PROTECT
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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

DRUG CONSUMPTION DATABASES IN EUROPE

Master document

WP2 Framework for pharmacoepidemiological studies

WG3 Drug utilization data

PROTECT: Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

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PREFACE

This report delivers the work done after one of the goals set by the PROTECT project , to build up an inventory on drug consumption databases across Europe. The interest behind this inventory was not only to gather information on governmental agencies collecting drug consumption data or the type of databases available in each country, but also to present the sources of drug utilization data in Europe from a researcher's point of view, i.e. in a structured manner to facilitate the handling of such information for research purposes. This report provides information on non-commercial and commercial drug consumption sources and on international network groups working in drug utilization research. The description of the characteristics of national drug consumption databases allows for the establishement of the degree of comparability between these databases.

The report is organised in 7 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 is dedicated to the methodology to get the information to build-up the inventory. There is a general methods subheading that 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 in drug utilization research. As this information can be collected either in an outpatient or inpatient healthcare setting, specific methodology is referred. Chapter 3, provides the results of the search on information on drug consumption and is divided into 3 subsections: background data, outpatient drug utilization resources and inpatient drug utilization resources. Chapter 4 is entirely dedicated to describe the validity of national drug consumption

databases. Chapter 5 discusses the findings in light of what has already been done in this field and the stated objectives. Chapter 6 and chapter 7 go on with the conclusions and recommendations for future actions in this field.

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

The International Standard point and thousand comma are applied in tabulated statistics

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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

AFMPS, Belgian Federal Agency for Medicines and Health Products

AFSSAPS, French Agency for the Safety and Health Products

AEMPS, Spanish Agency for Medicines and Health Products

AGES, Austrian Agency for Health and Food Safety

AIFA, The Italian Drug Agency

AMI, Acute Myocardial Infarction

ANM, (Romanian) National Medicines Agency

ARITMO, Arrhytmogenic potential of drugs

ARPAC, Antibiotic Resistance Prevention and Control

ATC, Anatomic-Chemical-Therapeutic classification system

BfArMI, 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 Utilization Research

CNHIM, (French) National Hospital Center on Medicines Information

CPN, Central Pharmaceutical Number

CSD, Cegedim Strategic Data

CU, Counting Units

DDD, Defined Daily Doses

DIMDI, German Institute of Medical Documentation and Information

DKMA, Danish Medicines Agency

DoHC, (Irish) Department of Health and Children

DU, Drug Utilization

DRUID, Driving under the influence of Drugs, Alcohol and Medicines

DURQUIM, Drug Utilization 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 Organization 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

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

HMUD, Scottish Hospital Medicines Utilization 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

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 Pharmaco-Epidemiology

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 Center for Biotechnology Information

NeLM, British National electronic Library on Medicines

NHS, United Kingdom National Health System

NIC, Net Ingredient Cost

NMUU, The Scottish National Medicines Utilization 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 Utilization

PEI, Paul-Ehrlich Institute

PGRx, Pharmacoepidemiologic General Research eXtension group (by LA-SER)

PHIS, Pharmaceutical Health Information System

PK, (Austrian) Pricing Committee of the Ministry of Health

PPRI, Pharmaceutical Pricing and Reimbursement Information System

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 Utilization Research

SPA, Scottish Prescription Analyses

TEDDY, Task-force in Europe for Drug Development for the Young

TUPP, The Users Perspective Project

UNCAM, (French) National Union of Health Insurance Organizations

UK, United Kingdom

UKMi, British National Health System pharmacy medicines information service

US, 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, Working Package

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EXECUTIVE SUMMARY

Different initiatives have arisen in Europe to gather information on drug utilization (DU) for the last 15 years. Knowledge of the quantitative and qualitative patterns of drug use is a key element for 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, 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 or through wholesalers, and (iii) reimbursement data. This data may be collected by governmental agencies or stored in pharmacies' databases or insurance compapanies databases. These sources of data are known as non-commercial data providers. In addition, data mining companies can conduct market surveys and thereafter 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. Second, sources of data on drug exposure obtained from the prescriptions registered in clinical databases. Third, interviews to patients collecting the current ingestion of medicines and finally, pharmacoepidemiological studies from which the utilization rate for a class of drugs can be obtained.

Furthermore, the growth of new technologies with the establishement of automated databases, results in an increasing number of patient- healthcare

encounters electronically registered. These databases cover large sizes of population, and the data is 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 of the association drug-adverse event 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, leaving out a segment of the population.

The objective of the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) 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 organized into seven working packages (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 organized in 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 World Health Organisation (WHO) recommendations on the adoption of the Anatomical Chemical Therapeutic classification (ATC) of drugs and the measurement of drug exposure in defined daily doses (DDD).The PROTECT project includes the following drug-adverse events: 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.

To find out information on national drug consumption databases we elaborated a search strategy that allowed for getting different sources of data on drug consumption considered of interest for drug utilization studies. Data providers, pricing and reimbursement agencies, information on marketed active substances, healthcare systems and reimbursement decisions adopted in each European country, and international drug utilization working groups. The European countries included in this inventory were limited according to their population, tradition in DU research and participation in the PROTECT project. We conducted, first, a specific website search from global European institutions to country-specific governmental websites; second, a bibliographic database search to find articles published by international working groups; third, google search, and finally interviews with experts. 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, 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, we reviewed the main available information on hospital drug utilization for the PROTECT selected drugs by means of 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 in the selected PROTECT countries.

One of the aspects of interest was to determine the validity of the national drug consumption databases. In the context of the PROTECT project, validity is understood as to which degree the results obtained from these national databases are comparable across different countries and over time. Considering the vast bibliography available on the validity and application of automated databases in research we elaborated a questionnaire including most of the items considered of relevance when measuring drug exposure and interpreting the results obtained in drug consumption studies. The key items referred to the definition of in- and outpatient drug consumption, population coverage, drug- and patient-based information, database internal validity and accessibility.

This complex methodology yielded to 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: data providers of authorised medicinal products (table 4), healthcare systems (Appendix 3), pricing and reimbursement agencies (table 5), pharmaceutical data sources by country(table 6) and international networks and working groups in pharmacoepidemiology. For each of the international working groups, the following information was collected: website, definition, objectives, work period, country-participants, information, funding and publications. At the same time, these international networks have been divided in those offering general information: general research groups, and those groups studying either

specific diseases or groups of drugs of interest for the PROTECT project, the specific research groups(points 3.1.5.1 and 3.1.5.2).

Information on national drug consumption databases in Europe is provided for Denmark, Finland, France, Germany, Italy, Norway, Poland, Spain, Sweden, the Netherlands and the United Kingdom (point 3.2.1.1). Appendix 7 and 8 show the data available at the Foundation Catalan Institute of Pharmacology (FICF), both from non-commercial and commercial data providers. Only Denmark, France, Italy and Norway can provide data on the inpatient sector. The consumption at ATC level 1 for the cardiovascular system (C), nervous system (N) and respiratory system (R) for the inpatient sector, year 2009, represented in Denmark < 4% (table 9, for ATC level 3 or 4, table 11), in Sweden < 3%, and in France (ATC level 3 or 4) <7%. From the bibliographic database search in the inpatient sector, regardless of the country concerned and the type of drug utilization research study, the majority of articles were set in the oupatient setting and expressed drug consumption as a percentage of the active substance (table 13,appendix 6). For inpatient antibacterial consumption, the PubMed search conducted yielded up to 20 papers with relevant data (table 14 and 15). The results of the website search for antibacterial consumption are summarized in table 16.

The questionnaires were received from Denmark, France (AFSSAPS), Italy, Norway, the Netherlands and Sweden. Table 17 summarizes the comparability of national drug consumption databases.

The PROTECT inventory provides information on 18 European working groups, 12 national drug consumption databases and 3 national sources of sales of medicines from wholesalers (France, Norway, Sweden). In addition,

sources of inpatient antibacterial consumption were identified from 7 countries and 1 region of Spain. For Denmark, France, Italy, Norway and Sweden inpatient drug consumption is available for other drugs than antibacterials. As expected, the Nordic countries and the Netherlands with their long tradition in drug utilization research, are the ones to provide drug consumption data free online. For the rest of the countries, information should be applied for. Finland recommends to give 1-1.5 years ahead of the planning study to receive such information.

The interest in compiling such information has evolved in the last 15 years. From the EuroMedicines project that elaborated a drug directory for 14 European countries, through the EUROMEDSTAT project and CNC (Cross National Comparison) project, to the EuroDURG-ISPE (European drug utilization group and International Society of Pharmacoepidemiology) collaboration and the ENCePP (European Network of Centres fro Pharmacoepidemiology and Pharmacovigilance). Also, several specific international working groups have been established around a disease that indirectly implies drug utilization research. Other specific groups targeted a specific drug group.

Generally speaking, there is a scarcity of national 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 WHO recommendations of adjusting drug consumption to clinical activity are barely followed. In contrast with this lack of information on inpatient drug utilization from non-commercial data providers, IMS Health started in 2008 the Hospital Audit Presciption which collects

information on drugs dispensed from hospital pharmacies to the patient, containing more clinical information (diagnostic) of utter interest in research.

The evaluation of validity of national drug consumption databases within the scope of the PROTECT project , provides enough information regarding the comparability of the results in drug consumption across different countries. 3 European databases collect dispensed medicines which best assess drug exposure, as they include over-the-counter (OTC) drugs. 5 databases collect reimbursed data, and 3 prescription data. The population coverage of most of these databases reaches 100%, except for 3. Only one of them provided the weighting methodology. ATC/DDD methodology has been adopted by all the databases, even the British database which collects information according to the British National Formulary/Average Daily Quantity (BNF/ADQ) provides ATC codes and DDD upon request. Most of the databases update retrospectively the ATC codes and DDD according to the WHO guidelines released every year. The problem of the ATC/DDD methodology is still the same that have been pointed out by other authors: the lack of an ATC code or the not assignation of a DDD to some of the marketed drugs. In this case, the strategy adopted for each of the databases varies considerably. The questionnaire allowed to evaluate the different degrees of ascertainment of those variables considered potential confounders of the drug exposure. Very few databases provide age and sex of the patient, some provide information on the prescriber and the community pharmacy where the patient purchased the drug.

The PROTECT inventory is a comprehensive and structured source of information on drug consumption that should promote the correct interpretation of the results of a study comparing different European countries.

In addition a brief summary of the data provided by IMS Health is available.For academic researchers the PROTECT offers the basis for future collaborations, and for regulatory agencies and pharmaceutical companies, the possibility of supporting post-marketing and safety studies. This inventory would not have been possible without the previous initiatives in compiling such 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 the usual clinical practice. In particular, patients exposed to new medicines in usual clinical practice differ from those in clinical trials in terms of sex, age, indication for use, dose, dosage patterns, duration of use, concomitant medications and co-morbidities. In addition, pre-approval drug trials are usually done in highly qualified study centers with experienced investigators. All these factors may alter the benefit-risk ratio of the drug of interest as soon as the drug becomes available on the market(1).

The economic development in the 1950s led governements to establish a public health system. A raising number of medicines became more readily available in the market parallel to the economic development. The pharmaceutical industry and a more universal access to health, transformed the pharmaceutical market. Soon, monitoring drug consumption was important not only from an economic perspective (health expenditure in terms of drug costs, sales of medicines and a highly competitive pharmaceutical market), 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 of the West Germany market(2).

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(3). Quantitative data on drug consumption is available from national databases, mantained 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(4).

Besides the storage of quantitative data on drug use collected in non-commercial and commercial data providers, its validity needs to be assessed if used for research. In the context of the PROTECT project, validity has been defined as to which degree the results on drug use obtained from national databases are comparable across different countries and over time. It includes validity in terms of drug-exposure measurement and validity in terms of potential biases introduced in a drug utilization study by the information contained in these databases.

1.2 RATIONALE

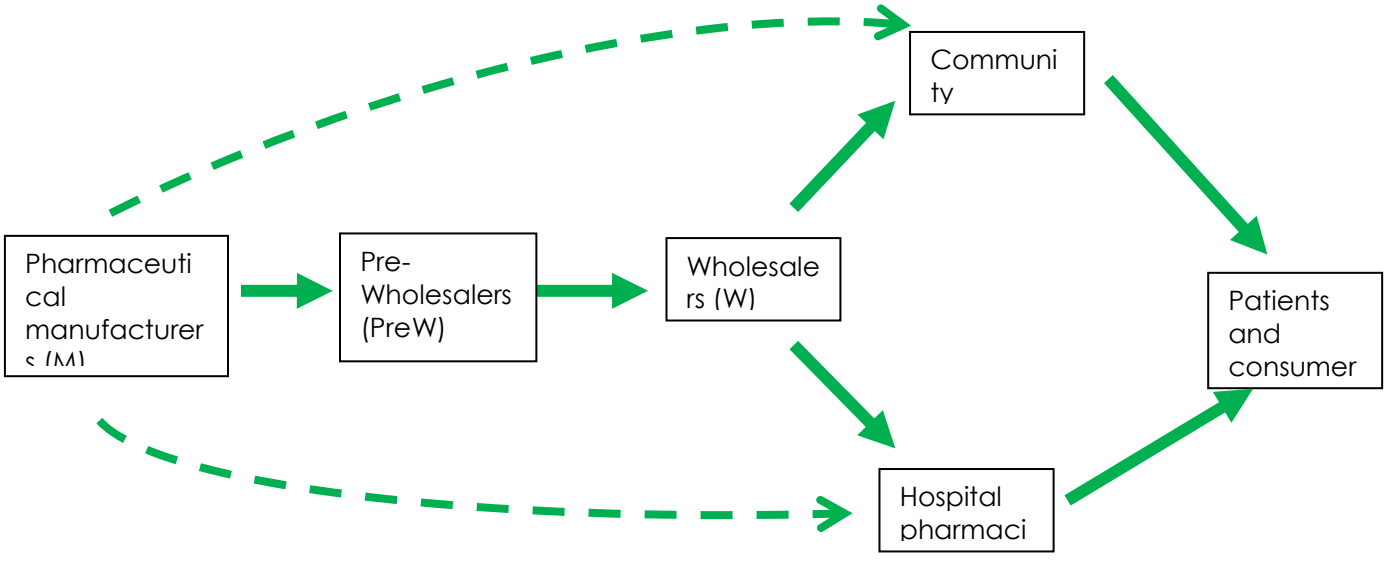
The establishement of automated databases, monitoring drug use, is the result of an increasing number of patient-health care encounters electronically registered and the advance of the new technologies. In drug utilization studies information on prevalence, incidence, indication and duration of a treatment can be derived from different sources(4):

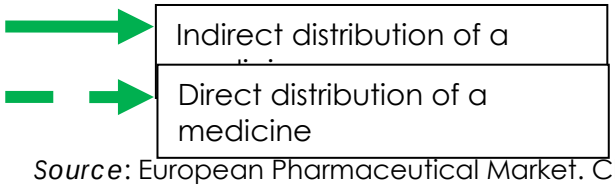
(a) distribution data (see Figure 1): dispensing (with or without prescription), purchasing (of medicines by hospital/community pharmacies or other outlets) or reimbursement data. It usually stems from governmental agencies, pharmacies' databases, and insurance companies. These sources are generally named non-commercial drug utilization data providers. Another source of drug consumption data are market surveys. (b) prescribing data, from clinical databases. Medical audits allow the collection of the individual extent and profile of drug use on a continuing basis and it can be correlated with healthcare utilization data.

(c) information on actual ingestion of medicines through interviews to patients.

(d) pharmacoepidemiological studies from which the utilization rate for a class of drugs can be obtained.

Figure 1. Medicines chain distribution





Source: European Pharmaceutical Market. Chapter 1. National Bureau of Economic Research.2010

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. The measures of drug exposure will differ in each of the healthcare settings.

Furthermore, the PROTECT project proposed to collect drug consumption data for medicinal substances of hospital or specialist use, for which neither national drug consumption databases, nor commercial data providers held. However, when the project started and the drug-adverse event pairs were selected, none of the groups of medicines belonged to such category. See appendix 1 for a detailed list of medicines and appendix 2 for the pairs drug-adverse event, included in the PROTECT project.

When the interest is on studying drug exposure in inpatient settings at national level, the task becomes more complex. 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. In a survey conducted by the European Association of Hospital Pharmacists (EAHP) in 2005, figures showed that around 54% of European hospitals purchased the drugs from wholesalers and 47% directly from the pharmaceutical industry(5). Also, some hospitals got their medicines supplied by larger hospitals (e.g. Belgium) or partly by local community

pharmacies (e.g. United Kingdom). The percentage of hospital pharmacies per total number of hospitals varied from 2% in Finland, where the number of pharmacies in small hospitals or in dispensaries is unknown, to 100% in Portugal, where it is compulsary by law to have a hospital pharmacy in all public hospitals(6).

A third aspect influencing the measure of inpatient drug use is the existence of therapeutic drug formularies that list the active ingredients currently in use in a specific hospital. Among the drugs included in the therapeutic drug formularies, there are those classified by the national authorities as hospital-only-medicines (HOM). The number of pharmaceutical substances included in these formularies can range from 225 in Norway, up to 1500 in Greece(5).

Finally, there is a confusion between the definition of inpatient and outpatient drug consumption. Some countries may include as inpatient consumption those medicines prescribed to outpatients by specialists independently of whether the specialist is settled in a hospital or in an ambulatory health centre. On the contrary some countries may include as outpatient consumption medicines prescribed in long-term health care institutions, such as nursing homes, psychiatric healthcare centres, drug abuse centers, and private institutions. Also, those HOMs dispensed by the hospital pharmacy to outpatients may be included as inpatient consumption. For instance, France and Italy are two of the countries with the highest rate of inpatient pharmacies serving to outpatients (67% and 61% respectively), whereas in Finland and Norway only 12% of the hospital pharmacies dispensed medicines to outpatients(5).

Hospital pharmaceutical expenditure represents 15% of the total pharmaceutical expenditure. A previous report ("Proportion of utilization in hospital setting of selected groups of drugs") established that the bulk of drug consumption of medicines in ATC groups C08, N03, N05BA, N05CD, N06A, N06CA, R03AC and R03AK was in the outpatient sector, thus their consumption in the inpatient sector would not be further explored. Only J01 and J01CR02 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(7). Also their costs in hospitals have grown from 10% to over 15%, being the object of institutional guidelines to influence their prescription(8).

Historically, drug consumption databases were created with an administrative purpose: to record drug use in the outpatient setting for 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(2). In research, these databases offer several advantages: they cover large sizes of population; the data is already available and it is easy to access. This is translated into lower costs and less time spent in getting results(9-11).

These databases have also their downsides. First, they are secondary data sources: data may have been initially collected for purposes different to that of the current research question(12). Not all variables regarded as potential confounders of the association under study (drug exposure-adverse event) may be collected(13). Second, there is not a 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(9-11). Finally, the information is only registered for those individuals that have an encounter with a health service: doctors, nurses, pharmacists.These problems may become more obvious when the objective of the study is to describe and compare patterns of drug use across countries or trends of drug use over time.

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 determined best by comparing with medical records at an individual patient level(14) or conducting surveys with interviews and home inventory with patients(15).

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 Work Packages. The overall objective of Work Package 2 (WP2, Framework for Pharmacoepidemiological Studies) is to develop, test and disseminate methodological standards for the design, conduct and analysis of pharmacoepidemiological studies. The specific objective of this WP2 is to study five pairs of selected adverse drug events and to develop new methods to enhance the detection of adverse drug events (ADEs). Working Package (WP) 2 is organised in 3 Working Groups (WG).

1.3.1 General objective

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

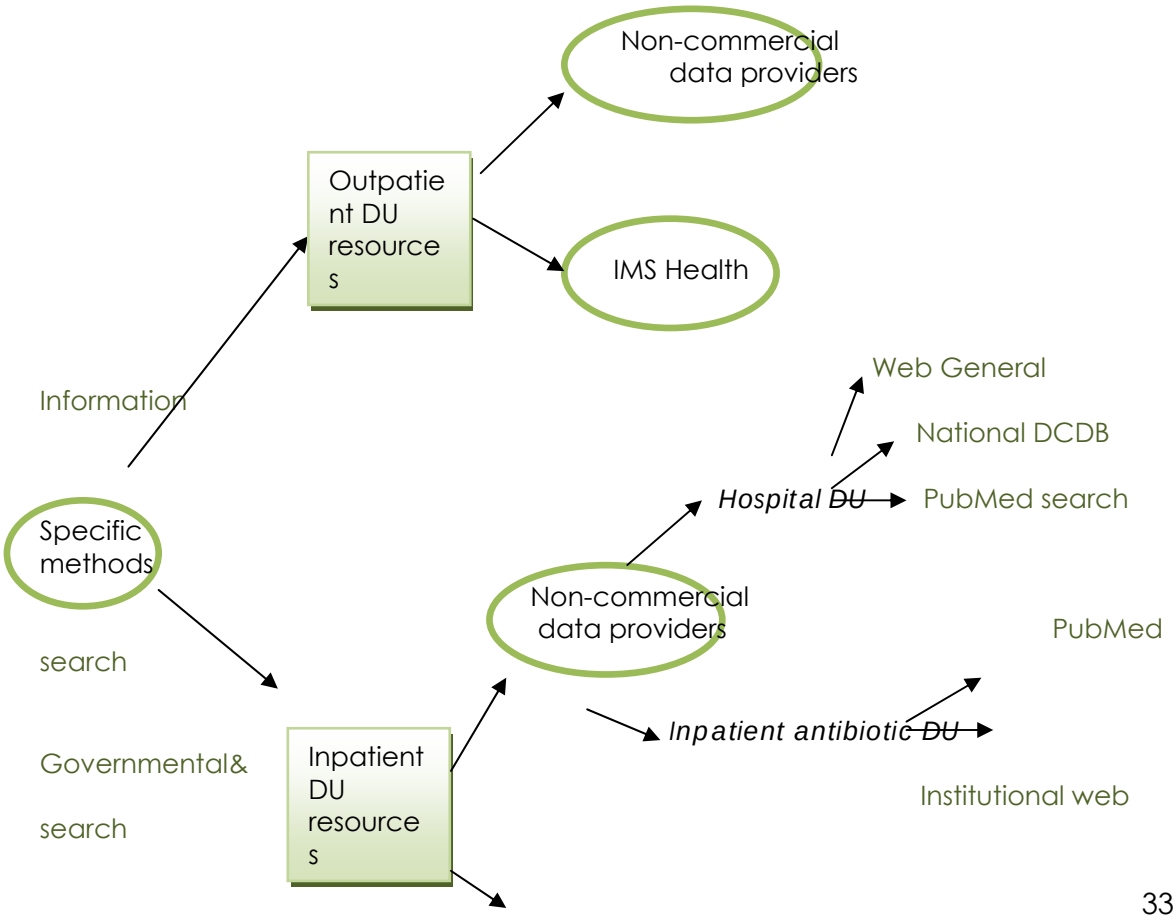
This document is intended to be an updated list of drug consumption data sources in Europe with details on the information that may have an influence on the patterns of medicines usage. It aims to revise and complete the information already available from similar initiatives conducted previously, to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

1.3.2 Specific objectives

- To describe the characteristics of non-commercial providers of drug consumption data in the selected European countries
- To describe the main characteristics of the market data collected internationally by IMS Health
- To provide an updated list of national drug consumption databases in selected European countries.
- To describe the main characteristics and accessibility of these national drug consumption databases
- To outline the performance of these databases (validity)
- To explore the availability of inpatient drug consumption data at national level in the selected European countries

2 METHODOLOGY

Because of the complexity of the subject under study, an schematic overview of the methodology is offered at this point to facilitate its understanding and organization.



2.1 GENERAL METHODS

Under this heading, the intention is to explain the methods used to get different types of data on drug consumption, including information on drug consumption data providers, pricing and reimbursement agencies, and international working groups on drug utilization as a means to eventually obtain the actual national drug consumption databases. In addition, we also searched for sources that provided information on the marketed active substances and the reimbursement decisions adopted in each country.

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 data and information of interest for DU research studies.

Search strategy

1. We consulted the European Union (http://europa.eu) and the European Medicines Agency –EMA- (www.ema.europa.eu) websites. The goal was to find institutions, networks and research projects related to DU in Europe.
2. We sought information regarding national health systems policies and national competent authorities that regulated licensing, pricing and

reimbursement of drugs in Europe. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) website (www.ispor.org) was targeted. The objective was that these national authorities might be directly involved in collecting drug consumption data.

3. Bibliographic database search: The goal was to find articles published by European or international –with European collaboration- groups, working on pharmacoepidemiology and/or drug utilization 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.

The search was conducted on PubMed and SIETES (Spanish electronic information system database on pharmacoepidemiology). PubMed (http://www.ncbi.nlm.nih.gov/books/NBK3827/#pubmedhelp.PubMed_Quick_Start last accessed 10/5/2011) is a database maintained by the National Center for Biotechnology Information (NCBI), at the United States National Library of Medicine. It provides access to MEDLINE and other web sites and links to the other NCBI molecular biology resources, life science journals and e-books. SIETES (www.icf.uab.es/informacion/Papyrus/sietes.asp , last accessed 10/5/2011) is an electronic drug information system in Spanish maintained by the Catalan Institute of Pharmacology. A selected number of journals are periodically reviewed, and the articles in the database are selected accordingly to the objectives of the SIETES database. Approximately 3000 new articles are included every year in

the database. The majority of these articles are critically reviewed and the comments introduced in the database (http://www.icf.uab.es/websietesdb/fonament.asp , last accessed 10/5/2011).

