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The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP)

Guide on Methodological Standards in Pharmacoepidemiology (Revision 1)

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List of Acronyms

Agency for Healthcare Research and Quality (AHRQ)

Case Report Form (CRF)

Confidence Interval (CI)

Consolidated Standards for Reporting Trials (CONSORT)

Council for International Organisations of Medical Sciences (CIOMS)

Clinical Practice Research Datalink (CPRD)

Disease Risk Score (DRS)

Empirical Bayes Geometric Mean (EBGM)

Enhancing the Quality and Transparency of Health Research (EQUATOR)

EuroDURG Quality Indicator Meeting (DURQUIM)

European Commission (EC)

European Forum for Good Clinical Practice (EFGCP)

European Medicines Agency (EMA)

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)

European Surveillance of Antimicrobial Consumption (ESAC)

European Union (EU)

Exposure Propensity Score (EPS)

Food and Drug Administration (FDA)

General Practice Research Database (GPRD)

German Society for Epidemiology (DGEpi)

German Society for Social Medicine and Prevention (DGSPM)

Guideline on good pharmacovigilance practices (GVP)

High Dimensional Propensity Score (hd-PS)

Individual Case Safety Report (ICSR)

Information Component (IC)

International Classification of Diseases (ICD)

International Classification for Primary Care (ICPC)

International Committee of Medical Journal Editors (ICJME)

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

International Epidemiological Association (IEA)

IEA Good Epidemiological Practice Guidelines (GEP)

Instrumental Variables (IV)

International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
International Society for Pharmacoepidemiology (ISPE)
International Society of Pharmacovigilance (ISOP)
ISPE Good Pharmacovigilance Practice Guidelines (GPP)
Large Simple Trials (LST)
Marginal Structural Models (MSM)
Meta-analysis of Observational Studies in Epidemiology (MOOSE)
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
Post-authorisation Safety Studies (PASS)
Postmarketing commitments (PMC)
Postmarketing requirements (PMR)
Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)
Propensity Score Calibration (PSC)
Proportional Reporting Ratio (PRR)
Quality Assurance (QA)
Quality control (QC)
Quality of Reporting of Meta-analyses (QUORUM)
Randomised Controlled Trial (RCT)
Reporting Odds Ratio (ROR)
Risk Evaluation and Mitigation Strategies (REMS)
Strengthening the Reporting of Observational studies in Epidemiology (STROBE)
United States (US)
Working Group for the Survey and Utilisation of Secondary Data (AGENS)

All hyperlinks in the document were last accessed on-line on 10 June 2012.

1. Introduction

The [European Network of Centres for Pharmacoepidemiology and Pharmacovigilance \(ENCePP\)](#) aims to support high quality pharmacoepidemiological studies and to stimulate innovation that benefits patients and public health at large. This guide has therefore been developed to offer a single overview document and web resource for methodological guidance for both experienced and new researchers in pharmacoepidemiology and pharmacovigilance. For each topic covered, direct electronic access is given to internationally agreed recommendations and key points from important guidelines, published articles and textbooks after an introductory review. The focus is on scientific rather than regulatory guidance although relevant legislation and good pharmacovigilance practice are cited, where appropriate.

The guide has been developed by the ENCePP Working Group on Research Standards and Guidances and has been subject to public consultation. The first step was to identify and review [a list of existing English language guidances](#). That review consisted of documenting the objective, scope, target audience, content and relevance of each guidance. Gaps in guidance in areas important to collaborative pharmacoepidemiology research were also identified. Where relevant, such gaps have been addressed with what ENCePP considers good practice.

The guide is updated annually by structured review to maintain its dynamic nature. It may also be amended as necessary on an ad-hoc basis in response to comments received. Researchers are therefore kindly requested to refer any additional guidance document that they consider relevant, to encepp_comments@ema.europa.eu. In the interim, to facilitate access to methodological aspects that are not specifically covered in textbooks or existing guidance, the researcher is referred to a list of published papers addressing a number of methodological challenges and lessons learned (see Section 6.2).

Readers are also referred to the ENCePP [Checklist for Study Protocols](#), the objective of which is to increase awareness about scientific and methodological developments in the field of pharmacoepidemiology, and the ENCePP [Code of Conduct](#) that seeks to provide a set of rules and principles for studies.

Researchers are also requested to self-refer to standard textbooks in epidemiology and pharmacoepidemiology research, in addition to those cited in the present document.

2. Context

In Europe, European Union (EU) and national laws are the keys to what may and may not be done with regard to data access, data linkage and consent issues, including such domains as human rights and duty of confidentiality. While differing data custodians currently have differing requirements related to what approvals are needed before data can be released, the requirements will fit within the overall need to meet all applicable EU and national laws and guidelines for the actual study. This includes situations where multi-country studies are being conducted and there may be transfer of data or information. In addition to meeting legislative requirements, studies also need to adhere to a set of principles that meet with the requirements of scientific and ethical reviews.

2.1. Legal provisions

New pharmacovigilance legislation has been implemented in the EU since July 2012 ([Regulation \(EU\) No. 1235/2010](#) and [Directive 2010/84/EC](#)). This legislation includes the possibility for regulatory authorities to impose on marketing authorisation holders the conduct of post-authorisation safety studies (PASS) as a condition of the marketing authorisation, a PASS being defined as *“any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard,*

confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures. The legislation also provides obligations as regards the submission of study protocols, progress reports and final study reports in a standard format to regulatory authorities. The [Guideline of good pharmacovigilance practices \(GVP\) Module VIII - Post-authorisation safety studies](#) describes practical aspects for the implementation of the new legislation and the operation of the EU medicines regulatory network. It provides a general guidance on the development, conduct and reporting of PASS conducted by marketing authorisation holders, voluntarily or pursuant to an obligation. Of note, the legislation provides legal definitions of the *start of data collection* (the date from which information on the first study subject is first recorded in the study dataset, or, in the case of secondary use of data, the date from which data extraction starts) and of the *end of data collection* (the date from which the analytical dataset is completely available). These dates provide timelines for the commencement of the study and the submission of the final study report to the competent authorities.

2.2. The ENCePP Code of Conduct

The objective of the [ENCePP Code of Conduct](#) is to promote scientific independence in pharmacoepidemiology and pharmacovigilance studies. It aims to do so by providing a set of rules and principles for best practice of the investigator-study funder relationship and transparency

By applying the principles of transparency and scientific independence, the Code aims to strengthen the confidence of the general public, researchers and regulators in the integrity and value of pharmacoepidemiology research. To this end, the Code addresses critical areas in the planning, conduct and reporting of such studies. At its core are a requirement to register studies before they start and an obligation to publish all study findings irrespective of positive or negative results.

The '[ENCePP Study](#)' concept has been developed to uphold high standards throughout the research process based on the principles of transparency and scientific independence. Such 'ENCePP Studies' are required to comply with the provisions of the Code in their entirety and investigators seeking an accompanying ENCePP Study seal need to confirm their intention to do so by submitting a completed and signed [Checklist of the ENCePP Code of Conduct](#) and [Declaration on compliance](#) as part of their application.

2.3. Scientific standards, review and approval

The methodological standards for designing a pharmacoepidemiological and pharmacovigilance study are captured in the [ENCePP Checklist for Study Protocols](#).

Many research organisations (including those owning or hosting databases) have scientific review boards that ensure scientific standards are met. Some national competent authorities also have their own review board for registering/approving studies. In addition, it is good practice to invite experts to review the study results, as well as the protocol and any publications and/or communications thereof. The role of scientific committees in governance is also emphasised as being of particular importance.

2.4. Ethical conduct, patient and data protection

The [Declaration of Helsinki](#) and the provisions on processing of personal data and the protection of privacy as laid down in [Directive 95/46/EC](#) and [Regulation \(EC\) No. 45/2001](#) of the European Parliament and of the Council need to be followed in the EU in terms of the ethical conduct of studies. For interventional research, the corresponding [Clinical Trial Directive \(Directive 2001/20/EC\)](#) applies.

As post-authorisation studies are carried out with authorised medicinal products, relevant European and national legislation applies as previously detailed in Section 2.1. Module VIII of the GVP and, for clinical trials, the [Guidelines for Good Clinical Practice \(Commission Directive 2005/28/EC\)](#) should also be followed.

Consideration of ethical issues, data ownership and privacy is an important part of the [International Society for Pharmacoepidemiology \(ISPE\)](#) guideline for [Good Pharmacoepidemiology Practices \(GPP\)](#), section IV. It includes a sub-section (IV.A) on protection of human subjects and a reference to the ISPE guidelines on [Data Privacy, Medical Record Confidentiality, and Research in the Interest of Public Health](#). The ISPE GPP also recommends a stand-alone section within a study protocol that contains a description of plans for protecting human subjects. Such a section should include consideration of the need for submitting the protocol to an Institutional Review Board/Independent Ethics Committee and the requirement of informed consent. According to [Directive 2001/83/EC](#) of the European legislation, marketing authorisation holders and investigators must follow relevant national legislation and guidance of those Member States where the study is being conducted. The legislation on data protection must be followed in accordance with [Directive 95/46/EC](#) on the protection of individuals with regard to the processing of personal data and on the free movement of such data. Article 36 of the [Commission Implementing Regulation \(EU\) No. 520/2012](#) specifies that, for post-authorisation safety studies imposed as an obligation, marketing authorisation holders shall ensure that all study information is handled and stored so as to allow for accurate reporting, interpretation and verification of that information and shall ensure that the confidentiality of the records of the study subjects remains. It shall also ensure that the analytical dataset and statistical programmes used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection. The [Guideline of good pharmacovigilance practices \(GVP\) Module VIII - Post-authorisation safety studies](#) recommends that these provisions should also be applied to PASS voluntarily initiated, managed or financed by a marketing authorisation holder.

The main scope of the [International Epidemiological Association \(IEA\) Good Epidemiological Practice \(GEP\)](#) guideline for proper conduct in epidemiological research is on the ethical principles of pharmacoepidemiological field studies, which could also apply to interventional studies, such as the role of ethics committees, patients' informed consent, use and storage of personal data and publication of results.

The [Council for International Organisations of Medical Sciences \(CIOMS\)](#) 2002 International Ethical Guidelines for Biomedical Research Involving Human Subjects that were prepared in collaboration with the World Health Organisation (WHO) consist of a statement of general ethical principles, a preamble and 21 guidelines indicating how the ethical principles that should govern the conduct of biomedical research involving human subjects could be effectively applied. The CIOMS 2009 [International Ethical Guidelines for Epidemiological Studies](#) set forth ethical guidance on how investigators - as well as those who sponsor, review, or participate in the studies they conduct - should identify and respond to the ethical issues that are raised by such research.

The [Agency for Healthcare Research and Quality \(AHRQ\)](#) of the United States has published [Registries to Evaluate Patient Outcomes: a User's guide, Second Edition, 2010](#), which is a reference for establishing, maintaining and evaluating the success of registries created to collect data about patient outcomes. Section 1: 'Creating a registry' is a specific chapter dedicated to ethics, data ownership, and privacy. The concepts within are useful although focused on US law.

The [Uniform Requirements for Manuscripts Submitted to Biomedical Journals](#) by the [International Committee of Medical Journal Editors \(ICJME\)](#) includes clear statements on ethical principles related to publication in biomedical journals addressing authorship and contributorship, editorship, peer review, conflicts of interest, privacy and confidentiality and protection of human subjects and animals in research.

