in Latvia: Regional differences and pharmacists' observations. Medicina (Kaunas) 2011;47 (Suppl 2):97-104. Zavadska D, Bērzina D, DrukaĮska L, Pugačova N, Miklaševics E, Gardovska D. Macrolide resistance in group *A beta haemolytic Stretococcus*isolated from outpatient children in Latvia. APMIS 2010; 118:366-370.

3.3.6.1.15 Lithuania

National Health Insurance Fund database	
Organisation	National Health Insurance Fund under the Ministry of Health.
Web	http://www.vlk.lt/
Source	Reimbursed prescriptions.
Setting	Outpatient.
Population coverage	98%
Accessibility	Application data provider (Kristina.Garuoliene@vlk.lt)
Drug codification	ATC
Data	**Prescribed medicines:** ATC code, drug name, dose, number of doses in each prescription; DDD, diagnosis. **Patient:** date of birth, gender, sex, place. of living. Prescriber and pharmacy data.
Record period	1998
Language	Lithuanian and English
Record linkage	No
Other databases	The data on total sales in Lithuania could be obtained from IMS Health.
References	Report about National Health Insurance Fund at: http://www.vlk.lt/vlk/files/2007/2007_VLK_overview.pdf [English]

3.3.6.1.16 The Netherlands

	GIP databank	---
Organisation	College voor Zorgverzekeringen Health Care Insurance Board	Foundation for Pharmaceutical Statistics (SFK).
Web	http://www.gipdatabank.nl/	http://www.sfk.nl
Source	Drugs prescribed by general practitioners and specialists and dispensed by pharmacists, as well as dispensing general practitioners and other outlets being reimbursed under The Health Care Insurance Act.	SFK directly gathers its data from a panel of pharmacies (1836 of 1981 community pharmacies). Drug dispensed data.
Setting	Outpatient.	Outpatient.
Population coverage	95%	95% of the pharmacies
Accessibility	Free online. Further data can be applied for. JF Piepenbrink infogip@cvz.nl	Application to data provider info@sfk.nl
Drug codification	ATC	ATC
Data	**Patient related**: insurance identification, gender, age and region. Drug-specific:name, dosage form, ATC-code, DDD. **Prescriber's:** type of prescriber (general practitioner, type of specialist). **Dispenser's:**pharmacists, dispensing general practitioners, other outlets. **Prescription:**date, dispensed amount and prescribed daily dose (PDD), pharmacy price, dispensing fee, VAT, reimbursement and personal contribution.	**Patients**: age, gender. **Prescriber**: specialist, general practitioneror others. **Pharmacy**: department, province, urbanization rate. **Drug information**: ATC, cost, DDD, number of prescriptions, cost/DDD, gross profit, degree of substitution, claw back, parallel import. **Insurers**: Health insurance sector, private

	Output freely available online : total cost reimbursed, number of patients receiving at least one prescription, DDD, number of prescriptions, total costs per patient receiving at least one prescription, number of DDD/patient, number of prescriptions/patient, total costs/prescription, number of DDD/prescription.	insurance sector, insurer, institution.
Record period	2004-onwards	From 1990-onwards.
Language	Dutch and English	Dutch and English
Record linkage	No	No
References	F Dekker, NJ Wiendels, V de Valk, C van der Vliet, A Knuistingh Neven, WJJ Assendelft and MD Ferrari. Triptan overuse in the Dutch general population: A nationwide pharmaco-epidemiology database analysis in 6.7 million people. Cephalgia 2011; 31:943. Timmers L, Beckeringh JJ, van Herk-Sukel MPP, Boven E, et al. Use and costs of oral anticancer agents in The Netherlands in the period 2000-2008. Pharmacoepidemiol Drug Saf 2011. Doi: 10.1002/pds.2225. College voor zorgverzekeringen. GIPeilingen 2009. Ontwikkelingen genees-en hulmiddelengebruik. Genees- en hulmiddelen Informatie Project, september 2010, nr 31.	Data en feiten 2013. SFK. Het jaar 2012 in cijfers. http://www.sfk.nl/nieuws-publicaties/data-en-feiten/jaaroverzicht-data-en-feiten. Available only in Dutch. De Bont A, Grit K. Unexpected advantages of less accurate performance measurements. How simple prescription data works in a complex setting regarding the use of medications. Public Administration 2012; 90: 497-510. Teichert M, Visser LE, Dufour M, Rodenburg E, Straus SM, De Smet PA, Stricker BH. Isotretinoin use and compliance with the Dutch preganancy prevention programme. Drug Saf 2010;33:315-326.

3.3.6.1.17 Norway

	Norwegian Prescription Database (NorPD).	Norwegian Drug Wholesales-statistics Database
Organisation	Norwegian Institute of Public Health.	Norwegian Institute of Public Health.
Web	www.norpd.no	www.fhi.no
Source	All prescribed drugs, reimbursed or not, dispensed at Norwegian pharmacies to individual patients outside institutions. Regarding patients in nursing homes and hospitals, the register receives figures on drug use at aggregate level.	Sales of drugs from wholesalers to pharmacies, hospitals/nursing homes and non-pharmacy outlets with persmission to sell drugs. All sales of drugs both on prescription and OTC.
Setting	Outpatient.	Out- and inpatient
Population coverage	100 %	100%
Accessibility	Free. Further data can be applied for dataaccess@fhi.no	Application to data provider lmfin@fhi.no
Drug codification	ATC	ATC
Data	**Patient**: person-identifier (encrypted), month/year of birth, month/year of death,gender, place of residence (municipality and county); **Prescriber**:	Number of packages, wholesales price (wholesaler purchasing price and retailer purchasing price), pharmaceutical product number.

	person-identifier (encrypted) month/year of birth, gender, profession, speciality; **Drug:** nordic article number (brand name or generic substitution, strength, package size), number of packages, DDD, category of prescription, code of reimbursement, area of aplication and prescribed dosis (free-text), dispensing date, price (Pharmacy retail price). **Pharmacy**: name, license number, municipality and county. Free online number of users/1000 inhabitants, population figures used to calculate number of users per 1000 inhabitants, turnover by value, turnover by dosage (DDD).	Wholesaler intern number, municipality number, Pharmacy license number, municipality, Wholesales license number.
Record period	2004-onwards	1977-onwards. Monthly updated
Language	Norwegian and English	Norwegian and English
Record linkage	Yes. Medical Birth Registry of Norway, Cancer register, Causes of Death Register, Central Tuberculosis Surveillance Register, System for Immunization Surveillance of Infectious Diseases, Norwegian Patient Register, Health Surveys, Biobanks, Patient Records, Data from Statistics Norway.	No
References	The Norwegian Prescription Database 2008-2012. http://www.fhi.no/dokumenter/09dff4ea6c.pdf [Norwegian and English]. Jonasson C, Tvete IF, Hatlebakk JG. Patterns of proton pump inhibitorzutilization in gastroesophageal reflux diseaseand the effect of restrictions on reimbursement: a nationwideprescription database study. Scand J Gastroenterol 2013;48:1010-7. Steffenak AKM, Nordström G, Wilde-Furu K. Establishment of the nationwide Norwegian Prescription Database (NorPD) - new opportunities for research in pharmacoepidemiology in Norway. Nor Epidemiol 2008; 18: 129-136	Sakshaug S, Strøm H, Salvesen Blix H et al. Drug consumption in Norway 2008-2012. Legemiddelstatistikk 2013:1. Folkehelseinstituttet. http://www.legemiddelforbruk.no/english/ Norwegian Institute of Public Health. Usage of antivirals and the occurrence of resistance to antivirals in Norway 2011-2012.Report 2013:5. http://www.fhi.no/dokumenter/44641956be.pdf [Norwegian and English] Hauge SH, Blix HS, Borgen K, Hungnes O, Dudman SG. Sales of oseltamivir in Norway prior to the emergence of oseltamivir resistant influenza A (H1N1) viruses in 2007-08. Virology Journal 2009, 6:54

3.3.6.1.18 Poland

National Health Fund database	
Organisation	Narodowy Fundusz Zdrowia (National Health Fund, NHIF).
Web	www.nfz.gov.pl
Source	Values of Reimbursed medication.Information provided bypharmacies to the National Health Fund.
Setting	Outpatient.
Population coverage	100%
Accessibility	Barbara Wójcik-Klikiewicz. Room 3.14.tel. 22 572 61 89 fax:+22 572 63 43

	rzecznikprasowy@nfz.gov.pl
Drug codification	ATC
Data	Prescribing doctor, identification number of the pharmacy, prescription number assigned to the prescription filled and number of repeated prescriptions, patient identifier, type of patient (e.g. military war invalid), medicine identification number, number of packages issued, reimbursement code (free of charge, flat rate, 30% or 50%), date of prescription issued, provincial branch of the NHF identifier, the identification number of the branch.Turnover, code of reimbursement, number of packages, package size, strength, dosage form, total DDD, DID. ***Currently the NHIF holds data only on the value of medicines. Drug consumption data comes from IMS Health*** (personal communication).
Record period	A report for 2004 and 2005 is available on the website.
Language	Polish
Record linkage	No
References	National Health Report on reimbursed medicines, for year 2004 and 2005, as wellas a description of the NFZ database http://www.nfz.gov.pl/new/index.php?katnr=0&dzialnr=2&artnr=1627&b=1&szukana=ATC [Polish] (accessed on 10/2013). Godman B, Srank W, Wettermark B, Andersen M, Bishop I, Burkhardt T, Garuolienè K, Kalaba M, Laius O, Joppi R, Serment C, Schwabe U, Teixeira I, Tulunay FC, Wendykowska K, Zara C, Gustafsson L. Use of Generics – A critical cost containment measure for all healthcare professionals in Europe?. Pharmaceuticals 2010;3:2470-2494. Dziurda D, Polak S, Skowron A, Kuschill-Dziurda J, Brandys J. Analysis of non-hospital antibacterial pharmacotherapy in Poland. Int J Infect Dis 2008;12(5):483-489.

3.3.6.1.19 Portugal

INFARMED's database	
Organisation	Autoridade Nacional do Medicamento e Productos de Saüde I.P. National Authority of Medicines and Health Products, IP.
Web	http://www.infarmed.pt/portal/page/portal/INFARMED
Source	Prescribed and dispensed in community pharmacies Hospital-only-medicines dispensed to outpatients are considered inpatient. It is possible to get sales from wholesalers from the same data provider. OTC sales available. Nursing homes, dental care or other healthcare institutions are not included specifically in these database.
Setting	Out and inpatient.
Population coverage	100%
Accessibility	Application to the data provider: demps-omps@infarmed.pt
Drug codification	ATC code
Data	Manual and electronical prescriptions, date of dispensation, quantity of drug dispensed, package size, number of packages dispensed, dose, strength, dosage form, DDD. Database is updated retrospectively every year. Current version 2012. No information on other hospital variables, no sociodemographic variables.
Record period	?
Language	Portuguese and English.
Record linkage	No
References	Ribeiro M, Jorge A, Macedo AF. Off-label drug prescribing in a Portuguese paediatric emergency unit. Int J Clin Pharm 2013;35:30-6. Torre C, Guerreiro J, Costa S. Trends in the consumption of antidepressants,

	anxiolytics, hypnotics, and sedatives in Portugal, over the National Health Plan period (2004-2010). Proceedings of the 27th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Chicago, 14-17 August 2011. Pharmacoepidemiol Drug Saf 2011; 20:S112. Carmona MF. PhD thesis: Caracterização (farmaco) epidemiológica da diabetes tipo 2 em Portugal. http://hdl.handle.net/10451/5869 .

3.3.6.1.20 Russia

No national drug consumption database (personal communication)

3.3.6.1.21 Slovenia

Organisation	The National Institute of Public Health (NIPH)
Web	http://www.ivz.si/
Source	Dispensed prescription medicines.
Setting	Outpatient.
Population coverage	99%
Accessibility	Application to data provider: marjetka.jelenc@ivz-rs.si
Drug codification	ATC
Data	**Prescribed medicines:** data dispensed, quantitiy of drug dispensed, oackage size, number of packages dispensed, dose, strength, dosage form, DDD, ATC code (last version). **Prescriber**: ID of doctor and his/her speciality. **Patient:** unique patients identification number, age, gender, place of residence (down to municipalities)
Record period	Since 1976. Since 1998 prescriptions are reported in ATC/DDD methodology.
Language	Slovenian
Record linkage	No
References	Report of dispensing drugs in Slovenia in 2011 (in Slovenian):http://www.ivz.si/zdravila_druge_publikacije?pi=5&_5_Filename=attName.png&_5_MediaId=6018&_5_AutoResize=false&pl=137-5.3 Pal M, Leskošek BL, P Ferk. Consumption of antihypertensives in Slovenia and comparison with Norway.ZdravVestn 2011;80: 386-394.# Svab V, Subelj M, Vidmar G. Prescribing changes in anxiolytics and antidepressants in Slovenia. PsychiatrDanub 2011;23:178-82.

3.3.6.1.22 Spain

DGFPS database	
Organisation	Ministry of Health, Social Policy, and Equity. DGFPS: Dirección General de Farmacia y Productos Sanitarios (General Directorate of Pharmacy and Health Products.
Web	www.msc.es/profesionales/farmacia/organizacion.htm
Source	Drugs dispensed by community pharmacies reimbursed by the National Health System. Data is collected at regional level and centralised in the Ministry of Health. Not included are medicines consumption reimbursed by other health insurances that specifically cover civil servants or military personnel.
Setting	Outpatient.
Population coverage	100%
Accessibility	Application to data provider abenedi@msssi.es oiac@msssi.es If of interest, application at regional level is possible (a list of the regional health authorities is available on the website).
Drug	ATC

codification	
Data	Region, DDD, turnover, prescriber's code, national pharmaceutical code, pharmacist's code, strength, dosage form. Some regions collect data on age and gender,
Record period	Since 1985 (computerised data).
Language	Spanish
Record linkage	No
References	Lallana Alvarez MJ, Feja Solana C, Malo Fumanal S, Abad Diez JM, Bjerrum L, Rabanaque Hernández MJ; grupo de investigación en Servicios Sanitarios de Aragón. Variations in the prescription of antibiotics among primary care areas in the autonomous region of Aragon,Spain]. Rev Esp Salud Publica 2012;86:627-35. Agencia Española de Medicamentos y Productos sanitarios. Observatorio del uso de medicamentos. http://www.aemps.gob.es/medicamentosUsoHumano/observatorio/home.htm (accessed on 10/2013).

3.3.6.1.23 Sweden

	Swedish Prescribed Drug Register	---
Organisation	The National Board of Health and Welfare (http://www.socialstyrelsen.se/)	Apoteket AB (The National Corporation of Swedish Pharmacies)
Web	http://192.137.163.49/sdb/lak/val.aspx	http://www.apotekensservice.se/lakemedelsstatistik/sok_statistik/sok_statistik_databaser/sokfunktion_recept/
Source	Prescribed medicines dispensed by community pharmacies.	All sales of medicines from pharmacies to individuals and medicines supplied to hospitals by manufacturers.
Setting	Outpatient.	Out- and inpatient.
Population coverage	100%	100%
Accessibility	Free online. Specific data may be delivered on request for statistics or research. Approval from ethical committee is needed when data is used for research Andrejs.Leimanis@socialstyrelsen.se Helena.Schioler@socialstyrelsen.se .	Application to data provider: servicedesk@apotekensservice.se
Drug codification	ATC	ATC
Data	**Patient**: personal identification number, age, gender, residency (county, municipality and parish). **Prescriber:** workplace code,prescriber's profession, prescriber's speciality, characteristics of workplace (ownership, type of healthcare institution). The prescriber and the health care institution cannot be identified. **Drug**: prescribed and dispensed drug, date of prescription and dispensing, generic substitution, dosage, DDD, expeditures total and reimbursed and parallel import. Annual period prevalence available on the website by age, sex and region down to ATC5th level.	Turnover, wholesale price (wholesaler purchasing price and retailer purchasing price), national pharmaceutical code number, DDD, manufacturer's organisation and identification number, type of transaction, organisation's code receiving the supplies, GLN code of type of health care institution, date of sales, number of packages, total turnover in Swedish crowns/national pharmaceutical package code.
Record period	July 2005-ongoing (online). Prescribing	

	records kept since 1974.	
Language	Swedish and English.	Swedish and English.
Record linkage	Yes Cancer Register, Medical Birth and Congenital Malformations Register, Cause of Death Register, National Patient Register and other Registers (e.g. migration, taxation, education and sick-leave) as well as national healthcare quality registers for certain diseases.	No
References	Yearly report on medicines statistics, published every March. Data is for prescribed and dispensed medicines in the out- and inpatient. http://www.socialstyrelsen.se/publikationer2013/2013-3-21 Nordin M, DacquehaqM, Gerdtham UG. Socioeconomic inequalities in drug utilization for Sweden: evidence from linked survey and register data. Frisk P, Kälvemark-Sporrong S, Wettermark B. Selection bias in pharmacy-based patient surveys. Pharmacoepidemiol Drug Saf. 2013; published ahead online. Doi: 10.1002/pds.3488	www.apotekensservice.se Wilking N,Jönsson B, Wettermark B. Användningen av cancerläkemedel i Sverige och Europa. Läkartidningen 2010;107: 1075-1080. Merlo J, Broms K, Lindblad U, Björck-Linné A, Liedholm H, Östergren PO, Erhardt L, Råstam L, Melander A. Association of outpatient utilisation of non-steroidal anti-inflammatory drugs and hospitalised heart failure in the entire Swedish population. Eur J Clin Pharmacol 2001; 57:71-75.