- → Keywords: "pharmacoepidemiology", "drug utilization", "international cooperation", "databases" and "Europe".
- → Working groups studying a single medical condition and/or those focusing on drugs of no interest for the PROTECT project were excluded.
- → Variables of interest collected for each working group: website, definition of the group, objectives, period of work, participant countries, and information on the group activities from their websites or publications, source of funding, and publications.

4. Google search: The same keywords used in the electronic bibliographic database search, as well as the first author's name from published articles were entered in the search engine.
5. Web-cross links
6. Interviews with experts and EuroDURG contacts (see Table 1 for a list of contacts that needs to be confirmed), to find out drug consumption data specific for a country.

Table 1. European Drug Utilization Research Group. National Groups and Contact Persons

Country	Contact Person	e-mail
ARMENIA	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

Country	Contact Person	e-mail
BELGIUM	Monique Elseviers University of Antwerp Campus drie Eiken Universiteitsplein 1 B-2610 Wilrijk Belgium	monique.elsevier@ua.ac.be
BOSNIA AND HERZEGOVINA	Begler Begovic Department of Clinical Pharmacology Clinical Centre University of Sarajevo Bolnicka 25 71 000 Sarajevo	bbegovic@bih.net.ba
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	Ria Benkö Department of Clinical Pharmacy University of Szeged Szikra utca 8 Szeged H-6725 Hungary	benkoria@gmail.com
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	Elisabetta Poluzzi Department of Pharmacology University of Bologna Via Irnerio, 48 I 40126 Bologna Italy	elisabetta.poluzzi@unibo.it
THE NETHERLANDS	Peter Mol Department of Clinical Pharmacology University of Groningen P.O.box 196 9713 AV Groningen	P.G.M.Mol@med.umcg.nl
NORWAY	Ingebjorg Buajordet Senior Adviser/MSc Pharm, PhD Norwegian Medicines Agency Pharmacovigilance Section Svein Oftedalsvei 6 0950 Oslo Norway	ingebjorg.buajordet@noma.no
RUSSIA	Svetlana Ratchina, MD, PhD Smolensk State Medical Academy	Svetlana.ratchina@antibiotic.ru

Country	Contact Person	e-mail
	Department of Clinical Pharmacology, Assistant Professor Institute of Antimicrobial Chemotherapy, Senior Research Fellow 28 Krupskaya str, PO Box 5 Smolensk 214019 Russian Federation	
SWEDEN	Björn Wettermark Centre for Medical Knowledge Stockholm County Council SE-118 91 Stockholm Sweden	Bjorn.wettermark@sll.se
UNITED KINGDOM and IRELAND	Prescribing and Research in Medicines Management (PRIMM) www.primm.eu.com Prof. Colin Bradley (chairman) Rm 2. 40 Western Gateway Building University College Cork Cork Ireland Prof. Stephan Chapman (honoray secretary) Head of School of Pharmacy Keele University Keele, Staffordshire ST5 5BG	primm@mema.keele.ac.uk gp@ucc.ie s.r.chapman@mema.keele.ac.uk

Names no shadowed: same names of executive committee published in Eurodurg last bulletin and eurodurg website with contact names as in April 2007
Green shadowed. Eurodurg website contact names as in April 2007
Blue shadowed: checked in their own webpage
Purple shadowed: information extracted from last bulletin and checked in their webpage.

Inclusion criteria

Setting: Countries included in the inventory

Initially, we limited the number of European countries to be included in the inventory according to the following inclusion 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
- Country of origin of participants in the PROTECT project with available clinical databases (Denmark, France, Germany, The Netherlands, Spain and United Kingdom), or

- Member states of the EEA known to have a long tradition in collecting drug consumption data and/or with on-line accessible drug consumption data (Denmark, Sweden, Norway, Finland and The Netherlands).

Table 2. Economic European Area countries

27 EU countries and 3 European Economic Area[1] members (Iceland, Norway and Liechtenstein)			
Countries in alphabetic order (Total population, inhabitants, in 2011)			
Country	***Total population (inhabitants) in 2011***	***Country***	***Total population (inhabitants) in 2011***
Austria	8,404,252	Latvia	2,229,641
Belgium	10,918,405	Liechtenstein	36,152
Bulgaria	7,504,868	Lithuania	3,244,601
Cyprus	804,435	Luxembourg	511,840
Czech Republic	10,532,770	Malta	417,608
Denmark	5,560,628	Netherlands	16,654,979
Estonia	1,340,194	Norway	4,920,305
Finland	5,375,276	Poland	38,200,037
France	65,075,310	Portugal	10,636,979
Germany	81,751,602	Romania	21,413,815
Greece	11,329,618	Slovakia	5,435,273
Hungary	9,986,000	Slovenia	2,050,189
Ireland	4,480,176	Spain	46,152,926
Iceland	318,452	Sweden	9,415,570
Italy	60,626,442	United Kingdom	62,435,709

Source: www.europa.eu. For the total population: www.epp.eurostat.ec.europa.eu (both accessed 20/7/2011) [1]The European Economic Area Agreement was signed in 1992 and came into force in 1994. Since 1 May 2004, is formed by the 27 EU member states and 3 European Free Trade Association (EFTA) countries: Iceland, Liechtenstein and Norway.

Language criterion

No language restriction. For those languages that none of the authors mastered, the google translator was used as a customized 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

Measured as the availability of current and complete information and their independence from commercial sponsorship.

2.2 SPECIFIC METHODS FOR OUTPATIENT DRUG UTILIZATION RESOURCES

2.2.1 NON-COMMERCIAL DATA PROVIDERS

See the above general methods as they provide the way through which the information from non-commercial data providers was obtained. Information on the following characteristics was gathered for all national drug consumption databases: data provider, website, source of drug consumption, setting, population coverage, accessibility, drug codification, variables collected related to unit of measurement, drug-based information, prescriber and pharmacy information, potential confounders: age, sex, indication for use, co-morbidities, co-treatment, language of the database, record period and record linkage. We also provide references, that is, reports or published articles that have used these databases in pharmacoepidemiological studies or that have described their characteristics.

Once the source of a national drug consumption database was located, if the data was available free online, we downloaded the total number of DDD or DDD/1000 inhabitants/year for the PROTECT selected drugs, years 2007, 2008 and 2009. Otherwise, we requested the data to the contact person found.

2.2.2 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).

Interview with experts provided information on another company collecting information on drug consumption data in Germany: Pharmafakt (www.pharmafakt.de , last accessed 24/8/2011) . This company sells reimbursement drug consumption data. No further contact was established with this company.

Also experts provided a website address wich led to find another worldwide market and medical research company: Cegedim Strategic Data (CSD) (https://www.cegedimstrategicdata.com , last accessed 24/8/2011) . No further contact was established with this company.

2.3 SPECIFIC METHODS FOR INPATIENT DRUG UTILIZATION RESOURCES

2.3.1 NON-COMMERCIAL DATA PROVIDERS

First, we reviewed the main available information on hospital drug utilization for the PROTECT selected drugs. 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.

2.3.1.1 HOSPITAL DRUG UTILIZATION (GENERAL OVERVIEW)

See appendix 6 for the full report "Proportion of utilization in hospital settings of selected groups of drugs"

There were 3 potential sources of information on DU studies in hospital settings: general information available on the web, public national databases and electronic bibliographic databases.

Website General information

From the general search methods, we extracted general information on hospital medicines management from the Pharmaceutical Health Information System website http://phis.goeg.at/index.aspx?_nav0027 (last accessed 24/8/2011).Through links from this website index, three other websites of general information were identified: the European Association of Hospital Pharmacists website http://www.eahp.eu/ (last accessed 24/8/2011), the European Hospital and Healthcare Association website, www.hope.be (last accessed 24/8/2011), and the Organization for Economic Cooperation and Development (OECD) website, http://www.oecd.org/home/0,2987,en_2649_201185_1_1_1_1_1,00.html (last accessed 24/8/2011).

National Public Databases

Information on the type of drug consumption data and the sector covered by the 12 (16)different European national databases was already available. In addition, we explore the National Medicines Agencies websites to find whether they had published reports on inpatient drug consumption data.

Bibliographic database search

A search in PubMed was conducted. This search was not intended to be a systematic review of hospital medicines consumption but rather a broad overview of the number of drug utilization studies conducted in a hospital setting, for the selected PROTECT drugs.

Search strategy

A search for the terms "hospital drug utilization"," calcium channel blockers"," antiepileptics", "beta-2-agonists", "antidepressants" and "benzodiazepines" was conducted, with the following strategy: Each of the medicine groups was combined with "hospital drug utilization", using the Boolean logic AND.

Inclusion criteria

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 included nursing homes, psychiatric clinics or any other institution categorized as 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, drug utilization studies can be divided into 4 different categories: studies covering the patterns of use, quality of use, determinants of use, and outcome of use(16). Only articles related to patterns of drug use, regardless of indication, were included. All units and methods of measurement were valid for the review. Those abstracts classifying medicines according to the ATC codification and/or quantifying drug use in defined daily doses (DDD) were reported. Active pharmaceutical ingredients classified in ATC level 5 of the selected PROTECT drugs were considered drugs of interest.

No restrictions regarding the type of study design were imposed. Any article published in a language understood by any of the group members were included: English, Spanish or any other Roman languages and Swedish.

2.3.1.2 ANTIMICROBIAL (J01FA, J01CR02) DRUG UTILIZATION IN HOSPITALS

This part of the project was undertaken by Amgen and was conducted by EPIPharmaCo.

The current project aims to determine the availability and nature of information in the public domain on hospital consumption of macrolides and amoxicillin-clavulanate in Europe reported between 2000 and 2010. Two sources of information on inpatient use of macrolides and amoxicillin clavulanate were explored: Bibliographic database and the web search.

Bibliographic database search

It was conducted on PubMed on the 8th of April 2011.

Search strategy:

Search 1:[antibiotic OR antimicrobial] AND hospital AND audit AND [country name]

Search 2:[antibiotic OR antimicrobial] AND hospital AND registry AND [country name]

Search 3 (drug specific): [drug name] AND epidemiology AND hospital AND [country name]

Inclusion criteria:

- Relevant countries: Denmark, France, Germany, Italy, Norway, Poland, Spain, Sweden, the Netherlands, United Kingdom

- Relevant antimicrobials: erythromycin, spiramycin, midecamycin, oleandomycin, roxithromycin, josamycin, troleandomycin, clarithromycin, azithromycin, miocamycin, rokitamycin, dirithromycin, flurithromycin, telithromycin, amoxicillin (co-amoxiclav)
- Time period: from year 2000 up to current
- Language: English articles

Reviewers:

Dr Tracey Lonergan and Dr Louise Watson

Web-based search

An internet search was undertaken in order to determine whether government/health-service-driven data was available. In addition to a free search -using terms including drug name, antibiotic, audit, prescribing and hospital, country specific government and health-services websites were also targeted.

Data collected by ESAC was explored in their database to see whether they had inpatient antibacterial consumption for the selected PROTECT countries.

2.3.2 COMMERCIAL DATA PROVIDERS

Because the only commercial data provider mentioned in this report is IMS Health, the information which has been 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 have been classified accordingly to the website search strategy (See table 3).

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

Comprehensive institutional European websites	More specific institutional websites providing information on drug data providers, pricing and reimbursement agencies, and national medicines agencies.	Websites of international networks on DUR studies providing information similar to the more specific institutional websites and on drug consumption databases
www.europa.eu Gateway to the European Union (EU)	www.ispor.org International Society for Pharmacoeconomics and Outcomes Research	www.encepp.eu Information on research and medical-care centers, helathcare databases, electronic registers and existing networks
www.ema.europa.eu European Medicines Agency	www.eudrapharm.eu It is part of the EU Telematics Implementation Plan. It is a source of information on all medicinal products approved by the EU and EEA.	www.eurodurg.com European forum on medical, socioeconomic, and ethical issues of the determinants of drug utilization and its effects.
www.who.int World Health Organization	www.euro.who.int/observatory The European Observatory on Health Care Systems and Policies	www.euromedstat.cnr.it (latest update 2007) Database holding information on sources of drug utilization data, their reliability and comparability across countries
	www.oecd.org Organization for Economic Co-operation and Development	www.pharmacoepi.org International Society of Pharmacoepidemiology. With a special group interested in DUR
	www.ppri.oebig.at Pricing and Reimbursement Information(PRI) system. Network providing PRI for the 27 EEA members and with the collaboration of EMA,OECD, WHO and World Bank institutions	www.nhv.se/norpen Nordic network on pharmacoepidemiological research

Comprehensive institutional European websites	More specific institutional websites providing information on drug data providers, pricing and reimbursement agencies, and national medicines agencies.	Websites of international networks on DUR studies providing information similar to the more specific institutional websites and on drug consumption databases
	www.eahp.eu European Association of Hospital Pharmacists.	www.piperskagroup.com Group of professionals involved in reimbursement, formulary listing and rational use of drugs
	www.hope.be European Hospital and Healthcare Association	See specific tables for specific drug utilization networks
	www.bridgetodata.org Online subscription website providing information on more than 140 databases from 21 countries	

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 from information provided by comprehensive institutional websites to specific national databases. This background data offers information on the national health systems, medicines regulatory agencies, drugs marketed in each PROTECT selected country and the patient summary characteristics leaflet, and international research working groups. The second category is termed national drug consumption databases found in each of the PROTECT selected countries.

3.1 BACKGROUND DATA

3.1.1 DATA PROVIDERS OF AUTHORISED MEDICINAL PRODUCTS

From the EudraPharm website we have retrieved information for 30 European countries (See table 4). Each website listed on table 4 has been

checked to confirm that is still available (date of update 11/05/2011). The medicinal product data provider is given in the national language and in English. The English translation was provided either by Eudrapharm or by the own national website.

Table 4. List of providers on information about European medicinal products, organised by alphabetical order

Country	Medicinal product data provider	Website
Austria	Österreichische Agentur für Gesundheit und Ernährungssicherheit - AGES Austrian Agency for Health and Food Safety (AGES)	www.ages.at
Belgium	Agence Fédérale des Médicaments et des Produits de Santé - AFMPS Federal Agency for Medicines and Health Products	www.fagg-afmps.be
Bulgaria	Изпълнителнаагенцияполекарствата Bulgarian drug agency	www.bda.bg
Cyprus	ΥπουργείοΥγείαςτηςΚυπριακήςΔημοκρατίας Ministry of Health of the Republic of Cyprus	www.moh.gov.cy
Czech Republic	Státní ústav pro kontrolu léčiv State Institut for Drug Control	www.sukl.cz
Denmark	Lægemiddelstyrelsen Danish Medicine Agency	www.laegemiddelstyrelsen.dk
Estonia	Ravimiamet State Agency of Medicines	www.ravimiamet.ee
Finland	Lääkealan turvallisuus- ja kehittämiskeskus Finnish Medicines Agency	www.fimea.fi
France	Agence Française de Sécurité Sanitaire des Produits de Santé - AFSSAPS The French Agency for the Safety of Health Products	www.afssaps.fr
Germany	Bundesinstitut für Arzneimittel und Medizinprodukte - BfArM Federal Insitute for Drugs and Medical Devices Deutsches Institut für Medizinische Dokumentation und Information - DIMDI German Institute of Medical Documentation and Information Paul-Ehrlich-Institut - PEI Paul-Ehrlich-Institut	www.bfarm.de www.dimdi.de www.pei.de
Greece	ΕθνικόςΟργανισμόςΦαρμάκων - EOF National Organizationfor Medicines	www.eof.gr
Hungary	Országos Gyógyszerészeti Intézet The National Institute of Pharmacy	www.ogyi.hu
Iceland	Lyfjastofnun Icelandic Medicines Agency	www.lyfjastofnun.is
Ireland	Irish Medicines Board	www.imb.ie
Italy	Agenzia Italiana del Farmaco - AIFA The Italian Drug Agency	www.agenziafarmaco.it

Country	Medicinal product data provider	Website
	Istituto Superiore di Sanità Institute of Health Ministero della Salute Ministry of Health	www.iss.it www.salute.gov.it
Latvia	Zāļu valsts aģentūra The State Agency of Medicines	www.zva.gov.lv
Liechtenstein	Amt für Gesundheit Board of Health	www.llv.li/amtsstellen/llv-ag-home.htm
Lithuania	Valstybine vaistu kontroles tarnyba prie Lietuvos Respublikos sveikatos apsaugos ministerijos The State Medicines Control Agency (SMCA)	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.public.lu/fr/
Malta	Medicines Authority the Medicines Authority	www.medicinesauthority.gov.mt
Netherlands	College ter Beoordeling van Geneesmiddelen Medicines Evaluation Board	www.cbg-meb.nl
Norway	Statens legemiddelverk Norwegian Medicines Agency	www.legemiddelverket.no
Poland	Urzad 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
Romanía	Agentia Nationala a Medicamentului - ANM National Medicine Agency	www.anm.ro
Sweden	Läkemedelsverket Medical Products Agency	www.lakemedelsverket.se
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
Slovakia	Štátny ústav pre kontrolu liečiv - ŠÚKL State Institute for Drug Control	www.sukl.sk
Spain	Agencia Española de Medicamentos y Productos Sanitarios-AEMPS Spanish Agency of Drugs and Medical Devices	www.aemps.es
Sweden	Läkemedelsverket Medical Products Agency	www.lakemedelsverket.se
United Kingdom	Medicines and Healthcare products Regulatory Agency - MHRA	www.mhra.gov.uk

3.1.2 HEALTH SYSTEMS

European countries have a variety of approaches to the organization of health systems and are diverse in terms of language, history and wealth (www.euro.who.int/en/what-we-publish/abstracts/european-health-report-2009-the.-health-and-health-systems, last accessed 29/7/2011). Knowledge of the different health systems gives us important information about financing, population coverage, and the type of turnover/update of the data registry. Also knowing how each country records the prescriptions, sales or other information may be helpful to understand the data gathering process and the characteristics of the databases.

In appendix 3 there is a table with the main characteristics of each country health systems.The table describes the health care provider, population coverage, the model of health care financing and the pharmaceutical financing.

3.1.3 PRICING AND REIMBURSEMENT AGENCIES

Table 5 offers a list of pricing and reimbursement agencies, updated on 5/2011. Source of information is from ISPOR website and EUROMEDSTAT website.

Table 5. Pricing and reimbursement agencies

Country	Pricing agency	Reimbursement agency
Austria	Bundesministerium für Gesundheit(BMG) assisted by Preiskommission (PK). Federal Ministry of Health. Pricing Committee. www.bmg.gv.at	Hauptverband der Österreichischen Sozialversicherungsträger Federation of Austrian Social Insurance www.sozialversicherung.at
Belgium	SPF Economie, PME, Classes moyennes et Energie. Service des Prix Federal Minister of Economic Affairs.	Institute National d'Assurance Maladie-Invalidité Rijksinstituut voor ziekte- en invaliditeitsverzekering

Country	Pricing agency	Reimbursement agency
	Price Services FOD Economie, KMO, Middenstand en Energie. Prijzendienst www.economie.fgov.be/fr/consommateurs/Prix_reglementes/	Commissie Tegemoetkoming Geneesmiddelen Commission de Remboursement des Médicaments www.riziv.fgov.be
Denmark	Indenrigs-og Sundhedsministeriet The Ministry of Interior and Health www.im.dk	Lægemiddelstyrelsen The Danish Medicines Agency www.laegemiddelstyrelsen.dk
Finland	Sosiali –ja Terveysministeriö. Lääkkeiden hintalautakunta Ministry of Social Affairs and Health. Pharmaceuticals 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) Committee of Health Products Economics www.sante.gouv.fr/comite-economique-des-produits-de-sante-ceps.html	Commission d'Evaluation des Médicaments. Ministery of Health and Sports. Ministère du Travail, de l'Emploi et de la Santé 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 free to set price 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 Gesetzliche Krankenversicherung (GKV) Statutory Health Insurance http://www.g-k-v.de/gkv/
Greece	Υπουργείο Ανάπτυξης Γενική Γραμματεία Εμπορίου Διεύθυνση Εσωτερικής των τιμών βιομηχανικών προϊόντων και φαρμάκων.Ministry of Development www.ypan.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.yyka.gov.gr Social Security Funds(based on a recovery price) www.ika.gr(the largest one 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
Irland	The Department of Health and Children (DoHC) .www.dohc.ie	The Department of Health and Children (DoHC). ww.dohc.ie

Country	Pricing agency	Reimbursement agency
	The Health Services Executive (HSE). Corporate Pharmaceutical Unit. www.hse.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
Norway	Statens Legemiddelverk Norwegian Medicines Agency www.legemiddelverket.no	Statens Legemiddelverk Norwegian Medicines Agency www.legemiddelverket.no Helse-og omsorgsdepartementet Ministry of Health and Care Services www.regjeringen.no
Poland	**Ministerstwo Zdrowia** Ministry ofHealth Zespół zarządzający narkotyków Drug Manegament Team www.mzios.gov.pl	**Ministerstwo Zdrowia** Ministry of Poland www.mzios.gov.pl
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
Spain	Ministerio de Sanidad , Política Sociale Igualdad Dirección General de Farmacia y Productos Sanitarios. Ministry of Health and Social Policy Department of Pharmacy and Health Products. www.msc.es/profesionales/farmacia/organizacion.htm	Ministerio de Sanidad ,Política Social e Igualdad. Dirección General de Farmacia y Productos Sanitarios. Ministry of Health and Social Policy Department 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
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
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

3.1.4 PHARMACEUTICAL INFORMATION

Pharmaceutical information websites are mainly of general information and do not include consumption data, but can serve as supplementary information to compare trade names, prices, specific dates a drug has been marketed or withdrawn, and approved indications.

We updated on 5/2011 the pharmaceutical data sources listed in the Euro Medicines project(17). See table 6.

Table 6. Pharmaceutical data sources by country

Country	Source of pharmaceutical information	Information provided	Website
Austria	Austria Codex		--
Belgium	Association Pharmaceutique Belge	Internal list with all the prices of medical specialties online	www.apb.be www.apbtarif.be (no free access)
	Centre Belge d'Information Pharmaceutique Belgisch Centrum voor Farmacotherapeuh sche Informatie	Repertoire of medicines with comments on them	www.bcfi.be
	Compendium des medicaments	List of drugs marketed in Belgium ?	--
Denmark	Danish Medicines Agency	Prices of medicines, and other information of the different pharmaceutical products (summary of product characteristics, package leaflet)	www.laegeiddelstyrelsen.dk www.produktresume.dk
	Earlier Laegemiddelkatalo get	Lists with information about medicinal products updated daily.	www.medicin.dk
		Information on medicinal products for	

Country	Source of pharmaceutical information	Information provided	Website
		both the patients and health care professionals	
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 (part of CMP Medica) Centre National Hospitalier d'Information sur le Médicament (CNHIM) AFSSAPS. French Health Products Safety Agency	Information on drugs for healthcare professionals and patients A database for Health care professionals have been developed with information on all drugs available in France ECODEX database with information on all drugs marketed in France	http://www.vidal.fr/les-produits-professionnels/dictionnaire-vidal http://www.cnhim.org/ http://www.theriaque.org (no free access) http://afssaps-prd.afssaps.fr/php/ecodex/index.php
Germany	(Internal file) Bundesvereinigung Deutscher Apothekerverbände Apothekerkammer Niedersachsen Rote list Fachinfo Fachinformationsve	A pdf file is available with information on German pharmacies. Information mainly for pharmacists. It contains a database (AMINO-datenbak) that contains information on medicine products Information on drugs for pharmacists and medical doctors Information on drugs	www.abda.de http://www.apothekerkammer-niedersachsen.de/cms/arzneimittelinformation/amino-datenbank/amino_datenbank.html http://www.rote-liste.de www.fachinfo.de (no free access)

Country	Source of pharmaceutical information	Information provided	Website
	rzeichnis Deutschland	for medical doctors and pharmacists	
Ireland	(internal list) of Irish Medicines Board Monthly Index of Medical Specialties (MIMS) Irish Pharmaceutical Healthcare Association	 It is an index of prescribed medicines in Ireland updated monthly Summary of product characteristics and patient information leaflet.	www.imb.ie http://www.imt.ie/mims http://www.medicines.ie/default.aspx
Italy	Elsevier editorial Repertorio Farmaceutico Italiano (ReFI) Supplemento ordinario a la Gazetta Ufficiale della Republicca Italiana	Information on drugs marketed in Italy. The information is available online and as a book **Online** database containing information (partly from ReFI) regarding drugs for pharmacists and other healthcare professions **Book**: L'Informatori farmaceutico (updated yearly) It is a collection of nearly 4200 summaries regarding medicines information participated by the Ministry of Health and the Pharmaceutical Industry Extra legislative decrees regarding health issues	www.prontuario.it www.codifa.it (no free access) Online version available. No free access -- --
Luxembourg	Ministère de la Santé (ministry of health).Division de la Pharmacie et des Medicaments (Pharmacies and drug division)	Liste des medicaments admis à la vente dans le Grand-Duché de Luxembourg Pricing list	http://www.ms.public.lu/fr/ (no free Access to this list)
Portugal	Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.	Prontuário Terapêutico (for drugs dispensed in the community) Formulário Hospitalar	http://www.infarmed.pt/portal/page/portal/INFARMED/PUBLICACOES

Country	Source of pharmaceutical information	Information provided	Website
		de Medicamentos (FHNM). Both available online. INFOMED database: Access to information on all drugs marketed in Portugal	http://www.infarmed.pt/infomed/inicio.php
Spain	Consejo General de Colegios Oficiales de Farmacéuticos Agencia Española de medicamentos y productos sanitarios (AEMPS)	Catálogo de Especialidades Farmacéuticas. Reference drug information book edited Database with information about drugs by region (summary of product characteristics, patient leaflet, patient counseling) CIMA database. Centro de información online de Medicamentos de la AEMPS. Information on all drugs marketed in Spain	Not online https://botplusweb.portalfarma.com/ (no free access) https://sinaem4.agemed.es/consaem/fichasTecnicas.do?metodo=detalleForm&version=new
Sweden	FASS Läkemedelsverket (Medical Products Agency)	Information on drugs marketed in Sweden for the general public and health care professionals (Internal list)? Information on all medicines registered in Sweden since 2004	www.fass.se http://www.lakemedelsverket.se/malgrupp/Halso---sjukvard/Sok-lakemedelsfakta/
The Netherlands	College ter Beoordeling van Geneesmiddelen (Medicines Evaluation Board) Internal list of Z-association	Database on information about all drugs marketed in the Netherlands	http://www.cbg-meb.nl/CBG/nl/humane-geneesmiddelen/geneesmiddeleninformatiebank/default.htm
United Kingdom	The electronic Medicines Compendium (eMC)	Information about UK licensed medicines (summary product characteristics and	http://www.medicines.org.uk/emc/

Country	Source of pharmaceutical information	Information provided	Website
		patient information leaflet	
	NHS Business Services Authority, NHS Prescription Services	NHS Electronic Drug Tariff (for England and Wales). Information on prices of drugs for GP, pharmacy contractors and appliance contractors. Updated monthly	http://www.ppa.org.uk/edt/May_2011/mindex.htm (free access)
	British Medical Association and the Royal Pharmaceutical Society	Information about the clinical use of medicines	www.bng.org (no free access except for UK residents and residents of low-and middle income countries listed in the web)
	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 are free access unless otherwise stated.

