Real-world data from the health decision maker perspective. What are we talking about?

Silvana Romio[1, 2], Miriam Sturkenboom[2], Giovanni Corrao[1]

ABSTRACT

Healthcare decision-makers are increasingly developing policies that seek information on "real-world" data providing "evidence" to support and monitor changes in clinical practice or policy decisions. Many strategies may be evaluated in experimental circumstances, but this does rarely reflect clinical practice. Due to the current focus on information and computer technology to provide safer and more efficient healthcare delivery, the amount of electronic medical records and other electronic healthcare data is increasing exponentially, and these real-world data can be used for evidence generation. This review describes why and how healthcare/policy decision making could benefit from real-world data, it introduces methods to investigate real-world clinical practice, lists potentialities of routinely collected real-world data, reviews their availability in the word, and outlines future challenges in this field.

Key words: Comparative Effectiveness Research; Healthcare Utilization Database; Medical records; New user design; Observational Studies; Pharmacoepidemiology

(1) Department of Statistics and Quantitative Methods, Division of Biostatistics, Epidemiology and Public Health, University of Milano-Bicocca, Milan, Italy
(2) Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands

CORRESPONDING AUTHOR: *Giovanni Corrao, Department of Statistics and Quantitative Methods, Division of Biostatistics, Epidemiology and Public Health, University of Milano-Bicocca, Via Bicocca degli Arcimboldi, 8, Building U7, 20126 Milan, Italy. Tel: +39 02 64485854. Fax: +39 02 64485899. e-mail: giovanni.corrao@unimib.it*
DOI: ***10.2427/8979***

WHY HEALTH DECISION MAKERS SHOULD BE INTERESTED IN REAL-WORLD DATA?

Healthcare decision making

Decisions about the deployment of health resources are taken by 2 subjects: by physicians for the individual patient and by public health policy makers on a population level. The target of public health care decision making is the population (which means less room for considering biological mechanisms of disease and more at the behavioural and social conditions that result in disease) and the decision makers are often public officials, rather than clinicians and their patients [1]. Nevertheless, most of the elements of public health decision making impact on the individual patients. For example, occult blood testing for screening of colorectal cancer is a public health decision, although it will impact on the individual patient. Drug safety presents similar concerns. For example,

regulatory decision making regarding drugs safety is based on population impact, although for a patient it is about having an adverse effect or not. Population impact played an important role in the discussions about rofecoxib, rosiglitazone and other widely used drugs. Although restriction of drugs may have an overall public health impact, for a single patient this may not be the case since the majority would not experience the rare effect anyway. Finally, decisions taken by insurance companies or National Health Services, about medical procedures to reimburse typically affect both, daily clinical practice, by limiting the therapeutic choice, and public health, by shifting resources from one domain of health care to another.

Real-world data and real-world evidence

Healthcare decisions preferably should be evidence-based and/or evaluated but reality shows that many decisions need to be taken on the basis of imperfect evidence and with uncertainty about the outcome of decisions [1]. Evidence about the real-world can best be obtained from the real world practice. With "real-world data" we mean data that are not collected under experimental conditions, but data generated in routine care. There is an enormous potential to improve cure and care if the information that is generated in clinical routine is exploited for evidence generation. Secondary use of these data has greatly contributed to the area of drug safety and outcomes research. A distinction between "real-world data" and "real-world evidence" is important. As noticed by the task force of the "International Society for Pharmacoeconomics and Outcomes Research" [2] the "data" conjures the idea of simple factual information, whereas "evidence" connotes the organization of the information to inform a conclusion or judgment. Evidence is generated according to a research plan and interpreted accordingly, whereas data is only a component of the research plan. Evidence is shaped, while data simply are raw materials and alone are non-informative.

Accordingly with this statement, the current paper firstly focuses general issues concerning data organization for obtaining "real-world evidence". Available "real-world data" will be considered afterwards.