From the examples provided above, it may be seen that there is a wide range of documents for protection of human subjects. The applicability of ethical requirements, however, varies based on the nature of the inquiry and the studies to be conducted. Certain human subject protections applicable to clinical studies (e.g. full informed consent) would not apply to other kinds of research (e.g. review of data from de-identified medical records). Furthermore, while protection of privacy is paramount, [ENCePP](#)

[considers](#) there are situations in which the use of healthcare data for secondary analyses, whilst fully protecting data confidentiality and individuals' right to privacy, has public health benefits.

3. General aspects of study protocol

The study protocol is the core document of a study. A protocol should be drafted as one of the first steps in any research project, and should be amended and updated as needed throughout its course.

Amendments should be justified. It must precisely describe everything that will be done in the study, so that the study can be reproduced. It is usually and profitably based on standard protocol outlines, which could be prepared for different types of studies (e.g. cohort or case-control studies based on field data or database studies that include different information according to study type).

Chapter II of the [ISPE GPP](#) provides guidance on what is expected of a pharmacoepidemiology study protocol. The guideline states that the protocol should include a description of the data quality and integrity, including, for example, abstraction of original documents, extent of source data verification, and validation of endpoints. As appropriate, certification and/or qualifications of any supporting laboratory or research groups should be included, as well as validation steps taken or considered to standardise laboratory methods proposed. The guidelines recommend description of data management, statistical software programs and hardware to be used in the study, description of data preparation and analytical procedures, as well as the methods for data retrieval and collection. It should be borne in mind that, as stated in the GPP, adherence to guidelines will not guarantee valid research. The [ENCePP Checklist for Study Protocols](#) also seeks to stimulate researchers to consider important epidemiological principles when designing a pharmacoepidemiological study and writing a study protocol.

The protocol should cover at least the following aspects:

- The research question the study is designed to answer, which might be purely descriptive, exploratory or explanatory (hypothesis driven). The protocol should include a background description that expounds the origin (scientific, regulatory, etc.) and the state of present knowledge of the research question. It will also explain the context of the research question, including what data are currently available and how this data can or cannot contribute to answering the question. The context will also be defined in terms of what information sources can be used to generate appropriate data, and how the proposed study methodology will be shaped around these.
- The main study objective and possible secondary objectives, which are operational definitions of the research question. In defining secondary objectives, consideration could be given to time and cost, which may impose constraints and choices, for example in terms of sample size, duration of follow-up or data collection.
- The source and study populations to be used to answer the research question. The protocol should describe whether this population is already available (such as, in a database) or whether it needs to be recruited *de novo*. The limits of the desired population will be defined, including inclusion/exclusion criteria, timelines (such as index dates for inclusion in the study) and any exposure criteria and events defining cases and exposed study groups.
- Exposures of interest that need to be pre-specified and defined, including duration of exposure or follow-up, visits or time-dependent appraisals and details of which data are collected when, using what methods.
- Outcomes of interest that need to be pre-specified and defined, including data sources, operational definitions and methods of ascertainment such as data elements in field studies or appropriate codes in database studies.
- The covariates and potential confounders that need to be pre-specified and defined, including how they will be measured.

- The statistical analysis of the resulting data, including statistical methods and software, adjustment strategies, and how the results are going to be presented.
- The identification of possible biases.
- Major assumptions, critical uncertainties and challenges in the design, conduct and interpretation of the results of the study given the research question and the data used.
- Ethical considerations, as described in the section on governance of the current document.
- The various data collection forms including the Case Report Form (CRF) or descriptions of the data elements may be appended to the protocol, allowing having an exact representation of the data collection. The study protocols could include a section specifying ways in which the CRF will be piloted, tested and finalised. Amendments of final CRFs should be justified. For field studies, physician or patient forms would be included depending on data collection methodology. Other forms may be included as needed, such as patient information, patient-oriented summaries, etc.

4. Research question

The research question and the associated objectives describe the knowledge or information to be gained from the study. It is important that current knowledge gaps are properly identified. Existing guidance on this aspect includes the [ISPE GPP](#) and the [ENCePP Checklist for Study Protocols](#).

These guidance documents emphasise that it should be clearly explained why the study is to be conducted (e.g. to answer an important public health concern, to confirm or further characterise a risk identified in a Risk Management Plan, to assess a new or emerging safety issue or to determine health outcomes or the benefit/risk profile). It also should be clear whether the results that will be reported represent pre-formed hypotheses or research questions, or are data driven. If there is no pre-formed hypothesis, this should be clearly stated. The [ENCePP Checklist for Study Protocols](#) also suggests that the research objective should briefly state the target population, primary endpoints, questions of dose-dependency and the main outcome measures.

A critical and thorough review of the literature usually forms the basis for the background description and theoretical framework of the research question and should be included in a protocol. Such review aims at evaluating the pertinent information and at identifying gaps in knowledge. According to the [ISPE GPP](#), the review should include findings of relevant animal and human experiments, clinical studies, vital statistics and previous epidemiological studies. The findings of similar studies should be mentioned and gaps in knowledge that the study is intended to fill should be described.

In addition, previous findings are useful for the methodological planning of the current study. They may be used to discuss how the findings of the previous research may support the background, significance, research question, hypotheses, and/or design of the proposed study. They may also serve to determine the expected magnitude of the event(s) under study and, if available, in the target population, to characterise the various risk factors for the event and to identify the outcomes and measures that have been used in previous studies. The review assists in providing an assessment of the feasibility of the proposed study.

In addition to seeking information, the review should be a critical appraisal of the evidence in order to assess, analyse and synthesise previous research, and place it in its current context. Several methods for reviewing and synthesising findings from the literature exist, including narrative review, for which guidance is available in [Writing narrative literature reviews](#) (Baumeister RF, Leary MR. *Rev of Gen Psychol* 1997; 1 (3): 311-320).

5. Approaches to data collection

There are different approaches for data collection. One is to use data already collected as part of administrative records or patient healthcare. The second option is primary data collection, which is collection of primary data specifically for the study. Increasingly often, a combination of approaches is used. In addition, networking among centres active in pharmacoepidemiology and pharmacovigilance is rapidly changing the landscape of drug safety research in Europe, both in terms of data networks and networks of interested researchers who may or may not have data sources that they can contribute.

5.1. Secondary use of data

The use of already available electronic patient healthcare data for research has had a marked impact on pharmacoepidemiology research. The last two decades have witnessed the development of key data resources, expertise and methodology that have allowed the conduct of landmark studies in the field. Electronic medical records and record linkage of administrative health records are the main types of databases from a data structure and origin perspective. Examples of the first and second are the [CPRD](#) in the UK and the national or regional databases in the Nordic countries, Italy, Netherlands and other countries, respectively. The [ENCePP Inventory of Databases](#) contains key information on the databases that are registered in the ENCePP Network.

A comprehensive description of the main features and applications of frequently used databases for pharmacoepidemiology research in the United States and in Europe appears in the book *Pharmacoepidemiology* (B. Strom, S.E. Kimmel, S. Hennessy. 5th Edition, Wiley, 2012, Chapters 11 - 18). It should be noted, however, that limitations exist in relation to pharmacoepidemiologic research using electronic healthcare databases, as detailed in [A review of uses of healthcare utilisation databases for epidemiologic research on therapeutics](#) (Schneeweiss S, Avorn J. J Clin Epidemiol 2005; 58: 323-337).

General guidance for studies including those conducted in electronic healthcare databases can be found in the [ISPE GPP](#), in particular sections IV-B (Study conduct, Data collection). This guidance emphasises the paramount importance of patient data protection.

The primary purpose of the ISPE endorsed [Guidelines for Good Database Selection and use in Pharmacoepidemiology Research](#) (Hall GC, Sauer B, Bourke A, Brown GS, Reynolds MW, Casale RL. Pharmacoepidemiol Drug Saf 2012; 21: 1 -10) is to assist in the selection and use of data resources in pharmacoepidemiology by highlighting potential limitations and recommending tested procedures. Although it refers in the title and objective to data resources or databases, it mainly refers to databases of routinely collected healthcare information and does not include spontaneous reports databases. It is a simple, well structured guideline that will help investigators when selecting databases for their research. If used, it will help database custodians to describe their database in a useful manner. A section is entirely dedicated to the use of multi-site studies. The entire document contains references to data quality and data processing/transformation issues and there are sections dedicated to Quality and Validation procedures. There are also separate sections on privacy and on security.

The Working Group for the Survey and Utilisation of Secondary Data (AGENS) with representatives from the German Society for Social Medicine and Prevention (DGSPM) and the German Society for Epidemiology (DGEpi) developed a [Good Practice in Secondary Data Analysis Version 2](#) aiming to establish a standard for planning, conducting and analysing studies on the basis of secondary data, i.e. data collected for other purposes such as population-based disease registers. It is also aimed to be used as the basis for contracts between data owners (so-called primary users) and secondary users. It is divided in 11 sections addressing, among other aspects, the study protocol, quality assurance and data protection.

The [International Society for Pharmacoconomics and Outcome Research \(ISPOR\)](#) established a task force to recommend good research practices for designing and analysing retrospective databases. The

Task Force has subsequently published a report that reviews methodological issues and possible solutions for studies of comparative effectiveness based on secondary data analysis. The report also discusses the strength of inferences from observational studies in comparison to randomised clinical trials. [Part I](#) of the report presents criteria for the definition of research questions and hypotheses, various study designs, a structured format for the study report and elements to be considered for the interpretation of results given the non-randomised nature of the data. [Part II](#) reviews misclassification and confounding and [Part III](#) reviews more advanced analytical techniques to control for confounding. Readers new to the field of comparative effectiveness might not be familiar with the mix of policy and methodological issues addressed in the report. Some important aspects of pharmacoepidemiological studies based on secondary use of data, such as data quality, ethical issues, data ownership and privacy, are not covered.

The use of technology including administrative databases for pharmacoepidemiological research has limitations including the following:

- Consistency and totality of data capture i.e. does the database reliably capture all of the patient's healthcare interactions or are there known gaps in coverage, capture, longitudinality or eligibility? Researchers using claims data rarely have the opportunity to carry out quality assurance of the whole data set. An example is provided in [Descriptive analyses of the integrity of a US Medicaid Claims Database](#) (Hennessy S, Bilker WB, Weber A, Strom B. *Pharmacoepidemiol Drug Saf* 2003; 12: 103–111), This article concludes that performing such analyses can reveal important limitations of the data and whenever possible, researchers should examine the 'parent' data set for apparent irregularities.
- Bias in assessment of drug exposure from an administrative database. The relevance of these biases for quality control in more clinical databases is explored in [European Surveillance of Antimicrobial Consumption \(ESAC\): Data Collection Performance and Methodological Approach](#) (Vander Stichele RH, Elseviers MM, Ferech M, Blot S, Goossens H; ESAC Project Group. *Br J Clin Pharmacol* 2004; 58: 419-28). This article describes the performance and methodological approach in a retrospective data collection effort (1997–2001) through an international network of surveillance systems, aiming to collect publicly available, comparable and reliable data on antibiotic use in Europe. The data collected were screened for bias, using a checklist focusing on detection bias in sample and census data; errors in assigning medicinal product packages to the [Anatomical Therapeutic Chemical Classification System](#); errors in calculations of [Defined Daily Doses](#) per package; bias by over-the-counter sales and parallel trade; and bias in ambulatory/hospital care mix. The authors conclude that methodological rigour is needed to assure data validity and to ensure reliable cross-national comparison.
- Validity of the data and the definitions used, which is not simply about source record validation of a particular endpoint. There are many possible ways to define endpoints and researchers that do validate may only seek to validate their choice. The following study investigated the range of methods used to validate diagnoses in a primary care database: [Validation and validity of diagnoses in the General Practice Research Database \(GPRD\): a systematic review](#) (Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. *Br J Clin Pharmacol* 2010; 69: 4-14). The findings concluded that a number of methods had been used to assess validity and that overall, estimates of validity were high. The quality of reporting of the validations was, however, often inadequate to permit a clear interpretation. Not all methods provided a quantitative estimate of validity and most methods considered only the positive predictive value of a set of diagnostic codes in a highly selected group of cases
- Discordance between data sources. [Discordance of databases designed for claims payment versus clinical information systems: implications for outcomes research](#) (Jollis JG, Ancukiewicz M, DeLong ER, Pryor DB, Muhlbauer LH, Mark DB. *Ann Intern Med* 1993; 119: 844-850) was a comparative study of a clinical versus an insurance claims database for predictors of prognosis in patients with ischaemic

heart disease. A finding was that claims data failed to identify more than half of the patients with prognostically important conditions when compared with the clinical information system.