3.1.5 INTERNATIONAL NETWORKS AND WORKING GROUPS IN PHARMACOEPIDEMIOLOGY

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

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

All websites and information updated 6/2011. See appendix 4 (a and b) for a summary table of all research groups.

3.1.5.1 GENERAL RESEARCH GROUPS

All the information provided by the general research groups was updated during 6/2011.

3.1.5.1.1 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 centers, healthcare databases, electronic registries and existing networks.
Objectives	To strengthen post-authorisation monitoring of medicinal products in Europe by facilitating the conduct of high quality, multicentre, independent post-authorisation studies focusing on safety and benefit risk.
Working period	2006-ongoing
Participants	EU countries
Information	**ENCePP Database of Research Resources**: public, fully searchable electronic index of the available EU research resources in pharmacoepidemiology and pharmacovigilance. The database has two components, the ***Inventory of ENCePP research centers and networks***, and the ***Registry of EU data sources***. **ENCePP Code of Conduct**: set of rules and principles for pharmacoepidemiology and pharmacovigilance studies about best practice and transparency. **Checklist of Methodological Standards for ENCePP Study Protocols** developed to stimulate researchers to consider important epidemiological principles when designing a pharmacoepidemiological study and writing a study protocol, to promote transparency regarding methodologies and design used in pharmacoepidemiological studies performed in the EU, and to increase awareness about developments in science and methodology in the field of pharmacoepidemiology. **E-register of studies:** in pharmacoepidemiology and pharmacovigilance
Funding	European Medicines Agency
Publications	http://www.encepp.eu/publications/index.html It is mainly a list of documents regarding different meetings and work plans

3.1.5.1.2 EuroDURG (European Drug Utilization Research Group)

Web	www.eurodurg.com
Definition	EuroDURG is a scientific forum for quantitative and qualitative research on drug utilization and prescribing. Recently, the organization merged with the International Society of Pharmacoepidemiology (ISPE) and it now constitutes the European chapter of ISPEs special interest group for Drug Utilization research. EuroDURG collaborates closely 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 drug utilization and pharmacoepidemiology. • Work towards the adoption of standards for international and national drug use research methodology to measure regional variations in drug utilization across Europe and to account for it. • Maximize the potential of the information available on drug utilization for improving patient care. • Cooperate with international and national drug regulatory authorities, such as the WHO and the EU, European Council, health insurance agencies, the pharmaceutical industry, academic departments and professional bodies in furthering drug utilization research and its applications. • Promote the incorporation of drug utilization research and its applications in educational programs.
Working period	1993-ongoing
Participants	20 national groups (as of April 2007): Armenia, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Germany, Greece, Hungary, Iceland, Israel, Italy, Netherlands, Norway, Portugal, Serbia, Spain, Russia, Sweden, UK. In 2009, EuroDurg changed its organization from national to individual membership
Information	Membership is open to European residents or collective legally constituted national research working groups Meetings jointly held with ISPE every year. **WORKING SUBGROUPS:** **TUPP** (The Users Perspective Project): To frame a protocol for pan-

	European research on the user perspective on mood modifying medicines (no website) **DRUID**(Driving Under the Influence of Drugs, Alcohol and Medicines): In collaboration with the University of Groningen, aims to combat the scourage of drink-driving and find answers to the question of the use of drugs or medicines that affect people's ability to drive safely. 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 EU countries.http://www.druid-project.eu/cln_031/Druid/EN/home/homepage__node.html?__nnn=true **HAPPY Audit** (Health Alliance for Prudent Prescribing, Yield and Use of Antimicrobial Drugs in the Treatment of Respiratory Tract Infections): In collaboration with the University of Southern Denmark, 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.http://www.happyaudit.org/ Participation in an European FP7 project on drug induced arrhythmias (**ARITMO,** see subheading 3.1.5.2.1).
Funding	Through ISPE
Publications	1. EuroDurg bulletins (Bulletin N°1 in April 2007-Bulletin N°21 in January 2011) 2. Ronning M, Blix HS, Strom H, Skovlund E, Andersen M, Stichele RV. Problems in collecting comparable national drug use data in Europe: the example of antibacterials. Eur J Clin Pharmacol 2003; 58:843-849. 3. Bergman U. The history of the Drug Utilization Research Group in Europe. Pharmacoepidemiol Drug Saf 2006;15:95-98 ***DRUID→*** 1. There is a list of public deliverables accessible, with information on psychoactive substances consumption in the general population http://www.druid-project.eu/cln_031/nn_107534/Druid/EN/deliverales-list/deliverables-list-node.html?__nnn=true (accessed 22/6/2011) ***TUPP→*** 1. Knudsen P, Hansen EH, Eskildsen K. Leading ordinary lives: a qualitative study of younger women's perceived functions of antidepressants. Pharmacy World and Science 2003;25(4):162-167. 2. Stevenson F. Images of nature in relation to mood modifying medicines: a user perspective. Health (London) 2004 8:241 http://hea.sagepub.com/content/8/2/241.full.pdf+html (accessed 22/6/2011) ***HAPPY Audit→*** 1. A report can be found on the website published in 2008. http://www.happyaudit.org/files/pub/4398.pdf (accessed 22/6/2011) 2. Llor C, Cots JM, Bjerrum L, et al. Prescripción de antibióticos en las infecciones del tracto respiratorio y factores predictores de su utilización. Atención Primaria 2009.

	Doi:10.1016/j.aprim.2009.04.018/j.aprim.

3.1.5.1.3 CNC (Cross-National Comparison of Drug Utilization Research)

Web	http://www.pharmacoepi.org/eurodurg/workgr/cross_national.cfm
Definition	In collaboration with ISPE's SIG-DUR, it gathers worldwide information on national drug utilization monitoring systems and drug utilization data for antibacterials, proton pump inhibitors, statins and clopidogrel.
Objectives	• To stimulate worldwide use of WHO indicators of rational drug use and cross-national monitoring DU programs for specific drugs • To record of DU in cross-national epidemiological disease registers • To enhance comparability of data on drug exposure in international databases
Working period	2008-ongoing
Participants	24 countries
Information	Information on DU monitoring and expenditure in each of the participants countries collected by a questionnaire, sent out to national contact persons in countries all over the world. All participant countries will work out the compariosn 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	1. Structured poster session presented on ISPE Conference in Copenhagen August 16-21, 2008 2. EuroDURG bulletin Nº20, January 2010.

	http://www.pharmacoepi.org/eurodurg/bulletins/gen_2010/EuroDURG_bulletin_2010.pdf (last accessed 13/7/2011).

3.1.5.1.4 DURQUIM (Drug Utilization Research Quality Indicator Meeting)

Web	**http://www.eurodurg.com/durquim.htm**
Definition	In collaboration with WHO, develop a list of indicators to be taken into account when evaluating the prescribing quality.
Objectives	To analyze the patterns of drug use and to implement strategies for improving the prescribing and use of drugs. To provide the framework for constructing prescribing quality indicators
Working period	2004-ongoing
Participants	19 European countries, US, Canada and Australia
Information	An expert meeting held in Belgium, regarding the potentials 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	1. 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. 2. Avorn J. An American Reflection on DURQUIM. Power point presentation http://www.pharmacoepi.org/EURODURG/AmericanReflectionDURQUIM.PDF (last accessed 13/7/2011)

3.1.5.1.5 EUROMEDSTAT (European Medicines Statistics)

Web	www.euromedstat.cnr.it
Definition	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 utilization of medicines in the EU.
Objectives	❁To develop a set of indicators, to be integrated in the EU Public Health Information network (EUPHIN) for monitoring price, expenditure and utilization of medicinal products, and to facilitate comparisons under a public health perspective. ❁To build a European database of licensed medicines.
Working period	2002-2003 (meetings until 2007)
Participants	A collaboration of academics and government agencies from most European Union 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 utilization 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. Utilization 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 Reports: List of participants in the EUROMEDSTAT projects List of competent authorities responsible for licensing, pricing and reimbursement of medicines Legal classification of medicines Reimbursement categories of medicines Relevant data sources The library of European Union pharmaceutical indicators Recommendations for national registers of medicinal products with validated ATC codes and DDD
Funding	European Commission (Directorate General of Health and Consumer Protection)
Publications	see www.euromedstat.cnr.it/publications/publications.asp (last accessed 22/6/2011)

3.1.5.1.6 ISPE'S SIG-DUR (International Society of Pharmaco Epidemiology's Special Interest Group on Drug Utilization/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	To create a global forum for discussion and cooperation between drug utilization researchers
Working period	2006-ongoing
Participants	Euro DURG members and other regional chapters (Australia, Canada, US)
Information	Website with a collection of national drug dictionaries, linked to the ATC and DDD . Information of a contact person on each group Project working subgroups: • ATC/DDD browser • Prescribing Quality indicators • Cross-national comparisons

	• Relationship with the health insurers • 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

3.1.5.1.7 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 o Initiating and designing new studies o Improving quality o Avoiding common pitfalls and duplication of efforts
Working period	2009-ongoing
Participants	Denmark, Finland, Iceland, Norway and Sweden
Informatio	They focus on rare exposures and rare events, prescribing quality

n	indicators, reproductive health, medicine use in children and mental health. Information about the meetings at the webpage.
Funding	Norden NordFosk, a Nordic research board operating under the Nordic Council of Ministers provides funding for Nordic research cooperation
Publications	1. Furu K, Wettermark B, Andersen M, Martikainen J, Almarsdottir AB, Sørensen HT. The Nordic Countries as a Cohort for Pharmacoepidemiological Research. Basic Clinical Pharmacol Toxicol 2009;106:86-94. http://www.nhv.se/upload/dokument/forskning/N%C3%A4tverk/NorPEN/Furu.pdf (last accessed 22/6/2011) 2. Power point presentation of NorPen by Helle Kieler. Centre for Pharmacoepidemiology. Karolinska Institutet. Sweden http://www.ema.europa.eu/pdfs/human/phv/encepp_scientific_convention_251108/ScConv_081125_Kieler.pdf (last accessed 22/6/2011)

3.1.5.1.8 PIPERSKA Goup

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	To 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 Joint alliance between PIPERSKA and European Cancer Initiative (OECI). Conference Berlin February 2010 http://www.oeci-eeig.org/Documents/Draft_Agenda_OECI_Piperska_8_6.pdf
Funding	---
Publications	Selection of recent publications at http://www.piperskagroup.com/documents/Piperska-Publications.pdf(last accessed 22/6/2011)

3.1.5.2 *DRUG RESEARCH GROUPS WITH FOCUS ON SPECIFIC DRUGS/DISEASES*

3.1.5.2.1 ARITMO (Arrhytmogenic potential of drugs)

Web	**http://www.aritmo-project.org**
Definition	To analyse the arrhythmic potential of antipsychotics**,** 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. ❁ To 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 - December 31, 2012
Participants	17 partners (listed in the web site)
Information	---
Funding	The Health Area of the European Comission under the 7th Framework Programme
Publications	No publications

3.1.5.2.2 ARPAC (Antibiotic Resistance Prevention and Control)

Web	**http://www.abdn.ac.uk/arpac/index.htm**
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 harmonize strategies for prevention and control of antibiotic resistant pathogens in European hospitals
Objectives	❁To identify antibiotic policies and prescription patterns associated with lower resistance rates. ❁To identify infection control policies associated with low incidence rates of "Alert organisms" i.e. transmissible antibiotic-resistant strains. ❁To 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 – December 31, 2004
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 use 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	1. MacKenzie FM, Struelens MJ, Towner KJ, Gould IM, ARPAC Steering Group. Report of the Consensus Conference of Antibiotic Resistance; Prevention and Control (ARPAC).Clin Microbiol Infec 2005;11:938-954. 2. Struelens M, Wagner D, Bruce J, MacKenzie FM, Cookson B, Voss A, van den Broek PJ, Gould IM, ARPAC Steering Group (2006). Status of Infection Control Policies and Organisation in European Hospitals. The ARPAC Study. Clin Microbiol Infec 2001;12:729-737 3. MacKenzie FM, Monnet DL, Gould IM, ARPAC Steering Group. Relationship between the number of different antibiotics used and the total use of antibiotics in European hospitals. J Antimicrob Chemoth 2006; 58:657-660. 4. Mackenzie FM, Bruce J, Van Looveren M, Cornaglia G, Gould IM, Goossens H, the ARPAC Steering Group. Antimicrobial Susceptibility Testing in European Hospitals: Report from the ARPAC Study. Clin Microbiol Infec

2006;12:1185-1192
5. 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.

3.1.5.2.3 ESGAP (European Study Group on Antibiotic Policy)

Web	http://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, identifying problems 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 to measure hospital antibiotic consumption as a number of Defined Daily Doses (DDD) per 100 bed-days
Funding	ESCMID supports economically all study groups under specific circumstances
Publications	http://www.escmid.org/research_projects/study_groups/esgap/presentations_publications/ (last accessed 22/6/2011)

3.1.5.2.4 ESAC (European Surveillance of Antimicrobial Consumption)

Web	http://app.esac.ua.ac.be/public/
Definition	European project coordinated by the University of Antwerp (Belgium), to collect data on the use of antimicrobial (ATC J01, J02, D01BA, J04A, J05, P01AB, A07AA09).
Objectives	❁To collect comprehensive out-and inpatient antimicrobial consumption. ❁To provide timely information on antimicrobial consumption. ❁The European database will be used to develop (i) health indicators of antimicrobial use and (ii) evidence-based guidelines and educational tools to manage the risk of infections and antimicrobial resistance. ❁To give regular feed-back to the relevant authorities of the participating countries. ❁To 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
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 2003 up to 2008, expressed in DID. The information gathered by country varies and specific results for all participating countries are available at the country sheets of the year concerned. Hospital-care data collected for individual hospitals with a linkage to the DRG (Disease Related Groups). Ambulatory-care data broken down by age and sex, specific prescriber groups, high consumers groups and by specific indications (in collaboration with existing networks of sentinel practices). Nursing homes, 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, by econometric models.
Funding	DG Sanco until 2006. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden (until June 2011).
Publications	1. List of publications at http://www.esac.ua.ac.be/main.aspx?c=*ESAC2&n=50012 (last accessed 22/6/2011) 2. Also the ESAC Electronic Library contains international publications and projects covering antimicrobial consumption

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

Web	**No**
Definition	European Study of the Epidemiology of Mental Disorders
Objectives	To collect data by 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, Netherlands and Spain
Information	Epidemiology of mental diseases. Data of use of any psychotropic drug (including antidepressants, ansiolytics, hypnotics, antipsychotics or mood stabilizers) in 2001-2003 – depending on the country-.
Funding	European Commission, national and regional health authorities, Glaxo Smithkline
Publications	1. Nutt DJ, Kessler RC, Alonso J, Benbow A, Lecrubier Y, Lépine JP, Mechanic D, Tylee A . Consensus statement on the benefit to the community of ESEMeD (European Study of the Epidemiology of Mental Disorders) survey data on depression and anxiety. JClin Psychiatry 2007;68 Suppl 2:42-8. 2. Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, et al. Psychotropic drug utilization in Europe: Results from the European Study of the epidemiology of Mental disorders (ESEMeD) project. ActaPsychiatrScand2004;Suppl 420:55-64

3.1.5.2.6 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**
Definition	EUROASPIRE is a European survey conducted under the auspices of the European Society of Cardiology (ESC) to describe current clinical practice in relation to secondary prevention of coronary heart disease.
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	1994-2007
Participants	15 European partners: Belgium, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Poland, Slovenia, Spain, Sweden and United Kingdom
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).
Funding	European Society of Cardiology
Publications	1. Kotseva K, Wood F, De Backer G, De Backquer D, Keil U on behalf of EUROASPIRE Study Group. Cardiovascular prevention guidelines in daily practice: a comparison of

	EUROASPIRE I,II and III surveys in 8 European countries. Lancet 2009;373(9667):929-940 2. EUROASPIRE II Study Group. Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries. Principal results from EUROASPIRE II. Euro Heart Survey Programme. Eur Heart J 2001;22:554-572 3. EUROASPIRE Study Group. A European Society of Cardiology survey of secondary prevention of coronary heart disease: Principal results. Eur Heart J 1997;18:1569-1582. http://eurheartj.oxfordjournals.org/content/18/10/1569.long (last accessed 22/6/2011)

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

Web	**http://www.teddyoung.org**
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	To establish a rationale for the safe and efficacious use of medicines in children. To identify unmet needs for the development and use of medicinal products and orphan drugs in children. To develop, validate and harmonise pre-clinical and clinical methods for assessing the safety and efficacy of current and new drugs in children. To 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. To 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 at 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 authorization holder, national availability, main pahtology. The results from the search offers the marketing authorization 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	1. Hsia Y, Neubert A, Sturkenboom MC, Murray ML et al. Comparison of antiepileptic drug prescribing in children in three European countries. Epilepsia 2010; 51:789-796 2. Neubert A, Sturkenboom MC, Murray ML, Verhamme KM, Nicolosi A, et al. Databases for pediatric medicine research in Europe –assessment and critical appraisal. Pharmacoepidemiol Drug Saf 2008;17:1155-1167. 3. Sturkenboom MC, Verhamme KM,Nicolosi A, Murray ML et al. Drug use in children: cohort study in three European countries. Brit Med J 2008;337:a2245

3.1.6 PROTECT PARTNERS' RESOURCES

The participants on PROTECT have access to several databases, some of them with drug consumption information.

Table 7. PROTECT Resources

DKMA Laeggemyddelstyrelsen (Denmark)
Register of Medicinal Products Statistics
Pharmacovigilance Database
Cancer Registry
Causes of Death Registry
Medical Birth Registry
Registry of Malformation
National Patient Registry
AEMPS Spanish Medicines Agency(Spain)
BIFAP. Healthcare records database from general practitioners
FEDRA. Spontaneous reporting database
Medicinal products database (including drug utilisation data)
LMU-Muenchen Ludwig Maximillian University (Germany)
Bavaria regional claims database

LA-SER Research and Development SME (France)
PGRx database: Registries of patients with myocardial infarction, multiple sclerosis, lupus, inflammatory arthritis, myositis, dermatomyositis, thrombocytopenia, diabetes, thyroiditis, Grave's disease, Guillain-Barré syndrome, acute liver injury, torsades de pointes, suicide attempts, depression, interstitial pneumonia and from general practice settings, collected in several countries; data collected on drug exposure and individual risk factors for the above mentioned diseases (not developed with IMI funds)
UU (The Netherlands)
Software developed by UU simulating patient cohorts to test methods to adjust for confounding Databases are currently incorporated in the Mondriaan project
General Practice Research Database (The United Kingdom)
Primary health care records database

3.2 OUTPATIENT DRUG UTILIZATION RESOURCES

3.2.1 NON-COMMERCIAL DATA PROVIDERS

3.2.1.1 NATIONAL DRUG CONSUMPTION DATABASES IN EUROPE

In the following paragraphs the information included is for the 11 European countries selected for the PROTECT project: Denmark, France, Finland, Germany, Italy, Netherlands, Norway, Poland, Spain, Sweden and The United Kingdom. More countries may be included in the process of updating this document.

Not all the data collected by these databases is free online. Detailed information on drug consumption data is mainly available upon request.

See appendix 5 for a summary of the national drug consumption databases

3.2.1.1.1 Denmark

The Danish Registry of Medicinal Products Statistics.	
Organization	Lægemiddelstyrelsen (Danish Medicines Agency)
Web	http://medstat.dk/statistics/#tabs-1
Source	For primary healt 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 centers and other similar institutions included. For hospital sector: dispensed medicines by ward codes
Setting	Out- and In-patients
Population coverage	100%
Accesibility	Free. Further data can be applied for.
Drug codification	ATC (all levels)
Data	Region, gender, age, DDD, DDD 1000 inhab/day, number of people treated, number of people treated/1000 inhabitants, turnover (including VAT-value added tax- and other prescription charges). Statistics can be drawn by medicines and group of medicines, or number of packages. *Other information*: date, time and place of sale; sales number; code for the sale (e.g. OTC), number of the person reporting the sale, 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; payment from patient.
Record period	From 2005 available online. The registry began in January 1995. In-hospital data since 1997
Language	Danish
Record linkage	Yes Health registers, demographic data (residence, migration, death, family), socioeconomic data (education, occupation, employment status, income).
Other databases	The Odense University Pharmacoepidemiological Database (1,2 million patients) and Pharmacoepidemiological Prescription Database in Northern Denmark (1,7 million patients).
References	✓ Nielsen LH, Lokkegaard E, Andreasen AH, Hundrup YA. Estimating the effect of current, previous and never use of drugs in studies based on prescription registries. Pharmacoepidemiol Drug Saf. 2009; 18 : 147-153. ✓ Sorensen R, Hansen ML, Abildstrom SZ, Hvelplund A, Andersson C, Jorgensen C, Madsen JK, Hansen PR, Kober L, Torp-Pedersen C, Gislason GH. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. Lancet 2009; 374: 1967-1974. ✓ Nielsen LH, Lokkegaard E, Andreasen AH, Keiding N. Using prescription registries to define continuous drug use: how to fill gaps between prescriptions. Pharmacoepidemiol Drug Saf. 2008; 17:384-388

	✓ Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. J Clin Epidemiol 2010; 2:273-279 ✓ Rochat P, Hallas J, Gaist D, Friis ML. Antiepileptic drug utilization: a Danish Prescription database analysis. Acta Neurol Scand 2001; 104:6-11 ✓ Ophævet. 816 af 28/08 2009 Bek. Om indberetning af oplysninger til lægemiddelstatistik. Ministeriet for Sundhed og Forebyggelse http://sik-lw.lovportaler.dk/showdoc.aspx?docId=bek20090816-full (accessed 17/5/2011)

3.2.1.1.2 Finland

Prescription reimbursement register	
Organization	Social Insurance Institution
Web	http://www.kela.fi/in/internet/english.nsf

Source	All reimbursed prescriptions
Setting	Out-patient
Population coverage	100%
Accesibility	Application to data provider
Drug codification	ATC (all levels)
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
Record period	Since 1994
Language	Suomi, Swedish, English
Record linkage	Yes Hospital discharge register, Cancer register, Causes of death register, Longitudinal database of population censuses with data on socioeconomic variables, Population information system
References	✓ Manderbacka K, Sund R, Koski S, Keskimäki I, Elovainio M.Diabetis and depression? Secular trends in the use of antidepressants among persons with diabetis in Finland in 1997-2007. Pharmacoepidemiol Drug Saf 2010; 13(5):425-434. ✓ Sihvo S, Wahlbeck K, McCallum A, Sevon T, Arffman M, Haukka J, Keskimäki I, Hemminki E. Increase in the duration of antidepressant treatment from 1994 to 2003: a nationwide population-based study from Finland. Pharmacoepidemiol Drug Saf 2010;19:1186-1193. ✓ Kajantie M, Manderbacka K, McCallum A, Notkola IE, Arffman M, Forssas E, Karvonen S, Kortteinen M, Leyland A, Keskimäki I. How to carry out register-based health services research in Finland?. Helsinki, 2006. Finland. http://www.stakes.fi/verkkojulkaisut/papers/DP1-2006.pdf [accessed 18/5/2011] ✓ Finnish Information Centre for register research http://retki.stakes.fi/EN/ [accessed 18/5/2011] ✓ Gissler M, Haukka J. Finnish health and social welfare registers in epidemiological research. Norsk Epidemiologi 2004;14(1):113-120.http://www.ntnu.no/ojs/index.php/norepid/article/viewFile/284/262

3.2.1.1.3 France

AFSSAPS database	
Organization	Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) French Agency of Health Safety and Health Products
Web	www.afssaps.fr
Source	Sales of medicines from pharmaceutical companies turnovers.
Setting	Out- and in-patient
Accessibility	Application to data provider
Population coverage	100%
Drug codification	ATC (all levels, except for those medicines with a single trademark grouped at ATC level 4)
Data	Units of measurement : DDD, DDD/1000 inhabitants/year, DDD/100 admissions in in-patient, sales of packages. Drug information : Package size, strength, form of dosage
Record period	Data available on the web since 1993. A report is published every year available online (http://www.afssaps.fr/Afssaps-media/Publications/Rapports-Syntheses-Medicaments , last accessed 19/7/2011).
Language	French and English
Record linkage	No
References	✓ MoulinG,CavalieP,Pellannel,ChevanceA,LavalA,MillemannY, ColinP,ChauvinC.A comparison of antimicrobial usage in human and veterinary medicine in France from 1999 to 2005. J Antimicrob Chemother 2008; 62(3): 617-625. ✓ Analyse des ventes de médicaments aux officines et aux hôpitaux en France 1999-2009 http://www.afssaps.fr/var/afssaps_site/storage/original/application/849879f9b33f8a16c739d28da79cb1d9.pdf

Extraction, Recherches, Analyses pour un Suivi Médico-Economique database (ERASME)	
Organization	Caisse Nationale d'Assurance Maladie des Travailleurs Salariés (CNAMTS) National Insurance Fund for salaried employees.
Web	http://www.ameli.fr/index.php
Source	Prescribed drugs dispensed by community pharmacies and reimbursed by the CNAMTS.
Setting	Out-patient
Population coverage	87%
Accesibility	Application to data provider.
Drug codification	ATC

Data	**Patients**: Identification number, registration date, date of tranfer, date of birht, address, sex marital status. **Prescriber**: prescriber identification number, speciality, age, sex, 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	Since 2001. Ongoing updates
Language	French
Record linkage	Yes *HIPPOCRATE* database : anonimysed medical information of patients with chronic diseases, professional diseases or that have had a work injury. Éhantillon Permanent des Assurés Sociaux (EPAS) : sample of people insured in CNAMTS.
Other databases	There are three 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. Échantillon Permanent Inter-regimes des Bénéficiaires de l'Assurance Maladie (EPIB-AM). It contains a standard sample of 1/100 patients of all 3 insurance schemes.
References	✓ Martin-Latry K,Bégaud B. Pharmacoepidemiological research using French reimbursement databases: yes we can!. Pharmacoepidemiol Drug Saf. 2010, 19 (3): 256-265. ✓ Acquaviva E, Legleye S,Auleley G.R, Deligne J,Carel D,Falissard B.B.Psychotropic medication in the French child and adolescent population: prevalence estimation from health insurance data and national self-report survey data. BMC Psychiatry 2009; 9:72. ✓ Latry P, Molimard M, Bégaud B, Martin-Latry K. How reimbursement databases can be used to support drug utilisation studies : example using the main French national health insurance system database. Eur J Clin Pharmacol 2010; 66 :743-748. ✓ Cœuret-Pellicer M, Zins M. Les bases de donnés de l'Assurance Maladie. INSERM Institut National de la Santé et de la Recherche Médicale. October 2006. http://www.rppc.fr/Les%20bases%20de%20la%20CNAM.pdf (last accessed 15/07/2011).