3.3.6.1.24 Switzerland

There is no national drug consumption database (personal communication)

3.3.6.1.25 The United Kingdom

Electronic Prescribing Database-England (ePACT)	
Organisation	NHS Business Services Authority. Prescription Services. Electronic Prescribing Analysis and Cost (ePACT).
Web	http://www.nhsbsa.nhs.uk/PrescriptionServices.aspx(accessed on10/2013). http://www.hscic.gov.uk/primary-care:It provides public information on quarterly prescription cost analysis statistics (accessed on 11/2013). For hospital, public available information at:http://www.hscic.gov.uk/article/2021/Website-Search?productid=9217&q=hospital+prescribing&sort=Relevance&size=10&page=1&area=both#topSource IMS Health Hospital Pharmacy Audit Index database and databases maintained by the Prescription Services Division of the Business Service Authority (EphMRA classification). Resources from ePACT for the rest of United Kingdom: **Scotland**: http://www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Community-Dispensing/Prescription-Cost-Analysis/ **Wales**: http://wales.gov.uk/statistics-and-research/prescriptions-dispensed-community/?lang=en **Northern Ireland:** http://www.hscbusiness.hscni.net/services/1806.htm
Source	Prescribed drugs.
Accessibility	Application to data provider. Data also available online. help@ppa.nhs.uk
Setting	Outpatient. It does not include prescriptions dispensed in mental health units, or private prescriptions.
Population	100%

coverage	
Drug codification	British National Formulary (BNF). ATC provided upon request.
Data	Free online: number of packages dispensed for each chemical substance, strength, dosage form and trademark. Upon request: Reporting period. Prescribing organisation (GP practice, health trust). BNF (from chapter to presentation level). Controlled drugs tag. Budget and expediture forecasts. Costs and volumes of prescribing.Prescribing totals by prescribers at all BNF levels. Prescribing from non-medical prescribers (independent pharmacists, nurses, optometrists). Working environment for nurses and supplementary prescribers (i.e community or practice). Patient list sizes. ADQ (Average Daily Quantities) and DDD. Low Income Scheme Index scores for practices.
Record period	Since 1988 (computerised).
Language	English
Record linkage	No
References	National Health Services. Business Services Authority. Prescription Services. Prescription data www.nhsbsa.nhs.uk/PrescriptionServices/3230.aspx[accessed on10/2013]. Davies M, Wilton L, Shakir S. Safety profile of modafinil across a range of prescribing indications, including off-label use, in a primary care setting in England: results of a modified prescription-event monitoring study. Drug Saf. 2013;36:237-46. Ilyas S, Moncrieff J. Trends in prescriptions and costs of drugs for mental disorders in England, 1998-2010. Br J Psychiatry 2012. Published online ahead doi 10.1192/bjp.bp.111.104.257. Majeed A, Evans N, Head P. What can PACT tell us about prescribing in general practice? Brit Med J, 1997;315:1515.

NORTHERN IRELAND (NI)		
	ePACT database-North Ireland.	**HSC BSO Enhanced Prescribing Database (EPD).**
Organisation	Health and Social Care. Business Services Organisation. General Pharmaceutical Services http://www.hscbusiness.hscni.net/services/1944.htm	NI's Department of health. Social Services and Public Safety. Business Services Organisation (NHS BSO). Electronic prescribing and eligibility system (EPES) project
Web	Business Services Organisation. http://www.hscbusiness.hscni.net/services/1806.htm(accessed on10/2013).	---
Accessibility	Some data free online. Further data may be purchased. Application to data provider Jacqueline.Sheridan@hscni.net.	---
Setting	Outpatient	Outpatient.
Population coverage	100%	85-90% of all prescriptions have incorporated these 2 barcodes.
Drug codification	BNF	BNF.
Source	All dispensed prescriptions by community pharmacists, dispensing doctors and personally administered by GPs.	Prescribed by GP and dispensed by community pharmacies.
Data	Name, strength and form of the drug dispensed. Quantity of the drug dispensed (number of items). DDD. Cost of the drug dispensed. The month and year in which the drug was dispensed. Prescriber information (GP, Practice, Area Health	The NHS BSO in NI implemented in 2008 an electronic prescribing system that added a two-dimensional barcode to paper prescriptions issued by the GP. It codes the

	Board). It does not collect patient information (age, sex, name or address), dosage or duration of treatment, or the indication.	patient's Health and Care number: a unique identifier which can track their dispensed prescriptions and details of the prescribed mediciation and information on the prescriber. It is scanned at the end of each calendar month and held in the EPD. 85-90% of all prescriptions result in usable data. BNF, dispensed drug item codes, drug name (brand and generic) strength, form, prescribed quantity, pack size and price, gross cost and prescriber practice information. Other demographic details can be retrieved through linkage. Diagnostic and other clinical outcomes are not recorded in the EPD.
Record period	From 2000 and onwards (online).	2008.
Language	English	English.
Record linkage	No	Yes, through the patients' unique identity number to other datasets in the NHS BSO.
References	Business Services Organisation. Information on Pharmaceutical Prescribing. Pharmaceutical Statistics. Prescription Cost Analyseshttp://www.hscbusiness.hscni.net/services/2437.htm(accessed on 10/2013). Alahdab OG, Crealey G, Scott MG, Mairs J, McElnay JC. Product standardisation as a tool to control prescribing costs - a case study of alginate liquid preparations.Int J Pharm Pract. 2013 Apr;21(2):73-81 Alabbadi I, Crealey G, Turner K, Rafferty T, Keenan L, Murray P, McElnay JC. Statin prescribing in Northern Ireland and England pre and post introduction of the quality and outcomes framework. Pharm World Sci 2010;32:43-51.	Maguire A, Hughes C, Cardwell C, O'Reilly D. Psychotropicmedications and the transition into care: a national data linkage study. J Am Geriatr Soc. 2013;61:215-21. Bradley MC, Fahey T, Cahir C et al. Potentially inappropriate prescribing and cost outcomes for older people: a cross-sectional study using the Northern Ireland Enhanced Prescribing Database. Eur J ClinPharmacol 2012;10:1425-33.

SCOTLAND		
	ePACT database-Scotland	HMUD database
Organisation	NHS National Services Scotland. Information Services Division (ISD) Scotland. Scottish Prescribing Analyses (SPA).	NHS Scotland. Information Services Division (ISD). National Medicines Utilisation Unit (NMUU): Hospital Medicines Utilisation Database(HMUD).
Web	http://www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/	http://www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/National-Medicines-Utilisation-Unit/
Accessibility	Application to data providernss.isdprescribing@nhs.net Free online http://www.isdscotland.org/Health-	Accessible only to NHS staff. Queries NMUU: Sharon.hems@nhs.net HMUD: nss.isdhmud@nhs.net

	Topics/Prescribing-and-Medicines/Community-Dispensing/Prescription-Cost-Analysis/	
Setting	SPA:Outpatient	HMUD: Inpatient aggregated at hospital level
Population coverage	100%	?
Drug codification	SPA:BNF	HMUD: BNF and ATC codification.
Source	SPA: All prescriptions from GP, nurses, dentists and pharmacists dispensed by community pharmacists in Scotland.Private prescriptions and dispensed in hospitals excluded. Prescriptions prescribed elsewhere in UK, but dispensed in Scotland included.	HMUD: All drugs dispensed by a hospital pharmacy with an end patient use (no drugs purchased).
Data	SPA: Costs and volumes of prescribing. ADQ (Average Daily Quantities) and DDD. BNF. Drug name. Number of dispensed items.Gross Ingredient Cost. Dispensed quantity measured in units depending upon the formulation of the product	HMUD: Hospital setting and location. Dates (financial and calendar). BNF code. DMD or NHS Dictionary of Medicines and Devices: unique identifier for the majority of products used in both Primary and Secondary care. DDD. Route of administration. ATC code. Formulary status. Cost. Hospital activity (occupied bed days, number of episodes, number of patients for a particular hospital). In-patient or daycase code. Estimated population for the health board.
Record period	SPA:Since 1993	NMUU set up in 2005. HMUD database 2007.
Language	English	English
Record linkage	No	?
References	Bennie M, Bishop I, Godman B, Barbui C, Raschi E, Campbell S, Miranda J, Gustafsson LL. Are specific initiatives required to enhance prescribing of generic atypical antipsychotics in Scotland?: International implications.Int J ClinPract 2013;67:170-80. Williams D, Singh M, Hind C.The effect of the withdrawal of rofecoxib on prescribing patterns of COX-2 inhibitors in Scotland.Br J ClinPharmacol. 2006;62:366-8	Hospital Medicines Utilisation Database. (HMUD)http://www.isdscotlandarchive.scot.nhs.uk/isd/6123.html(accessed on 10/2013). Bennie M et al. An investigation into the effect of advice from the Scottish Medicines Consortium on the use of medicines in Scotland's Health Service. Brit JClinPharmaco 2011;71:283-9.

WALES	
ePACT database-Wales	
Organisation	NHS Wales Informatics Service (NWIS) PartneriaethCydwasanaethau. GwasanaethauRhagnodi Shared Services Partnership. Prescribing Services
Web	www.wales.nhs.uk/sites3/home.cfm?orgid=428&redirect=yes
Accessibility	Application to data provider: stats.healthinfo@wales.gsi.gov.uk Some data is available free

	online.http://wales.gov.uk/topics/statistics/headlines/health2013/prescriptions-dispensed-community-2012/?lang=en
Setting	Outpatient
Population coverage	100%
Drug codification	BNF
Source	All prescriptions written by Welsh GPs and dispensed by chemists and dispensing doctors in England and Wales, or personally administered by Welsh GPs. It also includes prescriptions written by dentists and hospital specialists provided they are dispensed in the community.
Data	Drug:(proprietary or generic) preparation name, form and strength, number of prescribed items dispensed. Net Ingredient Cost (NIC). DDD. ADQ. General practice. Region.
Record period	Online since 2000
Language	English
Record linkage	No
References	Shared Services Partnership. Prescribing Services. Prescription Cost Analysis. PCA Explanatory Notes http://www.wales.nhs.uk/sites3/page.cfm?orgid=428&pid=13533 (accessed on 10/2013). Cohen D, Fasihul Alam M, Dunstan FDJ, Myles S, Hughes DA, Routledge PA. Abolition of Prescription Copayments in Wales: An observational Study on Dispensing Rates. Value Health 2010;13:675-680. Cheeta S, Schifano F, Oyefeso A, Webb L, Hamid Ghodse A. Antidepressant-related deaths and antidepressant prescriptions in England and Wales 1998-2000.Brit J Psych 2004;184:41-47.

3.3.6 COMMERCIAL DATA PROVIDERS

IMS Health, Inc (originally known as Intercontinental Marketing Services) collects medicines utilisation data worldwide according to the distribution channel of a medicine package in a country. Data is stored in the Multinational Integrated Analysis System Database (MIDAS), and is available for different healthcare settings: outpatient (or retail panel) and inpatient (hospital panel). The source of drug consumption data is sales from manufacturers and/or wholesalers to pharmacies and hospitals (retail sell-in data/hospital sell-in data, retrospectively), and prescribed and dispensed medicines from community pharmacies and hospitals to the patients (retail sell-out data and hospital consumption data, respectively). In some countries, information about direct distribution from the manufacturer to the pharmacy may also be obtained.

Access to these data is subject to contract. Most customers are pharmaceutical companies, with an interest in sales data at a national or regional level. In MIDAS database, data are registered by drug and for all its presentation forms. It attempts to do this in a standardized way (22). Samples are projected to get an estimation of total volume. Parallel trade will show only the destination of the product and not the source. Data on parallel trade are collected in most, but not all, countries.

IMS sales data are expressed in volume numbers (numbers of packages sold, counting units-CU-, Standard Units –SU-, number of prescriptions). CU are the

number of millitres (if liquid), or milligrams (if dry) per tablet. SU provide the amount of tablets or mililitres sold. The SUs are to be multiplied by the strength of dose of the drug to get a total volume in milligrams of the drug sold. A volume in milligrams can be converted into a total number of DDD. Using volume of DDDs sold over a given time period and a given population number, the number of DID can be calculated. Active pharmaceutical ingredients are classified according to the Pharmaceutical Products codification developed and maintained by the European Pharmaceutical Marketing Research Association (EphMRA). There is a document describing the differences between EphMRA and ATC codification.

In addition, IMS Health has medical data. It is collected from office-based doctors via a doctor's diary or patient records. It is a sample of doctors in each country representing different specialties and regions. It gives an overview of the prescribing practices in a country for patients that get their prescriptions from a community pharmacy.

3.4 INPATIENT DRUG UTILISATION RESOURCES

3.4.6 NON-COMMERCIAL DATA PROVIDERS

3.4.6.1 DRUG UTILISATION IN HOSPITAL SETTINGS

General website information:

The Pharmaceutical Heath Information System (PHIS) hospital pharma report (2010) described that European inpatient pharmaceutical consumption ranged from 3% in Sweden up to 14% in Latvia (7).

The website of the European Association of Hospital Pharmacists http://www.eahp.eu/ (accessed on 10/2013) published a report of a survey conducted in 2010 in Europe providing information on the organisation and activities of European hospital pharmacies, but not on medicines utilisation (23).

In 2009, the European Hospital and Healthcare Federation, www.hope.be (accessed on 10/2013) published a monography with information on the organisation of hospital health care in the 27 European Member States. No information on medicines consumption was given (23).

From the Organisation for Economic Cooperation and Development (OECD) website, a technical reporton the use of hospital administrative databases in health research was downloaded. Hospital administrative databases is understood as being those databases that collect information on diagnosis and pharmaceutical consumption for the whole population (24). Belgium, Denmark, Finland, France, Italy, Sweden and the United Kingdom were the European countries included in this report. In Belgium, hospital administrative databases collect further information on hospital pharmaceutical consumption at a national level: it uses the ATC codification and the total cost of drugs by ATC is part of the available information.

National Public Databases

From national public databases, Denmark has inpatient drug consumption data freely available on its website (25). Other countries such as Bulgaria, Croatia, Denmark, Estonia, Finland (26), France, Hungary, Italy (27), Latvia, Norway (28), Portugal, and Sweden (29) also have inpatient medicines consumption data available from national reports published by official governmental organisations or upon request. These reports reflect sales of medicines to hospital pharmacies, except in Italy where medicines are dispensed to the patients. The reason is that medicines dispensed to the inpatients in Italian hospitals are reimbursed by the local health authorities. Thus, they are registered in regional databases. The United Kingdom has also hospital drug consumption provided by IMS Health. However, the data cannot be released (http://www.ic.nhs.uk/services/prescribing-support-unit-psu/using-the-service/reference/datasets/hospital-database, last accessed on 10/2013). For the rest of the European countries included in the inventory, hospital drug consumption data is not collected at a national level. These reports express inpatient medicines consumption in DDDs or DID or in terms of expenditure.

Electronic bibliographic search:

All titles returned by the search in PubMed were screened and abstracts read. If an abstract was not available on the electronic database, we tried to retrieve the article in full to find out more information on its contents. If information was not available, the citation was excluded. All the abstracts published in or later than 1980 were reviewed to see whether they fulfilled the inclusion criteria. The search was conducted in March 2011 and updated in December 2011.

Because the search strategy did not consider the indication for use of the medicines, several articles were equally found under different groups of medicines, e.g. the same article could be found under antidepressant, antiepileptics and benzodiazepines. Duplicates were excluded from the total number of articles yielded by the search, and only included in one group of medicines.

Regardless of the country concerned and the type of DU research study, the majority of the articles were set in the outpatient setting. Most of the articles expressed the consumption as percentages of active ingredient out of the total consumption of the main anatomical group. For several articles that dealt with benzodiazepines and antidepressants indicated for mental illnesses, the prescribed doses were transformed into equivalents of diazepam or chlorpromazine.

3.4.7 COMMERCIAL DATA PROVIDERS

Information on the MIDAS database is also applicable to inpatient healthcare setting.

In addition,IMS Healthholds a hospital database (Hospital Prescribing Audit Index) that reflects the consumption of medicines sold into and distributed by hospital pharmacies. Thus, besides hospital sell-in data, it contains information on medicines dispensed by hospital pharmacies to patients, regardless of whether they are in- or outpatient, as long as the medical product has passed through the hospital pharmacy.

Hospital dispensation data reflects doses of drugs dispensed to the patients. Records report the dose but not the original pack. It measures usage by dose.

3.5 SUMMARY OF DRUG CONSUMPTION DATA SOURCES IN EUROPE

Tables 7-11 provide a summary of the main characteristics of national administrative drug consumption data sources.