Another example of the hazards of using large linked databases is provided in [Vaccine safety surveillance using large linked databases: opportunities, hazards and proposed guidelines](#) (Verstraeten T, DeStefano F, Chen RT, Miller E. *Expert Rev Vaccines* 2003; 2(1): 21-9).

In general it is clear that the quality of pharmacoepidemiological studies that rely heavily on clinical databases from medical practice could be greatly enhanced by stimulating the quality of medical registration in electronic health records, through the provision of elaborate end-user terminologies and classification aides at the point-of-care. The U.S. [Food and Drug Administration \(FDA\) Amendments Act of 2007](#) mandated that the FDA develop a system for using electronic healthcare data to identify risks of marketed drugs and other medical products.

Quality control and assurance are further addressed in section 8 of the present document.

5.2. Primary data collection

Case-control studies using hospital or community based primary data collection have allowed the evaluation of drug-disease associations for rare complex conditions that require very large base populations over several countries and in depth case assessment by clinical experts. Examples are [Appetite-Suppressant Drugs and the Risk of Primary Pulmonary Hypertension](#) (Abenhaim LA, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, Higenbottam T, Oakley C, Wouters E, Aubier M, Simonneau G, Bégaud B. for the International Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996; 335: 609-616); [The design of a study of the drug etiology of agranulocytosis and aplastic anemia](#) (Shapiro S. for the International Agranulocytosis and Aplastic Anemia Study. *Eur J Clin Pharmacol* 1983; 24: 833-6); [Medication Use and the Risk of Stevens–Johnson Syndrome or Toxic Epidermal Necrolysis](#) (Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, Auquier A, Bastuji-Garin S, Correia O, Locati F, Maja Mockenhaupt M, Paoletti C, Shapiro S, Shear N, Schöpf E, Kaufman DW. *N Engl J Med* 1995; 333: 1600-1608).

For some conditions, case-control surveillance networks that have been developed can be used for selected studies and for signal generation and clarification e.g. [Signal generation and clarification: use of case-control data](#) (Kaufman DW, Rosenberg L, Mitchell AA. *Pharmacoepidemiol Drug Saf* 2001; 10: 197-203).

General guidance on proper conduct of prospective patient-based studies can be found in the [ISPE GPP](#) and the [IEA GEP](#). The GPP is especially useful for its recommendations on aspects rarely covered by guidelines, such as data quality issues and archiving. Both guidelines address the importance of patient data protection and the ethical principles of research using patient healthcare and personal data.

Patient registers are sometimes requested by regulators at the time of authorisation of a medicinal product in order to determine clinical effectiveness and monitor safety. A registry should be considered a structure within which studies can be performed, i.e. a data source, where entry is defined either by diagnosis of a disease (disease registry) or prescription of a drug (exposure registry). AHRQ has published a comprehensive document on 'good registry practices' entitled [Registries for Evaluating Patient Outcomes: A User's Guide. Second Edition](#), the purpose of which is to guide the planning, design, implementation, analysis, interpretation, and evaluation of the quality of a registry. A section also covers linking of registries to other data sources. References to research review, funding and regulatory bodies are however US centric and specific recommendations, in particular on ethical, privacy ownership and regulatory aspects, cannot be transferred to the European situation.

Surveys in pharmacoepidemiology, in the areas of disease epidemiology and risk minimisation evaluation efforts, are increasing. Such surveys require a sampling strategy that allows for external validity and maximised response rates. Useful textbooks on these aspects are *Survey Sampling* (L. Kish, Wiley, 1995)

and *Survey Methodology* (R.M. Groves, F.J. Fowler, M.P. Couper, J.M. Lepkowski, E. Singer, R. Tourangeau, 2nd Edition, Wiley 2009). Depending of the purpose of the survey, questionnaires are often used. They should be validated based on accepted measures including, if appropriate, construct, criterion and content validity, inter-rater and test-retest reliability, sensitivity and responsiveness. Although primarily focused on quality of life research, the book *Quality of Life: the assessment, analysis and interpretation of patient-related outcomes* (P.M. Fayers, D. Machin, 2nd Edition, Wiley, 2007) offers a comprehensive review of the theory and practice of developing, testing and analysing questionnaires in different settings. *Health Measurement Scales: a practical guide to their development and use* (D. L. Streiner, G. R. Norman, 4th Edition, Oxford University Press, 2008) is a very helpful guide to those involved in measuring subjective states such as attitudes, feelings, quality of life, educational achievement and aptitude, and learning style in patients and healthcare providers. Many other examples of the development and testing of questionnaires have also been published in the scientific literature.

RCTs are a form of primary data collection. There are numerous textbooks and publications on methodological and operational aspects of clinical trials, although they are not covered here. An essential guideline on clinical trials is the European Medicines Agency [Note for Guidance on Good Clinical Practice](#), which specifies obligations for the conduct of clinical trials to ensure that the data generated in the trial is valid.

5.3. Research networks

Although collaborations for multinational studies are not new, they have been strongly encouraged over the last years by the drug safety research funded by the European Commission (EC). The funding resulted in the conduct of groundwork necessary to overcome the hurdles of data sharing across countries.

Networking implies collaboration between investigators, which is based on trust and willingness to share and to maximise the advantage of bundling expertise. The [ENCePP Database of Research Resources](#) may facilitate such collaborations by providing an inventory of research centres and data sources available for specific pharmacoepidemiology and pharmacovigilance studies in Europe. It allows the identification of centres and data sets by country, type of research and other relevant fields. In addition, an important component of ENCePP is the potential for meta-analyses to maximise the information gathered for an issue that is addressed in different databases. ENCePP also provides opportunities to perform pooling of person level analytical datasets of individual studies (person level meta-analysis). In the US, [the HMO Research Network](#) is a consortium of health maintenance organisations that have formal, recognised research capabilities.

From a methodological point of view, data networks have many advantages:

- By increasing the size of study populations, networks may shorten the time needed for obtaining the desired sample size. Hence, networks can facilitate research on rare events and accelerate investigation of drug safety issues;
- Heterogeneity of drug exposure across countries allows studying the effect of more individual drugs;
- Multinational studies may provide additional knowledge on whether a drug safety issue exists in several countries and on reasons for any differences between countries, which can lead to important information for regulators and marketing authorisation holders;
- Involvement of experts from various countries addressing case definitions, terminologies, coding in databases and research practices provides opportunities to increase consistency of results of observational studies;
- Requirement to share data forces harmonisation of data elaboration and transparency in analyses, and benchmarking of data management.

Different models have been applied for combining data from various countries ranging from a very disparate to a more integrated approach:

- Meta-analysis of results of individual studies with potentially different design e.g. [Variability in risk of gastrointestinal complications with individual NSAIDs: results of a collaborative meta-analysis](#) (Henry D, Lim Lynette L-Y, Garcia Rodriguez LA, Perez Gutthann S, Carson JL, Griffin M, Savage R, Logan R, Moride Y, Hawkey C, Hill S, Fries JT. *BMJ* 1996; 312: 1563-1566), which compared the relative risks of serious gastrointestinal complications reported with individual NSAIDs by conducting a systematic review of twelve hospital and community based case-control and cohort studies, found a relation between use of the drugs and admission to hospital for haemorrhage or perforation.
- Pooling of results from common protocol studies conducted in different databases, allowing assessment of database/population characteristics and of choices of study design and analysis as determinants of variability of results (e.g. [IMI PROTECT](#) project).
- The five Nordic countries with similar healthcare systems and databases have developed a collaborative cross-national pharmacoepidemiological network which covers the entire population of 25 million inhabitants ([The Nordic countries as a cohort for pharmacoepidemiological research](#) Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sorensen HT. *Basic Clin Pharmacol & Toxicol* 2010; 106: 86 – 94). This network has been used for analytical pharmacoepidemiological studies linking drug exposure to other health registries ([Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic Countries](#) Kieler H, Artama M, Engeland A, Ericsson Ö, Furu K, Gissler M, Nielsen RB, Nørgaard, Stephansson O, Valdimarsdottir U, Zoega H, Haglund B. *BMJ* 2012; 344: d8012).
- Distributed data approach in which data partners maintain physical and operational control over electronic data in their existing environments (e.g. [Mini-Sentinel](#) project). A common data model standardises administrative and clinical information across data partners, whom execute standardised programs provided by an operations centre or project workgroups and typically share the output of these programs in summary form. Methods are available to allow multivariate adjusted analyses in federated databases without violating patient privacy ([Multivariate-adjusted pharmacoepidemiologic analyses of confidential information pooled from multiple healthcare utilisation databases](#). Rassen JA, Avorn J, Schneeweiss S. *Pharmacoepidemiol Drug Saf* 2010; 19: 848-57). The Mini-Sentinel pilot focuses on drugs, vaccines, other biologics, and medical devices (the vaccine safety activities together constitute the [Post-Licensure Rapid Immunisation Safety Measurement \(PRISM\) Program](#)).
- Pooling of aggregated data (person-time based) extracted locally from databases or electronic health records using a common data model and common software, and transmitted electronically to a central data warehouse for further analysis (e.g. [EU-ADR](#) project).
- Pooling of properly non-identifiable individual level data gathered locally (either from databases or field studies) to a central data warehouse for statistical analysis (e.g. [VAESCO](#) project).
- Pooling of elaborated individual-level data extracted locally from databases or electronic health records using common software and transmitted electronically to a central location for further analysis by multiple collaborators (e.g. [SOS-NSAIDS](#) project).

These different models have different strengths and weaknesses and present different challenges. These may include:

- Differences in culture and experience between academia, public institutions and private partners;
- Different ethical and governance requirements in each country regarding processing of anonymised or pseudo-anonymised healthcare data;

- Mapping of differing disease coding systems ([International Classification of Diseases](#), 10th Revision (ICD-10); [Read codes](#) in the United Kingdom, [International Classification of Primary Care \(ICPC-2\)](#)) and languages of narrative medical information.
- Choice of data sharing model and access rights of partners;
- Validation of diagnoses and access to source documents for validation;
- Issues linked to intellectual property and authorship;
- Sustainability and funding mechanisms, especially when private funding (e.g. from pharmaceutical companies) is involved and when the study receives funding from several sponsors.

Experience has shown that many of these difficulties can be overcome by full involvement and good communication between partners, and a project agreement between network members defining roles and responsibilities and addressing issues of intellectual property and authorship.

Technical solutions also exist for data sharing and mapping of terminologies. A distributed data model and a JAVA (freely available) based data elaboration software was developed by the [EU-ADR](#) project to allow for pooling of data from drug safety studies across borders. This distributed data model and way of data sharing has been shown to be feasible, fast and to deal effectively with ethical and governance issues. It has been used in several other EC funded projects and in the United-States.