3.2.1.1.4 Germany

Organization	Wissenschaftliches Institut der AOK (WidO). The Research Institut of the AOK. (AOK is the major German public health insurance company).
Web	http://wido.de/arzneiverordnungs-rep.html
Source	Prescribed and dispensed and reimbursed drugs within the public sickness fund system.
Setting	Out-patient
Population coverage	85%
Accesibility	Application to data provider.
Drug codification	ATC
Data	Subject identification number assigned by the statutory health insurance, central pharmaceutical number (CPN), 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 (SHI): socio-demographic variables, hospital and outpatient data.
Other databases	German Pharmacoepidemiological Database (GePaRD-BIPS database). It is a health insurance database covering approximately 17% of German population with information on prescriptions.
References	✓ 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. ✓ Grimmsmann T, Himmel W. Polypharmacy in primary care practices: an analysis using a large health insurance database. Pharmacoepidemiol Drug Saf. 2009; 18:1206-

	1213. ✓ Ufer M, Meyer SA, Junge O, Selke G, Volz HP, Hedderich J, Gleilter H. Patterns and prevalence of antidepressant drug use in the German state of Baden-Wuerttemberg: a prescription-based analysis. Pharmacoepidemiol Drug Saf. 2007; 16:1153-1160.

3.2.1.1.5 Italy

OsMed database	
Organization	Agenzia Italiana del Farmaco. Osservatorio sull'impiego dei medicinali (OsMED) The Italian Medicines Agency. The Medicines Utilization Monitoring Centre.
Web	http://www.agenziafarmaco.it/it/content/osservatorio-sull%E2%80%99impiego-dei-medicinali-osmed
Source	Dispensed medicines (reimbursed and non-reimbursed) by public and private pharmacies. 2 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 ADESFARMA and FEDERFARMA, and by IMS Health, respectively. Medicines dispensed in hospitals to patients are reimbursed by regional health authorities, thus registered in regional databases.
Population coverage	100%
Setting	Out- and in-patient
Accesibility	Application to data provider
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: DDD/1000 inahbitants/day; 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 available in 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 in other databases which can be linked through patient and physician keys present in the prescription.
Other databases	Project Health Search Database (HSD) collects information from general practitioners on drug prescription, demographic

	factors, morbidity, outpatient specialist care, laboratory data and disability data of population over 14 years-old registered in a Medici di Medicina Generale (MMG) or General Practitioner list Pedianet database for children<14 years-old
References	✓ Grupo di lavoro OsMed. L'uso dei farmaci in Italia. Rapporto nazionale anno 2009. Roma. Il Pensiero Scientifico Editore, 2010. ✓ Mirandola M, Andretta M, Corbari L, Sorio A, Nosè M, Corrado B. Prevalence, incidence and persistence of antypsichoticdrugprescribing in theItalian general population: retrospectivedatabaseanalyses, 1999-2002. PharmacoepidemioLand Drug Saf 2006; 15:412-420. ✓ Nobili A, Pasina L, Tettamanti M, Lucca U, Riva E, Marzona I, Monesi DL et al. Potentially severe drug interactions in elderly outpatients: results of an observational study of an administrative prescription database. J Clin Pharm Ther 2009; 34:377-386. ✓ Filippi A, Vanuzzo D, Bignamini AA, Mazzaglia G, Cricelli C, Catapano AL. The database of Italian general practitioners allows a reliable determination of the prevalence of myocardial infarction. Ital Heart J 2005;6(4):311-314.

3.2.1.1.6 Norway

Norwegian Prescription Database (NorPD).	
Organization	Norwegian Institute of Public Health
Web	http://www.norpd.no/Prevalens.aspx
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.
Setting	Out-patient
Population coverage	100 %
Accesibility	Free. Further data can be applied for (datatilgang@fhi.no)
Drug codification	ATC (all levels)
Data	**Patient**: person-identifier (encrypted), month/year of birth, month/year of death,gender, place of residence (municipality and county); **Prescriber**: 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.
Record period	2004-onwards
Language	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.
References	✓ Furu K. Establishemnt of the nationwide Norwegian Prescription Database (NorPD) - new opportunities for research in pharmacoepidemiology in Norway. NorskEpidemiologi 2008; 18 (2): 129-136 ✓ Johannessen Landmark C, Larsson PG, Rytter E, Johannessen SI. Antiepileptic drugs in epilepsy and other disorders – A population-based study of prescriptions. Epilepsy Research 2009; 87: 31-39. ✓ FOR 2003-10-17 nr 1246: Forskriftominnsamlingogbehandlingavhelseopplysninger i Reseptbasertlegemiddelregister (Reseptregisteret). Kappitel 1 §1.8 Opplysninger i Reseptregisteret. http://www.lovdata.no/cgi-wift/ldles?doc=/sf/sf/sf-20031017-1246.html#1-2 (last accessed 18/5/2011)

Wholesaler-based drug statistics	
Web	www.fhi.no
Source	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
Sectors	Out- and In-patient
Population coverage	100%
Accesibility	Application to data provider (lmfin@fhi.no)
Drug codification	ATC (all levels)
Data	Number of packages, wholesales price (wholesaler purchasing price and retailer purchasing price), pharmaceutical product number. Wholesaler intern number, municipality number, Pharmacy license number, municipality, Wholesales license number
Record period	1977-onwards. Data is updated monthly.
Language	Norwegian and English
Record linkage	No

References	✓ Drug consumption in Norway 2006-2010. http://www.legemiddelforbruk.no/ (last accessed 18/5/2011) ✓ Legemiddelstatistikk-grossistbasert. Folkhelseinstituttet. http://www.fhi.no/eway/default.aspx?pid=233&trg=MainArea_5661&MainArea_5661=5565:0:15,4217:1:0:0:::0:0 (last accessed 18/5/2011)

3.2.1.1.7 Poland

National Health Fund database	
Organization	Narodowy Fundusz Zdrowia (National Health Fund)
Web	www.nfz.gov.pl
Source	Reimbursed medication. Information provided by pharmacies to the National Health Fund
Setting	Outpatient
Population coverage	100%
Accesibility	Application to data provider
Drug codification	ATC (all levels)
Data	Turnover, code of reimbursement, number of packages, package size, strength, dosage form, total DDD, DDD/1000 inhabitants/day
Record period	Information available for 2 years 2004 and 2005. A report for these 2 years is available on the website
Language	Polish
Record linkage	No
References	✓ National Health Fund. Report on reimbursed medicines downloadable from the website http://www.nfz.gov.pl/new/index.php?katnr=0&dzialnr=2&artnr=1627&b=1&szukana=ATC (accessed 19/7/2011) ✓ Dziurda D, Polak S, Skowron A, Kuschill-Dziurda J, Brandys J. Analysis of non-hospital antibacterial pharmacotherapy in Poland. Int J Infect Diseases 2008;12(5):483-489.

	✓ 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, FC Tulunay, 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.

Impossible to contact anyone at the NFZ who could provide further information or data on drug consumption in Poland

3.2.1.1.8 Spain

Organization	Department of Pharmacy and Health Products (Ministry of Health, Social Policy and Equity).
Web	www.msc.es/profesionales/farmacia/organizacion.htm
Source	Drugs dispensed by community pharmacies reimbursed by the National Health System.
Setting	Out-Patient.
Population coverage	100%
Accesibility	Application to data provider (Ministerio de Sanidad. Paseo Prado, 18. 28014 Madrid)
Drug codification	ATC (all levels)
Data	Region, DDD, turnover, some regions collect data on age and sex, but the Ministry of Health provides only total consumption, prescriber's code, national pharmaceutical code, pharmacist's code, strength, dosage form.
Record period	Since 1985 (computerized data)
Language	Spanish
Record linkage	No
References	✓ Garcia del Pozo J,Carvajal A,Viloria JM,Velasco A,Garcia del Pozo V.Trends in the consumption of opioid analgesics in Spain. Higher increases as fentanyl replaces morphine. Eur J Clin

	Pharmacol 2008; 64:411-415. ✓ Ruiz-Bremón A, Ruiz-Tovar M, Pérez-Gorricho B, Díaz de Torres P, López-Rodríguez R. Non-hospital consumption of antibiotics in Spain: 1987-1997. J Antimicrob Chemoth 2000; 45:395-400 ✓ García del Pozo J, Isusi Lomas L, Carvajal A, Martín Rodríguez I, Sáinz Gil M, García del Pozo V, Velasco Martín A. Evolución del consumo de fármacos antipsicóticos en Castilla y León (1990-2001). Rev Esp Salud Pública 2003; 77:725-733 ✓ Agencia Española de Medicamentos y Productos sanitarios. Observatorio del uso de medicamentos. http://www.aemps.es/profHumana/observatorio/home.htm#presenta (Accessed 19/5/2011) ✓ Álvarez Luna F. Farmacoepidemiología. Estudios de utilización de medicamentos. Parte I: Concepto y metodología. Pharmacy Practice, july-september, año 2008/vol 2, número 003. Centro de Investigaciones y Publicaciones Farmacéuticas Granada. España (pages 129-136)

3.2.1.1.9 Sweden

Swedish Prescribed Drug Register	
Organization	The National Board of Health and Welfare
Web	http://192.137.163.40/epcfs/index.asp?kod=engelska
Source	Prescribed medicines dispensed by community pharmacies
Setting	Out Patient
Population coverage	100%
Accesibility	Free online http://192.137.163.49/sdb/lak/val.aspx (only in Swedish) Specific data may be delivered on requests for statistics or research. Approval from ethical committee is needed when data is used for research
Drug codification	ATC (all levels)
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
Record	July 2005-ongoing (online). Prescribing records kept since 1974

period	
Language	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.
References	✓ Wettermark B,HammarN,ForedC.M,LeimanisA,Otterblad OlaussonP,BergmanU,PerssonI,SundströmA,Westerholm B,RosenM. The new Swedish Prescribed Drug Register – oportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf. 2007; 16:726-735. ✓ Jonasson JM, Ljung R, Talbäck M, Haglund B, Gudbjörnsdòttir S, Steineck G. Insulin glargine use and short-term incidence of malignancies –a population-based follow-up study in Sweden. Diabetologia 2009; 52:1745-1754. ✓ Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sørensen HT. The Nordic Countries as a Cohort for Pharmacoepidemiological Research. Basic Clin Pharmacol Toxicol. 2010;106:86-94 ✓ Wessling A. Continuous recording of drug prescribing in Sweden 1974-1983. Methods and examples of utilization of data. Eur J Clin Pharmacol 1987;33(1):7-13.

Apotek AB database	
Organization	Apotek AB (The National Corporation of Swedish Pharmacies)
Web	www.apotekensservice.se
Source	All sales of medicines from pharmacies to individuals and supplied to hospitals by manufacturers
Setting	Out- and inpatient
Population coverage	100%
Accessibility	Free online for OTC and total sales per county Further information: application to data provider statistik@apotekensservice.se
Drug codification	ATC (all levels)
Data	Turnover,wholesales price (wholesaler purchasing price and retailer purchasing price), national pharmaceutical code number, DDD, manufacturer's organisation and identification number, type of transaction, organization'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	2006 (online)
Language	Swedish
Record linkage	No
References	✓ http://www.apotekensservice.se/Om_statistik/ (last accessed 19/5/2011) ✓ 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.

3.2.1.1.10 The Netherlands

GIP Database	
Organization	Health Care Insurance Board
Web	http://www.gipdatabank.nl/
Source	Drugs prescribed by generalpractitioners and specialists and dispensed by pharmacists, as well as dispensing general practitioners and other outlets being reimbursed under The Health Care Insurance Act.
Setting	Out-patient.
Population coverage	95%
Accesibility	Free online. Further data can be applied for.
Drug codification	ATC (all levels)
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. ***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
Record period	2004-onwards
Language	Dutch and English
Record linkage	No
Other databases	InterAction Database (IADB, www.iadb.nl): Pharmacy dispensing records of the Northern Netherlands. Free data online down to ATC level 3.
References	✓ College voor zorgverzekeringen. GIPeilingen 2009. Ontwikkelingen genees-en hulmiddelengebruik. Genees- en hulmiddelen Informatie Project, september 2010, nr 31. ✓ Akkerman AE, Kuyvenhoven MM, Verheij T, van Kijk L. Antibiotics in Dutch general practice: nationwide electronic GP database and national reimbursment rates. Pharmacoepidemiol Drug Saf. 2008; 17:378-383. ✓ Dekker F, Wiendels NJ, van der Vliet C,de Valk V et al. Triptan use and overuse in the Netherlands –a national pharmaco-database analysis. In: Chronic frequent headache in the general population Wiendels NJ. Doctoral thesis, Leiden University. 2008. https://openaccess.leidenuniv.nl/bitstream/1887/12608/12/07.pdf (last accessed 20/5/2011). ✓ Knoster P, Deckers C, van der Vaart R, Leufkens B, Hekster Y. Volume and market share of anti-epileptic drugs in the Netherlands: impact of new drugs. Pharm World Sci 2005;27:129-134.

Database of the Foundation for Pharmaceutical Statistics	
Organization	Foundation for Pharmaceutical Statistics (SFK)
Web	http://www.sfk.nl
Source	SFK directly gathers its data from a panel of pharmacies (1836 of 1981 community pharmacies). Drug dispensed data.
Setting	Out-patient
Population coverage	92.3%
Accesibility	Application to data provider
Drug codification	ATC (all levels)
Data	**Patients**: age, gender. **Prescriber**: specialist, general practitioner,or 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 insurance sector, insurer, institution.
Record period	From 1990 and upwards
Language	Dutch and English
Record linkage	No
References	✓ Griens AMFG, Lukaart JS, van der Vaart RJ. Foundation for Pharmaceutical Statistics (Stitchting Farmaceutische Kengetallen). February 2011. http://www.sfk.nl/algemeen/2010fandf (last accessed 20/5/2011). ✓ 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 (4):315-326. ✓ Teichert M, van der Aalst A, de Wit H, Stroo M, De Smet PAGM. How useful are prescribing indicators based on the DU90% method to distinguish the quality of prescribing between pharmacotherapy audit meetings with different levels of functioning? Eur J Clin Pharmacol 2007;63:1171-1177. ✓ Florentinus SR, Souverein PC, Griens FA, Groenewegen PP, Leufkens HG, Heerdink ER. Linking community pharmacy dispensing data to prescribring data of general practitioners. BMC Med Inform Decis Mak. 2006; 6, 18.

3.2.1.1.11 The United Kingdom

ENGLAND	
Electronic Prescribing Database-England (ePACT)	
Organization	NHS Business Services Authority. Prescription Services. Electronic Prescribing Analysis and Cost (ePACT)
Web	http://www.nhsbsa.nhs.uk/PrescriptionServices/960.aspx
Source	Prescribed drugs by community pharmacists. It does not include prescriptions dispensed in mental health units, or private prescriptions.

Accesibility	Application to data provider
Setting	Outpatient
Population coverage	100%
Drug codification	British National Formulary (BNF) ATC provided upon request. Equivalences between both codification systems provided by NHS upon request.
Data	Reporting period. Prescribing organization (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 enviornment for nurses and suplementary 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 (computerized)
Language	English
Record linkage	No
References	✓ National Health Services. Business Services Authority. Prescription Services. Prescription data www.nhsbsa.nhs.uk/PrescriptionServices/3230.aspx[accessed 20/5/2010] ✓ Langley TE, Szatkowski L, Gibson J, Huang Y, McNeill A, Coleman T, Lewis S. Validation of the Health Improvement Network (THIN) primary care database for monitoring prescriptions for smoking cessation medications. Pharmacoepidemiology and drug safety 2010;19:586-590. ✓ Bennie M, Bishop I.Routine prescribing data. In: Bond C, editor. Using medicines information. 1st ed. Oxford:Radcliffe; 2008. p.101-123 http://www.radcliffe-oxford.com/books/samplechapter/6908/Bond%20chpt%2007-11ed6ac0rdz.pdf (accessed 23/5/2011). ✓ Guillaume L, Cooper R, Avery A, Mitchell S, Ward P, Anderson C, Bissell P, Hutchinson A, James V, Lymn J, McIntosh A, Murphy E, Ratcliffe J. Supplementary prescribing by community and primary care pharmacists: an analysis of PACT data, 2004-2006. J Clin Pharm Ther 2008;33:11-16 ✓ Majeed A, Evans N, Head P. What can PACT tell us about prescribing in general practice? British Medical Journal, 1997;315:1515.

NORTHERN IRELAND	
ePACT database-North Ireland	
Organizati	Health & Social Care in Northern Ireland

on	www.n-i.nhs.uk (accessed 23/5/2011)
Web	Business Services Organization http://www.hscbusiness.hscni.net/(accessed 23/5/2011)
Accesibility	Some data free online. Further data must be purchased.
Setting	Out-patient.
Population coverage	100%
Drug codification	British National Formulary
Source	All dispensed prescriptions by community pharmacists, dispensing doctors and personally administered by GPs.
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 Board). It **does not** collect patient information (age, sex, name or address), dosage or duration of treatment, or the indication.
Record period	From 2000 and onwards (online)
Language	English
Record linkage	No
References	✓ Business Services Organization. Information on Pharmaceutical Prescribing. Pharmaceutical Statistics. Prescritption Cost Analyses. http://www.hscbusiness.hscni.net/services/Family Practitioner Services/Information and Research Unit/statistics/Pharmaceutical Statistics/Prescription Cost Analysis/index.html#TopOfPage (accessed 23/5/2011) ✓ 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.

SCOTLAND	
ePACT database-Scotland and HMUD database	
Organization	NHS National Services Scotland. Information Service Division (ISD) Scotland. Scottish Prescribing Analyses (SPA) National Medicines Utilization Unit (NMUU): Hospital Medicines Utilization Database(HMUD)
Web	www.isdscotland.org
Accesibility	Application to data provider
Setting	SPA:Outpatient HMUD: Inpatient aggregated at hospital level
Population coverage	100%
Drug codification	SPA:British National Formulary 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 (oocupied 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 HMUD since 2007
Language	English
Other databases	MEMO database (Medicines Monitoring Unit at the University of Dundee). It collects all dispensed drugs by the pharmacists covering the population of Tayside. It contains patient and prescriber information
Record linkage	No
References	✓ The effect of the withdrawal of rofecoxib on prescribing patterns of COX-2 inhibitors in Scotland. Williams D, Singh M, Hind C Br J Clin Pharmacol. 2006 Sep;62(3):366-8 ✓ Statistics on prescribing in Scotland (produced by the Information Services Division of NHS Scotland). Assessment report 60. October 2010. Pdf document downloaded from www.statisticsauthority.gov.uk/assessment/assessment/asse

	ssment-reports/index.html [accessed 23/5/2011] ✓ Hospital Medicines Utilisation Database(HMUD).www.isdscotland.org/isd/6123.html [accessed 23/5/2011] ✓ Hospital Medicines Utilization Database (HMUD) http://www.isdscotland.org/isd/6542.html HMUD Data manual.pdf ✓ Development of a system to allow comparison of Secondary Care medicines utilisation across Scotland-the Hospital Medicines Utilisation Database (HMUD). Abstracts of DURG (UK and Ireland). 21st Annual Scientific Meeting (February 2010).Pharmacoepidemiology and Drug Safety, (2010). DOI:10.1002/pds. ✓ Libby G, MacDonald TM, Evans MM. Record-linkage methodology for prescribing research. Journal of Clinical Pharmacy and Therapeutcis. 2001(26): 241-246.

WALES	
ePACT database-Wales	
Organization	NHS Wales Informatics Service (NWIS) Partneriaeth Cydwasanaethau. Gwasanaethau Rhagnodi Shared Services Partnership. Prescribing Services
Web	www.wales.nhs.uk/sites3/home.cfm?orgid=428&redirect=yes
Accesibility	Application to data provider Some data is available free online.
Setting	Out-patient
Population coverage	100%
Drug codification	British National Formulary
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 strenght, 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 23/5/2011) ✓ Cohen D, FasihulAlam M, Dunstan FDJ, Myles S, Hughes DA, Routledge PA. Abolition of Prescription Copayments in Wales: An observational Study on Dispensing Rates. Value in Health 2010;13(5):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

3.2.2 COMMERCIAL DATA PROVIDERS

IMS (Intercontinental Medical Statistics) collects drugs utilization data worldwide. Access to these data is subject to contract. Most customers are pharmaceutical companies, with an interest in sales data at national or regional level. In IMS Multinational Integrated Analysis System (MIDAS), data are registered by drug and for all its application forms and it attempts to do this in a standardized way (18-20)

Collection of data

In general, there are two different ways of data collection:

1) Drugs sales from pharmacy to consumer (sell-out)

2) Distribution from wholesaler to pharmacy (sell-in)

In some countries, direct distribution from the manufacturer to pharmacy may also be captured. In may countries, IMS uses sell-in panels.

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 data: volume and classification

IMS sales data are expressed in volume numbers (numbers of packs sold). More detail provide Counting Units (CUs). CU are the number of millitres (if liquid), millgrams (if dry) per tablets. The CUs 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 Defined Daily Doses, as defined by WHO-DDD(16).

Using volume of DDDs sold over a given time period and a given population number, the number of DDDs per 1,000 inhabitants per day (DDD/1,000 persons/day) can be calculated.

Expression of drug utilization in DDDs/1,000 persons/day allows aggregation of data that differ in administration form and strength of dose and makes it possible to compare drug use between countries(16).

Products are classified by IMS using the anatomical classification of Pharmaceutical Products developed and maintained by the European Pharmaceutical Marketing Research Association (EphMRA).

It should be noted for some recently marketed products, WHO ATC/DDD Index does not provide a DDD. There are indeed delays in assigning DDDs to new drugs. For studies, these DDDs have to be estimated. Recent reference works such as Martin Dale can be checked for the recommended dose, for an ad-hoc DDD. Else, literature on randomized clinical trials (RCTs) may be available and the given dose in these studies can be used to estimate a DDD. If no RCTs were found, the most frequent strength of dose in the IMS data can be used. In case only an oral DDD is available while there are also parenteral forms of application, an oral DDD may be used for the parenteral forms.

Estimating numbers of users

IMS can provide data on volume of drugs sold, not however on numbers of users. By transforming sales data to DDDs as described above, utilization expressed as DDD/1000 persons/day can be estimated, a proxy for the point prevalence of users.

To extrapolate IMS volume data to a number of different users over a given period (period prevalence), the few publicly accessible databases can be used.

Databases that contain both volume data and the number of users are available from Denmark, the Netherlands and Norway: the Register of Medicinal of Product Statistics of the Danish Medicines Agency(21), the Dutch GIPdatabank(22) and the Norwegian Prescription Database (NorPD)(23).