Table 7. National administrative drug consumption databases in Europe (I)

Countries	BELGIUM	BULGARIA	CROATIA	CZECH REPUBLIC	DENMARK		ESTONIA	
Database name	Pharmanet	Not provided	Not provided	Not provided	Register of medicinal products statistics	Danish National database of Prescriptions Reimbursed	EHIF Database	SAM Database
Data provider	National Institute for Health and Disability Institute (INAMI)	Bulgarian Medicines Agency	Croatian Drug Agency	The State Institute for Drug Control	Danish Health and Medicines Authority	Department of clinical epidemiology at Aarhus University	Estonian Health Insure Fund	State Agency of Medicines
Website	www.inami.fgov.be	www.bda.bg	www.almp.hr	www.sukl.eu	http://laegemiddelstyrelsen.dk	http://kea.au.dk/en/research/thedanishnationaldatabaseofreimbursedprescriptions/	www.haigekassa.ee	www.sam.ee
Accessibility	Application http://www.inami.fgov.be/drug/fr/statistics-scientific-information/pharmanet/request/index.htm	Application Medicines use control department maria.popova@bda.bg	Application viola.malocic@halmed.hr	Application Press and Information Department infs@sukl.cz	Free online www.medstat.dk Further data upon request	Application to regional board. Only for Danish researchers	Application infor@haigekassa.ee	Application info@raviamet.ee
Data source	Reimbursed	Sales	Sales	Sales (2006) Dispensed (2011)	Dispensed	Reimbursed	Reimbursed	Sales
Healthcare setting	Outpatient	Out/Inpatient	Out/Inpatient	Outpatient	Out/Inpatient	Outpatient	Outpatient	Out/Inpatient
Population coverage	99%	100%	100%	100%	100%	100%	95%	100%
ATC/DDD[a]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
OTC[b]	No	Yes	Yes	Yes	Yes	No	No	Yes
Data by age/gender	Yes	No	No	Yes (since 2011)	Yes	Yes	Yes	No
Record linkage	Yes (within INAMI)	No	No	No	Yes	Yes	No	No

[a] Anatomical Therapeutic Chemical codification (ATC). Defined Daily Doses (DDD) as unit of measurement of drug use [b]OTC: Over the counter medicines

Table 8. National administrative drug consumption databases (II)

Countries	FINLAND		FRANCE		GERMANY	HUNGARY	ICELAND	
Database name	Prescription Register Database	Drug sales register	ERASME database	ANSM database	WiDO database	Not provided	Not provided	The Icelandic Pharmaceutical Database
Data provider	Social Insurance Institution	Finnish Medicines Agency	National Insurance Fund-CNAMTS	The French National Agency for Medicines and Health Products Safety (ANSM)	The Research Institute of the General Medical Insurance Plans (AOK)	Directorate General of National Institute of Pharmacy	Icelandic Medicine Agency	Directorate of Health (Landlæknir)
Website	www.kela.fi	www.fimea.fi	www.ameli.fr	www.ansm.sante.fr	http://www.wido.de/	www.ogyi.hu	www.imca.is	www.landlaeknir.is
Accessibility	Applica-tion to KELA research department tutkimus@kela.fi	Application communications@fimea.fi	Application http://www.ameli.fr/l-assurance-maladie/contacts.php	Application communication@ameli.fr	Application valentina.coca@wido.bv.aok.de helmut.schroeder@wido.bv.aok.de	Application ogyi@ogyi.hu	Free online http://www.imca.is/imca/statistics/nr/235	Application http://www.landlaeknir.is/um-embaettid/abendingar
Data source	Reimbursed	Sales	Reimbursed	Sales	Reimbursed	Sales	Sales	Dispensed precription
Healthcare setting	Outpatient	Out/Inpatient	Outpatient	Out/Inpatient	Outpatient	Out/Inpatient	Outpatient	Outpatient
Population coverage	100%	100%	87%	100%	85%	100%	99%	93%
ATC/DDD[a]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
OTC[b]	No	Yes	No	Yes	No	No	Yes	No
Data by age/gender	Yes	No	Yes	No	Yes	Yes	No	Yes
Record linkage	Yes	No	Yes (within CNAMTS)	No	Yes (within AOK)	No	No	Yes

[a] Anatomical Therapeutic Chemical codification (ATC). Defined Daily Doses (DDD) as unit of measurement of drug use [b]OTC: Over the counter medicines [c]HOM: Hospital-only-medicine

Table 9. National administrative drug consumption databases (III)

Countries	IRELAND	ITALY	LATVIA	LITHUANIA	THE NETHERLANDS	
Database name	(HSE-PCRS) pharmacy claims database	OsMED database	Not provided	NHIF Database	GIP database	SFK database
Data provider	Department of Health and Children. The Health Service Executive (HSE)	Italian Medicines Agency	State Medicines Agency of Latvia	National Health Insurance Fund under the Ministry of Health	Health Care Insurance Board	Foundation for pharmaceutical statistics
Website	http://www.hse.ie/eng/staff/PCRS/About_PCRS	www.aifa.it	http://www.vza.gov.lv/index.php?id=305&sa=305&top=298	www.vlk.lt	www.cvz.nl	www.sfk.nl
Accessibility	Application BENNETTK@tcd.ie	Application farmaciline@aifa.gov.it	Application info@zva.gov.lv	Application to Kristina.Garuoliene@vlk.lt	Free online www.gipdatabank.nl Further data	Application info@sfk.nl
Data source	Reimbursed	Dispensed	Sales	Reimbursed prescriptons	Reimbursed	Dispensed
Healthcare setting	Outpatient	Out/Inpatient	Out/Inpatient	Outpatient	Outpatient	Outpatient
Population coverage	37%	100%	100%	98%	92.2%	95%
ATC/DDD[a]	Yes	Yes	Yes	Yes	Yes	Yes
OTC[b]	No	Yes	Yes	No	No	Yes (the 50% sold by pharmacies)
Data by age/gender	Yes	Yes	No	Yes	Yes	Yes
Record linkage	Yes	Yes at regional level	No	No	No	No

[a] Anatomical Therapeutic Chemical codification (ATC). Defined Daily Doses (DDD) as unit of measurement of drug use

[b]OTC: Over the counter medicines

Table 10. National administrative drug consumption database (IV)

Countries	NORWAY		POLAND	PORTUGAL	SLOVENIA	SPAIN
Database name	Norwegian Prescription Database	Wholesalers drug statistics	National Health Fund database	Infarmed database	Unknown	Not provided
Data provider	Norwegian Institute of Public Health	Norwegian Institute of Public Health	National Health Fund	National medicines agency	Ministry of Health. Directorate of Pharmacy and Health Products	The National Institute of Public Health
Website	www.fhi.no	www.fhi.no	www.nfz.gov.pl	www.infarmed.pt	www.msc.es/profesionales/farmacia/organizacion.htm	www.ivz.si
Accessibility	Free online www.norpd.no Further data upon request datatilgang@fhi.no	Application lmfin@fhi.no	Application to data provider: Barbara Wójcik-Klikiewicz. Room 3.14.tel. 22 572 61 89 fax:+22 572 63 43	Application demps-amps@infarmed.pt	Application farmacoepi@aemps.es	Aplication to marjetka.jelenc@ivz-rs.si
Data source	Prescribed	Sales	Value of Reimbursed drugs?	Prescribed Dispensed HOM[c]	Reimbursed	Dispensed prescription medicines
Healthcare setting	Outpatient	Out/Inpatient	Outpatinet	Out/Inpatient	Outpatient	Outpatient
Population coverage	100%	100%	100%	100%	100%	99%
ATC/DDD[a]	Yes	Yes	Yes	Yes	Yes	Yes
OTC[b]	No	Yes	No	No	No	No
Data by age/gender	Yes	Yes	Yes	No	No	Yes
Record linkage	Yes	No	No	No	No	No

[a] Anatomical Therapeutic Chemical codification (ATC). Defined Daily Doses (DDD) as unit of measurement of drug use [b]OTC: Over the counter medicines [c]HOM: Hospital-only-medicines

Table 11.National administrative drug consumption databases (V)

Countries	SWEDEN		THE UNITED KINGDOM
Database name	The Swedish Prescribed Register	Apoteket AB database	ePACT database
Data provider	The National Board of Health and Welfare	National Corporation of Swedish Pharmacies	NHS Business Services Authority. Prescription Services. Electronic Prescribing Analysis and Cost (ePACT).
Website	www.socialstyrelsen.se	www.apotekensservice.se	http://www.nhsbsa.nhs.uk/PrescriptionServices.aspx
Accessibility	Free online http://192.137.163.49/sdb/lak/val.aspx Further data: andrejs.leimanis@socialstyrelsen.se	Free online http://www.apotekensservice.se/lakemedelsstatistik/sok_statistik/ Application: servicedesk@apotekensservice.se	ENGLAND: Free online http://www.ic.nhs.uk/statistics-and-data-collections/primary-care/pharmaciesFurther data: help@ppa.nhs.uk NORTHERN IRELAND: Free online: http://www.hscbusiness.hscni.net/services/1806.htm Further data: Jacqueline.Sheridan@hscni.net WALES Free online: http://wales.gov.uk/topics/statistics/headlines/health2012/1203281/?lang=en Further data: stats.healthinfo@wales.gsi.gov.uk SCOTLAND[d] Free online: http://www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/Community-Dispensing/Prescription-Cost-Analysis/ Further data: nss.isdprescribing@nhs.net
Data source	Prescribed	Sales	Prescribed
Healthcare setting	Outpatient	Out/Inpatient	Outpatient
Population coverage	100%	100%	100%
ATC/DDD[a]	Yes	Yes	British National Formulary/Average Daily Quantities. ATC/DDD upon request
OTC[b]	No	Yes	No
Data by age/gender	Yes	No	No
Record linkage	Yes	No	No

[a] Anatomical Therapeutic Chemical codification (ATC). Defined Daily Doses (DDD) as unit of measurement of drug use [b]OTC: Over the counter medicines

[d]In Scotland, there is the National Medicines Utilisation Unit set up in 2005, with patient-level data. http://www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/National-Medicines-Utilisation-Unit/

4 VALIDITY OF DRUG CONSUMPTION DATA

4.3 INTRODUCTION

There is a vast bibliography regarding the validity and application of automated databases or secondary data sources in research, from a more conceptual point of view (12,30) to reviews of uses of these databases in pharmacoepidemiology (11,31,32), to studying different aspects of the databases that can affect their comparability (33-36).

Sørensen claims that there are 5 aspects that determine the value of an automated database in epidemiological research: completeness of registration of individuals (proportion of individuals that are correctly classified as exposed, drug coverage), comprehensiveness of the information registered (variations in coding, incompleteness in coding of variables collected or of variables not collected - e.g. confounders-, proportion of missing data), size of the data source (population coverage), registration period, accessibility, availability and cost, data format (e.g. available age categories), and record linkage (unique personal identifying number allowing one to link with independent automated databases, or a probabilistic view) (13).

Quality of data registered in automated databases has mainly been identified with the accuracy and the completeness of the database (37). Accuracy is the degree to which the value of a registered variable represents the truth. Completeness is the extent to which data on the variables contained in the database have actually been filled out (37,38). The discussion focuses on administrative drug consumption databases, leaving out clinical databases.

Sensitivity (completeness) and specificity (accuracy) would be the two measures of validity of an automated database when compared to a golden standard, considered in the scientific literatureas either the electronic medical records (16) or patient questionnaire with a home inventory (17).

This kind of validation of the national drug consumption databases is beyond the scope of the PROTECT project. However, the validity of the data extracted from these automated databases can still be evaluated if it is understood as those variables that may introduce potential biases when comparing drug consumption across countries and/or over time (39).

The ESAC group when studying antibacterial consumption in Europe listed the problems encountered when evaluating antibiotic consumption data across European countries. Data collected from different national drug consumption databases raised concerns about population coverage –including parallel export for sales of medicines, drug coverage and the mix between what was considered hospital (inpatient) or ambulatory (outpatient) drug consumption. According to this list each national drug consumption database was scored as valid, valid with a minor bias, or not valid (39).

Several factors, including those proposed by ESAC, may help to interprete the results of medicines consumption when comparing different countries, such as reimbursement policies, prevalence of the diseases treated by the group of medicines, cultural differences, national clinical guidelines. These factors have been studied mainly for antihypertensives (40,41), acid suppressants (42), and antibiotics (43). The impact of reimbursement policies is the most studied factor (41,44-46).

4.4 SPECIFIC METHODOLOGY

To evaluate the validity of medicines consumption data, we undertook several steps. First of all, we built a table with the consumption in numbers of DID of the drugs included in the PROTECT project, allowing for a descriptive comparison across different countries (47). Secondly, we searched for studies published on the sensitivity and specificity of drug exposure measurement for the national administrative drug consumption databases. Thirdly, we developed a questionnaire aiming attrying to collect information on the items considered of relevance when measuring drug exposure, but also that couldbe key elementsin interpreting the results obtained across countries (see Appendix 7.4 for a sample of the questionnaire).

For completeness, the items selected for the questionnaire are listed below:

a. Definition of in- and outpatient drug consumption. There is an interest in knowing whether drugs used in nursing homes, drug abuse centres, private institutions are collected, as well as whether prescriptions by specialists or hospital medicines dispensed to outpatients are classified as in- or outpatient.
b. Population coverage of the database. If the coverage is below 90%, what was the weighting system. If the database covers only a sample of the population, what was the sampling methodology.
c. Drug-based information. This item covers many different aspects that may be of interest for establishing the proportion of a population exposed to drugs:

c1. Source of the data

- wholesalers sales: sales of medicinal products from wholesalers to the community or hospital pharmacies and other outlets. They are usually provided at an aggregate level.

- dispensed: medicines dispensed by the community pharmacy to the patient, either prescribed or not prescribed. Thus, it includes over-the-counter (OTC) medicines;

- prescribed: prescription medicines dispensed at community pharmacies. It does not include OTC medicines, except if there is an authorised indication for which these OTC medicines may be prescribed.

- reimbursed: medicines prescribed by a healthcare professional, dispensed by a pharmacist and reimbursed by a healthcare provider. It excludes OTC medicines, and those prescription-only-medicines (POM) that are not reimbursed.

c2. The time intervals of drug exposure (days of supply, quantity of drug dispensed, dose).

c3. Characteristics of the package sold.

c4. Date of prescription and dispensation; proportion of electronic prescriptions not collected by the patient in the pharmacy –as a means to measure secondary compliance.

c5. Proportion of missing information on the database.

c6. Indication for use.

c7. The use of the ATC/DDD methodology, trying to establish how often the database is updated with the yearly ATC/DDD guidelines, released by the WHO,as well as the handling in the database of those drugs that do not have an ATC code or who have not a DDD assigned.

d. Patient-related information collected, either straight from the database, such as age, gender, unique patient identifier number or other sociodemographic factors, or through linkage to other databases.

e. The way the internal validity of the database is checked and how often these checks take place.

f. Accessibility of the data for research purposes.

The questionnaire was structured under four headings, three of which specifically covered items a, b and c. The fourth heading termed *other information* covered items d, e and f. It was sent by e-mail to the contact persons. A cover letter and instructions to fill and return the questionnaire followed. The questionnaire consisted of closed-questions, but also included the possibility of adding any comments or further information for each of the headings. In order to facilitate the responsiveness, the questionnaire was partially completed for those databases where information existed either from published articles (48-52) or from their own websites.Thus, participants were asked to complete and amend any errors found. At least two reminders were sent. Information was requested from nationwide medicines consumption databases for the out- and if available, inpatient setting.

Fourthly, several factors were deemed to have an impact on medicines utilisation: population demographic characteristics; prevalence of the condition for which the drug is mainly used according to the ATC guidelines; clinical guidelines for the treatment of the main indication for use of the drug, according to the ATC guidelines; reimbursement policies; medicines advertisement policies; and other factors, such as cultural dimensions (43).

4.5 SPECIFIC RESULTS

4.5.6 Table with drug consumption data

A table with drug consumption data expressed in DID for the selected PROTECT drugs have been built-up to compare prevalence of expsoure across countries (results not shown).