EVIDENCE FROM REAL-WORLD CLINICAL PRACTICE

Health insurers, regulators, physicians, and patients need information on the comparative effectiveness and safety of drugs in routine care [3]. This means that experimental designs should not be used, but real-life care should be studied. Although the need is evident, there is controversy around non-experimental, i.e. observational studies, even more so if they study effectiveness [4]. Several controversies have arisen, for example the effectiveness of HRT as evidenced in the Nurses Health Study that was not supported in a subsequent trial, the effect of NSAIDs on Alzheimer's disease that could not be proven in clinical trials, the effects of statins on fractures which could not be seen in clinical trials. Methodological issues concerning the design, confounding, conduct of the study and interpretation of results needs special attention in an epidemiologic observational framework.

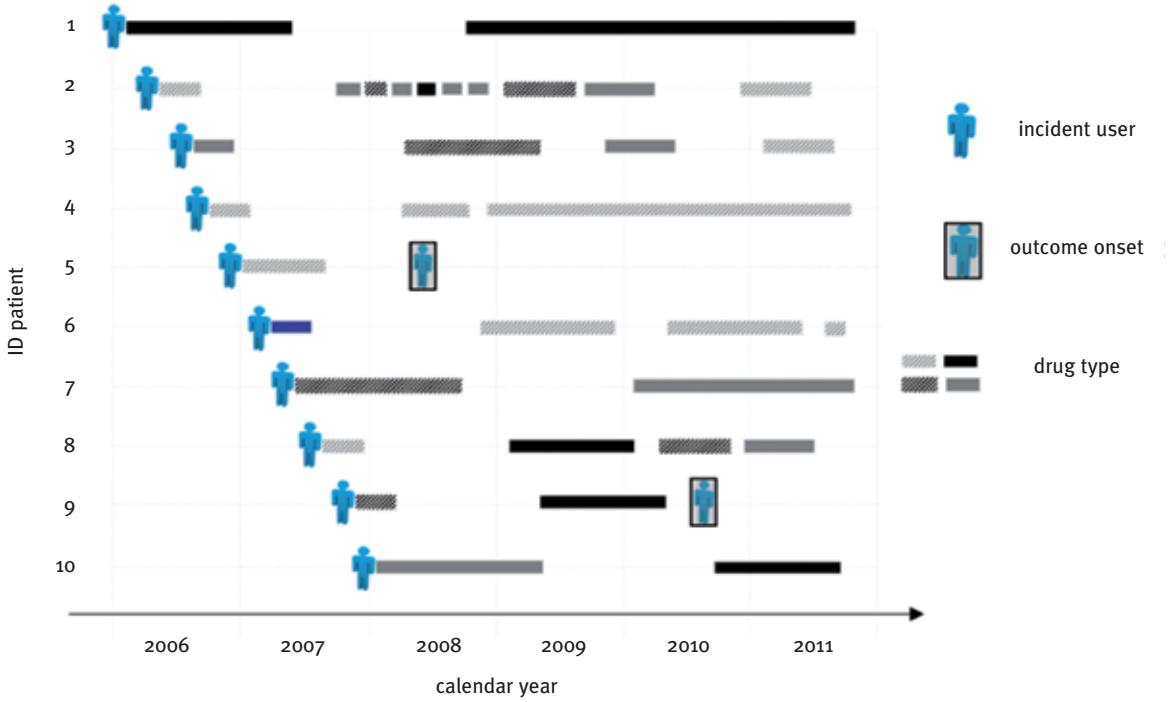
The basic observational design

We now introduce a basic design in an observational epidemiologic framework, the so called population-based cohort design. A cohort is defined by subjects meeting a set of eligibility criteria and by entry and exit time points. Consider, as hypothetical example, a cohort investigation for studying issues concerning antidiabetic therapies. Entry in the cohort may be defined by calendar time (e.g., any time after January 1, 2004), by age (any age before 40th birthday), by events (the first use of oral hypoglycaemic medication), and/or by disease status (the date of diagnosis of type 2 diabetes). Exit from the cohort may be defined by the first occurrence of specific calendar time (e.g., December 31, 2010), age (exit at 80th birthday), events (death; exit from the study; the first switching from oral hypoglycaemic therapy to insulin), and/or disease status (first occurrence of coronary heart disease).