Many of the current research networks have operated mainly with EC funds and under EC grant agreements. The coming years should demonstrate whether and how the expertise and infrastructures could be maintained and used in the conduct of regulatory post-authorisation studies.

5.4. Spontaneous reports databases

Spontaneous reports of adverse drug effects remain a cornerstone of pharmacovigilance and are collected from a variety of sources, including healthcare providers, medical literature, and more recently, directly from patients. [EudraVigilance](#) is the European data processing network and management system for reporting and evaluation of suspected adverse drug reactions (ADRs). It deals with the electronic exchange of Individual Case Safety Reports (ICSR), the early detection of possible safety signals and the continuous monitoring and evaluation of potential safety issues in relation to reported ADRs.

The increase in systematic collection of ICSRs in large electronic databases such as EudraVigilance has allowed the application of data mining and statistical techniques for the detection of safety signals. There are known limitations of spontaneous ADR reporting systems, which include limitations imbedded in the concept of voluntary reporting, whereby known or unknown external factors may influence the reporting rate and data quality. ADRs may be limited in their utility by a lack of data for an accurate quantification of the frequency of events or the identification of possible risk factors for their occurrence. For these reasons, the concept is now well accepted that any signal from spontaneous reports needs to be verified or validated in a clinical context before further communication.

[Validation of statistical signal detection procedures in EudraVigilance post-authorisation data: a retrospective evaluation of the potential for earlier signalling](#) (Alvarez Y, Hidalgo A, Maignen F, Slattery J. *Drug Saf* 2010; 33: 475 – 87) has shown that the statistical methods applied at the European Medicines Agency (EMA) for signal detection in EudraVigilance can provide significantly early warning in a large proportion of drug safety problems. Nonetheless, this approach should supplement, rather than replace, other pharmacovigilance methods.

Chapters IV and V of the [Report of the CIOMS Working Group VIII 'Practical aspects of Signal detection in Pharmacovigilance'](#) present sources and limitations of spontaneously-reported drug-safety information and databases that support signal detection. Appendix 3 provides a list of international and national spontaneous reporting system databases.

6. Study design and methods

There exists a number of evolving methodological challenges that recur in pharmacoepidemiological research, that are still in development or that to date have not been adequately covered by recommendations. The following section presents such methodological challenges relating to study design, use of electronic healthcare data, bias and confounding and methods for controlling for confounding.

6.1. General considerations

The choice of study design and methods is a crucial part in every pharmacoepidemiological study and starts with the formulation of a relevant research question (whether non-steroidal anti-inflammatory drugs [NSAIDs] increase the risk of gastro-intestinal bleeding is cited throughout the present document as an illustrative working example). The study design and methods should follow the research question and are naturally interrelated.

Pharmacoepidemiological studies involving multiple objectives are not so uncommon. One approach for a given study might be to consider the study population as a cohort in which to implement the most appropriate design for each objective, thus ensuring alignment of each objective to the best possible design and analysis. Indeed, for studies involving primary collection of data, it may be particularly useful to adopt an approach that also incorporates strategies for appropriate minimisation of the possible sources of bias and confounding problems identified by the design.

In a descriptive study, the research question is to describe a population with respect to pre-defined parameters. In analytical studies, the research question drives three key sequentially structured phases in the design and conduct of an epidemiological study:

- Relation of a parameter of incidence to a determinant or a set of determinants (e.g. the incidence rate ratio of gastro-intestinal bleeds among users and non-users of NSAIDs),
- Collection of data to empirically document this relation (e.g. collection from a database of exposure [use of NSAIDs] and outcomes data [gastro-intestinal bleeding] in a cohort of patients that are/have been NSAIDs users), and
- Analysis of data (from raw data to quantification of associations).

These three phases are not independent. A hypothesised relation may lead to an array of designs for data collection based, in this example, on different data sources available on use of NSAIDs (exposure) and occurrence of gastro-intestinal bleeds in patients (outcomes). Each design for data collection, given a well-defined research question, will be followed by only a few appropriate designs of data analysis. Note the selection of appropriate electronic health data sources is an important aspect of the design of data collection. Depending on the research question, other sources of data may be needed (e.g. some claims databases may not have a 'reason for stopping' a NSAID whereas another may have (see Section 5.1)).

The choice of epidemiological methods to answer a research question is not always carved in stone, but is rather based on principles than on rules. These principles may provide opportunities for creativeness and new innovative methods, when appropriate and needed. However, there are certain 'dos and don'ts' and certain standards in order to assure validity and robustness of the study results.

General aspects of study designs, their relevance to types of research question and issues relating to internal and external validity, including biases and confounding, are covered by many textbooks on epidemiology and pharmacoepidemiology. The following list proposes a list of textbooks recommended for consultation. Researchers may find other textbooks more appropriate to their specific needs.

- *Epidemiology: Principles and Methods 2nd Edition* (B. MacMahon, D. Trichopoulos. Lippincott Williams & Wilkins, 1996) offers an introductory understanding of epidemiological methods and processes, including on study designs and control for confounding.
- *Modern Epidemiology 3rd Edition* (K. Rothman, S. Greenland, T. Lash. Lippincott Williams & Wilkins, 2008) serves as a comprehensive textbook on methods in epidemiology. Chapter 8 deals with validity but rather than dichotomise validity into the two components, internal and external, details a view in which the essence of scientific generalisation is the formulation of abstract concepts relating the study factors.
- *Pharmacoepidemiology 5th Edition* (B. Strom, S.E. Kimmel, S. Hennessy. Wiley, 2012) provides a complete review of epidemiological methods applied to the study of drugs. In Chapter 41, it emphasises that, whatever the source of the data, the veracity of a study's conclusion rests on the validity of the data.
- *Pharmacoepidemiology and Therapeutic Risk Management 1st Edition* (A.G. Hartzema, H.H. Tilson and K.A. Chan, Editors. Harvey Whitney Books Company, 2008). In addition to a general review of drug-specific methodologies, this textbook illustrates practical issues with a large number of real life examples.
- *Encyclopedia of Epidemiologic Methods* (M.H. Gail, J. Benichou, Editors. Wiley, 2000). This compilation of articles complements existing textbooks by providing a large coverage of specialised topics in epidemiological and statistical methods.
- *Practical Statistics for Medical Research* (D. Altman. Chapman & Hall, 1990) presents a problem-based statistical text for medical researchers.
- *A Dictionary of Epidemiology 5th Edition* (M Porta, Editor. J.M. Last S. Greenland, Associate Editors. Oxford University Press, 2008), sponsored by the International Epidemiological Association (IEA), provides a definition and concise explanation of epidemiologic terms and is a key to understanding epidemiological concepts.
- *Dictionary of Pharmacoepidemiology* (Bernard Bégaud. Wiley, 2000) is a translation from the French original. Definitions are well illustrated with practical examples. It is particularly useful in terms of pharmacovigilance aspects of pharmacoepidemiology.

6.2. Challenges and lessons learned

6.2.1. Drug exposure/outcome/covariate definition and validation

Historically physicians relied on patient-supplied information on past drug use and illness to assist with the diagnosis of current disease. Given the rapid expansion of the use of and access to electronic health records this reliance is being reduced. Inadequate documentation of 'off-label' (outside of the terms of the marketing authorisation) use of medicines remains an issue, however, particularly in the paediatric population ([Off-label drug use in pediatric patients](#) Kimland E, Odland V. Clin Pharmacol Ther 2012; 91: 796 – 801). While there is no specific guideline for drug-utilisation studies targeting such off-label use it cannot be ignored that in prospective studies with data specifically collected to assess off-label use, clinicians may be more inclined to align diagnoses with approved indications than when working in their day-to-day clinical-care setting. This would lead to an underestimation of off-label use. However in studies where the indication is derived from medical information contemporary to the dispensing, rather than from surveys, this potential concern is not expected to be a problem.

Chapter 41 of *Pharmacoepidemiology* (B. Strom, S.E. Kimmel, S. Hennessy. 5th Edition, Wiley, 2012) includes a literature review of the studies that have evaluated the validity of drug, diagnosis and hospitalisation data and the factors that influence the accuracy of these data. The book presents

information on the two primary information sources available for pharmacoepidemiology studies: questionnaires and administrative databases and concludes with a summary of the current knowledge in the field as well as directions for future research.

In healthcare databases, the correct assessment of drug exposure/outcome/covariate will be crucial to the validity of research. Shapiro evaluates the validity of research conducted in automated databases according to a standard set of criteria, including validity of exposure, outcome and confounding in [The role of automated record linkage in the postmarketing surveillance of drug safety: a critique](#) (Shapiro S. Clin Pharmacol Ther 1989; 46:371-386), and points out that diagnosis obtained from review of codes of electronic record systems require validation.

In healthcare databases; validation of electronic information on drug exposure, outcome, or covariate definitions is database and item specific, and should constitute the technical handbook of each of the databases. [Validity of diagnostic coding within the General Practice Research Database: a systematic review](#) (Kahn NF, Harrison SE, Rose PW. Br J Gen Pract 2010; 60: e128 - 36) and *Pharmacoepidemiology* (B. Strom, S.E. Kimmel, S. Hennessy. 5th Edition, Wiley, 2012) contain examples of a kind.

Outcomes are defined differently at different levels of investigation. For case identification, a combination of codes is generally used. Initial plausibility checks may be done by algorithms applied to the database. This is followed by medical chart review for classification of cases by diagnostic certainty based on standardised case definitions applicable to epidemiologic studies. The [Brighton Collaboration](#) has developed standardised case definitions for adverse events following immunisation.

With the development of electronic, computerised patient record systems, the structured documentation of off-label use and the use of non-approved drugs, including the clinical outcomes of such treatments, could greatly improve the knowledge in this area

The [Inventory of Drug Consumption Databases in Europe](#) published by the [IMI PROTECT](#) consortium is the result of reviewing, compiling and updating knowledge about European sources of data on drug utilisation in the out- and inpatient healthcare sector. Information is available on Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Poland, Spain, Sweden and United Kingdom. The inventory aims to describe the characteristics of non-commercial drug consumption data providers in Europe. It outlines the validity of these European national drug consumption databases and explores the availability of inpatient drug consumption data at national level.

6.2.2. Bias and confounding

6.2.2.1. Choice of exposure risk windows

The choice of exposure risk window can influence risk comparisons. The paper [A study of the effects of exposure misclassification due to the time-window design in pharmacoepidemiologic studies](#) (van Staa TP, Abenheim L, Leufkens H. J Clin Epidemiol 1994; 47(2): 183 – 189) considers the effects of the time-window design on the validity of risk estimates in record linkage studies. In adverse drug reaction studies, an exposure risk-window constitutes the number of exposure days assigned to each prescription. The ideal design situation would occur when each exposure risk-window would only cover the period of potential excess risk. The time of drug-related risk depends on the duration of drug use as well as the onset and persistence of drug toxicity. With longer windows, a substantive attenuation of incidence rates was observed. The choice of prescription risk windows can, therefore, influence the estimate of exposure risks. Risk windows should be validated or a sensitivity analysis should be conducted.

6.2.2.2. Immortal time bias

Immortal time in epidemiology refers to a period of cohort follow-up time during which death (or an outcome that determines end of follow-up) cannot occur. It is defined in the book *Modern Epidemiology* (K. Rothman, S. Greenland, T. Lash. 3rd Edition, Lippincott Williams & Wilkins, 2008 p. 106-107).