The ratio volume/number of users can be calculated for a given product with the data contained in these three databases. The figure found can be used to calculate a number of users in other countries, using national volume data from IMS. One should remark however the ratio volume/number of users may be variable across countries, which will affect the precision of an extrapolation of number of users from the three publicly available databases to other countries covered by IMS data.

See appendix 7 and 8 for data available at FICF from non-commercial and commercial data providers.

3.3 INPATIENT DRUG UTILIZATION RESOURCES

3.3.1 NON-COMMERCIAL DATA PROVIDERS

3.3.1.1 DRUG UTILIZATION IN HOSPITAL SETTINGS

General website information:

The PHIS hospital pharma report (2010) states that European in-patient pharmaceutical consumption ranged from 3% in Sweden up to 14% in Latvia (6).

Table 8, extracted from this report, shows the top 10 active ingredients consumed in European hospitals during 2007.

Table 8. Top 10 active substances consumed (in volume) in European hospitals, 2007.

Paracetamol
Electrolyte solutions
Furosemide
Acetylsalicylic Acid
Epoetin beta
Albumin
Omeprazol
Ranitidine
Prednisolone
Coagulation factors IX, VII and X

The website http://www.eahp.eu/ published a report of a survey conducted in 2005, on 825 hospitals from 22 out of the 26 European member countries. It provides information on the organization and activities of European hospital pharmacies, but not on drug utilization (5).

The European Hospital and Healthcare Federation, www.hope.be has published a monography with information on the organization of hospital health care of the 27 European Member States. No information on medicines consumption is given(24).

From the OECD website, a technical report(25)on the use of hospital administrative databases in health research was downloaded. Hospital administrative databases is understood as those databases that collect information on diagnosis and treatment for the whole population. Belgium, Denmark, Finland, France, Italy, Sweden and the United Kingdom were the European countries included in this report. Only 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, only Denmark has hospital drug consumption freely available on its website, www.dkma.dk, expressed in DDD/1000 inhabitants/day. From national reports on medicines consumption, published by official governmental organizations, Sweden provides data on drug consumption in hospitals(26). Denmark also publishes an annual report with information on hospital drug utilization(21). Other countries collect information at a hospital level, such as France and Italy through the National Medicines Agency, but to obtain the data, a further application is needed. These reports reflect sales of medicines to hospital pharmacies. The United Kingdom has also hospital drug consumption provided by IMS Health; however, the data cannot be released. For the rest of the European countries included in the inventory, hospital drug consumption data is not collected at national level. Figures extracted from the Denmark database, France AFSSAPS database and Swedish annual report will serve as an example to show the level of drug consumption in hospital settings for the ATC groups C, N and R.

Table 9 shows drug consumption in Denmark, for 2009, in the primary health sector and hospital sector, by ATC level 1: C (cardiovascular system), N (nervous system) and R (respiratory system). The consumption is expressed in DDD/1000 inhabitants/day and the proportion out of the total drug consumption for primary health care and hospital sector is given.

Table 9. Primary health sector and hospital sector drug consumption in Denmark in 2009. ATC level 1. Expressed in DDD/1000 inhabitants/day

ATC level 1	Primary health care sector or outpatient DDD/1000 inh/day(%)	Hospital sector or inpatient DDD/1000 inh/day(%)	Total DDD/1000inh/day
C Cardiovascular system	482.2 (98.8)	6 (1.2)	**488.2**
N Nervous system	258 (96.9)	8.3(3.1)	**266.3**
R Respiratory system	121.4 (98.4)	2(1.6)	**123.4**
Total	**1,351 (96.5)**	**49 (3.5)**	**1,400**

Source: Data extracted from Lægemiddelstatistik I Danmarkwww.dkma.dk/medstat [Accessed 18/3/2011]

The total drug consumption in Denmark for the cardiovascular, respiratory and nervous system, excluded over-the-counter (OTC) drugs, amounted to 1400 DDD/1000inhabitants/day. Only 3.5% of the total ATC group C, N and R use was consumed at the hospital level, representing only 1.2%, 3.1% and 1.6%, respectively.

A similar table (Table 10) could be elaborated for Sweden from data extracted from the annual report published by the Swedish National Board of Health and Welfare(26). This information is given in millions of DDD and was converted into DDD/1000inhabitants/day considering that the Swedish

population in 2009 was 9,340,682 inhabitants

(http://www.scb.se/Pages/TableAndChart____25897.aspx Statistics in Sweden

[Accessed 19/3/2011]).

Table 10. Primary health sector and hospital sector drug consumption in Sweden in 2009, by ATC level 1. Expressed in DDD/1000 inhabitants/day

ATC level 1	Primary health care sector or outpatient DDD/1000 inh/day(%)	Hospital sector or inpatient DDD/1000 inh/day(%)	Total DDD/1000inh/day
C Cardiovascular system	424.4 (98.7)	5.63(1.3)	**430.03**
N Nervous system	220.57(96.2)	8.79(3.8)	**229.36**
R Respiratory system	100.02(97.5)	2.55(2.5)	**102.57**
Total	**1,639.6 (97.1)**	**48.2 (2.9)**	**1,687.8**

Source: Data extracted from http://www.socialstyrelsen.se/publikationer2010/2010-3-28.Läkemedelstatistik förår 2009. [Accessed 20/3/2011].

In Sweden as in Denmark, similar trends of drug consumption in hospitals can be described. A very low percentage of drugs coded as acting on the cardiovascular system (1.3%), nervous system (3.8%) and respiratory system (2.5%) are used at the hospital level.

Table 11 shows the consumption of the PROTECT selected drugs in Denmark, year 2009. The classification of the medicines is down to ATC level 3 or 4 and the unit of measure is DDD/1000 inhabitants/day.

Table 11. Outpatient and inpatient drug consumption in Denmark 2009, by ATC level 3 or 4. Expressed in DDD/1000 inhabitants/day

ATC level 3 or 4	Primary health	Hospital sector	Total

	care sector or outpatient DDD/1000 inhabitants/day(%)	**or inpatient** DDD/1000 inhabitants/day(%)	
C08 Calcium channel blockers	68 (99.3)	0.5 (0.7)	**68.5**
N03 Antiepileptics	13.5 (97.1)	0.4 (2.9)	**13.9**
N05BA Benzodiazepine derivatives (anxiolytics)	12.3 (96.1)	0.5 (3.9)	**12.8**
N05CD Benzodiazepinesderivatives (hypnotics and sedatives)	5.3 (96.4)	0.2 (3.6)	**5.5**
N06A Antidepressants	77 (98.5)	1.2 (1.5)	**78.2**
R03AC Selective beta-2-adrenoreceptor agonists	18.6 (97.4)	0.5 (2.6)	**19.1**
R03AK Adrenergics and other drugs for obstructive airway diseases	16.8 (97.1)	0.5 (2.9)	**17.3**

Source: Data extracted from Lægemiddelstatistik I Danmarkwww.dkma.dk/medstat

[Accessed 18/3/2011]

The consumption of some of the different groups of medicines in hospitals in Denmark is as low as 2.6% for selective beta-2 adrenoreceptor agonists (R03AC) and 2.9% for adrenergics and other drugs for obstructive airway diseases (R03AK), or 0.7% for calcium channel blockers (C08). Benzodiazepine derivatives (N05BA and N05CD) correspond to a higher proportion of inpatient drug consumption. Yet, compared to outpatient sector, inpatient consumption does not represent more than 5% of the total consumption of anxiolytics and no more than 5% of hypnotics and sedatives.

As part of the PROTECT project we obtained data on inpatient drug consumption from the AFSSAPS, another example of drug consumption in inpatient settings in France, year 2009. This data is provided by the pharmaceutical manufacturers straight to the French government for taxes purposes.

Table 12. Drug consumption in the inpatient and outpatient sector in France, by ATC level 3 or 4, year 2009. Expressed in DDD/1000 inhabitants/day.

ATC level 3 or 4	**Primary health care sector or outpatient** DDD/1000 inhabitants/day(%)	**Hospital sector or inpatient** DDD/1000 inhabitants/day(%)	**Total**
C08 Calcium channel blockers	50.89 (97.8)	1.16 (2.2)	**52.05**
N03 Antiepileptics	12.55 (94.0)	0.81 (6.0)	**13.35**
N05BA Benzodiazepine derivatives (anxiolytics)	39.98 (93.6)	2.73 (6.4)	**42.71**
N05CD Benzodiazepinesderivatives (hypnotics and sedatives)	7.91 (93.1)	0.59 (6.9)	**8.5**
N06A Antidepressants	47.68 (95.7)	2.15 (4.3)	**49.83**
R03AC Selective beta-2-adrenoreceptor agonists	16.28 (95.9)	0.69 (4.1)	**16.97**
R03AK Adrenergics and other drugs for obstructive airway diseases	21.88 (98.5)	0.34 (1.5)	**22.22**

Source: Data provided by AFSSAPS as part of the PROTECT project.

As shown in the above tables, the utilization of the drugs ATC group C, N and R in hospitals is below 10%. The greatest difference between the outpatient and inpatient sectors, is seen in the consumption of adrenergics and other drugs for obstructive airway diseases (R03AK), where only 1.5% is consumed in hospitals. Also calcium channel blockers (C08) are used in 97.8% of all the cases in the outpatient sector.

Bibliographic search:

All titles returned by the search in PubMed were screened and abstracts read. If an abstract was not available in the electronic database, the article in full was searched in order to try to find out more information on its contents. All the abstracts published in or later than 1980 were reviewed to see whether they

fulfilled the inclusion criteria. If the abstract was not available, the citation was excluded.

Because the search strategy did not take into account the indication for use of the medicines, several articles were equally found under different medicines groups, 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.

The results of the search in the electronic database PubMed are shown in table 13.

Table 13. Key search terms and citations retrieved from PubMed dating back to 1980

Key search terms	Calcium channel blockers	Antiepileptics	Beta-2-agonists	Antidepressants	Benzodiazepines
Hospital drug utilization	138	201	33	253	245
Titles earlier than 1980	0	2	0	13	6
Duplicates	3	0	1	4	18
No abstract available	0	0	0	1	1
Articles included (references)	5 (27-32)	16 (33-48)	0	20 (49-68)	23 (69-91)

Articles classified as not being drug utilization research studies, were either studying the metabolism of the active pharmaceutical ingredient in animals or were guidelines of the use of the drugs in clinical practice.

Articles categorized as containing drugs of no interest, provided information on magnesium sulphate, in the case of calcium channel blockers;

leukotriens and devices used in the administration of inhaled medicines, in thecase of beta-2-agonists. In the case of antidepressants, antiepileptics and benzodiazepines, antipsychotics and opioids were catalogued as drugs of no interest.

Regardless of the country concerned and the type of drug utilization 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. This calculation eased the comparison of drug use among different diagnoses or across countries.

Articles concerning antiepileptic drugs, benzodiazepines and antidepressants included in this review were conducted in nursing homes or in other long-term care institutions, and therefore the study subjects were mainly elderly people or people with learning disabilities.

3.3.1.2 ANTIBACTERIAL UTILIZATION IN HOSPITAL SETTINGS

Below we present the results obtained from the PubMed search (table 14 and table 15) and the website search (table 16)

PubMed search

Table 14. Results of PubMed search on antibiotic utilization in hospitals

Drug	Citations identified	Citations included for full review
Search 1	149	38
Search 2	196	20
Search 3	362	38

Erythromycin	178	
Spiramycin	2	
Midecamycin	0	
Oleandomycin	0	
Roxithromycin	4	
Josamycin	1	
Troleandomycin	0	
Clarithromycin	39	
Azithromycin	23	
Miocamycin	2	
Rokitamycin	2	
Dirithromycin	0	
Flurithromycin	0	
Telithromycin	10	
Amoxicillin (co-amoxiclav)	101	
Totals	707	96
	After exclusion of duplicates	88
	Papers with relevant data	20

Papers that were deemed not to contain relevant data (n=68), were mainly because no antibiotic consumption data was collected (n=35; 51.5%), because data on antibiotics did not come from the inpatient setting (n=11; 16.2%), because the antibiotics listed in the publication were not of interest (n=15; 22%), or there was no online access to the article (n=7; 10.3%).

Table 15 shows the information extracted from the 20 publications by country and active substance.

Table 15. Results from the PubMed search split by country

Country	Citation	Study year	Setting	Unit of measurement
Denmark	(92)	1997-2001	All public hospitals	DDD/100 bed-days for macrolides
Finland	No information identified			
France	(93)	11/1998 to 4/1999	7 Infectious disease wards	Percentage of patients prescribed a single macrolide or co-amoxiclav and percentage of patients prescribed combination therapy out of the total patients with community-acquired pneumonia
	(94)	1/1983 to	13 hospitals	Percentage of patients receiving clarithromycin as part of a

Country	Citation	Study year	Setting	Unit of measurement
		12/2003		combination therapy to treat M xenopi
	(95)	5/1997 to 12/2001	Neurosurgical unit of one hospital	Percentage of patients receiving co-amoxiclav as prophylaxis (20%)
	(27)	1/1999 to 12/2000	2200-bed teaching hospital	Percentage of patients receiving coamoxiclav out of the total patients undergoing first or revision total hip replacement
Germany	(96)	1994	4 university hospitals (1000-1700 beds)	Percentage of macrolides prescribed out of all the patients admitted
	(97)	2001-2004	40 ICU	DDD/1000 patient-days for macrolides
Italy	No information identified			
Norway	No information identified			
Poland	No information identified			
Spain	(98)	11/1998 to 10/1999	9 hospitals	DDD/1000 inhabitants/year (calculated from wholesaler sales) for macrolides
	(99)	1986 to 2004	6 hospitals	Percentage of patients prescribed erythromicyn or coamoxiclav in combination therapy to treat endophthalmitis
	(31)	2/1999 to 6/1999	25 hospitals	Percentage of coamoxiclav prescriptions
Sweden	No information identified			
The Netherlands	No information identified			
United Kingdom	(100)	1/1995 to 3/1997	1 hospital	DDD/patient-days for macrolides
	(101)	2003 (1 day)	10 acute hospitals	Percentage of patients receiving a macrolide out of the total patients
	(102)	5/2008 and 5/2009	1 hospital	Percentage of patients prescribed a macrolide out of the total patients
	(103)	2002 to 2007	426-bed district general hospital	DDD/100 bed-days for macrolides and coamoxiclav
	(104)	9/1994 to 8/1995 10/1996 to 9/1997	1 hospital Children with CAP	Percentage of patients receiving a prescritpion of a erythromycin, clarythromycin, or coamoxiclav
	(105,106)	1/1996 to 12/2000	1 surgical ward	Percentage of patients with erythromycin, clarythromycin, co-amoxiclav prescribed out of the total patients
	(107)	2003 to 2007	1 hospital	Percentage of children out of the total children that underwent major airway surgery receiving coamoxiclav
	(108)	Not	1 hospital	Percentage of patients receiving

Country	Citation	Study year	Setting	Unit of measurement
		specified		clarythromycin to treat suspected or confirmed bacterial meningitis
	(109)	1/1996 to 12/2000	1 hospital	Percentage of patients receiving co-amoxiclav out of the total children admitted for neck abscess

Web-based search

Table 16 shows potential sources of inpatient antibacterial consumption, that hold information at national level. Several of these data sources may potentially provide information on other groups of medicines. The last row of the table shows the data on antibacterial consumption provided by the ESAC interactive database.

Table 16. Sources of information on antibiotic consumption. Countries(§) with information on other drug groups

	DENMARK[§]	FRANCE[§]	ITALY[§]	NORWAY[§]	SPAIN (Catalonia: 7,364,078)	SWEDEN[§]	THE NETHERLANDS	UNITED KINGDOM[§]	
								England	Scotland
Data provider	Danish Medicines Agency	French Medicines Agency	Italian Medicines Agency	Norwegian Institute of Public Health	Regional Catalan Authority	Apoteket AB[§] STRAMA	SWAB	NHS Information Cener. HPAI (Hospital Prescribing Audit Index database)	Scotland National Medicines Utilization Unit
Data source	Danish Prescription Registry	AFSSAPS database	OsMED database	Wholesaler-based drug statistics	VinCAT database (Nossocomial Infection Surveillance in Catalan Hospitals)	Apoteket AB STRAMA-Point-prevalence survey (PPS) on AB consumption across Swedish hospitals	Questionnaire sent to hospital pharmacies	IMS Health. Hospital Pharmacy Audit Index	Hospital Medicines Unit
Type of data	Dispensed medicines by ward	Sales from wholesalers	Reimbursed prescriptions	Sales from wholesalers	Dispensed Inpatient antibiotics and antifungals	Sales from wholesalers STRAMA-PPS: Dispensed AB by hosp pharmacy to hosp departments	Dispensed medicines	Supplies from hospital pharmacies to wards, departments, theatres, satellite sites and patient in outpat clinics and on discharge	Dispensed medicines
Population coverage(%)	100	100	100	100	66 Catalan Hospitals	100	53 Dutch Hospitals	97% of all NHS acute beds	100
Record period	1997	1992	Online reports since yr 2000	1997	2008	Online since yr 2006	Online report since 2003	1991	2007
ATC/DDD methodology	Yes *DDD/100 occupied bed-days* *DDD/100*	Yes *DDD/100 admissions* *DID*	Yes	Yes *DID*	Yes *DDD/100 patient-days* *DDD/100 discharges*	Yes *DDD/100 patient-days* *DDD/100 admissions*	Yes *DDD/patient-days* *DDD/100 admissions*	EPhMRA/ATC codification *Total DDD*	Yes Also BNF codification

	discharges *DID*								

.../...

	DENMARK[§]	FRANCE[§]	ITALY[§]	NORWAY[§]	SPAIN (Catalonia)	SWEDEN[§]	THE NETHERLANDS	UNITED KINGDOM[§]	
								England	Scotland
Patient data collected	No	No	Age and gender Demographic data available on patients and physicians through linkage to other DB	No	Yes Age and sex	Yes in PPS: Diagnosis, infection focus, indication (4 pre-established groups), immunodef, culture before tx, route of administration, dose, prescription	Yes. Age and sex	Not specified	Yes Age and sex
Other data collected	Outpatient	Outpatient	Outpatient	For specific AB consumption, there exists the Hopital Pharmacies Drug Statistics database: Sales from hospital pharmacy to wards and hospitals	Type and localization of infection. Medical devices used. Type of surgery. Type of prophylaxis. Indication according to 3 pre-established categories	Outpatient STRAMA also has ICU AB consumption	Type of hospital. Region. Department of hospital	Volume of use of medicines in packs. Estimated costs	Health care board, Pharmaceutical product ID, formulary status, costs, inpatient or daycase, occupied bed-days, number of episodes of care, type of hospital
Accessibiity	http://laegemiddelstyrelsen.dk	www.afssaps.fr	www.agenziafarmaco.it	www.fhi.no	http://www20.gencat.cat	www.apotekensservice.se	www.swab.nl	http://www.ic.nhs.uk	http://www.isdscotland.org/Healt

	Free online	Application	Application	Application	Application	Application www.strama.se Application	Free data on the report.	Data not released	h-Topics/Prescribing-and-Medicines/Hospital-Medicines-Utilisation/ Application
AB consumption in ESAC web	It provides in- and outhospital	It provides in- and outhospital	It provides in- and outhospital	It provides in- and outhospital	Spain provides only outpatient	Out and inhospital	The Netherlands contributes with outhospital	England provides outpatient	PPS participating 39 Scottish hospitals

4 VALIDITY OF DRUG CONSUMPTION DATABASES

4.1 SPECIFIC METHODOLOGY

Vander Stichele et al (110) listed the problems encountered when evaluating antibiotic consumption data across European countries, including potential biases these factors could have introduced in study results. Data collected from different national drug consumption databases raised concerns about population coverage, 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.

Sørensen(11) 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), the size of the data source (population coverage), the registration period, the accessibility, availability and cost, data format (e.g. available age categories) and record linkage (unique personal identifying number allowing to link with independent automated databases, or through probability scores(111)).

There is a vast bibliography regarding the validity and application of automated databases in research, from a more conceptual point of view

(10,112) to reviews of uses of these databases in pharmacoepidemiology (9,113,114), to studying different aspects of the databases that can affect their comparability (115-118). (119,120)Specifically for drug utilization studies, several articles have evaluated the comparability of data sources across European countries, both among national drug consumption databases (119,121)and between national databases and commercial databases(118). As stated in the introduction, validity of the national drug consumption databases is understood as the degree of comparability of these databases in measuring drug exposure across countries and/or over time.

A questionnaire was elaborated trying to collect information on the items considered of relevance when measuring drug exposure and that could also be key elements in interpreting the results obtained. See appendix 9 for a sample of the questionnaire sent. For completeness, the items selected for the questionnaire are listed below:

a. Definition of in- and outpatient drug consumption. Interest in knowing whether drugs used in nursing homes, drug abuse centers, private institutions were collected and if so, classified as in- or outpatient. Also whether prescriptions by specialists or hospital medicines dispensed to outpatients, were included as in-or outpatients

b. Population coverage by the database.If the coverage was below to 90%, what weighting system was used. If the database covered only a sample, the sampling methodology.

c.Drug-based information. This item covered many different aspects that may be of interest for establishing the proportion of a population exposed to drug.

c1) Source of the data (wholesalers sales, dispensed –drugs purchased by an individual in the pharmacy, prescribed –issued prescriptions by a healthcare professional dispensed in a pharmacy, independently of their reimbursement status-, or reimbursed medicines- drugs prescrribed and reimbursed by the government that are dispensed in a pharmacy)

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

c3) Characteristics of the package sold to check the calculations supplied by the database.

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

c5) Proportion of missing information in 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 DDD assigned.

d. Patient-related information collected, either straight in the database, such as age, sex, 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 the periodicity of these checkings

f. Accessibility of the data for research purposes.

The questionnaire was structured in 4 headings, 3 of them 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 of the initial 12 national drug consumption databases selected by the PROTECT project. A cover letter and and the instructions to fill and return the questionnaire followed. The questionnaire comprised closed- questions, but also included the possibility to add 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(122-127) or from their own websites. Thus, participants were asked to complete and ammend any errors found. Two remainders were sent.

4.2 SPECIFIC RESULTS

Questionnaires were sent to the following databases: The Danish Registry of Medicinal Products Statistics, CNAMTS and AFSSAPS, Research Institute of AOK, OsMed, NorPD, NHF Poland, Spanish Ministry of Health, division of pharmaceutical products, Swedish Prescription Register, GIP databank and SFK, and the central ePACT Services.

Questionnaires were received from: The Danish Prescription Register, AFSSAPS, OsMed, NorPD, GIP, SFK and The Swedish Prescription Register.

For Spain, Germany, Poland, and UK no answer was received by July 2011.

Results from the questionnaires received

A summary of the answers provided in the questionnaire can be seen in table 17 and 18

Table 17. Comparability of national consumption databases (Denmark, France, Italy, Norway)

Items	Danish Registry of Medicinal Products Statistics	AFSSAPS	OsMed	NorPD
Type of data source	-Dispensed medicines in outpatient sector -Sales from wholesalers in inpatient sector	-Sales from wholesalers	-Reimbursed medicines from regional local authorities databases (LHA) -Dispensed medicines from IMS Health	-Dispensed prescription medicines
Data included as outpatient drug consumption	-Community pharmacies - Hospital drugs dispensed to outpatients	-Sales to ommunity pharmacies	-Nursing homes -Specialist care to outpatients -Hospital drugs dispensed to outpatients (partly)	-Dental care -Specialist care to outpatients -Drug abuse centers -Private institutions
Data included as inpatient drug consumption	-Sales from wholesalers 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

Items	Danish Registry of Medicinal Products Statistics	AFSSAPS	OsMed	NorPD
If applicable, sampling or weighting methodology	--	--	--	--
OTC sales	Yes	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)	No	Yes (Quantity of drug dispensed and dose)	No No information on quantity of drug dispensed, nor days of supply provided. Dose is available only as free text
ATC/DDD updatings	Yearly, all retrospective data is updated	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 drug is assigned to an ATC 4th level group according to WHO guidelines	For anticancer drugs, dispensing units.	No information provided
Linkage to other registers	Yes (through unique ID number)	No	No	Yes (through unique ID number
Register of sociodemographic and economic variables	Yes. Age, sex and place of residence.	No	Yes. Age, sex and place of residence	Yes. Age, sex and place of residence
Other variables collected	Yes. Number of people treated, number of packages. Indication for use in 75% of the prescriptions	No	No	Yes. Information on prescribers and the pharmacy
Internal validity	Every month, large validation process	Data is contrasted with other sources of drug sales	For treacibility data on a monthly basis, for health card register, the process is ongoing. For reimbursed data it depends on the LHA	Monthly and every 6 months the database is checked for inconsistencies and errors
Proportion of missing prescriptions	No information provided	N/A	Regarded as unclear question	1% in 2010
Accessibility	Part of the data is free online. Furhter data can be applied for.	Due to confidentiality conflicts not all data is available. Specifically for those active substances marketed by a single manufacturer	Open to study specific requests	Part of the data is free online. Guidelines on access to further information and fees available at their website

Table 18. Comparability of national drug consumption databases (Sweden and GIP and SFK from Netherlands)

Items	The Swedish Prescription Register	GIP	SFK
Type of data source	-Dispensed prescription medicines	-Reimbursed medicines	-Dispensed medicines
Data included as outpatient drug consumption	Community pharmacies Nursing homes (not completely) Hospital clinics also included	Specialist care to outpatients and hospital drugs dispensed to outpatientInformation on dental care, nursing homes, drug abuse centers and private	Dental care Specialist care to outpatients Hospital drugs dispensed to outpatients

Items	The Swedish Prescription Register	GIP	SFK
		institutions is not collected s	
Data included as inpatient drug consumption	No	No	Nursing homes (partly)
Population coverage (%)	100	95	90
If applicable, sampling or weighting methodology	--	Extrapolation to the total Dutch population through 20 age subgroups and by sex	No information provided
OTC sales	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)	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 updatings	ATC/DDD codes are a separate product register. Although the data is always updated with the last 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	A list with national assigned DDD/ATC exists in the productr register, updated every month	A list with national assigned DDD/ATC exists	No information provided
Linkage to other registers	Yes (Through a unique personal identiy number)	No	No
Register of sociodemographic and economic variables	Yes Age, sex and place of residence	Yes. Age, sex and place of residence	Yes. Age, sex and place of residence
Other variables collected	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	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	<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 is not accessible for researchers although they can post a request

When individual electronic medical records are not available, drug exposure is best studied with databases providing information on dispensed medicines(9). Dispensed medicines covers all prescribed and not prescribed items purchased in a community 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 and NorPD data for

all prescriptions dispensed in a community pharmacy. GIP databank provides information on medicines reimbursed. AFSSAPS collects information on sales of medicinal products from wholesalers.