4.5.7 Sensitivity and specificity

Table 12. Studies published on sensitvity and specificity of national drug consumption databases

COUNTRY	DATABASE	REFERENCES
Denmark	The Danish National Prescription Registry	Johannesdottir et al. 2012(53) Comparison of the general practitioner prescription data with the Aarhus prescription database which is a regularly updated research copy of the regional prescription records. They checked full ATC agreement and therapeutic group agreement. Kildemoes et al. 2011(54) For hormone replacement therapy (patient questionnaire gold standard), sensitivity 74.8% and specificity 98% in 1999.
Finland	The Finnish National Prescription Registry	Haapea M et al. 2010(55) Comparison of a postal questionnaire data and reimbursed prescriptions. Antipsychotics (κ=0.77), antidepressants (κ=0.68), antiepileptics (κ=0.84) and antidiabetics (κ=0.92) and beta-blockers (κ=0.55). Rikala et al 2010(56) Psychotropic drugs in elderly (patient questionnaire). *No access* Haukka et al 2007(57) Psychotropic drugs in patients with schizophrenia (patient questionnaire as gold standard, Cohen's κ 0.96 for Li to 0.37 for BZD
France	Reimbursement databases	Noize et al. 2012(58) Validity of chronic drug exposure from repeated surveys with reimbursement data (golden standard) from the national health insurers. Cardiovascular and antithrombotic Se, 85.3–95.4%; Sp, 67.1–97.6%; PPV, 65.9–86.6%; NPV, 93.3–99.3%. Benzodiazepines, NSAIDs, analgesics very low validity with PPV (15.8–51.4%). Noize et al. 2009(59) Comparison of health insurance claims and patient interviews in assessing drug use: data from the Three-City (3C) study. All classes of drugs in the general population (patient questionnaire as gold standard). Values of correlation and sensitivity/specificity varied with reimbursement time frame. 30-day κ= 0.03-0.59; Se 2.4%-47.4%; Sp 89.1-99.9%.60-dayκ= 0.05-0.20; Se 70%; Sp 77.6-99.8% Latry P 2010 (60) Comparison of sales of drugs with reimbursement drug data. Depending on the ATC, the capture of the drugs in the reimbursement database ranged from 32% to 81%.
Germany	Health insurance medication claims data	Hoffmann. 2009(61) Review article on use of German Health Insurance data. None of the articles published conducted a validation study about drug exposure. Hoffmann et al. 2008(62) Validity of information relevant to research in routine medication claims data from 2000 to 2006. Article in German. *No access*. Information on claims data was compared with the scanned original prescriptions (gold standard) for 1 health board. They check the accuracy of prescription and dispensing date, physician and pharmacy identifiers with an accuracy for all variables >85%.
Italy	OsMed/regional pharmacy databases	No information found

COUNTRY	DATABASE	REFERENCES
Ireland	HSC-PCRS pharmacy records databases	Richardson et al.,2013(63). Comparison of in-home interviews and pharmacy dispensing records. Drugs checked (ATC codification): A02 (κ=0.67), A10(κ=0.86), A12(κ=0.66), B01(κ=0.72), C01(κ=0.72), C03(κ=0.77), C07(κ=0.80), C08(κ=0.77), C09(κ=0.78), C10(κ=0.73), G04(κ=0.70), H03(κ=0.81), M01(κ=0.54), M05(κ=0.67), N02(κ=0.20), N05(κ=0.59), N06(κ=0.69), R03(κ=0.64), S01(κ=0.37). The effect of interviewer was not statistically significant
Netherlands	Pharmacy records (pharmacy databases)	Lau et al, 1997(17). Validity of pharmacy records (legend time method: supply and dosages determine drug exposure) compared with home inventory interview (gold standard) in people aged ≥70yrs. Se 70%; Sp 98% (variations seen upon different drug classes) Heerdink et al. 1995(16). Comparison of pharmacy, GP and patient data on drug use in the elderly. Home interviews as gold standard. Pharmacy records 80%; GP data 40%. Variability among classes of drugs.
	CVZ (reimbursed records)	No information found
	SFK (dispensed records)	No information found
Norway	Norwegian Prescription Database	Furu et al. 2011(64). High validity of mother-reported use of antiastmatics among children: a compariosn with a population-based prescription database Maternal questionnaire compared with NorPD. Sensitivity 85%. Specificity 96.8%. Furu 2009(49). Explains the quality checks conducted in NorPD Skurtveit 2008(65). Comparison of self-reported prescription medication and NorPD (gold standard) in adolescents. Sensitivity for questions varied among drug classes from 48.5% for painkillers to 99.2% contraceptive pills
Spain	Ministry of Health database	No information found.
Sweden	The Swedish Prescription Registry	Stephansson et al. 2011(66). Drug use during pregnancy in Sweden –Prescribed drug register and medical birth register concordance. It varied across drug class. The agreement was high for chronic conditions (85.3% for thyroid treatment), whereas for occasional drugs agreement was 42.5% for antihistamines. Neovius et al. 2010(67). Comparison of people registered in a the Swedish biologic register and people receiving tx with etanercept and adalimumab from the Swedish prescribed register (gold standard).
United Kingdom	ePACT	Langley et al. 2010(68). Validation of prescription in THIN database compared with ePACT (gold standard)

4.5.8 Questionnaire results

Questionnaires were sent to the contact person of the following databases or institutions: Pharmanet database, The Bulgarian Medicines Agency database, The Czechian Medicines Agency database, The Danish Registry of Medicinal Products Statistics, ANSM, Research Institute of AOK, Prescription Register at The Social Insurance Institution of Finland (Kansaneläkelaitos, Kela), The Hungarian Medicines Agency Database, OsMed, NorPD, Portuguese INFARMED, Spanish Ministry of Health, Swedish Prescription Register, GIP databank and SFK, the central ePACT Services,

Austria Regional Health Insurence company (Burgenländische Gebietskrankenkasse), Agency for Medicinal Product and Devices of Bosnia and Herzegovina, Croatian Medicines Agency Database, Estonian Health Insure Fund Database, State Agency of Medicines Database of Estonia, Icelandic Medicines Agency Database, (HSE-PCRS) Pharmacy Claims Database, State Agency of Medicines Database of Latvia, National Health Insurance Fund (NHI) Database of Lithuania, Serbian Institute for Health Insure, The Slovenian National Institute of Public Heath.

Questionnaires were received with information from: Pharmanet database, Bulgarian database, Czechian Database, The Danish Prescription Register, ANSM, Hungarian database, OsMed,NorPD, INFARMED. GIP, SFK, The Swedish Prescription Register,Croatian Medicine Agency Database, Estonian Health Insure Fund (EHIF) Database, State Agency of Medicines (SAM) Database of Estonia, Prescription Register at The Social Insurance Institution of Finland (Kansaneläkelaitos, Kela), Icelandic Medicines Agency Database, (HSE-PCRS) Pharmacy Claims Database, State Agency of Medicines Database of Latvia, National Health Insurance Fund (NHI) Database of Lithuania, The Slovenian National Institute of Public Heath (NIPH),Spanish Ministry of Health.

For Russia and Switzerland, the contact persons replied back and explained that none of the countries had any nationwide administrative database monitoring trends in drug consumption.

For the National Insurance Fund in Poland, the questionnaire was not replied becuase their information was only for value of reimbursed drugs, and drug consumption data was available from IMS Health which characteristics have already described.

For Spain, the information contained in the questionnaire was filled through a telephone interview.

For Germany and UK, no remainders were sent this year.

A summary of the answers provided in the questionnaire can be seen in tables 13-17.

Table 13. Information retrieved from the questionnaire (I)

Items	Danish Registry of Medicinal Products Statistics (Denmark)	Danish National Database of Prescriptions Reimbursed[1]	ANSM (France)	OsMed (Italy)	NorPD (Norway)
Type of data source	Dispensed medicines in outpatient sector Medicines dispensed by ward code in inpatient sector.	Reimbursed medicines dispensed in.	Sales from wholesalers.	Reimbursed medicines from regional health authorities databases (LHA) Dispensed medicines from IMS Health.	Dispensed prescription medicines.
Data included as outpatient drug consumption	Community pharmacies. Hospital drugs dispensed to outpatients.	Community pharmacies and hospital-based outpatient pharmacies.	Sales to community pharmacies.	Nursing homes Specialist care to outpatients Hospital drugs dispensed to outpatients (partly)	Dental care Specialist care to outpatients Drug abuse centres Private institutions.
Data included as inpatient drug consumption	Sales to hospital pharmcies dispensed by ward codes (number of patients undergoing treatment in hospitals is not available).	--	Sales to hospital pharmacies.	Hospital drugs dispensed to outpatients (partly) Drugs dispensed to patients during hospital stay are reimbursed, thus registered by LHA.	Nursing homes are sent to the register on an aggregated level.
Population coverage (%)	100	100	100	100	100
If applicable, sampling or weighting methodology	n/a	n/a	n/a	n/a	n/a
OTC sales	Yes	No	Yes	Yes	No
Possibility to estimate the time intervals of drug exposure (days of supply or quantity of drug dispensed, dose and DDD)	Yes (Quantity of drug dispensed and dose)	Yes (Quantity of drug dispensed and dose)	No	Yes (Quantity of drug dispensed and dose)	No (Dose is available only as free text)
ATC/DDD updatings	Yearly, all retrospective data is updated.	Yearly	Yearly, all retrospective data is updated.	Yearly, all retrospective data is updated.	Yearly, with all retrospective data updated.
Coding of drugs with non ATC/DDD assigned	National DDD assigned which are accounted as WHO-DDD. A list is available on the website.	--	When the drug is not classified within ATC system, the drugis assigned to an ATC 4th level group according to WHO	For anticancer drugs, dispensing units.	No information provided.

Items	Danish Registry of Medicinal Products Statistics (Denmark)	Danish National Database of Prescriptions Reimbursed[1]	ANSM (France)	OsMed (Italy)	NorPD (Norway)
			guidelines.		
Linkage to other registers	Yes (through unique ID number).	Yes (through unique ID number).	No.	No.	Yes (through unique ID number).
Register of sociodemographic and economic variables	Yes. Age, gender and place of residence.	Yes. Age, age at dispensing date, gender and place of residence.	No.	Yes. Age, gender and place of residence.	Yes. Age, gender and place of residence.
Other variables collected	Yes. Indication for use in 75% of the prescriptions.	Yes.	No.	No	Yes. Prescribers and on the pharmacy.
Internal validity	Every month, large validation process.	Bar code scanning and own computerized accounting systems of the pharmacies.	Data is contrasted with other sources of drug sales.	For tracibility data on a monthly basis, for health card register, the process is ongoing. For reimbursed data it depends on the LHA database.	Monthly and every 6 months the database is checked for inconsistencies and errors.
Proportion of missing prescriptions	No information provided.	No information available.	n/a	Regarded as unclear question.	1% in 2010.
Accessibility	Part of the data is free online. Furhter data can be applied for.	Only for researchers in Denmark.	Data not available for those active substances marketed by a single manufacturer.	Open to specific study requests	Part of the data is free online. Guidelines on access to further information and fees available on their website.

n/a: Not applicable

[1]Johannesdottir SA et al. Clin Epidemiol 2012;4:303-313.

Table 14. Information retrieved from the questionnaire (II)

Items	The State Institute for Drug Control (Czech Republic)	The Swedish Prescription Register (Sweden)	GIP databank (Netherlands)	SFK (Netherlands)
Type of data source	Sales from wholesalers Dispensed medicines	Dispensed prescription medicines	Reimbursed medicines	Dispensed medicines
Data included as outpatient drug consumption	Community pharmacies (including medicines prescribed by specialists). Nursing homes, dental care, psychiatric clinics and other institutions not collected.	Community pharmacies Nursing homes (not completely) Hospital clinics also included.	Specialist care to outpatients and hospital drugs dispensed to outpatient information on dental care, nursing homes, drug abuse centres and private institutions is not collected.	Dental care Specialist care to outpatients Hospital drugs dispensed to outpatients.
Data included as inpatient drug consumption	No.	No.	No.	Nursing homes (partly).
Population coverage (%)	100	100	95	90
If applicable, sampling or weighting methodology	n/a	n/a	Extrapolation to the total Dutch population through 20 age subgroups and by sex.	No information provided.
OTC sales	Yes from wholesalers. Dispensed OTC also available with limits.	No.	No.	Yes, information on 50% of all OTC-sales. Other outlets sell also OTC drugs which are not included.
Possibility to estimate the time intervals of drug exposure (days of supply or quantity of drug dispensed, dose and DDD)	No. (Quantity of drug dispensed is available. No days of supply or dose available).	Yes. (Quantity of drug dispensed is available. No days of supply available. Dose collected as free text).	Yes. (Quantity ot drug dispensed, prescribed daily dose and days of supply available).	Yes. (Quantity of drug dispensed, dose and days of supply available).
ATC/DDD updates	Yes. Every April. Data is updated retrospectively for the whole database.	ATC/DDD codes are a separate product register. Although the data is always updated with the latest version.	Yes, twice a year.All data updated retrospectively.	Every January the database is updated with the latest version of ATC/DDD.
Coding of drugs with non ATC/DDD assigned	No.	A list with national assigned DDD/ATC exists in the products r register, updated every month.	A list with national assigned DDD/ATC exists.	No information provided.
Linkage to other registers	No.	Yes (Through a unique personal identiy number).	No.	No.
Register of sociodemographic and economic	Yes. Age and gender.	Yes. Age, gender and place of residence.	Yes. Age, gender and place of residence. Patient-level data.	Yes. Age, gender and place of residence. Patient-level data.

Items	The State Institute for Drug Control (Czech Republic)	The Swedish Prescription Register (Sweden)	GIP databank (Netherlands)	SFK (Netherlands)
variables		Patient-level data.		
Other variables collected	No.	Data can be split by primary health secrtor and hospital clinics, and prescriber's profession.	Yes. Information on prescribers, dispensers, cost and patient contribution.	Information on prescribers and dispensers. Cost and health insurance sector.
Internal validity	Controls are conducted continuously through data processing.	Once or twice a year, the proportion of missing information in certain variables is evaluated. No corrections can be introduced.	It is an ongoing process carried out during data collection and aggregation.	No information provided.
Proportion of missing prescriptions	Not requested.	<0.3% (2007) as measured for patient identity.	No information provided.	0%
Accessibility	Data freely available online. Further data can be requested.	Data freely available online. Further data can be requested.	Data freely available online. Further data can be requested.	Data is not accessible for researchers although they can post a request.

n/a: Not applicable

Table 15. Information retrieved from the questionnaire (III)

Items	Pharmanet (Belgium)	Bulgarian Medicines Agency Database (Bulgaria)	Hungarian Medicines Agency Database (Hungary)	INFARMED (Portugal)
Type of data source	Reimbursed dispensed prescriptions.	Sales from wholesalers.	Sales from wholesalers.	Prescribed, dispensed and reimbursed.
Data included as outpatient drug consumption	Medicines supplied by community pharmacies, regardless of doctor's specialty.	Community pharmacies and other outlets for outhospital.	Medicines sold by community pharmacies in the outpatient.	Medicines sold by community pharmacies.
Data included as inpatient drug consumption	No.	Hospital pharmacies for inpatient sector.	Medicines prescribed and supplied by the hospital to outpatients are included in the inpatient sector.	Medicines prescribed and supplied by the hospital to outpatients
Population coverage (%)	99	100	100	100 (it does not cover other systems such as private hospitals or private outpatient sector)
If applicable, sampling or weighting methodology	n/a	n/a	n/a	n/a
OTC sales	No.	Yes.	Yes.	No.
Possibility to estimate the time intervals of drug exposure (days of supply or quantity of drug dispensed, dose and DDD)	Yes (quantity of drug dispensed and days of supply, dose).	No (Package size, number of packages dispensed, dose, strength and dosage form).	Yes (Quantity of drug dispensed, days of supply, package size, number of packages dispensed, dose, strength, dosage form).	Yes (Quantity of drug dispensed, but not days of supply. Package size, number of packages dispensed, dose, strength, dosage form).
ATC/DDD updates	It is retrospectively updated every year around April-May.	ATC code as in the marketing authorisation of the product. No updates.	ATC/DDD updated retrospectively with the latest version.	Yearly updates during the first trimester.
Coding of drugs with non ATC/DDD assigned	Yes. The list is not publicly available.	--	No national list as all medicines approved in Hungary hold an ATC code.	--
Linkage to other registers	Yes INAMI's databases.	No.	No.	No.
Register of sociodemographic and economic variables	Yes: unique patient identification number, age, gender, and place of residence. Patient-level data.	No.	No.	No.
Other variables collected	Prescriber information.	No.	Indication for use. Number of beds, number of admissions and length of stay.	No.
Internal validity	Multilevel control	No.	Checked continuosly.	Monthly checkings.