Immortal time bias can arise when the period between cohort entry and date of first exposure, e.g., to a drug, during which death has not occurred, is either misclassified or simply excluded and not accounted for in the analysis. [Immortal time bias in observational studies of drug effects](#) (Suissa S. *Pharmacoepidemiol Drug Saf* 2007; 16: 241-249) demonstrates how several observational studies used a flawed approach to design and data analysis, leading to immortal time bias, which can generate an illusion of treatment effectiveness. This is frequently found in studies that compare against 'non-users'. Observational studies with surprisingly beneficial drug effects should, therefore, be re-assessed to account for this bias.

[Immortal time bias in Pharmacoepidemiology](#) (Suissa S. *Am J Epidemiol* 2008; 167: 492-499) describes various cohort study designs leading to this bias, quantifies its magnitude under different survival distributions, and illustrates it by using data from a cohort of lung cancer patients. The author shows that for time-based, event-based, and exposure-based cohort definitions the bias in the rate ratio resulting from misclassified or excluded immortal time increases proportionately to the duration of immortal time. The findings support the conclusion that observational studies of drug benefit in which computerised databases are used must be designed and analysed properly to avoid immortal time bias.

The paper [Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods](#) (Zhou Z, Rahme E, Abrahamowicz M, Pilote L. *Am J Epidemiol* 2005; 162: 1016-23) describes five different approaches to deal with immortal time bias. The use of a time-dependent approach had several advantages: no subjects were excluded from the analysis and the study allowed effect estimation at any point in time after discharge, however, exposure changes might be predictive of the study endpoint and need adjustment for time-varying confounders using complex methods. The authors of [Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes](#) (Lévesque LE, Hanley JA, Kezouh A, Suissa S. *BMJ* 2010; 340:b5087) describe how immortal time in observation studies can bias the results in favour of the treatment group and how they consider it not difficult to identify and avoid. They recommend that all cohort studies should be assessed for the presence of immortal time bias using appropriate validity criteria. However, [Re. 'Immortal time bias on pharmacoepidemiology'](#) (Kiri VA, MacKenzie G. *Am J Epidemiol* 2009; 170: 667 - 668) argues that sound efforts at minimising the influence of more common biases should not be sacrificed to that of immortal time bias.

6.2.2.3. Depletion of susceptibles

Depletion of susceptibles is the effect whereby patients who remain on a drug are those who can tolerate the product while those who are susceptible to an adverse event select themselves out of the population at risk. This was considered an issue in the risk of venous thromboembolism with 3rd generation oral contraceptives in Europe in the 1990s, but this hypothesis was not confirmed in [Risk of venous thromboembolism from oral contraceptives containing gestodene and desogestrel versus levonorgestrel: a meta-analysis and formal sensitivity analysis](#) (Hennessy S, Berlin JA, Kinman JL, Margolis DJ, Marcus SM, Strom BL. *Contraception* 2001; 64: 125 – 133). The article [Evidence of the depletion of susceptibles effect in non-experimental pharmacoepidemiologic research](#) (Moride Y, Abenham L. *J Clin Epidemiol* 1994; 47 (7): 731-7) provides empirical evidence of this effect. It describes a hospital-based case-control study on NSAIDs and the risk of upper gastrointestinal bleeding. Recent use (within 30 days prior to admission) of non-aspirin NSAIDs strongly increased the risk of upper gastrointestinal bleeding whereas use in the previous 3 years was associated with a lower increase in risk. Thus, past use should be

considered as a potential risk modifier in non-experimental risk assessment of events associated with drug use.

6.2.2.4. Confounding by indication

Confounding by indication refers to an extraneous determinant of the outcome parameter that is present if a perceived high risk or poor prognosis is an indication for intervention. This means that differences in care, for example, between cases and controls may partly originate from differences in indication for medical intervention such as the presence of risk factors for particular health problems. The latter has frequently been reported in studies evaluating the efficacy of pharmaceutical interventions.

A good example can be found in [Confounding and indication for treatment in evaluation of drug treatment for hypertension](#) (Grobbee DE, Hoes AW. *BMJ* 1997; 315: 1151-1154). The article [Confounding by indication: the case of the calcium channel blockers](#) (Joffe MM. *Pharmacoepidemiol Drug Saf* 2000; 9: 37-41) reviews conceptual issues regarding confounding by indication. It demonstrates that studies with potential confounding by indication can benefit from appropriate analytic methods, including separating the effects of a drug taken at different times, sensitivity analysis for unmeasured confounders, instrumental variables and G-estimation.

With the more recent application of pharmacoepidemiological methods to assess effectiveness, confounding by indication is a greater challenge and the article [Approaches to combat with confounding by indication in observational studies of intended drug effects](#) (McMahon AD. *Pharmacoepidemiol Drug Saf* 2003; 12: 551-8) focusses on its possible reduction in studies of intended effects. An extensive review of these and other methodological approaches discussing their strengths and limitations is discussed in [Methods to assess intended effects of drug treatment in observational studies are reviewed](#) (Klungel OH, Martens EP, Psaty BM, Grobbee DE, Sullivan SD, Stricker BH, Leufkens HG, de Boer A. *J Clin Epidemiol* 2004; 57: 1223-31).

Moreover, claimed advantages of a new drug may channel it to patients with special pre-existing morbidity, with the consequence that disease states can be incorrectly attributed to use of the drug (channelling). How channelling towards high risk gastrointestinal patients occurred in the prescribing of newer NSAIDs is well demonstrated in [Channelling bias and the incidence of gastrointestinal haemorrhage in users of meloxicam, coxibs, and older, non-specific NSAIDs](#) (MacDonald TM, Morant SV, Goldstein JL, Burke TA, Pettitt D. *Gut* 2003; 52: 1265–70).

6.2.2.5. Protopathic bias

Protopathic bias occurs when the initiation of a drug (exposure) occurs in response to a symptom of the (at this point undiagnosed) disease under study (outcome). For example, use of analgesics in response to pain caused by an undiagnosed tumour might lead to the erroneous conclusion that the analgesic caused the tumour. Protopathic bias thus reflects a reversal of cause and effect ([Bias: Considerations for research practice](#) T Gerhard. *Am J Health Syst Pharm* 2008; 65: 2159-68).

6.2.2.6. Unmeasured confounding

Large healthcare utilisation databases are frequently used to analyse unintended effects of prescription drugs and biologics. Confounders that require detailed information on clinical parameters, lifestyle, or over-the-counter medications are often not measured in such datasets, causing residual confounding bias. The article [Using directed acyclic graphs to detect limitations of traditional regression in longitudinal studies](#) (Moodie EE, Stephens DA. *Int J Public Health* 2010; 55: 701-703) reviews confounding and mediation (i.e. intermediate effects) in longitudinal data and introduces causal graphs to understand the relationships between the variables in an epidemiological study.

[Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics](#) (Schneeweiss S. *Pharmacoepidemiol Drug Saf* 2006; 15 (5) 291-303) provides a systematic approach to sensitivity analyses to investigate the impact of residual confounding in pharmacoepidemiological studies that use healthcare utilisation databases. In the article, four basic approaches to sensitivity analysis were identified: (1) sensitivity analyses based on an array of informed assumptions; (2) analyses to identify the strength of residual confounding that would be necessary to explain an observed drug-outcome association; (3) external adjustment of a drug-outcome association given additional information on single binary confounders from survey data using algebraic solutions; (4) external adjustment considering the joint distribution of multiple confounders of any distribution from external sources of information using propensity score calibration. The author concludes that sensitivity analyses and external adjustments can improve our understanding of the effects of drugs and biologics in epidemiological database studies. With the availability of easy-to-apply spread sheets (for download, for example, at <http://www.drugapi.org/dope-downloads/>), sensitivity analyses should be used more frequently, substituting qualitative discussions of residual confounding.

There has also been discussion about the amount of bias in exposure effect estimates that can plausibly occur due to residual or unmeasured confounding. In [The impact of residual and unmeasured confounding in epidemiologic studies: a simulation study](#) (Fewell Z, Davey Smith G, Sterne JAC. *Am J Epidemiol* 2007; 166: 646–55), the authors considered the extent and patterns of bias in estimates of exposure-outcome associations that can result from residual or unmeasured confounding, when there is no true association between the exposure and the outcome. With plausible assumptions about residual and unmeasured confounding, effect sizes of the magnitude frequently reported in observational epidemiological studies can be generated. This study highlights the need to perform sensitivity analyses to assess whether unmeasured and residual confounding are likely problems. Another important finding of this study was that when confounding factors (measured or unmeasured) are interrelated (e.g. in situations of confounding by indication), adjustment for a few of these factors can almost completely eliminate confounding by all these factors.

6.2.3. Methods to handle bias and confounding

6.2.3.1. New-user designs

The practice of most observational studies to include many prevalent users, i.e. patients taking a therapy for some time before study follow-up began, can cause two types of bias. First, prevalent users are “survivors” of the early period of pharmacotherapy, which can introduce substantial bias if risk varies with time (see Section 6.2.2.3 on ‘depletion of susceptibles’ above). Second, covariates for drug users at study entry are often plausibly affected by the drug itself. New user designs help avoid making the mistake of adjusting for factors on the causal pathway which may introduce confounding. Evaluating medication effects outside of clinical trials: new-user designs (Ray WA. *Am J Epidemiol* 2003; 158 (9): 915 – 920) reviews such designs, which avoid these biases by restricting the analysis to persons under observation at the start of the current course of treatment. In addition to defining new-user designs the article explains how they can be implemented as case-control studies and describes the logistical and sample size limitations involved.

6.2.3.2. Self-controlled designs

Case-crossover and case-time-control studies are especially useful for studying transient exposures with acute effects, and are less susceptible to confounding by indication.

Case-crossover studies use the exposure history of each case as his or her own control. It allows to further study the time relationship of immediate effects to the exposure. This design eliminates between-person confounding by constant characteristics, including chronic indications (The Case-Crossover

Design: A Method for Studying Transient Effects on the Risk of Acute Events Maclure M. Am J Epidemiol 1991; 133: 144-153).

The case-time-control design is an elaboration of the case-crossover design, which uses exposure history data from a traditional control group to estimate and adjust for the bias from temporal changes in prescribing (Case-crossover and Case-Time-Control Designs as Alternatives in Pharmacoepidemiologic Research Schneeweiss S, Sturmer T, Maclure M. Pharmacoepidemiol Drug Saf 1997; Suppl 3. S51-S59).

However, if not well matched, the control group may reintroduce selection bias. In this situation a 'case-case-time-control' method may be helpful as explained in Future cases as present controls to adjust for exposure trend bias in case-only studies (Wang S, Linkletter C, Maclure M, Dore D, Mor V, Buka S, Wellenius GA. Epidemiology 2011; 22: 568 – 74).

The self-controlled case series (SCCS) method was developed to investigate the association between a transient exposure (vaccines) and an adverse event. Each case's given observation time is divided into control and risk periods. Risk periods are defined during or after the exposure. Then the method compares the incidence in risk periods relative to the incidence in control periods. An advantage of the method is that confounding factors that do not vary with time, such as genetics, location, socio-economic status are controlled for implicitly and risks assessment is feasible even in highly exposed populations (Use of the self-controlled case-series method in vaccine safety studies: review and recommendations for best practice. Weldeselassie YG, Whitaker HJ, Farrington CP. Epidemiol Infect. 2011; 139: 1805 – 17).