There are few variables associated with the medicines exposure that are measured in these databases. Six out of the seven databases that replied the questionnaire collect age, sex and place of residence. No other relevant clinical information such as - indication for use or co-morbidities- are collected. However, the Danish Registry of Medicinal Products, the NorPD and the Swedish Prescription register allow the linkage of these registries to other databases through a unique identity number, which may be of interest when studying drug exposure. Time interval of exposure to a medicine can be estimated either through the days a drug is supplied or can be calculated through the quantity of drug dispensed, the dose prescribed and the DDD. AFSSAPS database, Norwegian wholesalers statistics and Apoteket AB data do not allow this calculation as they provide sales of medicines to community or hospital pharmacies. NorPD does not collect information on quantity of drug dispensed and dose is only available as free text. Time intervals of exposure can be estimated in the Danish Registry of Medicinal Products, OsMed, the Swedish Prescription Register, GIP databank and SFK.

The ATC/DDD methodology is adopted by all databases and updated yearly after the release of the WHO guidelines every October(128). However, consumption of those medicines without an ATC/DDD are handled differently. Several databases –The DanishRegistry of Medicinal Products, the Swedish Prescription Register and the GIP databank- use a national list with these medicines and a national DDD is assigned according to WHO guidelines. They

are usually counted as DDD. AFSSAPS assigns the drug into ATC level 4. For anticancer drugs, OsMed uses dispensing units. NorPD and SFK did not provide information.

5 DISCUSSION

The PROTECT inventory provides an account for collecting drug consumption data and, in addition to this, for planning drug utilization 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 drug utilization research at international level . The ultimate objective is to strengthen the monitoring of pubic health impact of a drug. It fulfills the objectives of the PROTECT project, WP2.

18 European working groups, 12 national drug consumption databases with information on dispensed, prescribed or reimbursed medicines, and 3 national sources of sales of medicines from wholesalers were identified. In addition, their characteristics and accessibility have been described. The majority provide information on the outpatient sector. For the 12 national drug consumption databases a questionnaire was sent compiling information on key items which could influence the study results. Complete information was obtained for 7 national drug consumption databases. A brief summary of market surveys conducted by IMS Health is also provided.

Antibacterial drugs were a focus as a therapeutic area. Sources of inpatient antibacterial consumption were identified for 7 countries and 1 region of Spain. For several countries(Denmark, France, Italy, Norway, Apoteket AB in Sweden) these sources of data allow also for estimating drug consumption other than antibacterials.

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

5.1 OUTPATIENT DRUG UTILIZATION 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(17,129). EUROMEDSTAT (2002 – 2007) was the second attempt, and it followed the EuroMedicines Project(129). They widened the initial EuroMedicines Project and developed a European database of licensed medicines and their prices in 20 EU countries and proposed indicators for price and drug utilization(130). Moreover, the database provided statistics on drug utilization across these countries. It showed the wide differences in the availability of data on drug use across the different countries, and the methodological difficulties encountered when comparing data across countries(118,131,132).

Yet, the EUROMEDSTATproject, was mainly focused on compiling potential resources of drug consumption data. 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 worlwide information on drug utilization data, specifically for antibacterials, proton pumb inhibitors, statins and clopidrogel(121). However these sources of data were not described in a comprehensive manner. The information was based on voluntary individual contacts in each country, and the work done by this group is not easily available. Information contained in the posters presented on the 24th ISPE Congress (133) have to be specifically requested.

EnCePP is the fourth attempt at European level. It was established to strengthen the postauthorisation monitoring of medicines. Its website contains, among other aspects involved in pharmacoepidemiological research, a registry of healthcare databases existing in Europe. 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, depending on the individual participating research centers or organizations(134).

In drug utilization studies the source of drug consumption data is a basic piece of information. As part of the objectives of the WG3-PROTECT project, the inventory represents the basis of DU research at a European national level. What comes to the fore from the PROTECT inventory is, first the structured manner in which the characteristics of the information collected by both international working groups and national drug consumption databases is presented. Second, the accessibility to drug consumption data provided by these national drug consumption databases. In addition, other potential sources of drug consumption data at national level are reported. Third, the PROTECT inventory should promote a correct interpretation of the results of a

study comparing the patterns of drug use across different European countries, and the trends over time on drug consumption. Fourth, the potential availabilty of drug consumption information by healthcare sector. Finally, the PROTECT project goes beyond the non-commercial drug data providers, and it also offers a brief summary of the information provided by IMS Health.

Up to now, we have offered a comparison on what has been done and what is new-compared to previous European experiences in collecting drug consumption data. Furthermore, the way the information has been compiled in the PROTECT inventory should offer several advantages: for academic researchers as a basis for future collaboration in drug utilization research; and, for regulatory agencies and pharmaceutical companies it offers the possibility of supporting post-marketing and safety studies.

As a recognition of what previous European initiatives have done, we would like to point out that it is always easier to update existing information than starting from scratch. All previous European projects mentioned earlier has provided us with valuable information, making the PROTECT inventory a comprehensive resource for drug utilization studies in Europe. The PROTECT project provides information on governmental agencies responsible for licensing, pricing and reimbursement of drugs; a brief description of the health policy systems reflecting the complexity of the reimbursement and pricing of drugs in each country; and pharmaceutical information. Having all this information at hand may help to understand some of the differences in patterns of drug consumption across different countries.

From a pragmatic point of view, we deemed of importance to provide information on the accessibility of drug utilization data. As expected the Nordic

countries and the Netherlands with their long tradition in drug utilization research have some of the information readily available online. Further information 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 drug utilization 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 to one of these projects. The information provided for the specific research groups tries to be comprehensive and gives an exact idea of what, within drug utilization research, the European scientific community is interested in.

To the best of our knowledge, such a compilation focused specifically on drug consumption is unique in Europe. All the work done may become almost meaningless, unless the inventory is kept updated in real time. In addition, these information resources on drug consumption must be accessible for researchers and the general public. 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, the fact that we limited ourselves according to the disease areas and medicines of interest for the PROTECT project goals, may have left some European drug utilization working groups out of this inventory. Another limitation is that drug consumption information is only available for 11 countries. However, these countries have been selected taking into consideration their population and tradition in drug utilization research. They represent 78.8% of the

total population of the 27 European Union countries. For researchers interested in conducting drug utilization studies in other European countries, we provide a list of the EuroDURG contacts.

5.2 INPATIENT DRUG UTILIZATION RESOURCES

Information on drug utilization in inpatient settings, understood as dispensation of drugs to patients admitted in hospitals, is sparse at national level. The majority of inpatient drug consumption databases refer to sales from wholesalers. The same applies to published articles regarding inpatient drug utilization studies at national level. Most of the research is set up in one hospital or in several hospitals within one country. Most of 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 authorities. These regional health authorities are the ones in charge of centrallly storing the data and elaborating more detailed drug consumption reports in the outpatient setting. Because of the complexity in the management of hospital medicines, this straight flow of information from hospitals to central health authorities is almost inexistent.

All European countries selected for the PROTECT project keep updated a national database of consumed medicines in the outpatient sector. Some of these countries collect information in inpatient drug use directly from wholesalers (Norway, Sweden or France) or from IMS Health (UK).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 (http://www.esac.ua.ac.be/main.aspx?c=*ESAC2&n=50297 , last accessed 27/6/2011).

Several factors may explain the scarcity of national hospital drug consumption information: First, the high heterogeneity in the management of medicines at a hospital level. From developing a hospital drug formulary, to the medicines distribution chain, up to the availability of a hospital pharmacy. Moreover, in some countries the absolute number of hospitals remains unknown difficulting the centralized collection of dispensed data by hospitals to their patients). These variations in hospital management of medicines are largely related to the variations in national health policies. Second, most of the countries collect sales from wholesalers to hospital pharmacies. Not only it may overestimate the drug exposure, as it includes stock movements in the pharmacy. But also it does only give data at an aggregated level, which means the loss of clinical, social and demographic information of interest when studying a drug exposure. Finally, linked to these general limitations, there are specific methodological problems when studying drug consumption in hospitals. It is usually recommended to adjust the DDD for clinical activity. Several denominators have been proposed: bed-days by the WHO(2); patient days(135), admissions(7), discharges(e.g. VinCAT database(136)), finished consultant episodes(137). Several authors have reviewed these different denominators(138), or tried to develop standardized methods when analyzing, for example, inpatient antibiotic consumption (139). In spite of all these recommendations, the majority of articles published on hospital drug consumption express the drug use as a proportion of a pharmaceutical active ingredient out of the total consumption for a specific group of medicines.

As an exercise for the PROTECT project, figures on drug consumption for the selected PROTECT drugs for Denmark, Sweden and France showed that these drugs are mainly used in the outpatient sector (appendix 6) and that among the top 10 most used drugs in inpatient settings less than a 50% are considered of specialist or only hospital use(6).

There are several limitations to the methodology in finding inpatient drug consumption information. The information on general hospital drug utilization is extracted from only three reports and one website. In addition, only one bibliographic database (PubMed) was used when searching information on inpatient drug utilization, both at a general level and, specifically, for antibacterial consumption. PubMed may have introduced a bias towards studies published in English, resulting in an under-representation of studies run in Europe.

The search strategy for general inpatient drug utilization information retrieved a large number of articles. There still exists the possibility that articles not indexed according to the terms specified in the search may have been excluded. Another limitation, is that the citations were included on the basis of what the abstract stated. For inpatient antibacterial drug utilization, the search strategy was highly restrictive to articles that included the terminology audit and registry. This might explain why the articles retrieved were more related to the quality of prescribing antibiotics.

Surely, more information is available on hospital drug utilization at European level, though not publicly available or not easily accessible making it almost invisible. However, IMS Health started in 2008 with the Hospital Audit Prescription which collects information on drugs dispensed from hospital

pharmacies to the patient, also containing more clinical (diagnostic) information that it is of most interest for research.

5.3 VALIDITY OF DATABASES

National drug consumption databases, were originally created for refund, that is, with an administrative purpose. Measuring validity of these secondary data sources, would formally require comparing the results obtained in drug consumption for each of these databases with primary sources 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(11). The validity of some European automated databases registering drug consumption has already been established for the ERASME database in France (140) and PHARMO database in The Netherlands (15). However, this way of establishing the validity of the databases is beyond the scope of the PROTECT project. Instead, as stated earlier, we have measured validity of a database in the sense of the value of these databases in measuring drug consumption, something that has already been done with Medicaid in the US(141). Other authors recommend other strategies to estimate the validity of automated databases, such as conducting descriptive analyses for several variables collected by the databases to identify the limitations of this data(142). If a primary source of data is not available for making comparisons, then the data quality can be assessed through the degree of matching of different datasets(143).

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 drug utilization study, was elaborated, and transformed into a questionnaire. We are aware that the questionnaire was not piloted which may explain that 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 (co-morbidities, severity of illness, other medications prescribed, diagnostic tests, hospital admission and discharge, and other sociodemographic and economic factors that might be of interest in order to study other factors that influence the patterns of drug use), relevant when studying drug exposure. However, the fact, that it also had open questions, allowed for gathering such information.

National drug consumption databases record 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 at patient level(144). The Danish Prescribed Register, the OsMed database and SFK database in Denmark, Italy and The Netherlands, respectively, contain dispensed medicines. Reimbursed databases (GIP databank, Spanish Ministry of Health, Polish National Health Funds, ERASME database and WiDO database) may 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(145). Reimbursed databases do not cover OTC drugs either, and this may be of importance when studying NSAIDs. Underdetection has been established to be important

for antibiotics in countries like Spain and Italy(146,147) where although not legal approximately 10% of antibiotics are sold as over the counter 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(3). These aspects are of special importance when we study trends 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 hence information on their use lost.

Prescription databases (Swedish, Norwegian and Finnish Prescription database) are in-between dispensed and reimbursed databases. Prescription registries lack information on OTC drugs, thus they may also underestimate the use of some groups of drugs. 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 primary compliance. However, uncollected prescriptions from the pharmacy may not be of importance when estimating drug exposure (148).

Population coverage is another item of importance, specially when studying drug adverse events, as they are usually very rare outcomes and large numbers of population are needed in order to detect a single event. In addition, the registry of the date the drug was dispensed, avoids recall bias. Almost all databases studied for the PROTECT project cover a large population. In fact, all of them are nationwide, except for the ERASME database which covers 87% of the French population, the GIP databank which

covers 95% of the Dutch population and the SFK which covers roughly 90% of the Dutch population. Following the checklist provided by Vander et al.(110), we asked for the weighting methodology used in case the population coverage was between 90% and 100%. SFK did not provide such information, but GIP databank extrapolated their drug consumption data through 20 age subgroups and by gender. No information is available from ERASME database.

ATC codification is recommended by the WHO (128). A single system of codification eases comparison of drug consumption across countries. The DDD is also recommended by the WHO as a measure for comparative drug statistics. It is considered a standard unit for quantifying drug use. The ATC/DDD methodology has been adopted in all databases. All retrospective data collected by these databases is updated yearly or twice a year with the release of the ATC/DDD guidelines by October. Several studies has pointed to the ATC/DDD methodology as a source of bias in drug utilization comparisons, either because the databases used different versions(115), or because DDD changes over time(116). Even the ePACT database in the United Kingdom which uses the British National Formulary and Average Daily Quantities(149)(148) for measuring drug consumption(149), 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 or DDD assigned. Each country adopts different approaches and this information is not easily available, except for Denmark, where a list of national assigned DDD is available on the National Medicines Agency website. In the case of the

PROTECT selected medicines, this problem was encountered for spiramycin (J01FA02) and midecamycin (J01FA03). The WHO has assigned an oral DDD for spiramycin and a parenteral DDD for midecamycin. In those countries, where these antibacterials are marketed, spiramycin is dispensed also as a parenteral drug (France and Poland) and midecamycin as only an oral drug (France, Italy and Spain). None of these countries provides information on how the DDD for these routes of administration is assigned.

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 for application in research. Readily available are age, sex and place of residence. Upon request information gathered by the database may be obtained. However, new epidemiological strategies have arised to adjust for such confounding (9,150,151). In addition, 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(122,152). However, usually information on important behavioral aspects, such as smoking, is missing.

Value of the automated databases

Drug exposure expressed in DDD/1000 inhabitants/day is an aggregate measure, derived from individual data. It 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(153). However, when the purpose of the study is to analyze the association between a drug and an adverse event, the aggregated nature

of the data often leads to ecological bias(154). Furthermore, most of these secondary data sources do not collect enough information on variables that may confound the association, misestimating the risk of an adverse drug event. Therefore, most of these ecological studies may give rise to new hypothesis that will need to be confirmed with primary data sources.

These databases may also be useful in the context of post-marketing surveillance.The proportion of population exposed to a drug can sometimes be used to calculate the population attributable fraction for an adverse event of interest, a relevant public health measure(9,144). Prevalence of a drug exposure is best estimated from individual data and some authors do not recommend the use of DDD/1000 inhabitants/day(155). The usefulness of the DDD/1000 inhabitants/day will depend on the differences between the DDD and the prescribed daily dose (PDD) and the indication for use of the medicine under study. Hence, for those drugs with only one indication and with a DDD that matches the PDD, the DDD/1000 inhabitants/day will most accurately reflect the population exposed(4).

6 CONCLUSIONS

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

- There is however wide interest in Europe in drug utilization research as shown by the wide range of European groups working on drug utilization research.

- It has been possible to collect information with some detail on the characteristics of national 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 national level. Most of the studies are set in a single hospital or several hospitals within one country.

7 RECOMMENDATIONS

To be fullfilled after the exposed population for the diferent drugs have been estimated . They will be part of the Guidelines for Drug Utilization Studies

8 APPENDICES

APPENDIX 1. ATC 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
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

J01CR02 amoxicillin 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
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

N06AANon-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

N06ABSelective serotonin reuptake inhibitors

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

N06AFMonoamine oxidase inhibitors , non-selective

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

N06AGMonoamine oxidase A inhibitors

ATC code	Name
N06AG02	moclobemide
N06AG03	toloxatone

N06AXOther 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

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 2. KEY PAIRS ADVERSE DRUG EVENTS-DRUGS, SELECTED FOR THE PROTECT PROJECT

Table 19. Adverse drug events-drug pairs selected for the PROTECT project

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

APPENDIX3. HEALTH POLICY SYSTEMS IN THE SELECTED EUROPEAN COUNTRIES.

	Health care provider	Population coverage	Model of health care financing	Pharmaceutical financing(3,156)
Denmark **5,4 millones** **5,560,628 (1Jan2011)** http://www.dst.dk (157)	Universal access to health services. No possibility of opting out of the system. Around 20% of Danish Population have purchased additional private insurance	100%	Municipal and central state taxes	Cost of drugs paid by official body Co-payment: Flat fee plus a percentage per prescription. Reimbursement depends on the individual yearly expenditure, there are 3 levels: 50%, 75%, 85% reimbursed. Max cost-ceiling above which the patient receives fully reimbursement
Finland **5,351.427 people (mid-2009)** http://www.stat.fi/tup/suoluk/suoluk_vaesto_en.html [Accessed 7/2/2011] (158,159)	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	Sickness Insurance covers the cost of outpatient drugs. There are 3 levels of reimbursement, with the first two levels subdivided into limited or non-limited. 42%, 72% and 100%. There exists a maximum annual individual out-of-pocket payments above which the patient receives fully reimbursement.
France **62,134,963 (1Jan2010)** http://www.insee.fr/fr/ppp/bases-de-donnees/recensement/populations-legales/france-regions.asp?annee=2008 [Accessed 9/2/2011] (160,161)	Public Universal access to health care services	Private health insurance provided by employment-based mutual associations which cover 87-90% of the population. People with low income (8%) which includes unemployed and receiving single-parent subsidies have been entitled complementary private coverage at little to no-cost.	Publicly financed health care, through a public health insurance scheme financed by the employer and the employee payroll taxes and other national taxes; the government that manages the public health insurance funds; private health insurance which reimburses the statutory cost-sharing for the services covered by the public health insurance scheme. Small private sector for profit that offers coverage for services not included in the public benefits package	Cost of drugs paid directly by the nationa insurance funds. Co-payment: Fixed rate per prescription plus a percentage of the retail price. There are 3 levels of reimbursement: 35%, 65% and 100% depending on the drug or condtion treated.
Germany **82,217,800 (2007)** http://www.destatis.de [Accessed 7/2/2011]	Public. Health insurance, either under the social or the private health insurance scheme. It is compulsory for all German citizens.	85% population covered by Social Health Insurance. People with low income are covered by a public health	Compulsory funds levied as a percentage of gross wages up to a certain threshold. Copayment: patient pays a flat-rate	Cost of drugs are directly paid by the health insurance board Co-payment: Fixed rate per outpatient prescription unless the

(162,163)	Universal access to health care services Around 10% of the population is covered by private health insurance. About 5% of population fall under special regimes	insurance scheme: Statutory Health Insurance. High income can opt out of the social health insurance scheme and purchase private health insurance	fee for several medical services including hospital stay and prescriptions. Private health care: Private health insurance covers mainly civil servants and self-employed. It usually covers some copayments, such as dentists	price is at least 30% below the so-called reference price. If the drug prescribed is priced at a higher level than the reference price, the patient also pays the difference between market and reference price

	Health care provider	Population coverage	Model of financing	Pharmaceutical financing (3,156)
Italy **60,340,328 (1Jan2010)** http://demo.istat.it/pop2010/index_e.html [Accessed 7/2/2011] (164-167)	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 (97%) and by patient co-payments	Cost of drugs paid directly by the national Insurance Scheme. Valid for outpatient and inpatient care. Co-payment: Flat-fee per item prescribed plus a percentage of the retail price of drug. Exemptions apply for class A drugs and specific groups of patients.
Norway **4,858.199 (1/1/2010)** http://www.ssb.no/folkemengde_en/tab-2010-03-11-34-en.html[Accessed 7/2/2011] (168)	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 co-payment 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 centers are opening up in urban areas, services only available to members.	Hospital expenses 100% covered. Cost of drugs paid by the National Insurance Scheme. Co-payment: Deductible.Max cost-ceiling above which the drugs are fully reimbursed
Poland **38,230,080 (year2002)** http://www.stat.gov.pl/ [Accessed 2/2011] (169,170)	Public. National Health Fund. Healthcare services are free at the point of delivery. However most services are subject to a series of formal and informal patient co-payments	100% Household expenditure: the share of private health expenditure as a percentage of total expenditure was 27.6% in 2002. No other reliable data is available on private health insurance or insurance policies that cover for extended medical options.	Public and private financing. Compulsory health insurance contributions at a percentage rate of the Population income. State financing through general taxation. Formal and informal out-of-pocket payments and to a lesser extent pre-payment scheme	Cost of drugs paid directly by the National health fund. Co-payment: Flat-fee per prescription. Only prescribed drugs group A can be reimbursed at levels of 30 and 50%

Spain **47,021,031 (1/1/2008)** **http://www.ine.es/welcoing.htm** **[Accessed 17/2/2011]** (171)	Public health sector. Universal access to health services 15% of the Spanish population are covered by private insurance.	99.5% (WHO 2005) includes low-income inhabitants and immigrants adults and children. Civil servants can opt out of the public financed system	Ttaxes and allocation from central government. 15% of the Spanish population are also covered by a private insurance	Cost of drugs payed by National Insurance Board. Co-payment: Percentage of the retail price up to a maximum price. 3 levels of reimbursement: Basic, the user pays 40% of the prize of prescribedrugs. For patients with prescribed drugs for chronic illnesses pay 10%. Fully reimbursed for inpatients, retired, handicapped, occupational accidents. Users of civil servant's mutual funds pay 30% of the pharmaceutical cost.

…/…

	Health care provider	**Population coverage**	**Model of financing**	**Pharmaceutical financing**(3,156)
Sweden **9,412,851 (30/11/2010)** http://www.scb.se/Pages/Product___25799.aspx [Accessed 17/2/2011] (172)	Public: Universal access to health care Around 2.3% of Swedes have a private medical insurance.	All residents in Sweden regardless of their nationality.	Mainly proportional income taxes, supplemented by Government grants and patient co-payment	Cost of drugs paid directly by an official body. Co-payment: Deductible: Up to a certain amount of money spent by the patient, above which a rising scale of reimbursement applies. There is a yearly maximum individual expenditure above which, the drugs are fully reimbursed.
The Netherlands **16,578,693** http://statline.cbs.nl [Accessed 9/2/2011] (173-175)	Private. All residents have to purchase a basic benefit package which might be complemented by 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	97% Population. It is calculated that in 2007 approx 1.5% of Dutch population were not insured and that another 1.6% were defaulters	Government funds and percentage contributions of taxable income. Co-payment by the insured The money is distributed to health insurers based on a risk-adjustment scheme to compensate for differences in the risk profiles of insured people	Cost of drugs paid by the Health Insurance Co-payment: fixed rate per prescribed item plus a deductible system: there is a conditional reimbursement for two positive lists of drugs that are being reimbursed. For chronic illnesses, drugs are also reimbursed after the patient has paid for the first 15 days.

The United Kingdom **61,792,000 (mid-2009)** http://www.statistics.gov.uk/pdfdir/pop0610.pdf [Accessed 7/2/2011]	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 central taxation (about 80%). But also National Insurance (12%) and user charges, mainly prescriptions charges(2.1%). Miscellaneous. Dental and ophthalmic care are partially funded	Cost of drugs paid directly by an official body. Co-payment: Fixed rate per prescription. For those with a chronic disease or higher users of drugs can purchase a prepaid certificate to obtain drugs at a lower cost. Drugs may be free of charge for specific social groups.