The cohort of incident users of oral hypoglycaemic drugs may be illustrated graphically as in Figure 1. In the graph, ten subjects who entered in the cohort at the time of their first prescription of the considered drugs (e.g. incident users of oral hypoglycaemic agents) are ranked according to their cohort entry date. The restriction to new

FIGURE 1

ILLUSTRATION OF A FIXED COHORT OF TEN INCIDENT USERS OF A GIVEN DRUG THERAPY WHO WERE GENERATED FROM A WELL-DEFINED DYNAMIC POPULATION FROM 2006 THROUGH 2007



Cohort members are followed until December, 31 2011. During follow-up drug exposure and outcome onset experienced by cohort members are illustrated.

initiators of the study drugs (inception cohort) will mitigate those issues and will also ensure that patient characteristics are assessed before the start of the study drug and can therefore not be the consequence of the drug, similar to the principle of RCTs. Advantages of using the so-called "new user design" are recognized and well described by Ray [5].

It is important to stress that the included ten incident users reported in Figure 1 are, potentially, all individuals belonging to the target population who started therapy during the observational period. This is a first peculiarity of observational studies with respect to RCTs. As mentioned above, RCTs often select patients from clinical excellence centres, excluding patients who are more vulnerable to adverse effects of therapy in the absence, however, of a target population from which incident users arise. This means that population-based cohort studies, such as that described in Figure 1, are virtually free from external selection bias (lack of generalizability) and, hence, adequately should describe real data generated from unselected target populations.

Cohort members of incident drug users are followed to record two categories of data. The first one concerns drug exposure. Figure 1 depicts a strong heterogeneity of drug exposure for both type and duration (respectively represented by sketching and base length of rectangles). This is the second substantial peculiarity of observational studies with respect to RCTs. The last ones, in fact, are based on the minimization of exposure heterogeneity. Conversely, one main characteristic of observational studies is that they are aimed to describe drug exposure heterogeneity observed in real-world clinical practice, including heterogeneity in the compliance to treatment and deviations from guideline-based clinical recommendations, and identifying components of heterogeneity affecting the outcome onset.

The second family of data recorded during follow-up is the outcome onset. Outcome may be the disease that would be avoided or postponed by the therapy (e.g. switching to insulin as proxy of disease worsening or macrovascular events avoided as effect of a given

treatment regimen) as well as events potentially linked with brief- or long-term drug safety (e.g. gastrointestinal bleeding or cancer). This is the third substantial peculiarity of observational studies compared to RCTs. The last ones, in fact, are often characterized by sample size and duration that do not allow for investigating rare outcomes and long-term effects of exposure. Conversely, large populations followed for several years from exposure starting are usually submitted to observational investigation.

Besides this reference design, other ways for observing a given population have been widely used for epidemiological purposes. Among these, the nested case-control design, a direct derivation of the cohort one, has received great attention owing its higher computational efficiency compared to the cohort design [6]. A complete review of observational designs proposed by the methodological and applicative literature, however, lies outside the objective of this introductive report. The review made by *Suissa* is a suitable introductive reading of modern approaches for designing and analysing observational studies [7].

The comparative effectiveness principle

There is a last substantial difference between observational studies and RCTs. As pointed out by Cochran about 40 years ago [8], RCTs on the efficacy of drugs for their regulatory approval study the extent to which an intervention does more good than harm under ideal circumstances ("Can it work?"). For most conditions, however, physicians have a choice of two or more medications that can prevent, cure, avoid progression of, and reduce suffering from diseases. For physicians, it is therefore not a question of whether to prescribe a drug [9] but which drug among several alternatives [10]. In such situations, physicians need to understand their comparative effectiveness and safety. As a matter of fact, effectiveness assesses whether an intervention does more good than harm compared to an alternative intervention, when provided under usual circumstances of healthcare practice ("Does it work in practice?").