6.2.3.3. Disease risk scores

An approach to controlling for a large number of confounding variables is to construct a multivariable confounder score which summarises potential confounding factors in a single score. [Stratification by a multivariate confounder score](#) (Miettinen OS. Am J Epidemiol 1976; 104: 609-20) demonstrates how the control of confounding may be based on stratification by the score, with stratum-specific contingency tables obtained and analysed in the usual manner. An example is a disease risk score (DRS) that estimates the probability or rate of disease occurrence conditional on being unexposed. The association between exposure and disease is then estimated, adjusting for the disease risk score in place of the individual covariates. DRSs are difficult to estimate if outcomes are rare. [Use of disease risk scores in pharmacoepidemiologic studies](#) (Arbogast P. Stat Methods Med Res 2009; 18: 67-80) includes a detailed description of their construction and use, a summary of simulation studies comparing their performance to traditional models, a comparison of their utility with that of propensity scores, and some further topics for future research.

6.2.3.4. Propensity scores

Databases used in pharmacoepidemiologic studies often include records of prescribed medications and encounters with medical care providers, from which one can construct surrogate measures for both drug exposure and covariates that are potential confounders. It is often possible to track day-by-day changes in these variables. However, while this information can be critical for study success, its volume can pose challenges for statistical analysis.

A propensity score (PS) is analogous to the disease risk score in that it combines a large number of possible confounders into a single variable (the score). The exposure propensity score (EPS) is the conditional probability of exposure to a treatment given observed covariates. In a cohort study, matching or stratifying treated and comparison subjects on EPS tends to balance all of the observed covariates. However, unlike random assignment of treatments, the propensity score may not balance unobserved covariates. [Invited Commentary: Propensity Scores](#) (Joffe MM, Rosenbaum PR. Am J Epidemiol 1999; 150: 327–33) reviews the uses and limitations of propensity scores and provide a brief outline of the associated statistical theory. The authors present results of adjustment by matching or stratification on the propensity score.

The following article discusses the emerging high dimensional propensity score (hd-PS) model approach: [High-dimensional Propensity Score Adjustment in Studies of Treatment Effects Using Healthcare Claims Data](#) (Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. Epidemiol 2009; 20(4): 512-22). hd-PS attempts to empirically identify large numbers of potential confounders in healthcare databases and by doing so extracts more information on confounders and proxies thereof. [Covariate selection in high-dimensional propensity score analyses of treatment effects in small samples](#) (Rassen JA, Glynn RK, Brookhart A. Schneeweiss S. Am J Epidemiol 2011; 173: 1404-1413) evaluates the relative performance of hd-PS in smaller samples. [Confounding adjustment via a semi-automated high-dimensional propensity score algorithm: an application to electronic medical records](#) (Toh S, Garcia Rodriguez LA, Herman MA. Pharmacoepidemiol Drug Saf 2012; 20: 849-857) evaluates the use of hd-PS in a primary care electronic medical record database. In addition, the article [Using high-dimensional propensity score to automate confounding control in a distributed medical product safety surveillance system](#) (Rassen JA, Schneeweiss S. Pharmacoepidemiol Drug Saf 2012; 21(S1): 41-49) summarises the application of this method for automating confounding control in sequential cohort studies as applied to safety monitoring systems using healthcare databases and also discusses the strengths and limitations of hd-PS.

The use of several measures of balance for developing an optimal propensity score model is described in [Measuring balance and model selection in propensity score methods](#) (Belitser SV, Martens EP, Pestman WR, Groenwold RH, de Boer A, Klungel OH. Pharmacoepidemiol Drug Saf 2011; 20: 1115-29).

In [Performance of propensity score calibration – a simulation study](#) (Stürmer T, Schneeweiss S, Rothman KJ, Avorn J, Glynn RJ. Am J Epidemiol 2007; 165(10): 1110-8) 'propensity score calibration' (PSC) was introduced. This technique combines propensity score matching methods with measurement error regression models to address confounding by variables unobserved in the main study by using additional covariate measurements observed in a validation study.

Although in most situations propensity score models, with the exception of hd-PS, do not have any advantages over conventional multivariate modelling in terms of adjustment for investigator identified confounders, several other benefits may be derived. Propensity score methods may help to gain insight into determinants of treatment including age, frailty and comorbidity, and it may help identify individuals treated against expectation. A mechanical advantage of PS analyses is that if exposure is not infrequent it is possible to adjust for a large number of covariates even if outcomes are rare, a situation often encountered in drug safety research.

6.2.3.5. Instrumental variables

Instrumental variable (IV) methods were invented over 70 years ago, but were used by epidemiologists only recently. Over the past decade or so, non-parametric versions of IV methods have appeared that connect IV methods to causal and measurement-error models important in epidemiological applications. [An introduction to instrumental variables for epidemiologists](#) (Greenland S. Int J of Epidemiol 2000; 29:722-729) presents those developments, illustrated by an application of IV methods to non-parametric adjustment for non-compliance in randomised trials. The author mentions a number of caveats, but concludes that IV corrections can be valuable in many situations. Including when IV assumptions are questionable, the corrections can still serve as part of the sensitivity analysis or external adjustment. When, however, the assumptions are more defensible, as in field trials and in studies that obtain validation or reliability data, IV methods can form an integral part of the analysis.

The complexity of the issues associated with confounding by indication, channelling and selective prescribing is explored in [Evaluating short-term drug effects using a physician-specific prescribing preference as an instrumental variable](#) (Brookhart MA, Wang P, Solomon DH, Schneeweiss S. Epidemiology 2006; 17(3): 268-275). This article also proposes a potential approach to control confounding by indication in non-experimental studies of treatment effects. The use of this instrument is

illustrated in a study comparing the effect of exposure to COX-2 inhibitors with non-selective NSAIDs on gastrointestinal complications. Contrary to randomised controlled trial (RCT) results showing that COX-2 inhibitors lead to a reduced risk of gastro-intestinal toxicity relative to non-selective NSAIDs, the author's conventional multivariable analysis found no evidence of a gastro-protective effect attributable to COX-2 inhibitor use. In contrast to the conventional analysis, a physician-level instrumental variable approach (a time-varying estimate of a physician's relative preference for a given drug, where at least two therapeutic alternatives exist) yielded evidence of a clinically significant protective effect due to COX-2 exposure, particularly for shorter term drug exposures. The authors also point out the possibility that a physician can influence the outcome in ways other than through the prescribing of an NSAID. For example, physicians who frequently prescribe COX-2 inhibitors may also be more likely to co-prescribe proton pump inhibitors for additional gastro-protection. In such a situation, the protective effect due to COX-2 exposure is partly attributable to the use of a proton pump inhibitor.

[Instrumental variable methods in comparative safety and effectiveness research](#) (Brookhart MA, Rassen JA, Schneeweiss S. *Pharmacoepidemiol Drug Saf* 2010; 19: 537 – 554) is a practical guidance on IV analyses in pharmacoepidemiology.

An important limitation of IV analysis is that weak instruments (small association between IV and exposure) lead to decreased statistical efficiency and biased IV estimates as detailed in [Instrumental variables: application and limitations](#) (Martens EP, Pestman WR, de Boer A, Belitser SV, Klungel OH. *Epidemiology* 2006; 17: 260-7). For example, in the above mentioned study on non-selective NSAIDs and COX-2-inhibitors, the confidence intervals for IV estimates were in the order of five times wider than with conventional analysis.

6.2.3.6. Handling time-dependent confounding in the analysis

6.2.3.6.1 G-estimation

G-estimation is a method for estimating the joint effects of time-varying treatments using ideas from instrumental variables methods. [G-estimation of Causal Effects: Isolated Systolic Hypertension and Cardiovascular Death in the Framingham Heart Study](#) (Witteaman JCM, D'Agostino RB, Stijnen T, Kannel WB, Cobb JC, de Ridder MAJ, Hofman A, Robins JM. *Am J Epidemiol* 1998; 148(4) 390-401) demonstrates how the G-estimation procedure allows for appropriate adjustment of the effect of a time-varying exposure in the presence of time-dependent confounders that are themselves influenced by the exposure.

6.2.3.6.2 Marginal Structural Models (MSM)

The use of Marginal Structural Models can be an alternative to G-estimation. The paper [Marginal Structural Models and Causal Inference in Epidemiology](#) (Robins JM, Hernán MA, Brumback B. *Epidemiology* 2000; 11: 550-560) introduces MSM, a class of causal models that allow for improved adjustment for confounding in these situations.

MSMs have two major advantages over G-estimation. Although useful for survival time outcomes, continuous measured outcomes and Poisson count outcomes, logistic G-estimation cannot be conveniently used to estimate the effect of treatment on dichotomous outcomes unless the outcome is rare. The second major advantage of MSMs is that they resemble standard models, whereas G-estimation does not (see [Marginal Structural Models to Estimate the Causal Effect of Zidovudine on the Survival of HIV-Positive Men](#) (Hernán MA, Brumback B, Robins JM. *Epidemiology*, 2000; 11:561–570)).

The article [Effect of highly active antiretroviral therapy on time to acquired immunodeficiency syndrome or death using marginal structural models](#) (Cole SR, Hernán MA, Robins JM, Anastos K, Chmiel J, Detels R, Ervin C, Feldman J, Greenblatt R, Kingsley L, Lai S, Young M, Cohen M, Munoz A. *Am J Epidemiol* 2003; 158: 687-694) provides a clear example in which standard Cox analysis failed to detect a clinically meaningful net benefit of treatment because it does not appropriately adjust for time-dependent

covariates that are simultaneously confounders and intermediate variables. Instead such a net benefit was shown using a marginal structural survival model.

Beyond the approaches proposed above, traditional and efficient approaches to deal with time dependent variables in the design of the study, such as nested case control studies with assessment of time varying exposure windows, should be considered.

6.3. Hybrid studies

The use of the term 'hybrid studies' in the current document relates to efforts at bridging the pharmacoepidemiological principles and practices of interventional and non-interventional study design, conduct and analysis. One of the primary aims for doing this is to better reflect 'real life' populations and circumstances.

6.3.1. Large simple trials

RCT are considered the gold standard for demonstrating the efficacy of medicinal products. This design can also be used to obtain unbiased estimates of the risk for adverse outcomes. However, large sample sizes are required when the risk is small or delayed (with a large expected attrition rate), when the population exposed to the risk is heterogeneous (e.g. different indications and age groups), when several risks need to be assessed in the same trial (e.g. risks of stroke and of myocardial infarction) or when many confounding factors need to be balanced between treatment groups. In such circumstances, the cost and complexity of a RCT may outweigh its advantages over observational studies. A study design which, ethical considerations permitting, allowed drug allocation to be randomised in an otherwise normal clinical setting, and which relied upon the routine collection of primary and secondary healthcare records, could overcome the size limitations and atypical settings of conventional clinical trials. It would also avoid the channelling bias that may, in some cases, make it impossible to interpret the results of purely observational studies. A Large Simple Trial (LST) is such a study design that keeps the volume and complexity of data collection to a minimum. Outcomes that are simple and objective can be measured from the routine process of care using epidemiological follow-up methods, for example by using questionnaires or hospital discharge records. LST methodology is discussed in Chapters 36 and 37 of the book *Pharmacoepidemiology* (Strom BL, Kimmel SE, Hennessy S. 5th Edition, Wiley, 2012), which includes a list of conditions appropriate for the conduct of a LST and a list of conditions which make a LST feasible. Examples of LSTs are [Assessment of the safety of paediatric ibuprofen: a practitioner based randomised clinical trial](#) (Lesko SM, Mitchel AA. JAMA 1995; 279: 929-933) and [Comparative mortality associated with ziprasidone and olanzapine in real-world use among 18,154 patients with schizophrenia: The Zodiac Observational Study of Cardiac Outcomes \(ZODIAC\)](#) (Strom BL, Eng SM, Faich G, Reynolds RF, D'Agostino RB, Ruskin J, Kane JM. Am J Psychiatry 2011; 168(2): 193 - 201).