Source: Authors' compilation from national references and the Observatory of Health Policy Systems

APPENDIX 4a. SUMMARY TABLE OF GENERAL DRUG UTILIZATION RESEARCH GROUPS

Name	Objectives	Number of Participant countries	Information	Drugs of interest	Website & Funding
EuroDURG ***European Drug Utilisation Research Group*** **1993- ongoing**	To provide an international forum for cooperation and communication to promote DU research, to work on:	EU countries	Working groups: **DRUID** **HAPPY AUDIT** **TUPP** **DURQUIM**	All drugs	EuroDURG bulletins http://www.eurodurg.com *Funds:* WHO European Office

CNC ***Cross National Comparison*** **2008-ongoing**	Collaboration EuroDurg with ISPE's SIG-DUR	24	**Poster presentation** • drug **consumption data** (2000-2007) • **DDD**, **€** or **$** • Ambulatory care. • Hospital care: Antibacterials (J01).	Proton Pump Inhibitors (A02BC), Statines (C10AA), and clopidogrel (B01AC04)	http://www.pharmacoepi.org/eurodurg/workgr/cross_national.cfm Abstract PDS2008
ISPE´s SIG-DUR ***Special Interest Group of Drug Utilisation Research*** **(2006-ongoing)**	To create a forum for discussion and cooperation between drug utilization researchers.	53 ISPE members from EU and non-EU countries.	**ATC** International ATC/DDD browser. **MTI** Methods for Testing Interventions. **PCI** Prescribing Quality Indicators . **RHI** Relationship with the Health Insurers	All drugs	http://www.pharmacoepi.org/resources/sigs_research.cfm
EUROMEDSTAT **2002-2007**	To establish an **inventory of national medicines data sources** and a survey of available data, to assess data reliability and comparability between countries.	19	• List of medicines data sources (available on-line) • competent authorities of each country, • list of licensed medicines per country.	All drugs	http://www.euromedstat.cnr.it/ *Funds:* European Commission
PIPERSKA GROUP **2008-ongoing**	To ensure robust systems are in place in Europe to **enhance the rational use of drugs**, including new expensive drugs, to improve health.	8	No consumption data	New expensive drugs	http://www.piperskagroup.com
NorPEN ***Nordic Pharmacoepidemiological Network***	To facilitate and promote pharmacoepidemiological research initiatives promoting safer and more efficient drugs and drug use in a	5	Each country has established a national database population-based to track **prescription drugs dispensed** to individuals in ambulatory care.	All drugs	http://www.nhv.se/customer/templates/InfoPage

2008-ongoing	public health perspective.				
ENCePP ***European Network of Centres for Pharmacoepidemiology and Pharmacovigilance*** **2006-ongoing**	To bring together the available expertise and research experience in the fields of Pharmacoepidemiology and Pharmacovigilance scattered across Europe in a Network of Excellence (research and medical-care centers, healthcare databases, electronic registries and existing networks)	31	**Registry of EU data sources** in the field of pharmacoepidemiology and pharmacovigilance,	All drugs	http://www.encepp.eu/ Lead by the EMA
DURQUIM ***Drug Utilisation Research Quality Indicator Meeting*** (2004-ongoing)	To analyse the patterns of drug use and to implement strategies for improving the prescribing and use of drugs. Framework for constructing prescribing quality indicators	19	Power point presentation with the **available European databases** (administrative, prescription, reimbursing, health assurance, …)	All drugs	http://www.eurodurg.com/durquim.htm Funds: WHO/EuroDURG, RIZIV

APPENDIX 4b. SUMMARY TABLE OF SPECIFIC DRUG UTILIZATION RESEARCH GROUPS

Name	Objectives	Number of Participants countries	Information	Drugs of interest	Website & Funding

Name	Objectives	Number of Participants countries	Information	Drugs of interest	Website & Funding
ARITMO ***Arrhythmogenic potential of drugs*** **(Jan. 2010-Dec. 2012)**	To analyse the arrhythmic potential of drugs in the following classes of study drugs (> 250 compounds).	8	Prospective case-control surveillance	Antipsychotics, anti-infectives (antibacterials, antimycotics and antivirals) and H1-antihistaminics.	http://www.aritmo-project.org *Funds:* FP7
ARPAC ***Antibiotic Resistence Prevention and Control*** **2002-2005**	To develop strategies for control and prevention of antibiotic resistance in European hospitals.	32	• Published data antibiotic hospital use • 170 hospitals • 2001 to 2005 • DDD/100 Beds-Day. • Cross-sectional survey study (questionnaire survey).	Antibiotic subgroups (4rth ATC level)	http://www.abdn.ac.uk/arpac *Funds:* European Commission
ESGAP ***ESCMID Study Group for Antibiotic Policies*** **1998-ongoing**	To improve antimicrobial prescribing policies and practices, to improve patient care and prevent/reduce the development of resistances (official recognition from the ESCMID).	31	• **ABC Calc:** to measure hospital antibiotic consumption in number of DDD/ 100 bed-days (available on the website). • Questionnaire distributed to hospital pharmacists	Antibiotic	http://www.escmid.org/research_projects/study_groups/esgap/
ESAC ***European Surveillance of Antimicrobial Consumption*** **2001- 2011**	To provide information on the consumption of antimicrobials and developing indicators and guidelines to help managing the risk of infections and resistences.	36	• Interactive database available online • Consumption data hospital-care, ambulatory-care and nursing homes • DDD/1000inh/d • ATC level 2 to 4 • Since 1998 (not all countries have all the information).	Antibiotic	http://app.esac.ua.ac.be/public/ *Funds: DG SANCO of the European Union*

Name	Objectives	Number of Participants countries	Information	Drugs of interest	Website & Funding
			• Annual reports by chemical group since 2006-2008. • Heterogeneous information source		
ESEMeD ***European Study of the Epidemiology of Mental Disorders*** **(2001-2003)**	To collect data by a cross-sectional survey, on prevalence, risk factors, health-related quality of life and use of services associated with common mental disorders .	6	• Published data • Out-hospital use (patients interview) • presented in % of the total sample • 2001-2003	Psychotropic drug	*Funds:* EC, Glaxo SmithKline
EUROASPIRE ***European Action on Secondary and Primary Prevention by Intervention to Reduce Events*** **1994-2007**	To determine if CV risk factors are recorded in patients medical records, to measure the modifiable risk factors, to describe therapeutic management after hospitalization in patients with coronary hearth disease.	**I:** 9. **II:** 15. **III:** 22	• Published data • Out- hospital • Review of medical records, and patient interview. • 1995-1996,1999-2000, 2006-2007.	Antiplatelets, beta-blockers, ace inhibitors, clacium chanel blockers, lipid-lowering drugs and anticoagulants by groups.	*Funds:* European Society of Cardiology registries
DRUID ***Driving under the Influence of Drugs, Alcohol and Medicines***	To combat the scourage of drink-driving and find answers to the question of the use of drugs or medicines that affect people's ability to drive	19	• Consumption of drugs with central nervous system (side)-effect • Out patient • 2000-2005. • Information is not available for	Ansiolytics, hypnotics, sedatives, antidepressants	http://www.pharmacoepi.org/eurodurg/workgr/druid_project.cfm 6th FP

Name	Objectives	Number of Participants countries	Information	Drugs of interest	Website & Funding
(2006-ongoing)	safely.		the moment.		
HAPPY AUDIT ***Health Alliance for Prudent, Yield and Use of Antimicrobial Drugs in the treatment of respiratory tract infections.*** **(2008-2010 planned)**	The aim of the HAPPY AUDIT is to improve the antibiotics prescription (quantity and quality) in respiratory tract infections in primary health care in Europe through development of intervention program targeting general practitioners (GPs), parents of young children and healthy adults.	10	• Report of the results (available on-line) • According to the APO (***Audit Project Odense***): auditing GP. • Antibiotic use in % by respiratory tract indication.	Antibiotic	http://www.happyaudit.org 6th FP
TUPP ***The Users Perspective Project*** **(1997-ongoing)**	The overall objective in the meeting is to frame a protocol for pan-European research on the user perspective on mood-modifying medicines.	11	Not information available	Mood-modifying medicines	http://www.eurodurg.com/workgr/tupp/index.htm
TEDDY ***Task Force in Europe for Drug Development for the Young*** **(2005-2010 planned)**	To promote the availability of safe and effective medicines for children by integrating existing expertise and good practices.	11	• Publications • Data sources containing information on medicines used in male/female children, out-patient data, prescription or drug dispensing data. • Prevalence drug of use by age and therapeutic level (ATC	All drugs	http://www.teddyoung.org/index ***Funds:*** FP6

Name	Objectives	Number of Participants countries	Information	Drugs of interest	Website & Funding
			2ond level) (2000-2005) in Netherlands, Italy and UK.		

APPENDIX 5. SUMMARY TABLE OF NATIONAL DRUG CONSUMPTION DATABASES

Countries/ Characteristics	DENMARK (Danish National Prescription Database)	FRANCE (ERASME)	FINLAND (Prescription register database)	GERMANY	ITALY (OsMED database)	NORWAY (Norwegian Prescription database)
Data provider *(accessibility)* Web site	**The Danish Medicines Agency** ***(Free online)*** www.medstat.dk/MedStatDataViewer.php	**Caisse Nationale d'Assurance Maladie des Travailleurs Salariés** ***(Application)*** www.ameli.fr	**Social Insurance Institution** ***(Application)*** http://kela.fi	**Wissenschaftliches Institut der AOK (Research Institut of the AOK)** ***(Application)*** www.wido.de	**Italian Medicines Agency. Osservatorio sull'impiego dei medicinali** ***(Application)*** www.agenziafarmaco.gov.it	**Norwegian Institute of Public Health** ***(Free online)*** www.norpd.no
Setting	**Out/Inpatient**	**Outpatient**	**Outpatient**	**Outpatient**	**Out/Inpatient**	**Outpatient**
Population coverage(%)	**100**	**87**	**100**	**85**	**100**	**100**
ATC/DDD methodology	**Yes**	**Yes**	**Yes**	**ATC**	**Yes**	**Yes**
OTC	**Yes**	**No**	**No**	**No**	**Yes**	**No**
Data by age and sex	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Linkage to other databases	**Yes** (Health, demographic and socioeconomic)	**Yes** (Health, demographic and socioeconomic)	**Yes** (Health, demographic and socioeconomic)	**Yes** (Within the Statutory Health Insurance, to sociodemographi	**No**	**Yes** (Health, demographic and socioeconomi

				c, hospital and outpatient data)		c)

Countries/ Characteristics	NETHERLANDS		POLAND NHF database	SPAIN	SWEDEN (The Swedish Prescribed Drug Register)	UNITED KINGDOM (ePACT database)
	GIP database	SFK database				
Data provider *(accessibility)* Web site	**Health Care Insurance Board** ***(Free online)*** www.gipdatabank.nl	**Foundation for Pharmaceutical Statistics** ***(Application)*** www.sfk.nl	**National Health Fund** ***(Application)*** www.nfz.gov.pl	**Department of Pharmacy and Health Products** ***(Application)*** www.aemps.es	**The National Board of Health and Welfare** ***(Free online)*** http://192.137.163.49/sdb/lak/val.aspx	**NHS Prescription Services** ***(Application)*** www.epact.net
Setting	**Outpatient**	**Outpatient**	**Outpatient**	**Outpatient**	**Outpatient**	**Outpatient**
Population coverage (%)	**85**	**92.5**	**100**	**100**	**100**	**100**
ATC/DDD methodology	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**BNF /ADQ** (upon request ATC/DDD)
OTC	**No**	**Yes**	**No**	**No**	**No**	**No**
Data by age and sex	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**No**
Linkage to other	**No**	**No**	**No**	**No**	**Yes** (Health,	**No**

databases					demographic and socioeconomic)	

APPENDIX 6. REPORT ON DRUG CONSUMPTION IN HOSPITAL SETTINGS FOR A SELECTED GROUP OF DRUGS

PROPORTION OF UTILIZATION IN HOSPITAL SETTINGS OF SELECTED GROUPS OF DRUGS

Authors: Ferrer P, Sabaté M, Ballarín E, Petri H, Ibáñez L.

Background:

Within the Framework for pharmacoepidemiological studies, Working Group 3 is in charge of reviewing and compiling knowledge about European sources of data on drug utilization in the outpatient and inpatient health care sector. This task has been developed for 10 European countries: Denmark, France, Germany, Italy, Norway, Poland, Spain, Sweden, The Netherlands and United Kingdom.

The PROTECT project proposal considered obtaining drug consumption data for medicinal substances of hospital or specialist use, for which Intercontinental Marketing Services(IMS Health) and national health service data are difficult to obtain, from manufacturers and/or specific studies. When the project started and the drug-event pairs were selected none of them included drugs specifically used in in-hospital setting. Preliminary data suggested that their use was scarce in hospital settings.

The medicines of interest for this framework, according the Anatomical Therapeutic Chemical (ATC[1]) code recommended by the World Health Organization (WHO) are: C08 Calcium channel blockers, J01FA Macrolides, J01CR02 Amoxicillin and enzyme inhibitor, N03A Antiepileptics, N05BA Benzodiazepine derivatives (anxiolytics), N05CD Benzodiazepine derivatives (hypnotics and sedatives), N06A Antidepressants, N06CA Antidepressants in

combination with psycholeptics, RC03AC Selective beta-2-adrenoreceptor agonists and, R03AK Adrenergics and other drugs for obstructive airway diseases. Henceforth, all these drugs except for macrolides and amoxicillin and enzyme inhibitor will be referred as the PROTECT selected drugs.

Objective:

The objective of this document is to review the main available information on in-hospital drug utilization for the PROTECT selected drugs concerning their use in Europe to provide information about the feasibility of using these sources to study the PROTECT drug event pairs. This data will be a key consideration in the decision to remove studying their in-hospital drug use as a project aim.
As a secondary goal, part of the content of this document will be added to the inventory of drug utilization data sources.

Introduction:

The information gathered about in-patient pharmaceutical consumption is mainly done at a hospital level. Broadly speaking, a hospital pharmacist monitors the medicines consumption in order to present the data and discuss it with the Pharmaceutical and Therapeutic Committee of the hospital. Very few countries collect information on hospital medicines consumption at a national level[2].

Increasingly numbers of hospitals in European countries have a therapeutic drug formulary which steers the inpatient drug consumption. It lists the different active ingredients currently in use in a specific hospital. Among the drugs included in these lists, those classified by the national authorities as hospital-only-medicines might be found. The numbers of substances included in these therapeutic formularies can range from 225 in Norway, up to 1500 in Greek hospitals[3].
Another aspect of the management of hospital drugs is the chain of distribution of medicines. In a survey conducted during 2005, by the European Association

of Hospital Pharmacists, figures showed that around 54% of European hospitals purchased the drugs from wholesalers, and 47% directly from the pharmaceutical industry[3]. Medicines might be supplied by either larger hospitals (e.g. Belgium) or partly by local community pharmacies (e.g. United Kingdom). The percentage of hospital pharmacies per total number of hospitals varies from 2% in Finland (the number of pharmacies in small hospitals or in dispensaries is unknown) to 100% in Portugal, where all public hospitals must have a hospital pharmacy[2].

Often, the distinction between what is considered outpatient consumption and inpatient consumption becomes blurred for specific subsets of population. Some countries may include as in-hospital drug utilization, medicines prescribed to outpatients by specialists as well as medicines prescribed in nursing homes, psychiatric clinics or other institutions with long-term inpatient care. Also, several medicines prescribed only by specialists at hospital level to outpatients might be included as either outpatient or inpatient consumption. France and Italy are two of the countries with the highest rate of inpatient pharmacies serving to outpatients (67% and 61%, respectively), whereas in Finland and Norway only 12% of the hospital pharmacies dispensed medicines to outpatients[3].

Besides, there is a great heterogeneity in the measurement of hospital pharmaceutical consumption. Packs, number of units administered, defined daily doses, total weight of active substance consumed in Kilograms or grams[2] or percentage of an active substance out of the total of the group of medicines.

Of the medicine groups studied in the PROTECT project, the importance of quantifying the utilization of antibacterials for systemic use in hospital settings is well known. There exists a close relationship between the emergence of

microorganisms resistance and the use and misuse of antibiotics. In fact, most of the European countries support programs on the rational use of antimicrobials. For instance, the STRAMA (the Swedish Strategic Programme against Antibiotic Resistence) in Sweden, www.strama.se , or the SWAB (the Dutch Working Party on antibiotic Policy) in The Netherlands, www.swab.nl. The European Center of Disease Control funds the European Surveillance of Antibiotic Consumption -ESAC, http://app.esac.ua.ac.be/public/ -Project Group. The ESAC Group is a collaborative project participated by 34 European countries, which collects data on medicines used to treat infectious diseases. The importance of antibiotic consumption in inpatient settings is also reflected by the fact that within the PROTECT project, one of the EFPIA partners is conducting a systematic review on antibiotic consumption in inpatient settings. Because of all these reasons, antibiotics will be excluded from this discussion and no data will be presented.

Methods:

There were 3 potential sources of information on drug utilization studies in hospital settings: general information available on the web, public national databases and electronic bibliographic databases.

Website General information

Through the established European networking on drug utilization studies, we extracted general information on hospital medicines management from the Pharmaceutical Health Information System website http://phis.goeg.at/index.aspx?_nav0027.Through links from this website index, three other websites of general information were identified: the European Association of Hospital Pharmacists website http://www.eahp.eu/,the European

Hospital and Healthcare Association website, www.hope.be, and the Organization for Economic Cooperation and Development (OECD) website, http://www.oecd.org/home/0,2987,en_2649_201185_1_1_1_1_1,00.html.

National Public Databases

As part of the inventory elaborated by Working Group 3, information on the type of drug consumption data and the sector covered by the 10 different European national databases was available.

Bibliographic database

A search in PubMed was conducted. This search was not intended to be a systematic review of hospital medicines consumption; rather a broad overview of the number of drug utilization studies conducted in a hospital setting, for the selected PROTECT drugs.

A search for the terms hospital drug utilization, calcium channel blockers, antiepileptics, beta-2-agonists, antidepressants and benzodiazepines on PubMed was conducted, with the following strategy: Each of the medicine group was combined with hospital drug utilization 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 included nursing homes, psychiatric clinics or any other institution categorized as 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.

Accordingly to the WHO criteria drug utilization studies can be divided into 4 different categories: studies covering the patterns of use, quality of use, determinants of use, and outcome of use.[6] Only articles related to patterns of drug use, regardless of indication, were included. All units and methods of

measurement were valid for the review. Those abstracts classifying medicines according to the ATC codification and/or quantifying drug use in defined daily doses (DDD) were reported. Active pharmaceutical ingredients classified in ATC level 5 of the selected PROTECT drugs were considered drugs of interest.
No restrictions regarding type of study design were imposed. Any article published in a language understood by any of the group members was included: English, Spanish or any other Roman languages and Swedish.

Results:

Website General information:

From the PHIS website, a hospital report from 2008 could be freely downloaded. It reported European in-patient pharmaceutical consumption, expressed as percentages of total pharmaceutical consumption. Inpatient drug use ranged from 3% in Sweden up to 14% in Latvia.

Table 1, extracted from this report, shows the top 10 active ingredients consumed in European hospitals during 2007.

Table1. Top 10 active substancesconsumed in European hospitals, 2007.

Paracetamol
Electrolyte solutions
Furosemide
Acetylsalicylic Acid
Epoetin beta
Albumin
Omeprazol
Ranitidine
Prednisolone

The website http://www.eahp.eu/ publishes a report of a survey conducted on 825 hospitals of 22 out of the 26 European member countries. The last survey was conducted in 2005. It provides information on the organization and activities of European hospital pharmacies, but not on drug utilization.

The European Hospital and Healthcare Federation, www.hope.be has published a book that contains information on the organization of hospital health care of the 27 European Member States. No information on medicines consumption is given.

From the OECD website, a technical report[4] on the use of hospital administrative databases in health research was downloaded. The report provides information of the type of data that is collected by different national hospital administrative databases in different countries. Among the countries studied, there are several European countries: Belgium, Denmark, Finland, France, Italy, Sweden and the United Kingdom. Only Belgium collects information on hospital pharmaceutical consumption at a national level: it uses the ATC codification and the total cost of drugs by ATC is available. None of the other national hospital databases collects information on pharmaceutical drug consumption.

National Public Databases

From national public data bases, only Denmark has hospital drug consumption freely available on its website, www.dkma.dk. From national reports on medicines consumption, published by official European organizations, Sweden provides data on drug consumption in hospital[7]. Denmark also publishes an annual report with information on hospital drug utilization[8]. Other countries

collect information at a hospital level, such as France through the National Medicines Agency, but to obtain the data, a further application is needed. For the rest of the European countries included in the elaboration of the inventory, hospital drug consumption is not collected at a national level.

Figures extracted from Denmark database, France database and Sweden annual report[7] will serve as an example to show the level of drug consumption in hospital settings for the 4 groups of medicines selected in the PROTECT project.

Table 2 shows drug consumption in Denmark, year 2009, in the primary health sector and hospital sector for the 3 main organs or systems on which the active substances selected act. The consumption is expressed in DDD/1000 inhabitants/day and a proportion out of the total drug consumption for primary health care and hospital sector is given.

Table 2. Primary Health sector andHospital sector drug consumption in Denmark 2009, by ATC level 1.Expressed in DDD/1000 inhabitants/day[i].

ATC level 1	**Primary health care sector or outpatient** DDD/1000 inh/day(%)	**Hospital sector or inpatient** DDD/1000 inh/day(%)	**Total** DDD/1000inh/day
C Cardiovascular system	482.2 (98.8)	6 (1.2)	**488.2**
N Nervous system	258 (96.9)	8.3(3.1)	**266.3**
R Respiratory system	121.4 (98.4)	2(1.6)	**123.4**
Total	**1351 (96.5)**	**49 (3.5)**	**1400**

[i]Data extracted from Lægemiddelstatistik I Danmarkwww.dkma.dk/medstat [Accessed 18/3/2011]

The total drug consumption in Denmark for the cardiovascular, respiratory and nervous system, excluded over-the-counter (OTC) drugs, amounted to 1400 DDD/1000inhabitants/day. Only 3.5% of the total drug use was consumed at the hospital level. From table 2, we can see that only 6 out of 1000 people consume a drug acting on the cardiovascular system in the inpatient sector, whereas there are in the outpatient sector, 482.2 persons out of 1000, that use a drug classified under the cardiovascular system. There are a very low percentage of drugs consumed at the hospital level acting on the three anatomical systems of interest. They represent 1.2%, 3.1% and 1.6% over the total amount respectively.

A similar table (Table 3) could be elaborated for Sweden from data extracted from the report that annually publishes the Swedish National Board of Health and Welfare[8]. The information is given in millions of DDD and they were converted into DDD/1000 inhabitants/day taking into account that the Swedish population in 2009 was 9,340,682 inhabitants (http://www.scb.se/Pages/TableAndChart___25897.aspx Statistics in Sweden [Accessed 19/3/2011]).

Table 3. Primary health sector and hospital sector drug consumption in Sweden 2009, by ATC level 1. Expressed in DDD/1000 inh/day[ii].

ATC level 1	**Primary health care sector or outpatient** DDD/1000 inh/day(%)	**Hospital sector or inpatient** DDD/1000 inh/day(%)	**Total** DDD/1000inh/day
C Cardiovascular system	424.4 (98.7)	5.63(1.3)	**430.03**
N Nervous system	220.57(96.2)	8.79(3.8)	**229.36**
R	100.02(97.5)	2.55(2.5)	**102.57**

Respiratory system			
Total	**1639.6 (97.1)**	**48.2 (2.9)**	**1687.8**

[ii]Data extracted from http://www.socialstyrelsen.se/publikationer2010/2010-3-28.Läkemedelstatistik förår 2009. [Accessed 20/3/2011].

In Sweden as in Denmark, similar trends of drug consumptionin hospitals can be described. A very low percentage of drugs coded as acting on the cardiovascular system (1.3%), nervous system (3.8%) and respiratory system (2.5%) are used at the hospital level. Thus, the bulk of the PROTECT selected drugs is mainly in the outpatient sector.

Table 4 shows the consumption of the PROTECT selected drugs in Denmark, year 2009. The classification of the medicines is down to ATC level 3 or 4. And the unit of measure is DDD/1000 inhabitants/day.

Table 4. Outpatient and inpatient drug consumption in Denmark 2009, by ATC level 3 or 4. Expressed in DDD/1000 inhabitants/day [iv].

ATC level 3 or 4	**Primary health care sector or outpatient** DDD/1000 inhabitants/day(%)	**Hospital sector or inpatient** DDD/1000 inhabitants/day(%)	**Total**
C08 Calcium channel blockers	68 (99.3)	0.5 (0.7)	**68.5**
N03 Antiepileptics	13.5 (97.1)	0.4 (2.9)	**13.9**

N05BA Benzodiazepine derivatives (anxiolytics)	12.3 (96.1)	0.5 (3.9)	**12.8**
N05CD Benzodiazepinesderivatives (hypnotics and sedatives)	5.3 (96.4)	0.2 (3.6)	**5.5**
N06A Antidepressants	77 (98.5)	1.2 (1.5)	**78.2**
R03AC Selective beta-2-adrenoreceptor agonists	18.6 (97.4)	0.5 (2.6)	**19.1**
R03AK Adrenergics and other drugs for obstructive airway diseases	16.8 (97.1)	0.5 (2.9)	**17.3**

[iv]Data extracted from Lægemiddelstatistik I

Danmarkwww.dkma.dk/medstat [Accessed 18/3/2011]

The consumption of some of the different groups of medicines in hospitals in Denmark is as low as 2.6% for selective beta-2 adrenoreceptor agonists (R03AC) and 2.9% for adrenergics and other drugs for obstructive airway diseases (R03AK), or 0.7% for calcium channel blockers (C08). Benzodiazepine derivatives (N05BA and N05CD) correspond to a higher proportion of inpatient drug consumption. Yet, compared to outpatient sector, inpatient consumption does not represent more than 5% of the total consumption of anxiolytics and no more than 5% of hypnotics and sedatives.

As part of the PROTECT project we obtained data on inpatient drug consumption from the Agence Française de Securité Sanitaire des Produits de Santé (AFSSAPS) and it will serve as a further example of the differences in drug consumption between the in- and outpatient settings.