Hence, Comparative Effectiveness Research (CER) tries to solve the issue of limited generalizability to routine care and the comparison with an active comparison group by secondary use of health care data, often from large healthcare utilization databases [11]. CER then aims to produce actionable evidence regarding the effectiveness and safety of medical products and interventions as they are used outside of controlled research settings (Figure 2) [12].

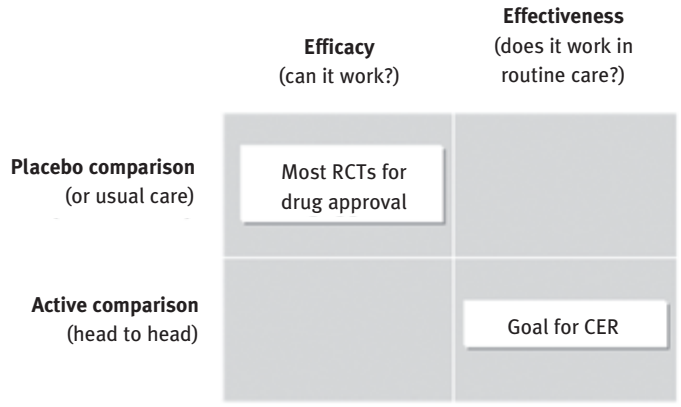
It is important to be explicit about the definition of comparative effectiveness as it is applied in this issue of EBPH. Regarding the term comparative, this report will focus on the majority of circumstances when comparisons can be made between two or more active treatments and it excludes the "no treatment" or placebo option [2].

Potentiality of observational approach

Observational studies utilizing existing health care data are suitable for studying several aspects of effectiveness in routine clinical practice. Two items have been considered

FIGURE 2

GOAL OF COMPARATIVE-EFFECTIVENESS RESEARCH (CER) IN CONTRAST TO RANDOMIZED CONTROLLED TRIALS (RCTS)



while the reference observational design was described: course of exposure (e.g. to a given therapy or, more in general, to health care services) and outcome onset (concerning therapy effectiveness and/or safety). Because both exposure and outcome generate costs for the National Health System (NHS), at least three types of studies are useful to understand the effects of interventions (e.g. drugs) in real life:

- profile of pharmacoutilization, or more in general of health care utilization, including the number of current (prevalent) users, new (incident) users, duration of use, to name a few [13-15];
- benefit-risk profile of a given therapy: effectiveness (that is efficacy in routine clinical practice) and safety outcomes that may be integrated by weights [1];
- cost-effectiveness profile of a given therapeutic strategy [16-18].

POTENTIALITY AND AVAILABILITY OF ROUTINELY COLLECTED REAL-WORLD DATA

The assessment of the comparative benefits and risks of various treatment options through the analysis of real-life data is controversial. Nevertheless, policymakers, stakeholders, and providers are more prone to use large electronic databases to answer a variety of questions, such as those above reported.

Defining healthcare database

It is important to be explicit about which definition of database is applied in this paper. With this term we will focus on electronic systems which are designed and fed for collecting and electronically storing all data of interest (e.g. drug prescriptions, hospital admissions, ambulatory visits, deaths, and so forth) concerning well defined dynamic populations (e.g. those residing a given administrative area or attending assistance from a network of general practitioners). We then will use the term database for implicitly meaning population-based databases.

Types and sources of healthcare database

Databases collecting health information can be classified into two broad categories: those that collect information for administrative purposes, such as filling claims for payment (denoted as administrative or healthcare utilization (HCU) databases), and those that serve as the patient's medical record and are therefore a primary tool by which physicians track health information on their patients (denoted as medical record (MR) databases) [19]. A basic description of HCU and MR data, in comparison to conventional sources of health care research, is provided in Table 1 [20-24].

HCU databases were initially created for administering payments to providers in nationally funded public or private healthcare delivery system [25]. Healthcare programs necessarily require a system of electronic database for their management. For example, data on drug dispensations, hospital admissions and outpatient visits carried out respectively by pharmacies, hospitals and physician ambulatories accredited by the health organization, are recorded and stored since these healthcare providers must be reimbursed for their supplied services. So conceived databases, usually containing patient-level data of health service for many millions of beneficiaries over long periods of time, can be electronically linked via a unique patient identifier. In this way, the care journey for each individual beneficiary of the health system may be tracked. In USA, typical examples of HCU databases are electronic healthcare records of large health insurance companies like United Health, or Health Maintenance Organizations like Kaiser Permanente, or of government-funded healthcare programs like Medicaid and Medicare [19].