Items	Pharmanet (Belgium)	Bulgarian Medicines Agency Database (Bulgaria)	Hungarian Medicines Agency Database (Hungary)	INFARMED (Portugal)
	process.			
Proportion of missing prescriptions	Not provided.	No.	Not provided.	Not provided.
Accessibility	Upon request. Fee for the data.	Data not available.	Upon request for research purposes.	Upon request.

n/a: Not applicable

Table 16. Information retrieved from the questionnaire (IV)

Items	Croatian Drug Agency (Croatia)	EHIF Database (Estonia)	SAM Database (Estonia)	Prescription Register at The Social Insurance Institution of Finland
Type of data source	Sales from wholesalers.	Reimbursed dispensed prescription drugs.	Sales from wholesalers.	Reimbursed prescriptions.
Data included as outpatient drug consumption	Yes.	Yes.	Yes.	Yes.
Data included as inpatient drug consumption	Yes.	No.	Yes.	No.
Population coverage (%)	100	95	100	100
If applicable, sampling or weighting methodology	n/a.	n/a.	n/a.	n/a.
OTC sales	Yes.	No.	Yes.	No.
Possibility to estimate the time intervals of drug exposure (days of supply or quantity of drug dispensed, dose and DDD)	Yes (Quantity of drug dispensed, but not days of supply. Package size, number of packages dispensed, strength, dosage form).	Yes (Quantity of drug dispensed but not days of supply. Package size, number of packages dispensed, dose, strength, dosage form).	No.	Yes (not availabe exact dosage).
ATC/DDD updates	Yes, at the beginning of the year.	Yes, updates March 1st.	Yes, updated March 1st.	Yes, ATC twice a month. DDD in spring with the last year's data.
Coding of drugs with non ATC/DDD assigned	No.	Yes (the list is not available). DDDs for combination products.	Yes (the list is not available). DDDs for combination products.	No.
Linkage to other registers	No.	No.	No.	Yes.
Register of sociodemographic and economic variables	No.	Yes, unique patient identification number, age, gender.	No.	Yes, unique patient identification number, age, gender, place of residence.
Other variables collected	No.	Yes, Indication for drug use (ICD-10), prescriber information (name and speciality).	No.	Yes, indication for drug use if the prescriber has stated the indication in the prescription (free text), prescriber and

Items	Croatian Drug Agency (Croatia)	EHIF Database (Estonia)	SAM Database (Estonia)	Prescription Register at The Social Insurance Institution of Finland
				dispenser information.
Internal validity	Yes, once a year.	Unknow.	Unknow.	Yes, certain purchases are checked every time and others weekly by spot checks.
Proportion of missing prescriptions	Not provided.	Not provided.	Not provided.	Not provided.
Accessibility	Upon request.	Upon request.	Upon request.	Upon request.

n/a: Not applicable

Table 17. Information retrieved from the questionnaire (V)

Items	Icelandic Medicines Agency (Iceland)	HSE-PCRS Pharmacy Claims Database (Ireland)	NHIF Database (Lithuania)	The National Institute of Public Health (Slovenia)	Ministry of Health, Social Policy and Equity (Spain)
Type of data source	Sales from wholesalers.	Reimbursed prescriptions.	Reimbursed prescriptions.	Prescribed medicines.	Reimbursed prescriptions.
Data included as outpatient drug consumption	Yes.	Yes.	Yes.	Yes.	Yes.
Data included as inpatient drug consumption	No.	No.	No.	No.	No.
Population coverage (%)	99	37	98	99	100
If applicable, sampling or weighting methodology	n/a.	n/a. It covers almost 100% of the prescriptions issued in the country.	n/a.	n/a.	n/a.
OTC sales	Yes.	No.	No.	No.	No.
Possibility to estimate the time intervals of drug exposure (days of supply or quantity of drug dispensed, dose and DDD)	Yes(number of packages dispensed, strength, dosage form).	Yes(packagesize, strength, quantity, method and unit of administration. Quantity prescribed).	Yes (dose, number of doses).	Yes (quantity of drug dispensed, package size, number of packages dispensed, dose, strength, dosage form).	Yes (national pharmaceutical code, strength, dosage form).
ATC/DDD updates	Yes, in January.	Not provided.	Not provided.	Yes, when the new medicine is added to the national base.	Not reported.
Coding of drugs with non ATC/DDD assigned	No.	No.	Not provided.	No.	In some cases, specially for drugs whith a high consumption.
Linkage to other registers	No.	Yes.	No.	No.	No.
Register of sociodemographic and economic variables	Yes, age and gender.	Yes, age, gender and health board.	Yes, age, gender, place of living.	Yes, unique patient identification number, age, gender, place of residence.	Some regionals databases have age and gender.
Other variables collected	Number of beds and average length of stay at country and hospital level.	--	The diagnosis, prescriber and pharmacy data.	Prescriber data (ID doctor, speciality).	Yes, prescriber's code and pharmacist's code.
Internal validity	Yes, yearly.	No provided.	Yes, financial audits and rules of agreed protocol to transfer data.	Yes, twice a year.	Yes, every daty.
Proportion of missing prescriptions	Not reported.	Not reported.	Not reported.	Not reported.	No reported.
Accessibility	Data freely available online.	Upon request.	Upon request.	Upon request.	Upon request.

n/a: not applicable

Dispensed medicines covers all prescribed and not prescribed items purchased in acommunity pharmacy by the individudual patient. Thus, it covers OTC-drugs.The Danish Registry on Medicinal Products, OsMed, and SFK, provide dispensed data. The Swedish Prescription Register, NorPD and the Slovenian Institute of Public Health database collect all prescriptions dispensed in a community pharmacy. The Danish National database of prescriptions reimbursed, GIP databank, HSE-PCRS, Spanish database from the Ministry of Health, INFARMED, the Lithuanian and Estonian health insurance funds, the Finnish Prescription Register at the Social Insurance Institution, and the Belgian Pharmanet provide information on reimbursed medicines. French (ANSM), Bulgarian, Croatian, Czechian, Hungarian, Estonian and Icelandic databasesform their corresponding national medicines agencies collect information on sales of medicinal products from wholesalers. In addition, it is possible to obtain sales of medicines from wholesalers in Norway and Sweden.

There are few variables associated with the medicines exposure that are measured in these administrative databases. Age, gender and place of residence are the additional variables collected. Only the DNPR, the Hungarian database and the EHIF database collect indication for use. The Danish National Registry of Medicinal collects partially indication for use in free text. No other relevant clinical information such as comorbidities are collected. However, the Danish Registry of Medicinal Products, DNPR, NorPD and the Swedish Prescription Register allow us the linkage of these registries to other databases through a unique identity number. The Belgian database allows to establish a record linkage system within the health insurance databases structure.Time interval of exposure to a medicine can be estimated either through the days a drug is supplied or, it can be calculated through the quantity of drug dispensed, the dose prescribed and the DDD. It can be estimated from the Danish Registry of Medical Products Statistics, DPNR, OsMED database, the Swedish Prescription Register, GIP databank, SFK database, Hungarian Medicines Agency database, and INFARMED database. For NorPD prescribed dose is only available as free text.

The ATC/DDD methodology is adopted by all databases and updated yearly after the release of the WHO guidelines every October (19). However, consumption of those medicines without an ATC/DDD are handled differently. Several databases –The DanishRegistry of Medicinal Products, the Swedish Prescription Registerand the GIP databank, use a national list with these medicines and a they assigne a national DDD according to WHO guidelines. The ANSM database assigns the drug into ATC level 4. OsMed database uses dispensing units for anticancer drugs.

Reimbursment and payment for drugs widely differs between countries. There are several characteristics that were first defined bySermeus in 1984 (69). These characteristics are: method of payment (cost of drugs may be paid directly by the health insurer or another governmental body; or the patient may pay fully or partly the costs of drugs that will then be reimbursed by an official body), beneficiaries (patients to whom the schemes apply), categories of reimbursable drugs (criteria under which a drug is reimbursed), the structure of reimbursement to the patient (or

patient copayment), the reimbursement level for the drugs (the percentage of costs of a drug that is reimbursed).

For reimbursement policies see Tables 18-22.

Table 18. Reimbursement characteristics of European countries (I)

CHARACTERISTICS	BELGIUM	BULGARIA	CROATIA	CZECH REPUBLIC	DENMARK
Method of payment	The patient only pays part of the total cost of a medicine and the sickness funds pay the remaining part to the pharmacist.	The patient only pays part of the total cost of a medicine and the sickness funds pays the remaining part.	The patient only pays part of the total cost of a medicine and the sickness funds pays the remaining part. Except for the basic list.	The patient pays part of the total cost of a medicine and the Health Insurance Funds pays the rest directly to the pharmacy.	The patient pays fully/partially the cost of the medicine and the municipality pays the remaining part to the pharmacist.
The beneficiaries	Reimbursement schemes differ for salaried and self-employed people, with the latter not receiving pharmaceutical reimbursement, except for oncological and AIDS drugs. The retired, widowers, orphans and people with disability benefits or people classified as preferentially insured persons are entitled to better benefits from the insurance system.	Reimbursement schemes are the same for all inhabitants.	Reimbursement is equal for all the citizens. But children, pregnant women, patients with HIV, chronic psychiatry patients, transplant patients, dialysis and cancer patients, citizens living under the poverty level are excepted from co-payment.	Reimbursement is equal for all Czech residents. Special reimbursement decisions on type of medicines and medical conditions. For dependent children, pensioners, women on maternity or parental leave, persons receiving parental benefits, job seekers, and adults with moderate to severe level of dependence and their carers, military and civil service are covered by the state.	Reimbursement schemes may differ for patients chronically or terminally ill. Supplementary reimbursement schemes for pensioners, people on low income, patients receiving cash assistance. Reimbursement schemes may also differ according to medicine.
Categories of reimbursable drugs	Positive reimbursable list. This list is subdivided into different chapters according to indication for use. It is valid for out- and inpatient sector.	Positive reimbursable list for the outpatient sector. Inpatient sector: there is a list of medicines available at hospital level.	There are "Basic" list with all essential medicines covered by mandatory insurance and the "Complementary" list with medicines covered partially through mandatory insurance and partially by out-of-pocket payments.	Positive reimbursable list of medicines. Special reimbursement may be granted for special medical purposes depending on the extent and severity of the disease (e.g. specific infectious diseases).	General reimbursement scheme for prescription-only medicines and OTC. Other medicines may be classified for general reimbursement when limited to certain diseases. Individual reimbursement scheme upon doctor's application for medicines non-reimbursed.

CHARACTERISTICS	BELGIUM	BULGARIA	CROATIA	CZECH REPUBLIC	DENMARK
Structure of reimbursement to the patient (patient co-payment)	Co-payment consists of a flat fee for medicine supplied and to a percentage of the real cost, and limited to a ceiling-fee.	Co-payment rates are product specific. Group IA (0%), IB (down to 0%), IC (up to 95%), II (up to 100%). The last co-payment category includes medicines listed in category II and III.	Prescription fee of HRK15 (roughly €2) per year on medicines. Above. The basic list: 0%.	Co-payment of a maximum ceiling of CZK5000 (roughly €200) per year on medicines. Above which the sickness funds reimburses 100% of the medicines, except for a fixed flat fee per prescription.	Positive list of medicines eligible for reimbursement. Co-payment consists to full payment of medicines up to a maximum cost for a period of 12 months. Above this maximum, different percentages are paid by the patient depending on patient's health expenditure with co-payment rates of 100%, 50%, 25%, 15%, and 0%).
Reimbursement level for drugs	Medicines are classified into 5 categories (reimbursement rate): A (100%), B (75 or 85%), C (50%), Cs (40%), and Cx (20%). The flat fee varies also by reimbursement category.	3 categories (reimbursement rate %): I (up to 100%), II (up to 100%), III (up to 75%).	100% for medicines included in the basic list.	50% of the medicines on the positive reimbursable list are fully covered by the sickness funds, only flat fee for prescription of €1.20.	4 reimbursement categories (reimbursement rate): General reimbursement POM (0,50,75,85,100%);general reimbursement POM limited to certain diseases (0,50,75,85,100%); general reimbursement OTC (0,50,75,85,100%); individual for a specific product (0,50,75,85,100).

Table 19. Reimbursement characteristics of European countries (II)

CHARACTERISTICS	ESTONIA	FINLAND	FRANCE	GERMANY	HUNGARY
Method of payment	The patient partially pays the cost of the medicine and the Estonian Health Insurance Fund (EHIF) pays the rest.	The patient partially pays the cost of the medicine. KELA pays the remaining to the pharmacist.	The patient partially pays the cost of the medicines and the health insurer pays the rest to the pharmacist.	The Statutory Health Insurance (SHI) directly pays costs of drugs to the pharmacist.	Cost of drugs paid by the National Health Insurance Fund Administration (NHFIA).
The beneficiaries	The reimbursement system is disease specific.	Reimbursement schemes differ by therapeutic value for basic reimbursement and by type of disease for special reimbursement categories. Municipalities additionally support people on low income, pensioners receiving support, children, and people with disabilities.	Reimbursement schemes differ by the therapeutic value of the medicine and disease severity as advised by the Health High Authority (HAS). People < 18 years are exempted of the flat-fee per prescribed medicine package.	Reimbursement schemes differ by age group. For some medicines, only approved indications are reimbursed. Children < 12 years exempt of co-payment.	Participation in the NHFIA is compulsory for all Hungarian citizens. Certain individuals are exempted (abandoned children, disability pensions, people receiving regular cash benefits) and means-tested which is determined by the patient household income and pharmaceutical expenditure.
Categories of reimbursable drugs	Positive reimbursable list. The reimbursement category is determinate according to the severity of the disease, efficacy of medication and social status of the patient.	Positive and negative reimbursable list. For special reimbursement, a doctor's application needs to be filled up. Some OTC medicines may also be granted basic or lower special reimbursement.	Positive reimbursable list. Within this list, the medicines are classified according to their clinical benefit assessment (Service Médicale Rendu, SMR): major or important, moderate, mild, and insufficient clinical benefit.	All medicines that hold a market authorisation are reimbursed by the SHI. However, the Ministry of Health, through the Quality Assessment Institute may exclude those medicines deemed not to be cost-effective or that do not provide additional benefit.	Positive and negative reimbursable list. Medicines are reimbursed depending on the severity of condition (specialist confirmation) and the indication and type of a prescription (fixed reimbursement type, valid for all indications licensed for a drug up to a fixed amount or on a percentage basis).

CHARACTERISTICS	ESTONIA	FINLAND	FRANCE	GERMANY	HUNGARY
Structure of reimbursement to the patient (patient co-payment)	Outpatient prescription are subject to co-payment of €3.20 (EEK 50) per prescription plus some of the price of the medicine. Drugs of the positive list prescribed by ambulatory provides: 50% of €393.40-639.00 per calendar year. 75% of €639.00-1278.00 per calendar year. 0% above €1278.00.	When patient's co-payment exceeds a maximum ceiling (€700.92, year 2012), the patient pays a flat fee for prescription of €1.50. The patient pays medicines not eligible for reimbursement, which are not included in the annual ceiling.	The patient pays a flat fee of €0.50 /package plus a co-payment of 85%, 70%, 35% and 0% depending of the therapeutic value of the medicine.	The patient pays 10% of the price of medicines with a minimum of 5€ and a maximum of 10€ per prescription up to an annual upper limit based on patient's income. Exception: For those drugs, which price is 30% below the reference price.	For the fixed reimbursement type, co-payment may be of 20%, 45% or 75% or up to a fix amount of €1.2/prescription (valid for generic medicines and to different products with different active ingredients with similar treatment effects). For the indication-related reimbursement, co-payment is 0% for more severe diseases with a package fee of €1. For less severe diseases, the co-payment is 10%, 30% or 50%.
Reimbursement level for drugs	List of medicines (27 indications/group) for severe diseases receive 100% reimbursed. Less severe but mostly chronic diseases (44) 75% reimbursed. In this group 90% reimbursed is applied for certain social group (children under 16, disabled and retired people). Children below 4 years 100% reimbursed. Other drugs belong the positive list that no belong the diagnoses outlined before are reimbursed at 50%.	There are 4 reimbursement categories (reimbursement rate): Basic reimbursement (42%); lower special reimbursement (72%); higher special reimbursement (100%; a flat fee of€3 is charged for prescription; additional reimbursement scheme when the maximum co-payment/year is reached.	There are 4 reimbursement categories: 100% for drugs with a barred white label. It corresponds to expensive, irreplaceable medicines; white label (65%) medicines deemed of major or important clinical benefit; blue label (30%) for moderate efficacy medicines; and 15% for medicines with mild clinical benefit assessment; 0% for insufficient value.	Adults: POM and for few OTC with specific indications: fully reimbursed (100%) except general co-payment. Children <12 years POM and OTC are fully reimbursed. Children < 18 years POM, and OTC for few indications are fully reimbursed (100%).	There are 5 reimbursement categories (reimbursement rate): Non-reimbursable drugs (0%); General or fixed reimbursement valid for any prescription medicine and indication (25, 55, and 80%); Indication-based reimbursement medicines (50, 70, and 90,100%); reimbursement based on social needs: NHIFA provides a maximum budget for chronic illnesses and acute illness/month to avoid abuse of the system.

Table 20. Reimbursement characteristics of European countries (III)

CHARACTERISTICS	ICELAND	ITALY	IRELAND	LATVIA	LITHUANIA
Method of payment	The patient pays part of the medicines and the remainder is reimbursed by the state outpatient health plan.	The Sistema Sanitario Nazionale (SSN) pays thecost of drugs.	The Health Service Executive Primary Care Reimbursement pays totally or partially the cost of the drugs under the Drug Payment Scheme.	The Nqtional Health Service through their regional branches pays partially the costs of drugs.	The Lithuanian Compulsory Health Insurance Fund.
The beneficiaries	Residents in Iceland.	All Italian citizens.	Residents in Ireland.	All Latvian residents.	Lithuanian residents.
Categories of reimbursable drugs	Positive list. Medicines are generally reimbursed for up to a 3-month or 100 day-supply at each dispensing for which the patient pays the price up to a fixed maximum amount. Reimbursement is based on clinical and economical value of the drug to its comparator together with the forecasted budget impact.	Positive list of potential reimbursable drugs. Class A drugs: essential drugs, drugs for chronic diseases, expensive drugs explicitly prescribed by the GP as part of a therapeutic plan initialized at the hospital; class H which are hospital-only-medicines and class C which correspond to OTC medicines.	Depending on income and other eligibility criteria, Irish fall into two categories: Category I: People who under the "Medical Card Scheme" with free medicines. Category II: people charged the monthly threshold amount of a medicine.	Positive reimbursable list of medicines with 3 sub-lists included in the general reimbursable scheme: List A: reference product list with interchangeable drugs; list B: non-interchangeable drugs; list C: expensive drugs with special reimbursement conditions. There is an additional individual reimbursement scheme upon patient status and medicines indication for use.	Only prescription-only medicines registered in Lithuania or the EU according to a positive list can be reimbursed by the NHIF on the basis of individual prescriptions.