Note that the use of the term 'simple' in the expression 'LST' refers to data structure and not data collection. It is used in relation to situations in which a small number of outcomes are measured. The term may not adequately reflect the complexity of the studies undertaken.

6.3.2. Randomised database studies

Randomised database studies can be considered a special form of an LST where patients included in the trial are enrolled in a healthcare system with electronic records. Randomised database studies attempt to combine the advantages of randomisation and observational database studies. In a randomised database study, eligible patients may be identified and flagged automatically by the software, with the advantage of allowing comparison of included and non-included patients. Database screening or record linkage can be used to detect and measure outcomes of interest otherwise assessed through the normal process of care. Patient recruitment, informed consent and proper documentation of patient information are hurdles that still need to be addressed in accordance with the applicable legislation for RCTs. These and other

aspects of randomised database studies are discussed in Chapter 17 of *Pharmacoepidemiology and Therapeutic Risk Management* (A.G. Hartzema, H.H. Tilson and K.A. Chan, Editors, 1st Edition, Harvey Whitney Books Company, 2008), which illustrates with examples the practical implementation of randomised studies in general practice databases. Another use of databases in RCT is the long-term follow-up of patients in observational studies after RCT termination, for example to assess long-term safety and effectiveness at regular intervals using objective outcomes. There are few published examples of randomised database studies, but this design could become more common in the near future with the increasing computerisation of medical records. The paper [Pragmatic randomised trials using routine electronic health records: putting them to the test](#) (van Staa T, Goldacre B, Gulliford M, Cassell J, Pirmohamed M, Taweel A, Delaney B, Smeeth L. *BMJ* 2012; 344: e55) describes a project to implement randomised trials in the everyday clinical work of general practitioners, comparing treatments that are already in common use, and using routinely collected electronic healthcare records both to identify participants and to gather results.

6.4. Systematic review and meta-analysis

Often more than one study is available for a research question so it is important to identify and integrate the evidence. In epidemiology, the focus of this activity is often not to obtain an estimate but to learn from the diversity of designs, results and associated gaps in knowledge.

A systematic review is a review of the literature aiming to answer a specific and clearly formulated research question. Systematic reviews use systematic and explicit methods to identify, select, critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. The key characteristics are that the methods used to minimise bias are explicit and the findings are reproducible as stated in the [Cochrane Handbook for Systematic Review of Interventions](#).

For example, it has long been recognised that persons using NSAIDs are at a significantly increased risk of gastrointestinal complications, for instance, injury to the intestinal lining that can result in ulcers and/or gastrointestinal bleeding. To reduce the morbidity associated with NSAIDs, specific estimates for individual drugs and individual groups of patients with different risk profiles are needed. Therefore, a systematic review of a number of studies is appropriate to determine specific pharmacologic features of NSAID-associated gastro-intestinal toxicity and to explore multi-factorial determinants in the risk of gastro-intestinal bleeding among NSAID users, including clinical background, use of concomitant medications or a possible genetic susceptibility.

Meta-analysis is a statistical technique used to analyse and summarise the findings of a systematic review by quantitative pooling of the data from individual studies addressing the same question included in the systematic review. How meta-analysis can provide more precise estimates of the effects of healthcare than those derived from the individual studies included within a systematic review is demonstrated in [Quantitative synthesis in systematic reviews](#) (Lau J, Ioannidis JP, Schmid CH. *Ann Intern Med* 1997; 127: 820-826). In addition meta-analysis evaluates the consistency of results across studies and facilitates the exploration of the heterogeneity (clinical, methodological and/or statistical). Indeed, as shown in [Investigating causes of heterogeneity in systematic reviews](#) (Glasziou PP, Sanders SL. *Stat Med* 2002; 21: 1503-11), when very significant heterogeneity exists, the heterogeneity itself may deserve more emphasis than the pooled summary estimates. In addition to direct comparisons, consideration should be given to the appropriateness of indirect comparisons through network meta-analysis of existing trials.

Systematic review and meta-analysis can be conducted with different sources of information including clinical trials or epidemiological studies for the assessment of safety and tolerability profiles of therapeutic interventions. An example of a meta-analysis addressing confounding to determine a safety profile is provided in [Risk of venous thromboembolism from oral contraceptives containing gestodene and desogestrel versus levonorgestrel: a meta-analysis and formal sensitivity analysis](#) (Hennessy S, Berlin JA,

Kinman JL, Margolis DJ, Marcus SM, Strom BL. *Contraception* 2001; 64: 125-133). Any systematic review and meta-analysis will, however, have the same limitations as the sources of information they use. There are also additional limitations pertaining to the actual statistical combination of data via a meta-analytic approach.

RCTs are considered the gold standard for establishing causal association for therapeutic interventions. They frequently have limitations relating to sample size, narrow population characteristics and indications, and short follow-up duration. Therefore RCTs alone and subsequent systematic review or meta-analysis of RCTs will not address issues relating to the incidence of diseases and will have little value in detecting rare events and in the evaluation of outcomes that are far in the future. Systematic review and meta-analysis of observational studies and other epidemiological sources are becoming as common as systematic review of published clinical trials and [Challenges in systematic reviews that assess treatment harms](#) (Chou R, Helfand M. *Ann Intern Med* 2005; 142:1090-9) shows why for different reasons both provide relevant information and knowledge for pharmacovigilance.

Section 5.3 further describes different approaches to integrating studies and pooling data.

6.5. Signal detection methodology and application

Quantitative analysis of spontaneous adverse drug reaction reports is increasingly used in drug safety research. [Quantitative signal detection using spontaneous ADR reporting](#) (Bate A, Evans SJW. *Pharmacoepidemiol Drug Saf* 2009; 18: 427-436) describes the core concepts behind the most common methods, the proportional reporting ratio (PRR), reporting odds ratio (ROR), information component (IC) and empirical Bayes geometric mean (EBGM). The authors also discuss the role of Bayesian shrinkage in screening spontaneous reports and the importance of changes over time in screening the properties of the measures. Additionally they discuss three major areas of controversy and ongoing research: stratification, method evaluation and implementation in addition to giving some suggestions as to where emerging research is likely to lead. [Methods for drug safety signal detection in longitudinal observational databases: LGPS and LEOPARD](#) (Schuemie MJ. *Pharmacoepidemiol Drug Saf* 2011; 20: 292 – 9) presents a sequential set of methods for detecting and filtering drug safety signals.

The 2010 report of [Council for International Organisations of Medical Sciences \(CIOMS\) Working Group VIII Practical Aspects of Signal Detection in Pharmacovigilance](#) provides a comprehensive resource for those considering how to strengthen their pharmacovigilance systems and practices in terms of signal management.

The [Guideline on the use of statistical signal detection methods in the Eudravigilance data analysis system](#) describes quantitative methods implemented in signal detection by the EMA together with the elements for their interpretation and their potential limitations in the frame of pharmacovigilance. It encompasses the use of quantitative methods in [EudraVigilance](#) applied to the evaluation of Individual Case Safety Reports (ICSRs) originating from healthcare professionals and involving authorised medicinal products.

Useful commentary and points of caution to consider before incorporating data mining as a routine component of any pharmacovigilance program is provided in [Data mining for signals in spontaneous reporting databases: proceed with caution](#) (Stephenson WP, Hauben M. *Pharmacoepidemiol Drug Saf* 2007; 16: 359–365), which also includes a review of data mining methodologies employed and their limitations.

Other large observational databases such as claims and electronic medical records databases are potentially useful as part of a larger signal detection and refinement strategy. In addition, there are a number of ongoing initiatives to develop observational data as electronic systems that will complement existing methods of safety surveillance e.g. the [IMI PROTECT](#), [EU-ADR](#) and [Mini-Sentinel](#) projects (see Section 5.3).

The [Guideline on good pharmacovigilance practices \(GVP\) Module IX - Signal Management](#) defines signal management as the set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, literature information or other data sources, there are new risks associated with an active substance or a medicinal product or whether risks have changed. Signal management covers all steps from detecting signals (signal detection), through their validation and confirmation, analysis, prioritisation and assessment to recommending action, as well as the tracking of the steps taken and of any recommendations made.

7. Statistical and epidemiological analysis plan

There is a considerable body of literature explaining statistical methods for observational studies but very little addressing the statistical analysis plan. A clear guide to general principles and the need for a plan is given in *Design of Observational Studies* (P.R. Rosenbaum, Springer Series in Statistics, 2010. Chapter 18, p. 385). This book also gives useful advice on how to plan complex hypotheses in a way that controls the chances of drawing incorrect conclusions. Planning analyses for randomised clinical trials is covered in a number of publications. These often give checklists of the component parts of an analysis plan and much of this applies equally to non-randomised design. A good reference in this respect is the [International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use \(ICH\) ICH E9 'Statistical Principles for Clinical Trials'](#). While specific guidance on the statistical analysis plan for epidemiological studies is sparse, the following principles will apply to most of the studies.

A study is generally designed with the objective of addressing a set of research questions. However, the initial product of a study is a set of numerical and categorical observations that do not usually provide a direct answer to the questions that the study is designed to address. The statistical analysis plan details the mathematical transformations that will be performed on the observed data in the study and the patterns of results that will be interpreted as supporting alternative answers to the questions. It will also explain the rationale behind this decision making process and the way that this rationale has influenced the study design. An important part of the statistical analysis plan will explain how problems in the data will be handled in such calculations, for example missing or partial data.

The statistical analysis plan should be sufficiently detailed so that it can be followed in the same way by any competent analyst. Thus it should provide clear and complete templates for each analysis.

Pre-specified statistical and epidemiological analyses can be challenging for data that are not collected specifically to answer the study questions. This is usually the case in retrospective observational studies. However, thoughtful specification of the way missing values will be handled or the use of a small part of the data as a pilot set to guide analysis can be useful techniques to overcome such problems. A feature common to most studies is that some not pre-specified analyses will be performed in response to chance observations in the data. It is important to distinguish between such data-driven analyses and the pre-specified findings. Post-hoc modifications to the analysis strategy should be noted and explained. The statistical analysis plan provides a confirmation of this process.

A particular concern in retrospective studies is that decisions about the analysis should be made blinded to any knowledge of the results. This should be a consideration in the study design, particularly when feasibility studies are to be performed to inform the design phase. Feasibility studies should be independent of the main study results.

The statistical and epidemiological analysis plan is usually structured to reflect the protocol and will address, where relevant, the following points:

1. A description of the study data source, the intended study population and the study design with discussion of strengths and weaknesses.

2. The effect measures and statistical models used to address each primary and secondary objective.
3. Formal definitions of any outcomes e.g. 'fatal myocardial infarction' might be defined as 'death within 30 days of a myocardial infarction'. Outcome variables based on historical data may involve complex transformations to approximate clinical variables not explicitly measured in the dataset used. These transformations should be discriminated from those made to improve the fit of a statistical model. In either case the rationale should be given. In the latter case this will include which tests of fit will be used and under what conditions a transformation will be used.
4. Formal definitions for other variable – e.g. thresholds for abnormal levels of blood parameters.
5. Sample size considerations should be presented, making explicit the data source from which the expected variation of relevant quantities and the clinically relevant differences are derived. It should be noted that in retrospective observational studies where no additional data can be collected sample size is not a relevant consideration and the ethical injunction against 'underpowered' studies has no obvious force provided the results, in particular the 'absence of effect' and 'insufficient evidence', are properly presented and interpreted.
6. Blinding to exposure variables of evaluators making subjective judgements about the study.
7. Methods of adjusting for confounding, including
 - 7.1. Which confounders will be considered;
 - 7.2. Criteria for any selection of a subset of confounders;
 - 7.3. Methods for assessing the level of confounding adjustment achieved;
 - 7.4. Sensitivity analyses for residual confounding.
8. Handling of missing data, including
 - 8.1. How missing data will be reported;
 - 8.2. Methods of imputation;
 - 8.3. Sensitivity analyses for handling missing data;
 - 8.4. How censored data will be treated, with rationale.
9. Fit of the model, including
 - 9.1. Criteria for assessing fit;
 - 9.2. Alternative models in the event of clear lack of fit.
10. Interim analyses – if considered:
 - 10.1. Criteria, circumstances and possible drawbacks for performing an interim analysis and possible actions (including stopping rules) that can be taken on the basis of such an analysis.
11. How the achieved patient population will be characterised:
 - 11.1. Description of target population;
 - 11.2. Description of the analysis population if different, e.g. after PS matching or in IV analyses.
12. Treatment of multiplicity issues not elsewhere covered.