A major weakness of these HCU databases is the instability of the population due to job changes, employers' changes of health plans, and changes in coverage for specific employees and their family members. The opportunity for longitudinal analyses is hindered by the continual turnover of plan members. Results from studies that use these databases may not be generalisable when data concerns an atypical population. For example, Medicare covers the elderly, Medicaid covers indigent and other special patient .groups, and the Veterans Administration database covers predominantly an older and possibly poorer male population. Employer-based databases, on the other hand, may represent patient populations of a relatively higher socioeconomic class. These factors limit the generalizability of study results obtained using such databases [20].

TABLE 1

COMPARISON OF MAJOR POPULAR DATA SOURCES FOR HEALTH RESEARCH: A GENERAL REPRESENTATION OF ADVANTAGES (+++) AND DISADVANTAGES (---)

	PROSPECTIVE DATA COLLECTION		ANALYSIS OF EXISTING DATABASE	
	CONTROLLED CLINICAL TRIALS	LONGITUDINAL OBSERVATIONAL STUDIES	HEALTHCARE UTILISATION DATABASES	MEDICAL RECORD RESEARCH DATABASES
Relatively less costly	---	---	+++	+
Timely availability of data	--	---	+++	+++
Nonintrusive	---	---	+++	+++
Usability in a variety of disease conditions from a single data source	---	-	+++	+++
Large patient groups	---	--	+++	++
Heterogeneous patient groups	---	++	+++	+
Resemblance to the actual clinical practice	---	+++	+++	+
Validity of information	+++	++	-	-
Comparable treatment groups (absence of confounding by indication)	+++	--	---	--
Easily accessible by health services researchers	---	--	+	---
Accurate coding	+++	+	-	+
No “upcoding” problems (a)	+++	+++	---	+++
Researcher control of the type and extension of information collection	+++	+++	---	---
Example	Scandinavian Simvastatin Survival Study [21]	The Framingham Heart Study [22]	Medicaid database [23]	General Practice Research Database [24]

(a) Upcoding: coding of diagnosis or services to maximize the reimbursement
Source: Gandy et al [20], partially modified

Several Member States of European Community provide universal coverage for many health services so that stable populations and generalisable findings may be easily obtained by linking data from public healthcare delivery system (i.e. the National Health Service). Nevertheless, the use of HCU databases for research aims, albeit with significant difference between States, is not as popular as in USA, mainly because of legal and privacy issues. Rather, whole segments of the healthcare delivery system rely on MR database from primary healthcare, e.g. in the UK, The Netherlands, and Italy [26]. The most prominent of these is the UK Clinical *Practice Research Database* (CPRD), a large physician-based computerized database of anonymous longitudinal patient records from hundreds of general practices that collect data on approximately three million patients, equivalent to approximately 5% of the UK population [24, 27]. Similarly, the Integrated Primary Care Information (IPCI) system from the Netherlands is a research-oriented database maintaining 500 general practitioners and covering over 1 500 000 people [28]. Finally, among structured electronic MR databases available in Italy, we here remind

those denoted *Health Search* and *ULNet* databases fed by approximately 900 and 220 general practitioners (GPs) respectively [29]. In addition, the Italian MR database specifically oriented at paediatric population, the so called *Pedianet* database, is also available for particular applications [30]. These databases include information on demographics, medical diagnoses, prescriptions, referrals to hospitals, smoking status, body mass index, immunizations, blood pressure measures and laboratory findings.