CHARACTERISTICS	ICELAND	ITALY	IRELAND	LATVIA	LITHUANIA
Structure of reimbursement to the patient (patient co-payment)	The level of co-payment depends on the 12-month pharmaceutical expenditure for the individual, which starts with the first drug purchased. Step 1: ≤ISK24,045:100% co-payment. Step2 ISK10,883: 15% co-payment. Step 3: ISK34,507: 7.5% co-payment. Total: ISK69,415. Above that amount the patient's co-payment is ISK0.	Class A drugs are fully reimbursed and patient does not pay. Class C are not reimbursed in the outpatient sector except for war veterans (100% co-payment). Medicines in the inpatient sector (A/H) are fully reimbursed. Regional variations in the reimbursement scheme.	There are 4 schemes: General Medical Services Scheme: the patient have to pay €2.50 per item prescription (up to a maximum charge of €25 per family/ month).Drug Payment Scheme: the patient pays a maximum of €144/month for approved medicines. Long Term Illness Scheme (LTI): free of charge for specific conditions. Hi-Tech Scheme: free of charge. Medicines are generally initiated or only prescribed in hospital.	For most severe diagnoses patients do not pay for the medicines. Otherwise, there are 4 different levels of co-payment: 0%, 25%, 50%, and 100%. In addition, generic substitution is compulsory: if a patient refuses, it is added 10%.	Free of payment: children ≤18 years, disabled and/or elderly people with a large need for specific care. Partially payment (90%, 80% and 50%) for specific diseases. 50% payment for pensioners and the disabled unless they fall into any of the prior categories. The rest of insured adults must pay the full cost of prescribed and OTC drugs. When the pharmaceutical price is higher than the reference price, the patient pays the difference.
Reimbursement level for drugs	From 4May2013, contributions to drugs are G-mark or 0-labeled. Exception for medicines with 100% coverage in palliative care at home, end stage of renal disease or severe psychotic illness.	Class A 100% reimbursed by SSN, class H 100% reimbursed and class C 0% reimbursement rate	No reimbursable levels.	Medicines are reimbursed 100%, 75%, 50%, and 0% either in the general or individual reimbursement scheme.	Full reimbursement of the reference price (for children 18 years or younger, the disabled and/or elderly people with a large need for specific care). Full or partial (90%, 80% or 50% of cost) reimbursement for patients diagnosed with specific diseases. 50% reimbursement for pensioners and the disabled unless they fall into any of the prior categories.

Table 21. Reimbursement characteristics of European countries (IV).

CHARACTERISTICS	NETHERLANDS	NORWAY	POLAND	PORTUGAL	SPAIN
Method of payment	Reimbursement of healthcare services is a patient's choice between in-kind (the patient pays the deductible to the health insurer and the health insurer directly reimburses the providers) or restitution (the patient pays the bill directly to the provider; the health insurer reimburses the patient, after deducting the out-of-pocket payment).	The National Insurance Scheme(NIS) pays fully or partially the costs of drugs.	The National Health Insurance Fund (NFZ) partially pays the medicines direct to the pharmacist.	There are 3 coexisting health systems in Portugal (public and private). In all of them patient partially pays the medicines and the rest is paid directly to the pharmacy by the health system.	The National Health System (SNS) partially pays reimbursed medicines. Patients pay the rest.
The beneficiaries	All Dutch residents and those with a Dutch employer.	All Norwegian residents.	All Polish residents.	All Portuguese residents.	All Spanish residents.
Categories of reimbursable drugs	Positive list of reimbursement. Reimbursement of medicines is based on a reference pricing system: the Medicines Reimbursement System (GVS) that categorizes pharmaceuticals into groups of treatment equivalents.	Several positive lists of reimbursable drugs. General, individual reimbursement (specific patient application for medicines not included in the general list or for other indications), and reimbursement scheme for medicines used to treat serious infectious diseases. There is a negative list.	Positive reimbursable list of drugs. Free of charge: proven effectiveness in cancer treatments, some psychiatric conditions, and severe infections. Other reimbursement categories established according to the length of treatment (fixed at 30 days), and a basic list of drugs reimbursable.	Positive list of reimbursable drugs. General scheme, with 4 categories according to the therapeutic value of the drug. Specific scheme for specific groups or diseases. Compound medicines are listed, annually updated, and have a specific level of reimbursement.	Based on negative lists that exclude pharmaceuticals with low treatment value or not proved to have adequate increased cost-effectiveness. Reimbursement of medicines depends upon the age and income of the patient. Special reimbursement category for people with specific treatments.
Structure of reimbursement to the patient (patient co-payment)	If the price of a medicine is above the level of the reference price, the patient pays the difference between the reimbursement price and the pharmacy retail price.	Patient co-payment is always 38% of the medicines price, up to a ceiling above which the NIS reimburses 90% of further expenditures. This ceiling includes all healthcare out-of-pocket expenditure. If patient	Patient co-payment: 0% for drugs free of charge; flat fee/package prescribed for drugs on the basic drug list and for drugs requiring 30-50% co-payment when treatment lasts longer	There are no flat fee charges for prescriptions in Portugal. General scheme: medicines categories (co-payment rate): A (10%), B (31%); C (67%); D (95%). Specific scheme:	*Retired people* pay 10% of the medicines price with a monthly maximum depending on annual income :>€100,000, co-payment is

CHARACTERISTICS	NETHERLANDS	NORWAY	POLAND	PORTUGAL	SPAIN
	Since 2009, benzodiazepines are not reimbursed anymore.	refuses generic substitution, there is additional co-payment	than 30 days and the monthly cost of treatment exceeds 5% or30% of the minimum wage. If treatment lasts less than 30 days,co-payment is of 50%. Other cases co-payment is up to 70%.	pensioners can get an extra percentage reduction of 5% for A drugs and 15% for B, C, and D drugs. Compound drugs 50% co-payment. Pensioners with a maximum annual income and patients chronically ill have a reduced rate of co-payment or are exempt from the cost of some courses of medication	60%;<€18,000 (max per month €8), between ≥€18,000-<€100,000 (max per month €18), ≥€100,000 (max per month €60). *Employees and beneficiaries*co-payment rate based on their annual income:<€18,000 40%; >€18,000-<€100,000 50%; >€100,000 60%. Exemptions: toxic syndrome and other disabilities, on social cash aid, retired with non-contributory pensions, unemployed not receiving any social aid, work derived diseases or injuries. For specific treatments, co-payment of 10% with a maximum of €4.13/package. There are regional variations.
Reimbursement level for drugs	Drugs *fully* reimbursed: unique medicines, proven clinical benefit and high cost-effectiveness; *limited*, for therapeutically interchangeable medicines; and *optionally*, reimbursed for specific indications for use. Most OTC is not reimbursed.	There are 4 reimbursement levels (reimbursement rate): *schedule2* (62%): specified diagnoses and for long-term treatment (LTT);*schedule 3a* (62%): after approval of an individual application and only for LTT. Medicines not in schedule 2, 3b, 4. *Schedule 3b*: rare diseases (62%). *Schedule 4:* serious contagious diseases (100%).	There are 4 reimbursement categories (reimbursement rate): 100%, 50%, 30%, and between 30 & 50%.	4 levels of reimbursement for the general scheme:A (90%), B (69%), C (37%), D (5%). 5-15% extra reimbursement for pensioners. Some disease specific reimbursement is 100%. For compound drugs, reimbursement is 50% of their price.	4 main levels: For employed and their beneficiaries reimbursement rate is between 40 to 60%. For pensioners between a 40-90% is reimbursed The reimbursement rates depend on annual income. For specific treatments, reimbursement is 90%.

Table 22. Reimbursement characteristics of European countries (V)

CHARACTERISTICS	SLOVENIA	SWEDEN	UNITED KINGDOM
Method of payment	The Health Insurance Institute pays medicines according with reimbursement scheme. Patients pay the rest.	The county councils partially pay the medicines direct to the pharmacists.	The National Health System pays the cost of medicines.
The beneficiaries	All Slovenian residents. There are no differences between different social groups of the Slovene society.	All Swedish residents. All children <18 years in a family unit are considered a single patient and the costs pooled together.	All residents in the UK.
Categories of reimbursable drugs	Limitations in terms of coverage by compulsory health insurance for expenditure on medicines are regulated by means of a positive list.	Positive list of reimbursable drugs with 3 exceptions: antismoking medicines, herbal remedies and certain medicines for external application are excluded. Medicines are granted a general reimbursement or a conditional reimbursement, according to specific indication for use or for specific group of patients. It is the doctor's obligation to make sure that the patient fulfils the conditions for reimbursement.	Medicines in the UK are fully reimbursed, except OTC medicines.
Structure of reimbursement to the patient (patient co-payment)	Free of co-payment: Children under 18 years, students, pregnancy and motherhood who take medicine from positive list. Specific diseases (most important contagious including AIDS and STDs, diabetes mellitus, major psychiatric diseases, epilepsy, muscular dystrophy, multiple sclerosis and psoriasis. 75% of payment: other people not specified in the above groups. If the price of drug is higher than the reference price, the difference will have to be paid by the patient.	Patients pay the full cost for prescribed and reimbursed medicines up to a ceiling. Thereafter the co-payment is progressively reduced according to his/her pharmaceutical expenditure. 50%, 25%, and 10%. The patient will pay for prescribed drugs a maximum of €244 annually.	The patient pays a flat fee per prescription. There is the possibility to buy a prescription pre-payment certificate for 3 or 12 months to get a discount on the fee per prescription. Exemptions to the flat-fee per prescription: m*edicines free of charge:* Prescribed contraceptives, medication personally administered by a GP, medication supplied at a hospital or Primary Care Trust for Sexually Transmitted Infections or Tuberculosis. *People aged ≥60 years, ≤16 years, or between 16-18 years and in full-time education*. *Conditions that grant a Maternity Exemption Certificate or a Medical Exemption Certificate*. People with a *valid war pensions exemption certificate* and the prescription is for the accepted disability. People entitled to an *NHS tax credit exemption certificate, or a valid HC2 certificate or if you receive income support*.

CHARACTERISTICS	SLOVENIA	SWEDEN	UNITED KINGDOM
Reimbursement level for drugs	Positive list: 75%-100% reimbursable of the price of the medicine. Intermediate list: 25% reimbursable of the medicine. There is also a negative pharmaceutical list, with products completely excluded from any kind of public reimbursement scheme.	There are 5 levels of reimbursement: 0% up to a ceiling; above the ceiling the reimbursement is 50%, 75%, and 90% depending on patient's pharmaceutical expenditure. 100% reimbursement above a pharmaceutical expenditure of €244. Several OTC medicines may also be reimbursed. For prescription drugs not reimbursed and OTC drugs, patients pay full price.	No reimbursable levels.

5 DISCUSSION

The PROTECT inventory provides a resource for collecting drug consumption data and, additionally, for planning DU studies, primarily in the field of patterns of drug use in Europe. Information is offered not only from a national perspective but also from the collaborative views of groups working in DU researchat an international level. The ultimate objective is to strengthenthe monitoring the impact of a drug on pubic health. The inventory fulfils the objective of compiling drug consumption data and determining the validity of this data within the PROTECT project.

Twenty-one European research WGs and thirty-one nationwide drug consumption databases were identified. Several countries collect inpatient sales from wholesalers.However,we did not identify administrative databases monitoring inpatient medicines utilisation, except for Belgium. We described the main characteristics and accessibility of the WGs and the nationwide administrative databases. The majority of the databases provide information on the outpatient sector. Additionally, a questionnaire was sent gathering information on key items which influence the interpretation of astudy results. We briefly described the characteristics of the MIDAS database.

The discussion will be subdivided according to out- and inpatient DU resources and the validity of drug consumption data.

5.3 OUTPATIENT DRUG UTILISATION RESOURCES

Interest in compiling such information and knowledge in Europe has evolved in the last 15-20 years. The first attempt was the EuroMedicines Project in 1998. It established a drug directory containing details on the ATC codes, trade names, licencing year of a drug, and reimbursement status in 14 EU countries and candidate countries at that time. This project highlighted the difficulty in finding out the information required to create such a directory (70,71). EUROMEDSTAT (2002 – 2007) was the second attempt, and it followed the EuroMedicines Project (71). The initial EuroMedicines Project was then extended and the result was a European database of licensed medicines and their prices in 20 EU countries. Also, it proposed indicators for price and DU (72,72). Moreover, the database provided statistics on DU across these countries. It showed the differences in the availability of data on drug use across the different countries, and the methodological difficulties encountered when comparing data across countries, over time and between commercial and non-commercial providers (35,36,73,74).

The CNC project in 2000, a EuroDURG-ISPE collaboration, took a step forward, offering a wide range of sources of drug consumption data, from clinical to administrative national databases. They collected information from around the world on DU data, specifically for antibacterials, proton pumb inhibitors, statins and clopidrogel (36). However, these sources of data were not described in a comprehensive manner.The information was based on voluntary individual contacts in each country. Information is available in the EuroDURG website.

EnCePP was established to strengthen the post-authorisation monitoring of medicines. Its website contains a"Resources database" that consists of two indices, one of which is the registry of European data sources. Thus, EnCePP indirectly has become a source of drug consumption data providers. An advantage of this initiative is that the EnCePP website is open to the general public. The disadvantage is that updates and registries are mantained on a voluntary basis. It depends on the individual participating research centres or organisations (75).

The inventory on nationwide drug consumption databases not only contributes towards the main objective of the PROTECT project, but is also the framework for DU research in Europe. The differences from previous European initiatives are firstly, the type of information and the way it is presented. Information on nationwide drug consumption databases has been retrieved from the perspective of a researcher. It offers an overview of the possibilities of working with aggregated and individual level drug consumption data. Secondly, a contact name and updated websites addresses are provided for those investigators requiring further information, promoting the accessibility to these databases.Thirdly, we have collected information on international WGs which directly or indirectly gather information on medicines utilisation at a national level. This offers the opportunity of being aware of ongoing research projects that interest the European research community. Fourthly,the content ofthe PROTECT inventory should promote a correct interpretation of the results of studies of patterns of drug use across different European countries or over time. Fifthly, it provides additional information related to DU research. Finally, all this information is publicly available on the IMI website which will help save time for researchers interested in the subject.

All the previous European projects mentioned earlier provided us with valuable information, making the work done within the PROTECT inventory easier and, making ita comprehensive resource for DU studies in Europe.

The PROTECT inventory could be regarded as a basis for future collaboration in DU at an academic level, but also for regulatory agencies and pharmaceutical companies. For the latter, it offers the possibility of supporting post-marketing and safety studies. For academic researchers,this report may be the basis for future collaboration in DU or pharmacoepidemiological studies.

We really value the information provided on the accessibility to DU data. The Nordic countries and The Netherlands with their long tradition in DU research have information at an aggregated level readily available online. Further information at an individual level can be applied for. In general, most of the sources of drug consumption data can be requested from the data provider.

Specific research groups provide information on the European networks working on DU in a particular disease or group of medicines. It is also a good starting point for those researchers and/or clinicians interested in working in a collaborative manner on one of these projects. The information provided for the general and specific research groups tries to be comprehensive and to give an exact idea of what, within DU, the European scientific community is interested in.

To the best of our knowledge, such a compilation is unique in Europe. All the work done may become almost meaningless, unless the inventory is keptupdated. To channel these efforts into the right direction, funding is a must.

One of the limitations of this inventory is that despite a comprehensive search through PubMed, Google scholar and other literature review resources, we limited ourselves to the disease areas and medicines of interest for the PROTECT project goals, excludingsome European DU working groups. However, groups with a general interest in DU have all been included.Although drug consumption information is not available for the whole Europe, we have compiled information for all those countries with the biggest population.The intention with every yearlyupdate is to add information from more European countries. In addition, we provide a list of the EuroDURG contacts. A third limitation is the focus on outpatient medicines consumption of these national databases. This is coherent with the fact that outpatient pharmaceutical expenditure represents roughly 80-85% of the total pharmaceutical expenditure and that most of the policies tackling pharmaceutical costs are directed to the outpatient sector.

5.4 INPATIENT DRUG UTILISATION RESOURCES

Information on DU in inpatient settings, understood as dispensation of drugs to patients admitted in hospitals, is sparse at a national level. The majority of inpatient drug consumption databases refer to sales from wholesalers. The same applies to published articles.There is a scarcity of articles providing inpatient drug consumption data ata national level. Most of the research is set up in one hospital or in several hospitals within one country. In addition, very few articles expressed consumption of inpatient medicines in DDDs (76).