Table 5 shows the in- and outpatient drug consumption by ATC level 3 or 4 in France, year 2009.

Table5. Drug consumption in the inpatient and outpatient sector in France, by ATC level 3 or 4, year 2009[v].

ATC level 3 or 4	**Primary health care sector or outpatient** DDD/1000	**Hospital sector or inpatient** DDD/1000 inhabitants/day(%)	**Total**

	inhabitants/day(%)		
C08 Calcium channel blockers	50.89 (97.8)	1.16 (2.2)	**52.05**
N03 Antiepileptics	12.55 (94.0)	0.81 (6.0)	**13.35**
N05BA Benzodiazepine derivatives (anxiolytics)	39.98 (93.6)	2.73 (6.4)	**42.71**
N05CD Benzodiazepinesderivatives (hypnotics and sedatives)	7.91 (93.1)	0.59 (6.9)	**8.5**
N06A Antidepressants	47.68 (95.7)	2.15 (4.3)	**49.83**
R03AC Selective beta-2-adrenoreceptor agonists	16.28 (95.9)	0.69 (4.1)	**16.97**
R03AK Adrenergics and other drugs for obstructive airway diseases	21.88 (98.5)	0.34 (1.5)	**22.22**

[v]Data provided by AFSSAPS as part of the PROTECT project.

As shown in the above table, over 90% of the utilization of the PROTECT selected drugs, takes place in the outpatient sector, being the greatest difference between the outpatient and inpatient sectors, the consumption of adrenergics and other drugs for obstructive airway diseases (R03AK), where only 1.5% is consumed in hospitals. Also calcium channel blockers (C08) are used in a 97.8% of the cases at the outpatient sector.

Table 6 lists the top 10 active substances ranked by consumption in inpatient settings in Sweden, year 2009.

Table 6. In-patient top-10 medicines consumption in Sweden, 2009[vi].

ATC level 5	ATC description

B03BB01	Folic acid
N02BE01	Paracetamol
C03CA01	Furosemide
H02AB01	Bethametasone
A02BC01	Omeprazol
B01AB04	Dalteparin
B03AA07	Ferrous Sulfate
B01AC06	Acetylsalicylic acid
A06AD11	Lactulose
L04AB02	Infliximab

[vi]Data extracted from http://www.socialstyrelsen.se/publikationer2010/2010-3-28.Läkemedelstatistik förår 2009. [Accessed 20/3/2011]
None of the medicines coded by ATC level 5, belongs to the group of medicines selected by the PROTECT project.

Bibliographic search:

All titles returned by the search in PubMed were screened and abstracts read. If an abstract was not available in the electronic database, the article in full was searched in order to try to find out more information on its contents. All the abstracts published in or later than 1980 were reviewed to see whether they fulfilled the inclusion criteria. For those titles that an abstract was not available, they were excluded from the review.

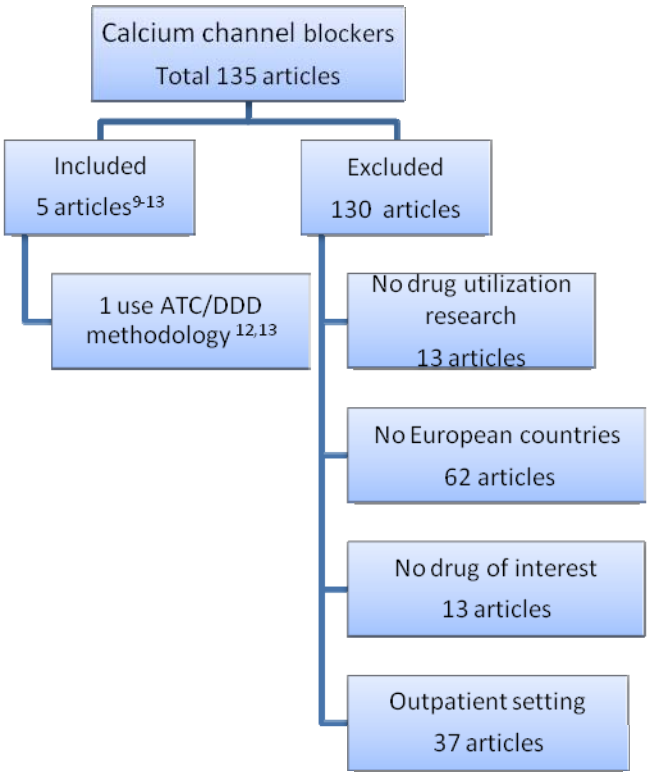
Because the search strategy did not take into account the indication for use of the medicines, several articles were equally found under antidepressant, antiepileptics or benzodiazepines. Duplicates have been excluded from the total number of articles yielded by the search, and only included in one group of medicines.

The results of the search in the electronic database PubMed are shown in table 7. For each group of medicines a flow chart has been elaborated.

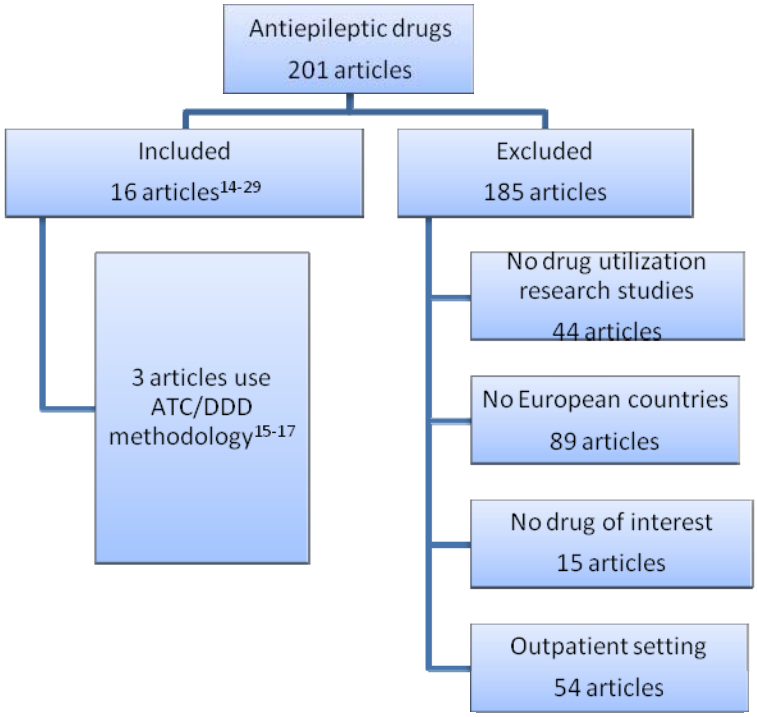
Table7. Key search terms and titles retrieved from PubMed dating back to 1980

Key search terms	Calcium channel blockers	Antiepileptics	Beta-2-agonists	Antidepressants	Benzodiazepines
Hospital drug utilization	135	201	33	253	245
Titles earlier than 1980	0	2	0	13	6
Duplicates	3	0	1	4	18
No abstract available	0	0	0	1	1

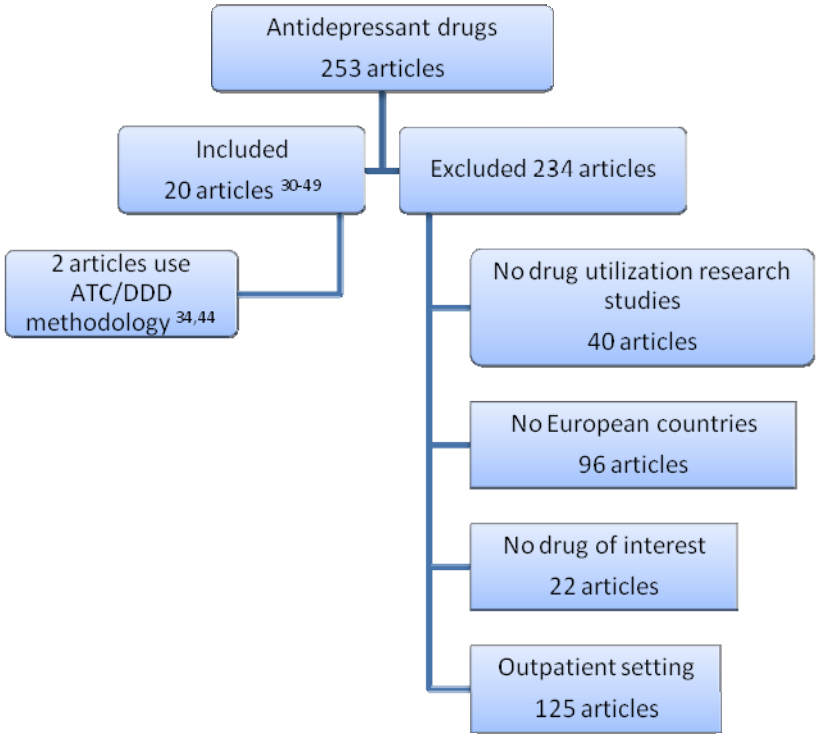
Flow chart 1. Calcium channel blockers and hospital drug utilization



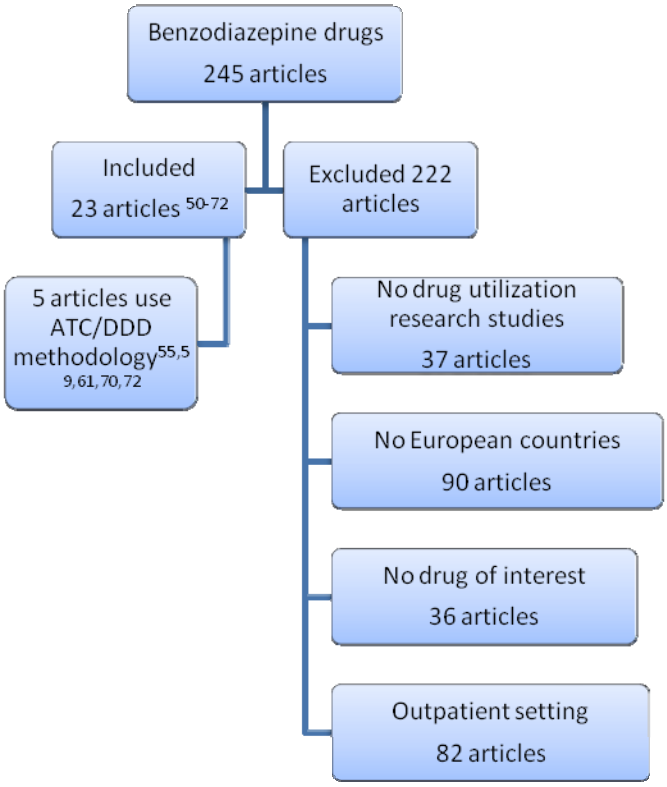
Flow chart 2. Hospital drug utilization and antiepileptics



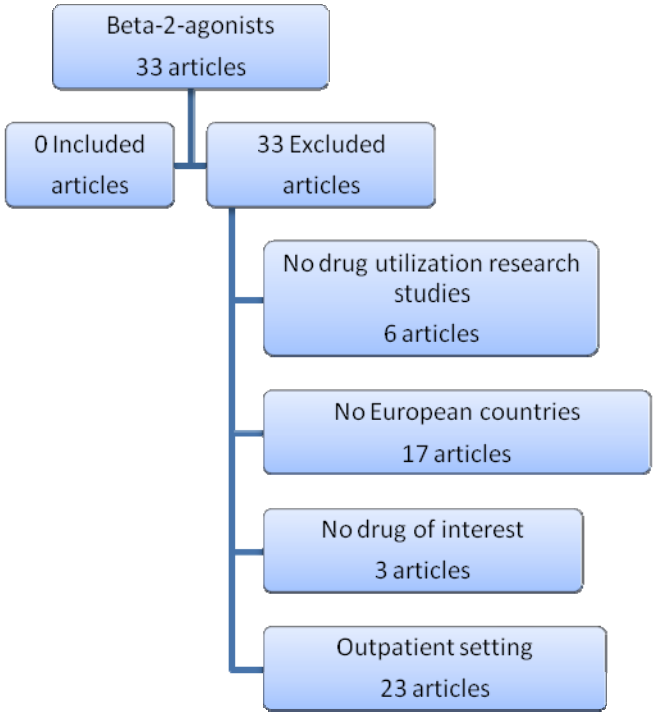
Flow chart 3. Hospital drug utilization and antidepressants



Flow chart 4. Hospital drug utilization and benzodiazepines



Flow chart 5. Hospital drug utilization and beta-2-agonists



The articles excluded because they were not drug utilization research studies, were either studying the metabolism of the active pharmaceutical ingredient in animals or were guidelines of the use of the drugs in clinical practice.

Drugs of no interest, retrieved in the search, were magnesium sulphate in the case of calcium channel blockers, leukotriens and devices used in the administration of inhaled medicines, in the beta-2-agonists; for antidepressants, antiepileptics or benzodiazepines, different antipsychotics were catalogued as drugs of no interest.

Regardless of the country or countries concerned and the type of drug utilization research study, the majority of the articles were set in the outpatient setting.

Another remarkable characteristic is the type of units of measurement of the patterns of use of the different groups of medicines. Most of the articles expressed the consumption as percentages of active ingredient out of the total consumption of the main anatomical group. Several articles that dealt with benzodiazepines, antidepressants, or antiepileptic drugs indicated for mental illnesses, prescribed doses were transformed into equivalents of diazepam or chlorpromazine. Thereafter, this calculation eased the comparison of drug use among different diagnoses or across countries.

Articles concerning antiepileptic drugs, benzodiazepines and antidepressants that were included in this review were conducted in nursing homes or in other long-term care institutions, being the studies mainly conducted among elderly people or people with learning disabilities.

Discussion

Figures reflecting drug utilization research in inpatient settings at a national level are sparse. Most of the found articles are centered in studying drug

consumption within one hospital or several hospitals within a single country. There are few articles that attempt to compare inpatient drug utilization research across different countries. To our knowledge, only the ESAC group launched in 2007 a study subgroup in charge of, among other goals, conducting point prevalence surveys on the inpatient antibiotic consumption across different European countries.

Several factors might have contributed to this fact:

- First, the high heterogeneity in the management of medicines at a hospital level, from the availability of a hospital drug formulary, to the distribution of the medicines, up to the availability of a hospital pharmacy. Moreover, for some countries the absolute number of hospitals remains unknown[2]. This fact might have hampered the possibilities of collecting valid drug consumption data. To this level the organization of the health system may influence in the management of medicines in the hospital sector.
- Second, most of the European countries collect information of prescribed drugs from community pharmacies with a straight flow of information from the community setting to the authorities, which are the ones in charge of centrally storing the data and elaborating drug consumption reports in the outpatient setting. Except Poland, for which information is not available, the rest of the European countries keep updated a national database of prescribed medicines in the outpatient sector. Some other countries collect information in inpatient drug use directly from wholesalers (Denmark, Sweden or France) or from IMS Health (Poland, Italy).

- Third, the division of inpatient or outpatient drug consumption varies among countries, probably reflecting their own health system.
- Finally, several problems are encountered regarding different methodological issues: The classification of drugs (the British National Formulary used in the United Kingdom), the Anatomical Therapeutic Chemical classification in Nordic countries and the EPhMRA classification by the IMS Health. The quantification of drug use: Defined Daily Doses is the recommended unit of measurement for drug consumption by WHO, even in the hospital setting. WHO recommends adjusting the calculation of the DDD to the hospital clinical activity, reflected by the bed-days. However, other denominators have been proposed as a measure of clinical activity by researchers in the field of antibiotic surveillance[73]. The ATC/DDD methodology is rarely used to measure the consumption of the PROTECT selected drugs. The quantification of drug use is mainly expressed as a proportion of an active pharmaceutical ingredient out of the total consumption for a specific group of medicines.

Figures from the PHIS report and from Denmark, Sweden and France show that the majority of the PROTECT selected drugs are used in the outpatient setting. Thus, the proportion of in-hospital drug utilization of calcium channel blockers, antidepressants, antiepileptics, benzodiazepines and beta-2-agonists can be assumed to be relatively small.

None of the 10 most used drugs in inpatient settings in Europe is one of the active pharmaceutical ingredients included in the PROTECT selected drugs. This statement is also valid for the top 10 most used drugs in Swedish hospitals. Moreover, 2 out of the 3 general reports found on the Internet do not provide information on in-hospital drug utilization, rather on the expenditure on drugs.

Calcium channel blockers and beta-2-agonists are drugs mainly indicated for chronic diseases, treated primary in the outpatient setting. This is clearly reflected in data on drug consumption in Denmark, where C08 use in inpatient sector represents only 0.5% of the total calcium channel blockers consumption. R03AC or beta-2-adrenoreceptor agonists and R03AK in hospital stand for 2.6% and 2.9% of the total consumption respectively. In addition, search on PubMed yielded to zero articles settled in a hospital setting studying the consumption of beta-2-agonists.

Antidepressants and benzodiazepines are widely prescribed in the community; use in psychiatric hospitals is small in comparison. Likewise, anticonvulsivants are mainly consumed outside of the hospital, with the exception of a smaller proportion of brain-damaged patients with epilepsy who are institutionalized. This is suggested by the results of the bibliographic database search. Of all included articles on antiepileptics, 50%(8) were conducted among patients living in long-term care settings. Also, data on inpatient drug consumption in Denmark and in Sweden, shows that drugs acting on the central nervous system (N) are less than 5% of the total drug consumption. Antiepileptic drugs, antidepressants and benzodiazepines are drugs all of them classified as acting on the central nervous system (N). It may be reasonable to assume that the consumption of antiepileptic drugs, antidepressants and benzodiazepines by ATC level 4 or 5 in inpatient settings is even lower. Not only antidepressants, antiepileptic drugs or benzodiazepines, are part of N anatomical group, but also anesthetics, analgesics, anti-Parkinson drugs, drugs used in addictive disorders and antivertigo drugs. This is also applicable to drugs classified as C and R.

There are several limitations to this study. Only three reports on general hospital information have been looked at and information extracted from them. Surely more information is available on hospital management from European organizations, although it is doubtful that further information on drug consumption in hospital setting is available as there are no national hospital databases that collect pharmaceutical report.

Second, data from only three European countries have been presented. Two of these countries are geographically closed and might have similar patterns of drug use, reflecting similar health systems or similar ways of understanding health. It is clear that these examples cannot be generalized to the rest of Europe. However, it is not expected that the proportion of in-hospital drug consumption would vary massively across countries.

Thirdly, only one bibliographic database PubMed was used. This may have introduced a bias towards studies conducted in North America, thus yielding to very few studies run in Europe. Although the search terms used allowed for a high number of articles to be retrieved, the key search terms did not include synonyms or MeSH terms, so there exists the possibility that articles not indexed according to the terms specified in the search may have been excluded. The articles were included on the basis of what was stated in the abstract.

Conclusions

The consumption of calcium channel blockers, benzodiazepines, antiepileptic drugs, antidepressants and beta-2-adrenergics in hospitals represent a very low percentage of their total consumption as it is inferred from consumption data in a few European countries.

Little published information is available on inpatient drug consumption at a national level. Most of the studies are set in a single hospital or very few hospitals within one country.

It is for all the above mentioned reasons that the interest of the PROTECT selected drugs in drug utilization research is inherent to their outpatient utilization.

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APPENDIX 7. SUMMARY TABLE OF DATA ON DRUG CONSUMPTION AVAILABLE AT FICF

Country		Data received	Organization	Type of data	ATC/DDD methodology	Validity assessment	
						Data Graphical description	Questionnaire received
Denmark (Danish National Prescription Registry)		Online	The Danish Medicines Agency	Outpatient (dispensed) Inpatient (sales)	Yes DDD/1000inh/day	Yes	No
France	CNAMTS (ERASME)	No (Declined collaboration)	National Insurance Company	Outpatient (reimbursed)	Yes	---	No
	AFSSAPS	Yes	AFSSAPS	In/Outpatient (sales)	Yes DDD/1000inh/day DDD/100 admissions	Yes	Yes
Germany (AOK database)		No (waiting for the agreement WIDO-LMU_FICF)	The Research Institute of the AOK	Outpatient (reimbursed)	Yes	No	No
Italy (OsMed database)		Incomplete,waiting for ATC 5 level	The Italian Drug Agency	Out-and inpatient (reimbursed+IMS Health)	Yes	No	Yes
Norway (Norwegian Prescription database (NorPD)		Online	Norwegian Institute of Public Health	Outpatient (prescribed and dispensed)	Yes	Yes	Yes
Poland (National Health Fund database)		No	National Health Fund	n/a	n/a	No	No
Sweden (The Swedish Prescribed Drug Register)		Online	National Board of Health and Welfare	Outpatient (prescribed and dispensed)	Yes	Yes	No
Spain		Yes	Spanish drug and health products agency	Outpatient (reimbursed)	Yes	Yes	No
The Netherlands	GIP	Online	Healthcare Insurance Board	Outpatient (reimbursed)	Yes	Yes	Yes
	SFK	No	Foundation for Pharmaceutical Statistics	Outpatient (dispensed)	Yes	No	Yes
United Kingdom (England and Wales) ePACT		Yes	NHS Prescription Services	Outpatient (reimbursed)	BNF/ADQ (ATC/DDD upon request)	Yes	No

APPENDIX 8. SUMMARY TABLE OF DATA ON ANTIBACTERIAL (J01FA and J01CR02) CONSUMPTION PROVIDED BY IMS HEALTH

Database name: MIDAS Monthly sales for retail and hospital panel			
Country	Data received	Panel	Data analyzed (2007-2009)
Denmark	Yes	Combined retail and hospital	Yes
France	Yes	Retail and hospital	Yes
Germany	Yes	Retail and hospital	Yes
Italy	Yes	Retail, hospital and distribution "per conto" [DPC] (for some drugs and regions may represent up to 20% of the market)	Yes
Norway	Yes	Retail and hospital	Yes
Poland	Yes	Retail and hospital	Yes
Sweden	Yes	Combined retail and hospital	Yes
Spain	Yes	Retail and hospital	Yes
The Netherlands	Yes	XPonent and hospital	Yes
United Kingdom	Yes	Retail and hospital	Yes

APPENDIX 9.SAMPLE OF THE QUESTIONNAIRE

QUESTIONNAIRE REGARDING DRUG CONSUMPTION DATABASES IN EUROPE

INSTRUCTIONS

One of the goals of the PROTECT research group is to identify and describe the health care databases at a national level that can be used in drug utilization research.

As part of an inventory on drug consumption databases (DCDB), the Working Group 3 of PROTECT Work Package 2 has elaborated this questionnaire about the characteristics of the database. Our aim is to collect additional information based on the population and drug coverage, as well as on the main characteristics of the individual patient. This information will let us know how comparable the different national databases are and could be used to conduct studies on drug utilization more effectively.

For more information regarding the PROTECT project www.imi-protect.eu

We would be most grateful if you could cooperate with us filling out the questionnaire. Please, specify the suggested citation for your person, as we would like to acknowledge all your support.

You will see that the questionnaire is partially filled out with the information we already have. Please, revise and amend any inaccuracy you may find.

Many thanks for your cooperation.

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

Contact person: Pili Ferrer
E-mail: pf@icf.uab.es
Catalan Institute of Pharmacology (FICF) http://www.icf.uab.es/en/index.html

1. DEFINITION: WHERE DO YOU RECORD INFORMATION ON DRUG USE IN THE FOLLOWING SETTINGS/SITUATIONS

If your information on drug use in nursing homes is included in outpatient care, tick under outpatient heading. If this information is not collected or does not apply to your database, tick under the appropriate heading.

DATABASE NAME:				
	Out-patient	In-patient	No information collected	No included
Nursing homes				
Dental care				
Specialist care to outpatients				
Drug abuse centers				
Private institutions				
Hospital drugs dispensed to outpatients				

Comments:

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

Estimated population coverage by your dc

Comments:

If you are using a sample of population, either for ***outpatient*** or ***inpatient***, please indicate your sampling method

Outpatient
Inpatient

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

3. DRUG-BASED INFORMATION.

3.1. Type of data available

Please answer yes or no. ***If applicable***, when the answer is positive, kindly provide the estimated proportion.

	Yes	%	No	Comments
Manually prescriptions (estimated proportion)				
Electronic prescriptions (estimated proportion)				
Sales of medicinal products				
Dispensed prescription data (reimbursed and not reimbursed)				
Dispensed prescription data reimbursed				
Over the counter drugs (estimated proportion)				
Prescriptions in the pharmacy not collected by the patient (estimated proportion)				
Completeness of registration of the prescription (Proportion of missing prescriptions)				
Indication of the prescription				
Date prescribed				
Date dispensed				
Duration of prescription				
Quantity of drug dispensed				
Package size/Number packages				
Days of supply				
Dose				
Strength				
Form of dosage				

Other data collected:

3.2 ATC/DDD methodology

❖ *When is your database updated with the new ATC/DDD codes? What is the currently version used?*

❖ *Does your database use the last ATC/DDD version for all retrospective data?*

❖ *Management of national assigned ATC/DDD codes in your database.*

4. OTHER INFORMATION OF INTEREST REGARDING YOUR DATABASE.

4.1 Patient-related information

❖*Is it possible to link this database with either other health register or other databases?*

❖*Please tick the items for which information is collected in your database*

Unique patient identification
Age
Sex
Ethnicity
Place of residence
Education
Income
Social class

Comments

4.2 Internal validity of the database

❖*Could you specify how and how often you ensure the internal validity of your database?*

4.3 Accessibility of data

❖*For research purposes, is all the data you collect publicly available?*

Thank you for your cooperation.

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