Strengths and weaknesses

Both, HCU and MR databases have four key advantages for performing comparative effectiveness and safety research [31]: (1) they are available at relatively low cost; (2) their representativeness of routine clinical care makes it possible to study real-world effects; (3) the large size of covered population will shorten the time necessary to identify a sufficient number of users of a newly marketed drug [32]; (4) patient's non-response bias and recall bias are non-existent in studies based on such records, as all data were recorded prospectively and independent of patients' recall or agreement to participate in a research study [11].

A major advantage of HCU data is that they even more reflect real-world clinical practice for large and unselected populations. This is particularly true where health assistance is assured by a National Health System -NHS- covering practically all citizens. However, studies based on HCU data have been criticized for the incompleteness of patients' information such as markers of clinical disease severity, lifestyle habits, and socio-economic status, among others. Indeed, because of HCU databases are aimed of reimbursing providers of health services there are not reasons for collecting information which do not influence costs of health service. In contrast, although MR data are richer of clinical and lifestyle information, they often suffer from the fact that any given practitioner provides only a piece of the care a patient receives, and specialist and hospital cares are unlikely to be recorded in a common MR database. Data quality issues, as well as the selection of general practitioners who carefully take care of their patients, are other potential limitations of studies based on MR data

FROM CURRENT EXPERIENCES TO FUTURE CHALLENGES

As said before, very large studies can be performed with real-world databases in a relatively quick and expansive way, their use being facilitated by the development of increasingly powerful computer technologies. However, their immense potential as a research resource has to be fully realized yet by administrators and database managers or information system specialists of individual health plans. With the experience gained through the use of these data and a careful understanding of the underlying healthcare system within the data were generated, computerized databases provide a highly useful data source for pharmacoepidemiology and healthcare research. Future studies should then move ahead in the direction of their more intensive, complete and integrated use.

A major concern in this field is the relatively scarce use of real-world data for decision making, most of all in some countries such as Italy. Currently, large databases are routinely used for administering payments to healthcare providers and managing care organizations. We hope however to have provided enough reasons to support the fact that potentialities of these data go beyond the simple healthcare accounting. From an academic point of view, the more natural way for stimulating intensive and complete use of HCU databases, is of increasing in-depth studies showing potentialities (and weaknesses) of this approach. For example, with the aim of assessing the association between use of oral bisphosphonates and their benefits (i.e. reduction of bone fractures risk) and suspected harms (i.e. increasing jaw osteonecrosis and gastrointestinal events) in real-world clinical practice, the Bisphosphonates Efficacy-Safety Tradeoff (BEST) study has been recently funded with grant from the Italian Drug Regulatory Agency (AIFA) [33]. This study has been carried out by means of creating a network of HCU databases as a whole containing records of almost 19 million Italian citizens from five Italian Regions and ten Local Health Authorities. Yet, a study still ongoing funded with grant from the AIFA as well, concerns the assessment inappropriateness of prescribing and outcome evaluation among elderly patients affected by cardiovascular disease and other chronic comorbidities assembling HCU data from three Italian Regions.

Another major concern in this field is the relatively scarce integration of HCU and MR data. As above reported, strengths and weaknesses of these data sources are in large part complementary between them. This suggest that, where feasible, multiple sources should be considered for investigating a given research question. For example, the strength of drug-outcome association estimated by HCU database may be biased by unmeasured confounders. However, if additional data sources can be identified (e.g. from MR database covering the same population and time-window as the HCU database), external adjustment of the drug-outcome association may be attempted [34]. Similarly, although errors in measuring exposure are an important source of bias mainly when HCU database is used (e.g. grossly approximations of drug dose assumed by a given patient are usually used), external adjustment to measure errors may be attempted, conditionally to the availability of MR data measuring the relationship between biased and approximately true exposure level [35].

There is no obvious method for combining different electronic medical records into a uniform repository. In-depth studies using this approach is ongoing from several studies funded by grants from European Community. For example, the "Safety Of non-Steroidal anti-inflammatory drugs" (SOS) project (http://www.sos-nsaids-project.org/), aimed of comparing the risk of cardiovascular and gastrointestinal events in users of any type of traditional nonsteroidal anti-inflammatory drugs (tNSAIDs) or Coxib, has been designed, and is still ongoing, by means of creating an international network for conducting common protocol database studies. In particular, both HCU and MR databases containing records of, in total, more than 40 million European citizens from four different countries (Italy, Germany, The Netherlands and UK) have been assembled. Similarly, a common-protocol multisource and multi-country database has been recently designed to address drug safety concerns diabetes and antidiabetic therapies (the Safeguard Project; http://www.safeguard-diabetes.org/).