Most European countries maintain databases that collect information of prescribed drugs dispensed by community pharmacies, with a straight flow of information from the community setting to the corresponding regional or national authority. These regional health authorities are the ones in charge of centrally storing the data and elaborating more detailed drug consumption reports in the outpatient setting.Some European countries collect inpatient information directly from wholesalers. In other countries, such as UK, the provider of inpatient pharmaceutical consumption at a national level is IMS Health. To our knowledge, only the ESAC group launched in 2007 a study subgroup in charge of, among other goals, collecting information on inpatient antibiotic use in a standardized way across different European countries. Point-prevalence surveys have been organised for one hospital in each participating country (http://www.esac.ua.ac.be/main.aspx?c=*ESAC2&n=50297 , last accessed on 11/2013).

5.5 VALIDITY OF DATA

National drug consumption databases were originally created to get a refund. Measuring validity of these secondary data sources, would formally require comparing the results obtained in drug consumption for each of these databases with a primary source of drug consumption, for example, the results obtained in a survey

interviewing a sample of patients about their drug consumption, or comparing drug consumption data from the databases with electronic medical records (13). There is no consensus on which is the best gold standard for these comparisons (18). The validity of some European automated databases registering drug consumption has already been established for the ERASME database in France (59) and community pharmaceutical databases in The Netherlands (17).However, this way of determining the validity of the drug consumption data is beyond the scope of the PROTECT project. Instead, as stated earlier, we have provided information for several items considered to determine the validity of the drug exposure, something that has already been done with Medicaid in the United States (77). Other authors recommend other strategies to estimate the validity of drug exposure data, such as conducting descriptive analyses for several variables collected by the databases to identify the limitations of this data (78,79). If a primary source of data is not available for making comparisons, then the data quality can be assessed through the degree of matching different datasets (80).

In order to know such value in the national drug consumption databases, a list of key items deemed of importance in interpreting the results of a study on patterns of drug use, was developed, and transformed into a questionnaire.We are aware that the questionnaire was not piloted which may explain why some of the questions were left unanswered by some of the participants. Nor did we cover all possible items, such as prescriber information, or problem or encounter-based information (comorbidities, severity of illness, other medications prescribed, diagnostic tests, hospital admission and discharge, and other sociodemographic and economic factors that might be of interest to study other factors that influence the patterns of drug use), which is relevant when studying drug exposure. However, the fact, that it also had open questions, allowed for gathering such information.

Nationwide drug consumption databases record sold, dispensed, prescribed or reimbursed medicines. Prevalence, incidence and duration of a treatment can best be assessed from databases that provide dispensed pharmacy information if dispensing is linked to patient level (81). The Danish Registry of Medicinal Products, the OsMed database and SFK database in Denmark, Italy and The Netherlands, respectively, provide dispensed medicines. Reimbursed databasesmay introduce an underestimation of drug exposure. They only collect information on drugs reimbursed, leaving out drugs that may need to be prescribed, but are not reimbursed, e.g. oral contraceptives in some countries (44). Reimbursed databases do not cover OTC drugs either, and this may be of importance when studying NSAIDs. Underascertainment of drug exposure has been established to be important for antibiotics in countries like Spain and Italy (82,83) where, although not legal, approximately 10% of antibiotics are sold as over the counter drugs. Sales of medicines from wholesalers may overestimate drug exposure of a population as they include pharmacy stocks and parallel trade in their databases.

Prescription databases are in-between dispensed and reimbursed databases. Prescription registries lack information on OTC drugs, underestimating the use of some groups of drugs.

Most of the European governments issue positive restrictive lists with the medicines reimbursed. Economical arguments, possibly more than health outcomes, lay behind reimbursement decisions (5). These aspects are of special importance when studyingtrends in drug consumption over time or across countries. Reimbursement decisions change over time and are not homogeneous across countries. Drugs currently being reimbursed and captured by the database, in several years time, may not be reimbursed,and the information lost.

In any case, all these national drug consumption databases may not reflect real-life use of a drug, as they do not register compliance. Only the Danish Prescription Register can to some extend, estimate secondary compliance for those prescriptions issued electronically that are not dispensed at the pharmacy. However, uncollected prescriptions from the pharmacy may be negligible when estimating drug exposure (84).

Population coverage is another item of importance, specially when studying ADEs. In post-marketing studies of safety, there is a need to know the proportion of population exposed to the drug of interest. These administrative databases provide an approximation of the population exposed to a drug, which is the denominator needed to determine the incidence of an adverse drug reaction of interest. For those databases with a population coverage below 90% and following the checklist provided by ESAC group (39), we asked for the weighting methodology. SFK did not provide such information, but GIP databank extrapolated their drug consumption data through 20 age subgroups and by gender.

Another advantage of these databases is that they collect the date the drug was dispensed. This avoids recall bias, present in studies where the information on drugs taken by a patient is retrieved through a questionnaire or interview.

ATC codification is recommended by the WHO (19). A single system of codification eases the comparison of the consumption of medicines across countries. The DDD is also recommended by the WHO as a measure to compare drug statistics. It is considered a standard unit for quantifying drug use and it represents the assumed average maintenance dose of a drug for its main indication for use in adults (19). The ATC/DDD methodology has been adopted for all databases. All retrospective data collected by these databases was updated yearly with the release of the ATC/DDD WHO guidelines in October. Several studies have pointed to the ATC/DDD methodology as a source of bias in DU comparisons, either because the databases used different versions (33), or because DDDs change over time (35). All European databases code medicines according to the ATC and use of medicines is measured in DDDs. Even the ePACT database in the United Kingdom which uses the British National Formulary and Average Daily Quantities (85) for measuring drug consumption, provides upon request DDD and a table of the equivalences between BNF and ATC codification.

Another problem when measuring drug consumption and linked to the ATC/DDD methodology is when a drug does not have an ATC code or aDDD is not assigned. Each country adopts different approaches and this information is not easily available.

The validity of a study conducted with these databases will also depend on the ascertainment of those variables considered potential confounders. Because the original purpose of these databases was merely administrative, this is their weakest side. Readily available are age, gender and place of residence. Upon request, other information gathered by the database may be obtained. However, the potential of some of these databases, specially in the Nordic countries, to link with other registries grant the possibility to ascertain counfounding variables and other health care information relevant for the study (48,86). Unfortunately, information on important behavioural aspects, such as smoking, is still missing.

Drug exposure expressed in DID allows for multiple descriptive studies, such as the comparison of a drug consumption across different countries and over time. It also allows for the evaluation of the effect of policy measures on drug consumption (20).However, when the purpose of the study is to analyse the association between a drug and an adverse event, the aggregated nature of the data often leads to ecological bias (87). Furthermore, most of these secondary data sources do not collect enough information on variables that may confound the association, misestimating the risk of an ADEs.

These databases may also be useful in the context of post-marketing surveillance.DU studies can describe the characteristics of those patients starting a new treatment, and they detect the misuse of medicines affecting patient's safety. One can evaluate the impact of risk minimising measures as well as interpreting spontaneous reports of adverse drug reactions (88).Finally, the proportion of population exposed to a drug can be used to calculate the population attributable fraction for an adverse event of interest, a relevant public health measure (11).

Prevalence of drug exposure is best estimated from individual data and some authors do not recommend the use of DID (89). The usefulness of the DID will depend on the differences between the DDD and the prescribed daily dose (PDD), the indication for use of the medicine under study and whether the medicine is used continuosly. Hence, for those drugs with only one indication and with a DDD that matches the PDD, and used chronically the DID will most accurately reflect the population exposed (6).

6 CONCLUSIONS

- Developing an inventory for the PROTECT project has been a daunting and time-consuming task.

- There is, however,a lot of interest in Europe in drug utilisation research as shown by the wide range of European groups working doing research in this field.

- It has been possible to collect information with some detail on the characteristics of nationwide administrative drug consumption databases.

- Information on most of the factors which influence interpretation of the results when using drug consumption databases were obtained through a questionnaire. This information allows for the comparison of drug consumption across countries and over time.

- However, little published information is available on inpatient drug consumption at a national level. Most of the studies are set in a single hospital or several hospitals within one country.

7 APPENDICES

APPENDIX 7.1ATC CODES OF DRUGS OF INTEREST FOR THE PROTECT PROJECT

C08 **Calcium channel blockers**

ATC code	Name
C08CA01	amlodipine
C08CA02	felodipine
C08CA03	isradipine
C08CA04	nicardipine
C08CA05	nifedipine
C08CA06	nimodipine
C08CA07	nisoldipine
C08CA08	nitrendipine
C08CA09	lacidipine
C08CA10	nilvadipine
C08CA11	manidipine
C08CA12	barnidipine
C08CA13	lercanidipine
C08CA14	cilnidipine
C08CA15	benidipine
C08CA16	Clevidipine
C08CA55	nifedipine, combinations
C08CX01	mibefradil
C08DA01	verapamil
C08DA02	gallopamil
C08DA51	verapamil, combinations
C08DB01	diltiazem
C08EA01	fendiline
C08EA02	bepridil
C08EX01	lidoflazine
C08EX02	perhexiline
C08GA01	nifedipine and diuretics

J01FAMacrolides

ATC code	Name
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

J01CR02Amoxicillin and enzyme inhibitor

N03AAntiepileptics

ATC code	Name
N03AA01	methylphenobarbital
N03AA02	phenobarbital
N03AA03	primidone
N03AA04	barbexaclone
N03AA30	metharbital
N03AB01	ethotoin
N03AB02	phenytoin
N03AB03	amino(diphenylhydantoin) valeric acid
N03AB04	mephenytoin
N03AB05	fosphenytoin
N03AB52	phenytoin, combinations
N03AB54	mephenytoin, combinations
N03AC01	paramethadione
N03AC02	trimethadione
N03AC03	ethadione
N03AD01	ethosuximide
N03AD02	phensuximide
N03AD03	mesuximide
N03AD51	ethosuximide, combinations
N03AE01	clonazepam
N03AF01	carbamazepine
N03AF02	oxcarbazepine
N03AF03	rufinamide
N03AF04	eslicarbazepine
N03AG01	valproic acid
N03AG02	valpromide
N03AG03	aminobutyric acid
N03AG04	vigabatrin
N03AG05	progabide
N03AG06	tiagabine
N03AX03	sultiame
N03AX07	phenacemide
N03AX09	lamotrigine
N03AX10	felbamate
N03AX11	topiramate
N03AX12	gabapentin
N03AX13	pheneturide
N03AX14	levetiracetam
N03AX15	zonisamide
N03AX16	pregabalin
N03AX17	stiripentol
N03AX18	lacosamide
N03AX19	carisbamate
N03AX21	Retigabine
N03AX22	Perampanel
N03AX30	beclamide

N05BABenzodiazepine derivatives(anxiolytics)

ATC code	Name
N05BA01	diazepam
N05BA02	chlordiazepoxide
N05BA03	medazepam
N05BA04	oxazepam
N05BA05	potassium clorazepate
N05BA06	lorazepam
N05BA07	adinazolam
N05BA08	bromazepam
N05BA09	clobazam
N05BA10	ketazolam
N05BA11	prazepam
N05BA12	alprazolam
N05BA13	halazepam
N05BA14	pinazepam
N05BA15	camazepam
N05BA16	nordazepam
N05BA17	fludiazepam
N05BA18	ethyl loflazepate
N05BA19	etizolam
N05BA21	clotiazepam
N05BA22	cloxazolam
N05BA23	tofisopam
N05BA56	lorazepam, combinations

N05CDBenzodiazepine derivatives(hypnotics and sedatives)

ATC code	Name
N05CD01	flurazepam
N05CD02	nitrazepam
N05CD03	flunitrazepam
N05CD04	estazolam
N05CD05	triazolam
N05CD06	lormetazepam
N05CD07	temazepam
N05CD08	midazolam
N05CD09	brotizolam
N05CD10	quazepam
N05CD11	loprazolam
N05CD12	doxefazepam
N05CD13	cinolazepam

N05CF Benzodiazepine relateddrugs

ATC code	Name
N05CF01	Zoplicone
N05CF02	Zolpidem
N05CF03	Zaleplon
N05CF04	Eszoplicone

N06AA Non-selective monoamine reuptake inhibitors

ATC code	Name
N06AA01	desipramine
N06AA02	imipramine
N06AA03	imipramine oxide
N06AA04	clomipramine
N06AA05	opipramol
N06AA06	trimipramine
N06AA07	lofepramine
N06AA08	dibenzepin
N06AA09	amitriptyline
N06AA10	nortriptyline
N06AA11	protriptyline
N06AA12	doxepin
N06AA13	iprindole
N06AA14	melitracen
N06AA15	butriptyline
N06AA16	dosulepin
N06AA17	amoxapine
N06AA18	dimetacrine
N06AA19	amineptine
N06AA21	maprotiline
N06AA23	quinupramine

N06AB Selective serotonin reuptake inhibitors

ATC code	Name
N06AB02	zimeldine
N06AB03	fluoxetine
N06AB04	citalopram
N06AB05	paroxetine
N06AB06	sertraline
N06AB07	alaproclate
N06AB08	fluvoxamine
N06AB09	etoperidone
N06AB10	escitalopram

N06AF Monoamine oxidase inhibitors , non-selective

ATC code	Name
N06AF01	Isocarboxazid
N06AF02	Nialamide
N06AF03	Phenelzine
N06AF04	Tranylcypromine
N06AF05	Iproniazide
N06AF06	Iproclozide

N06AG Monoamine oxidase A inhibitors

ATC code	Name
N06AG02	moclobemide
N06AG03	toloxatone

N06AX Other antidepressants

ATC code	Name
N06AX01	oxitriptan
N06AX02	tryptophan
N06AX03	mianserin
N06AX04	nomifensine
N06AX05	trazodone
N06AX06	nefazodone
N06AX07	minaprine
N06AX08	bifemelane
N06AX09	viloxazine
N06AX10	oxaflozane
N06AX11	Mirtazapine
N06AX12	bupropion
N06AX13	medifoxamine
N06AX14	tianeptine
N06AX15	pivagabine
N06AX16	venlafaxine
N06AX17	milnacipran
N06AX18	reboxetine
N06AX19	gepirone
N06AX21	duloxetine
N06AX22	agomelatine
N06AX23	desvenlafaxine
N06AX24	Vilazodone
N06AX25	Hyperici herba

N06CA Antidepressants in combination with psycholeptics

ATC code	Name
N06CA01	amitriptyline and psycholeptics
N06CA02	melitracen and psycholeptics

R03AC Selective beta-2-adrenoreceptor agonists

ATC code	Name
R03AC02	salbutamol
R03AC03	terbutaline
R03AC04	fenoterol
R03AC05	rimiterol
R03AC06	hexoprenaline
R03AC07	isoetarine
R03AC08	pirbuterol
R03AC09	tretoquinol
R03AC10	carbuterol
R03AC11	tulobuterol
R03AC12	salmeterol
R03AC13	formoterol
R03AC14	clenbuterol
R03AC15	reproterol
R03AC16	procaterol
R03AC17	bitolterol
R03AC18	indacaterol

R03AK Adrenergics and other drugs for obstructive airway diseases

ATC code	Name
R03AK01	epinephrine and other drugs for obstructive airway diseases
R03AK02	isoprenaline and other drugs for obstructive airway diseases
R03AK03	fenoterol and other drugs for obstructive airway diseases
R03AK04	salbutamol and other drugs for obstructive airway diseases
R03AK05	reproterol and other drugs for obstructive airway diseases
R03AK06	salmeterol and other drugs for obstructive airway diseases
R03AK07	formoterol and other drugs for obstructive airway diseases

APPENDIX 7.2 KEY PAIRS ADVERSE DRUG EVENTS-DRUGS, SELECTED FOR THE PROTECT PROJECT

Table 23. Adverse drug events-drug pairs selected for the PROTECT project

Drugs	Adverse event
Macrolides and amoxicillin-clavulanic acid	Drug induced liver injury
Calcium channel blockers	Malignancies
Benzodiazepines	Hip fracture
Antidepressants	Hip fracture
Beta-2 adrenergics	Acute Myocardial Infarction
Antiepileptics	Suicide/Suicide attempt/Suicidal thoughts