Despite these promising projects, observational studies using real-world databases suffer from limited research funding opportunities. This, of course, generates the risk that academic groups become too dependent on industry funding, both in term of study questions and credibility [36].

There is a great need of independent studies investigating use, equity, effects, and costs of healthcare with robust methodologies. We then hope that national and regional governments, particularly those where consolidated welfare systems operates through the NHS, begin to fund projects in this field more often.

In the meantime, with an attempt to stimulate health care decision makers and public health researchers to address resources towards real-world data, the current issue of EBPH is devoted to go into thoroughly methodological topics and privacy concerns of real-world data. Examples of MR and HCU databases will be also presented. Finally, the so called CRACK program (Carry out a Repository for Administrative and Clinical data Knotting), including methodological, health-related, and educational projects to evaluate management of chronic conditions in real world clinical practice, will be described.

References

[1] Sox HC, Goodman SN. The methods of comparative effectiveness research. Ann Rev Pubic Health 2012; 33: 425-45

[2] Garrison LP,1 Neumann PJ, Erickson P, et al. Using real-world data for coverage and payment decisions: The ISPOR Real-World Data Task Force Report. Value in Health 2007; 10: 326-35

[3] Berger ML, Mamdani M, Atkins D, et al. Good research practices for comparative effectiveness research: defining, reporting and interpreting nonrandomized studies of treatment effects using secondary data sources: The ISPOR Good Research Practices for Retrospective Database Analysis Task Force Report—Part I. Value in Health 2002; 12: 1044-52

[4] Sørensen HT, Lash TL, Rothman KJ. Beyond randomized controlled trials: a critical comparison of trials with nonrandomized studies. Hepatology 2006; 44: 1075-82

[5] Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 2003; 158: 915-920

[6] Essebag V, Platt RW, Abrahamowicz M, et al. Comparison of nested case– control and survival analysis

methodologies for analysis of timedependent exposure. BMC Med Res Methodol 2005; 5: 5

[7] Suissa S. Novel Approaches to Pharmacoepidemiology Study Design and Statistical Analysis. In: Pharmacoepidemiology (4th edn). Strom BL (ed). Wiley, New York, 2005;811-29

[8] Cochrane A. Effectiveness and efficiency: random reflection on health services. Nuffiled Provincial Trust; London, 1972

[9] van Luijn JCF, Gribnau FWJ, Leufkens HGM. Availability of comparative trials for the assessment of new medicines in the European Union at the moment of market authorization. Br J Clin Pharm 2007; 63: 159–62

[10] Pisano, DJ.; Mantus, D. FDA Regulatory Affairs: A Guide for Prescription Drugs, Medical Devices, and Biologics. CRC Press; Boca Rotan, FL: 2004

[11] Schneeweiss S. Developments in post-marketing comparative effectiveness research. Clin Pharmacol Ther 2007; 82: 143-56

[12] Schneeweiss S, Gagne JJ, Glynn RJ. Assessing the Comparative Effectiveness of Newly Marketed Medications: Methodological Challenges and Implications for Drug Development. Clin Pharmacol Ther 2011; 90: 777-90

[13] Hallas J, Gaist D, Bjerrum L. The waiting time distribution as a graphical approach to epidemiologic measures of drug utilization. Epidemiology 1997; 8: 666-70

[14] Hackshaw MD, Krishna A, Mauro DJ. Retrospective US database analysis of drug utilization patterns, health care resource use, and costs associated with adjuvant interferon alfa-2b therapy for treatment of malignant melanoma following surgery. ClinicoEconomics and Outcomes Research 2012; 4: 169-76

[15] Peterson AM, Nau DP, Cramer JA, et al. A checklist for medication compliance and persistence studies using retrospective databases. Value in Health 2007; 10: 3-12

[16] Berger M, Teutsch S. Cost-effectiveness analysis: from science to application. Med Care 2005; 43(Suppl.): S49-53

[17] Corrao G, Scotti L, Zambon A, et al. Cost-effectiveness of enhancing adherence to therapy with statins in the setting of primary cardiovascular prevention. Evidence from an empirical approach based on administrative databases. Atherosclerosis 2011; 217: 479-85

[18] Scotti L, Baio G, Merlino L. Cost-effectiveness of enhancing adherence to therapy with blood pressure lowering drugs in the setting of primary cardiovascular prevention. Value in Health 2013; 16: 318-24

[19] Strom BL. Pharmacoepidemiology, edn 4. Chichester 2005: John Wiley & Sons Ltd

[20] Gandhi SK, Salmon W, Kong SX, Zhao SZ. Administrative Databases and Outcomes Assessment: An Overview of Issues and Potential Utility. J Managed Care Pharm 1999; 5: 215-22

[21] Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 444 patients with coronary heart disease: the Scandinavian simvastatin survival study (4S). Lancet 1994; 344: 1383-89

[22] Wilson PWF, D'Agostino RB, Sullivan L, et al. Overweight and obesity as determinants of cardiovascular risk. The Framingham experience. Arch Intern Med 2002; 162: 1867-72

[23] Hennessy S, Carson JL, Ray WA, Strom BL. Medicaid Databases. In: Pharmacoepidemiology (4th edn). Strom BL (ed). Wiley, New York, 2005; 281-94

[24] Gelfand JM, Margolis DJ, Dattani H. The UK General Practice Research Database. In: Pharmacoepidemiology (4th edn). Strom BL (ed). Wiley, New York, 2005; 337-46

[25] Suissa S, Garbe E. Primer: administrative health databases in observational studies of drug effects—advantages and disadvantages. Nature Clin Pract Rheumatol 2007; 3: 725-32

[26] Ash J, Bates D. Factors and forces affecting EHR system adoption: report of a 2004 ACMI discussion. J Am Med Inform Assoc 2005; 12: 8-12

[27] Walley T, Mantgani A. The UK General Practice Research Database. Lancet 1997; 350: 1097-9

[28] Van der Lei J, Duisterhout JS, Westerhof HP, et al. The introduction of computer-based patient records in The Netherlands. Ann Intern Med 1993; 119: 1036-41

[29] Filippi A, Vanuzzo D, Bignamini AA, et al. Computerized general practice databases provide quick and cost-effective information on the prevalence of angina pectoris. It Heart J 2005; 6: 49-51

[30] Sturkenboom M, Nicolosi A, Cantarutti L, et al. Incidence of mucocutaneous reactions in children treated with niflumic acid, other nonsteroidal antiinflammatory drugs, or nonopioid analgesics. Pediatrics 2005; 116: e26-33

[31] Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol 2005; 58: 323-37

[32] Rodriguez EM, Staffa JA, Graham DJ. The role of databases in drug postmarketing surveillance. Pharmacoepidemiol Drug Saf 2001; 10: 407-10

[33] Lapi F, Cipriani F, Caputi AP, et al. Assessing the risk of osteonecrosis of the jaw due to bisphosphonate therapy in the secondary prevention of osteoporotic fractures. Osteoporos Int 2013; 24(2): 697-705

[34] Corrao G, Nicotra F, Parodi A, et al. External adjustment for unmeasured confounders improved drug-outcome association estimates based on health care utilization data. J Clin Epidemiol 2012; 65: 1190-9

[35] Spiegelman D, McDermott A, Rosner B. Regression calibration method for correcting measurement-error bias in nutritional epidemiology. Am J Clin Nutr 1997; 65: 1179S-86S

[36] Strom BL, Hennessy S. The future of pharmacoepidemiology. In: Pharmacoepidemiology (4th edn). Strom BL (ed). Wiley, New York, 2005; 833-9