APPENDIX 7.3EUROPEAN HEALTH CARE SYSTEMS

Table 24. Summary of the European health care systems

Country(total population)	Health care provider	Population coverage	Model of health care financing
Belgium 11,099,554 inhabitants (1/1/2013) http://statbel.fgov.be/fr/statistiques/chiffres/ (accessed on 11/2013)	Compulsory social insurance system. Population can opt to a voluntary health insurance, either from the public sickness funds or from private-profit making companies.	Universal access.	Compulsory system of health insurance which main sources of funding are the social security contributions depending upon a person's income (66%) and the subsidies from the federal government (10%). Other: indirect tax revenues (14%), allocated and diverse receipts (10%)..
Bulgaria 7,284,552 inhabitants (31/12/2012) http://www.nsi.bg/indexen.php (accessed on11/2013)	Social insurance system.	77% In early 2011, 23% did not pay their contributions to the National Health Insurance Fund, thus not covered.	Mixed public-private: compulsory statutory health insurance contributions, taxes, out-of-pocket payments, voluntary Health Insurance premiums, corporate payments, donations and external funding.
Croatia 4,267,558 inhabitants (mid-2012) http://www.dzs.hr/default_e.htm(accessed on 11/2013)	Compulsory public Health Insurance Fund (Croatian Institute for Health Insurance).	Universal access.	Mixed system of finanacing: health insurance contributions, co-payments, voluntary complementary health insurance, privately provided supplementary health insurance, the state budget and local self-administration county units' budgets.
Czech Republic 10,514,714inhabitants (March 2013) http://www.czso.cz/eng/redakce.nsf/i/population (accessed on11/2013)	It is provided on the basis of Statutory Health Insurance which is provided by 9 Health Insurance Funds.	100%.	Mixed public-private budget. The public health insurance system covers 76.6% of the total, state and territorial budgets cover 7.2% and the private expenditure is around 16.2%.
Denmark 5,599,741 (March2013) http://www.dst.dk (accessed on 11/2013)	Universal compulsory system. No possibility of opting out of the system.Around 20% of Danish population have purchased additional voluntary health insurance from non-for-profit organisations	100% Non-residents are entitled acute treatment.	Income taxes and block grants from the state finance municipalities. Regions are financed by the state through income taxes, VAT, other taxes and by the municipalities.
Estonia 1,286,479 inhabitants (1/1/2013) http://pub.stat.ee/px-web.2001/Dialog/varval.asp?ma=PO021&ti=POPULATION+BY+SEX+AND+AGE+GROUP%2C+1+JANUARY&path=../I_Databas/Population/01Population_indicators_and_composition/04Population_figure_and_composition/&lang=1 (accessed on 11/2013)	The National Health Service supervised by the Ministry of Social Affairs	Universal access.	It is mainly publicly funded through a general tax system. Social Health Insurance (SHI) contributions in the form of earmarked social payroll tax, which amounts to over 60% of total funding. Health Insured system operated through the Central Sickness Fund and 22 regional sickness funds. The Ministry of Social Affairs and its agencies are responsible for the financing and management of public health

Country(total population)	Health care provider	Population coverage	Model of health care financing
			services.In the last years private sources of health financing are rising mainly by out-of-pcket payments.
Finland 5,426,674inhabitants (end 2012) http://www.stat.fi/tup/suoluk/suoluk_vaesto_en.html (accessed on 11/2013)	Public. Universal access to health care. Three health care systems: municipal(35%), private (15%) and occupational (45%)	Municipal care covers all permanent residents. Asylum seekers, illegal immigrants, tourists, temporary students and workers for non-EEU countries are not covered by municipality health care, except for emergency care.	Municipal financing based on taxes (raised from municipal taxes, state subsidies and user-fees) and NHI based on compulsory insurance fees (sickness and income insurance). **Private health care system:** There are voluntary health insurance (not very common).Statutory motor accident and occupational accident, both compulsory
France 65,585,857 inhabitants (01/2013) http://www.insee.fr/fr/themes/detail.asp?reg_id=0&ref_id=bilan-demo&page=donnees-detaillees/bilan-demo/pop_age2b.htm (accessed on 11/2013)	Public through Statutory Health Insurance System. Universal access to health care services.	Statutory health insurance provided by mutual associations which cover 99.9%of the French residents. People with low income (minimum income of 9020 €/year in 2008) and non-residents are covered by the state medical help.	Mixed public and private financing. The Statutory Health Insurance (SHI) is responsible of 73.8% of French healthcare expenditure; 5.2% is financed by the State; and 20.2% by private sources.Initially the SHI was financed by the employer and the employee payroll taxes and other national taxes; currently, anyone can opt in to the system and pay a contribution to the SHI. In addition, 88% of population has a private-for-profit complementary Voluntary Health Insurance (VHI).
Germany 80,523,700 inhabitants (31/12/2012) https://www.destatis.de/DE/ZahlenFakten/GesellschaftStaat/Bevoelkerung/Bevoelkerungsvorausberechnung/Bevoelkerungsvorausberechnung.html (accessed on 11/2013)	Public. Statutory Health insurance system., compulsory for all German citizens. Universal access to health care services.	The SHI covers around 85% of population, Private Health Insurance covers 10% of the population About 5% of population fall under special regimes.	Uniform wage-related contribution plus taxes.

Country(total population)	Health care provider	Population coverage	Model of health care financing
Hungary 9, 908, 798 inhabitants (1/1/2013) http://www.ksh.hu/ (accessed on 11/2013)	Public Statutory Health Insurance System Universal access for all residents in Hungary	96% of population covered by the National Health Insurance Fund Administration (NHFIA). 4% of the population unclear.	Compulsory contributions to the SHI and general and local tax revenues. 23.7% is finaned by out-of-pocket payments (including informal payments).
Iceland 321,857 inhabitants (2013) http://www.statice.is/Statistics/Population/Overview (accessed on 11/2013)	Public. It is coverered by the State. Private health insurance hardly exists.	Universal. All persons resident in Iceland for at least six months are entitled to health care.	The healthcare system is largely paid by taxes (85%) and to some extent by service fees (15%).
Ireland 4,593.100 inhabitants (2013) http://www.cso.ie/px/pxeirestat/Statire/SelectVarVal/Define.asp?maintable=PEA15&PLanguage=0 (accessed on 11/2013)	Public:managed by the Health and Safety Executive who are accountable to the Department of Health. Private: private health insurance or co-payment.	All persons resident in Ireland are entitled to receive health care through the public health care system.	Predominatly tax funded (78%). Although approximately 50% of the population had private health insurance and around two thirds may a co-payment towards public healhcare, Approximately one third has free access to public services.
Italy 59,704,067 (1/1/2013) http://demo.istat.it/bilmens2013gen/index.html(accessed on 11/2013)	Public. All residents have access to a essential level of care defined by the government and provided by the regions. Regions are at liberty of providing other health services to their residents, but must finance these with own-source revenues	100%. Around 15% of the population have private health insurance	National and regional taxes (77.9%) and by patient copayments (19.7%)
Latvia 2,023,825 (2013) http://www.csb.gov.lv/en/category/tagi/population (accessed on 11/2013)	Public social insurance system. Universal access to healthcare	100%	It is tax-funded social insurance system. Money from inome, consumption and the social insurance taxes is collected centrally and through the Social Insurance Organisation (SCHIA) is redistributed to several regional branches. Private VHI to cover state user charge services or services not covered by SCHIA.
Lithuania 2,971,905 inhabitants (1/01/2013) http://www.osp.stat.gov.lt/en/web/guest/statistiniu-rodikliu-analize?id=1353&status=A (accesssed on 11/2013)	Public, funded by the National Health Insurance Fund (NHIF) through a national health insurance scheme and based on compulsory participation.	Entire population	NHIF has been the main financing agent for the health system, accounting for 61% of the total expenditure on health in 2010. National budget (11%), out-of-pocket payments (27%) and private insurance (1%).
The Netherlands 16,779,575inhabitants (1/1/2013) http://statline.cbs.nl/StatWeb/publication/?DM	Private. All residents have to purchase a basic benefit package which might be complemented by	97% Population. It is calculated that in 2008 approx 1-% of Dutch	Government funds (14%) and percentage compulsory contributions of taxable income (66%).

Country(total population)	Health care provider	Population coverage	Model of health care financing
=SLNL&PA=03759ned&D1=0,3,6,9,12&D2=129-132&D3=0-4&D4=24-25&VW=T (accessed on 11/2013)	a voluntary supplementary health insurance. In addition to the standard benefit package, all citizens are covered by the statutory Exceptional Medical Expenses Act scheme for a wide range of chronic and mental health illnesses	population were not insured and that another 1.5% were defaulters (premium not paid for 6 months) Exemptions those who refuse on grounds of religious beliefs or their philosophy of life and the armed forces as health care is organised by the Ministry of Defence.	Out-of-pcket payments 10% and 4% private voluntary health insurance. It is a free market controlled by the government. Of the 4 largest health insurers, only 1 has become a for-profit
Norway 5,063,709 (April 2013) www.ssb.no (accessed on 11/2013)	Public. Universal access to health care. In 2006, 0.65% Norwegians covered by private health system	All inhabitants covered by the National Insurance System.	Predominantly tax based. Patient copayment of treatment by a GP or for specialist tx as outpatient, visit psychologist/psychiatrist, prescription of certain drugs and travel expenses. **Private health care:** Voluntary Health Insurance: barely plays any role. A small number of private health care centres are opening up in urban areas, services only available to members.
Poland 38,533,299 (31/12/2012) http://www.stat.gov.pl/gus/5840_655_ENG_HTML.htm (accessed on 11/2013)	Public social insurance system (NFZ)	98% .	State budget covering mainly vulnerable groups. Private financing in form of out-of-pocket payments reaching 30%. Compulsory health insurance contributions at a percentage rate of the employee income. Unclear the market share of the private health insurance
Portugal 10,487,289 (2012) www.ine.pt (accessed on 11/2013)	3 coexisting systems: universal national health system (SNS, serviço nacional saúde); special public and private insurance schemes known as health subsystems; and private voluntary health insurance (VHI). Universal access to health services	The SNS covers all residents in Portugal. The Health subsystems covers 25% of the Population; private VHI covers 10-20%. The majority of the population can choose between 3 health systems	The SNS is covered by general taxation; health subsystems –which for some professions are compulsory- are financed with employee/employer contributions. Out-of-pocket payments represent about 30% of the healthcare expenditure in Portugal
Slovenia 2,060,533 inhabitants (march 2013) http://www.stat.si/eng/interaktivno.asp (accessed on 11/2013)	Public, funded mainly by the Health Insurance Institute of Slovenia(HIIS) based in compulsory participation.	99% population.	HIIS major source of finanancing 61,7%. Other sources: general national and municipal taxation (5,2%), voluntary health insurance (27,8%) [data from 2006].

Country(total population)	Health care provider	Population coverage	Model of health care financing
Spain 46,704,314 inhabitants (1/1/2013) http://www.ine.es/welcoing.htm (accessed on1/2013)	Public health sector. Universal access to health services	99.5%.It includes low-income inhabitants Civil servants can opt out of the public financed system. 88% of this population and their beneficiaries are covered for this non-for-profit private sector. 13% of the Spanish population are covered by private-for-profit VHI, with an important regional variation	Highly decentralised model with the allocation of block-grants –obtained through taxation-, from the central government to the autonomous communities, except for Navarre and the Basque Country with a high autonomy taxation. Taxation represents 94.1% of the funding of the social security system.
Sweden 9,647,695inhabitants (2013) www.scb.se (accessed on 11/2013)	Public: Universal access to health care	All residents in Sweden regardless of their nationality. Around 2.3% of Swedes have a private medical insurance.	Mainly proportional income taxes (80%), supplemented by Government grants and patient copayment (17%)
The United Kingdom 63,705,000inhabitants(mid-2012) http://www.ons.gov.uk/ons/index.html(accessed on 11/2013)	Public: Universal access to health care About 11% of the population is covered by a private health insurance.	All residents in the UK are eligible for NHS Services	Predominantly the government through general taxation, compulsory contributions to the NHS by employers, employees, self-employed and some local taxation. The first 2 sources of financing represent 94.6% of the NHS financing. Rest is financed through out-of-pocket payments and private health insurance

Source: Authors' compilation from national Ministries of Health, Social Health Insurance Funds and the WHO-European Observatory on Health Systems and Policies

APPENDIX 7.4 PROTECT QUESTIONNAIRE

BACKGROUND

One of the goals of the PROTECT research group is to identify and describe the sources of drug use at a national level of interest in drug utilisation research.

As part of an inventory on European national drug consumption databases (DCDB), Working Group 3 has developed this questionnaire. Our aim is to collect additional information on the database to let researchers to conduct and interpret cross-country drug utilisation comparisons.

For more information on the PROTECT project, see www.imi-project.eu. If you are interested in the inventory on drug consumption databases, see http://www.imi-protect.eu/frameworkRep.shtml.

	Number	Date
Final version	Questionnaire v1.0	June 2011
Ammendment (if any)	Questionnaire v1.0; a1.0 (Inclusion of inpatient information)	January 2012

INSTRUCTIONS

The questionnaire is intended to collect information on databases registering out- and inpatient drug consumption at national level.

The questionnaire is divided into four sections: (1) Definition of out- and inpatient drug consumption; (2) Population coverage; (3) Drug-based information; (4) Other information. Each of the sections collect different characteristics of out- and inpatient drug consumption databases at national level. In addition, there is the option of writing free comments. Also, there is the possibility of pointing out that the information requested is not collected or not applicable to your database. Further instructions are provided along the questionnaire.

If you have any questions, please do not hesitate to contact us at:

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Catalan Institute of Pharmacology (FICF)

http://www.icf.uab.es/en/index.html

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Thank you for your cooperation!

1. DEFINITION: WHERE DO YOU RECORD DRUG CONSUMPTION IN THE FOLLOWING SETTINGS?

Tick under the appropriate heading according to whether the information is registered as in- or outpatient drug consumption (D.U.).

	OUTPATIENT D.U DATABASE	INPATIENT D.U. DATABASE	NO COLLECTED
DATABASE NAME			
Medicines prescribed by specialists and supplied by community pharmacies to outpatients			
Medicines prescribed and supplied by the hospital to outpatients			
Nursing homes			
Dental care			
Drug abuse centres			
Psychiatric clinics			
Other long-term healthcare institutions			
Private institutions			

Comments:

2. POPULATION COVERAGE: WHAT IS THE ESTIMATED PROPORTION OF POPULATION COVERED BY YOUR DATABASES?

Outpatient D.U. database	Inpatient D.U. database
%	%

If the databases contain a population sample, either for outpatient or inpatient, please indicate your sampling method.

Outpatient D.U. database
Inpatient D.U. database

If population coverage is less than 90%, indicate your method of extrapolation or weighting data

Outpatient D.U. database
Inpatient D.U. database

3. DRUG-BASED INFORMATION

3.1 TYPE OF DATA COLLECTED

Please, tick under the appropriate heading whether your databases collect information on the listed characteristics. Additional information can be listed under the heading comments.

	Outpatient D.U. database		Inpatient D.U. database		Comments
	Yes (%)	No	Yes (%)	No	
Manually prescriptions					
Electronic prescriptions					
Electronic prescriptions in the pharmacy not dispensed (not collected by the patient)					
Sales of medicinal products obtained from wholesalers/ manufacturers					
Dispensed prescription data					
Reimbursed dispensed prescription data					
Over the counter drugs					
Proportion of missing prescriptions					
Indication for drug use. *Please specify how this information is obtained (free-text, Interntional Classification of Diseases, other codes)*					
Date prescribed					
Date dispensed					
Duration of prescription					
Quantity of drug dispensed					
Days of supply					
Package size					
Number of packages dispensed					
Dose					
Strength					

	Outpatient D.U. database		Inpatient D.U. database		Comments
	Yes (%)	No	Yes (%)	No	
Dosage form					
Prescriber information. *If possible, specify which information is collected*					

For **INPATIENT D.U. DATABASES:** Is the following information available?

	Country level		Hospital level	
	Yes	No	Yes	No
Number of beds				
Number of admissions				
Number of discharges				
Average length of stay				

Comments:

3.2ANATOMIC-THERAPEUTIC-CHEMICAL CODIFICATION OF MEDICINES AND THE DEFINED DAILY DOSES AS UNITS OF MEASUREMENT (ATC/DDD METHODOLOGY)

Please, provide the requested information for both types of databases

	OUTPATIENT D.U. DATABASE	INPATIENT D.U. DATABASE
Does your database use ATC codification?. If **not**, which drug codification system is in place?		
Does your database use DDD for quantifying drug use?. Please specify other units of measurement		
What is the currently ATC/DDD version used?		
When is your database updated with the new ATC/DDD codes		
Is your database retrospectively updated with the latest ATC/DDD version?		
Does your database assing a national ATC code or DDD unit for those drugs without an ATC/DDD code provided by the World Health Organisation?.		
Is this national ATC/DDD list available?. Please provide where to find this information.		

Comments:

4. OTHER INFORMATION

4.1 PATIENT-RELATED INFORMATION

	OUTPATIENT D.U. DATABASE	INPATIENT D.U. DATABASE
Is it possible to link DU databases with other health registries or other databases?		
Are the following socio-demographic factors collected in your databases?		
Unique patient identification number		
Age (date of birth)		
Gender		
Ethnicity		
Place of residence		
Education		
Income		
Social class		

Comments:

4.2 VALIDITY OF THE DATABASE

	OUTPATIENT D.U. DATABASE	INPATIENT D.U. DATABASE
How and how often do you ensure the internal validty (procedures that minimise errors during data collection) of your database?		
Are you aware of any study on the sensitivity and specificity of the database, published?. *If possible, provide the bibliographic reference*		

Comments:

4.3. ACCESSIBILITY OF DATA

	OUTPATIENT D.U. DATABASE	INPATIENT D.U. DATABASE
For research purposes, is drug consumption data publicly available?		
Is there any website providing further information on how to request data for research purposes?		

Comments:

Thank your for your time and cooperation!

The WG3, PROTECT project

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