8. Quality control and quality assurance

Quality control (QC) is the observation techniques and activities that are used to fulfill requirements for quality. Quality Assurance (QA) is defined as the planned and systematic activities implemented in a

quality system so that quality requirements for a product or service will be fulfilled. In general, QA defines the standards to be followed in order to meet the requirements, whereas QC ensures that these defined standards are followed at every step. The book *Modern Approaches to Quality Control* (A.B. Eldin, Editor. Croatia: InTech Open Access, 2011) demonstrates quality control processes in a variety of areas including in Chapter 14 on medical processes.

Excellence in scientific research involves the quality of the research that is conducted. The institution of quality is a strategic decision, the purpose of which is the continuous enhancement of research activities and their adaptation in line with the changes taking place in the research field. The quality of research, in general, is ensured by the implementation of three assumptions (postulates): (1) the establishment of a Quality assurance (QA) system, with (2) the implementation of Quality control (QC) parameters (or indicators) and their measurements, as well as (3) the introduction of an independent and objective audit of the QA/QC system and its outcomes.

The [ICH Guideline for Good Clinical Practice E6\(R1\)](#) defines Quality assurance (QA) as 'all those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice and the applicable requirements'.

The [European Forum for Good Clinical Practice](#) (EFCGP) considers Quality assurance (QA) encompasses all Quality control (QC) activities as well as auditing i.e. it is not audit by itself. From this it is clear that the responsibility for quality can only lie with the staff conducting the work initially.

Although quality assurance is the rule for RCTs, the practice is less well established for observational studies, which are also used to assess the safety and effectiveness of specific pharmacologic interventions. In an RCT the vast majority of data is quality assured but it may not be feasible because of time and budget constraints to do the same for large pharmacoepidemiological studies making secondary use of data collected for another purpose. [Training, Quality Assurance, and Assessment of Medical Record Abstraction in a Multisite Study](#). Reisch LM, Fosse JS, Beverly K, Yu O, Barlow WE, Harris E L, Rolnick S, Barton MB, Geiger AM, Herrinton LJ, Greene SM, Fletcher SW, Elmore JG. *Am J Epidemiol* 2003; 157: 546-551) describes a practical approach to assurance of good quality control in a large multisite study. The use of the results of pharmacoepidemiological studies in outcomes research requires at least some consideration and knowledge of the quality and validity of the data and of the studies themselves. In particular, there ideally needs to be some level of validation of the recording and coding for electronic data sets. It is considered the responsibility of database owners to provide researchers with the minimal level of validity and sensitivity of the coded data. It is also acknowledged that there is a need to move towards better quality control/assurance in terms of data quality assurance and study methodology. Quality should be mentioned in the study protocol in terms of quality assurance but this may, for example, lead to sensitivity analyses.

Aspects of research quality control that require close attention include data collection, data recording, numbers and qualifications of people making measurements and recording data, numbers. It also includes QC measures that are necessary to verify accuracy and consistency of the collected data, data entry into computer files, storage of originals and copies of data sheets and computer files, assignment of tasks and responsibilities, and data analyses. Quality criteria specific to a study should be defined to ensure scientific validity of the results. These criteria may involve the following items: independent scientific committee, sampling investigator recruitment, study organisation and quality control of the collected data and may include on-site control visits to participating researchers.

In general, the following are the steps to implement QA in the research plan: identifying the expectations; determining the standards; measuring and comparing performances; analysing; planning and controlling.

The two following articles are examples of quality control implementations in pharmacovigilance/pharmacoepidemiological studies. The [Norwegian Prescription Database \(NorPD\)](#) (Karu F. Norsk epidemiologi 2008; 18(2): 129-136) details the quality checks applied to the database. The article [Feasibility study and methodology to create a quality-evaluated database of primary care data](#) (Bourke A, Dattani H, Robinson M. Inform Prim Care 2004; 12(3): 171-7) details the study conducted to build and test a model for collection of computerised retrospective primary care data in the UK, to assess its quality for use in medical and pharmaceutical research. The main quality outcome measures were indicators of the completeness of data recording. It was concluded that in the group of practices studied, levels of recording were generally assessed to be of sufficient quality to enable a database of quality-evaluated, anonymised primary care records to be created.

Section II 'Operating Registries' of the AHRQ [Registries to Evaluate Patient Outcomes: a User's guide, Second Edition](#) provides a practical guide to the day-to-day operational issues and decisions for producing and interpreting high-quality registries. It is a very good reference, albeit US focused. Chapter 10 'Data Collection and Quality Assurance' reviews key areas of data collection, cleaning, storing, and quality assurance for registries. It contains a practical example of a performance-linked access system that ensures that only appropriate patients receive a treatment. It also details how these systems can help sponsors to monitor the patient population, and to learn more about adverse events and the frequency of these events

Section VII 'Archiving' in the [ISPE GPP](#) points out that copies of all quality assurance reports and audits should be included within the archived documents.

The [EuroDURG Quality Indicator Meeting \(DURQUIM\) Indicators of prescribing quality in drug utilisation research](#) is a report of a meeting at which a first draft of a database of prescribing quality indicators, already subjected to validation procedures, was made.

The following study [A systematic literature review: Prescribing quality indicators for type 2 diabetes mellitus and cardiovascular risk management](#) (Martirosyan L, Voorham J, Haaijer-Ruskamp FM, Wolffenbuttel BHR, Denig P. Pharmacoepidemiol Drug Saf 2010; 19(4): 319-34) describes the validity of existing prescribing indicators for type 2 diabetes mellitus and cardiovascular risk management.

The authors of [Validation and validity of diagnoses in the General Practice Research Database \(GPRD\): a systematic review](#) (Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Br J Clin Pharmacol 2010; 69: 4-14) assessed the quality of the methods used to validate diagnoses in the GPRD, a primary care database containing anonymised patient records for about 6% of the UK population that has been widely used for observational studies. The article contains methodological and reporting recommendations to further strengthen the use of the GPRD in research that are potentially applicable to other databases.

The following references are also useful guidance in terms of ensuring quality in pharmacoepidemiological research: the CIOMS [International Ethical Guidelines for Epidemiological Studies](#), the AGENS, DGSM and DGEpi [Good Practice in Secondary Data Analysis Version 2](#) and the [ENCePP Checklist for Study Protocols](#).

9. Reporting of adverse events to regulatory authorities

Observational studies or registers can provide the initial evidence leading to the identification of a new safety concern that may impact on patients and require a regulatory action to minimise the risk. Follow-ups of large numbers of persons using a structured data collection system may identify and characterise adverse reactions within the limits of study design, objectives, sample size and duration. Therefore, consideration should be given to the reporting of adverse reactions to competent authorities when designing a study and writing a protocol.

Chapter VI of the [ISPE GPP](#) provides general recommendations for adverse event reporting from pharmacoepidemiology studies. This text should be consulted by investigators when designing a non-interventional study. It specifies six conditions which, if obtained, generally require expedited individual

case reporting: 1) the study prospectively gathers data on individual patients, 2) the study involves direct contact with patients, 3) study personnel are trained on gathering and reporting adverse events and determining whether events might be considered "expected" for a specific product, 4) a serious event is identified by someone who has direct contact with the patient, 5) the event is considered unexpected, and 6) the reporter believes there is a causal association with the product or that causality cannot be ruled out. The GPP further specify that analyses of database studies can identify an unexpected increase in risk associated with a particular exposure but such studies typically do not require reporting of individual cases.

While these ISPE recommendations are helpful, the EU obligations to companies sponsoring a post-authorisation study are specified in [Module VI of the Guideline on good pharmacovigilance practice \(GVP\) - Management and reporting of adverse reactions to medicinal products](#):

- Marketing authorisation holders shall record all reports of suspected adverse reactions originating from within or outside the EU, which occur in non-interventional post-authorisation studies, compassionate uses, named patient uses, other patient support and disease management programmes, registries, surveys of patients or healthcare providers, and information gathering on efficacy or patient compliance.
- For non-interventional studies with primary data collection directly from patients and healthcare professionals, only reports of adverse reactions suspected to be related to the studied medicinal product should be reported. Reports of events should only be reported in the study report.
- For non-interventional study designs which are based on secondary use of data (such as studies based on electronic healthcare records or meta-analyses), adverse reactions reporting is not required. All adverse events/reactions should be summarised in the study report.
- In case of doubt, the marketing authorisation holder should clarify the reporting requirement with the concerned competent authorities in Member States.
- If the study qualifies as an interventional trial, the reporting criteria laid down in Directive 2001/20/EC and related guidance ([Volume 10 of the Rules Governing Medicinal Products in the European Union](#)) should be followed.

For a non-interventional post-authorisation study which is not sponsored by a marketing authorisation holder, there are no legal reporting obligations at the European level. Investigators should however enquire whether national obligations exist. Obligations or recommendations may also be specified by an ethical committee or a data safety monitoring board. In all circumstances, the adverse events/adverse reactions reported during the study should be summarised in the study report.

Chapter 12 of the AHRO [Registries to Evaluate Patient Outcomes: a User's guide, Second Edition](#) addresses the identification, processing, and reporting of adverse events detected in situations in which a registry has individual patient contact. This chapter should be read in the context of the regulatory requirements applicable in the US. It also presents the enforceable framework established by the FDA for risk management of products with known safety concerns, called Risk Evaluation and Mitigation Strategies (REMS).

10. Communication

Aspects of research communication include, but are not limited to, reports to health authorities, sponsors, presentations in scientific fora, scientific publications, patient focused communications and websites. One of the objectives of the new EU pharmacovigilance legislation is to increase transparency as regards drug-safety issues. [Regulation \(EU\) No. 1235/2010](#) (Art. 26) obliges the European Medicines Agency (EMA) to publish on-line protocols and public abstracts of post-authorisation safety studies (PASS) concerning centrally-authorized medicinal products and imposed as an obligation to the marketing

authorisation. [Directive 2010/84/EC](#) (Art 102) specifies that Member States shall ensure that the public is given important information on pharmacovigilance concerns relating to the use of a medicinal product. Such information may include protocols and results of PASS. The [Guideline on good pharmacovigilance practices \(GVP\) Module VIII - Post-authorisation safety studies](#) also recommends, for all PASS, registration of study information (including the protocol, amendments to the protocol, progress reports and final study report) in the [register of PASS maintained by the EMA](#).

This register of studies aims to provide a publicly accessible resource for the registration of pharmacoepidemiological and pharmacovigilance studies. Its purpose is to increase transparency, reduce publication bias, facilitate collaborations within the scientific community and facilitate optimal use of pharmacoepidemiology and pharmacovigilance expertise in Europe by preventing unnecessary duplication of research. Registration of studies in the register is mandatory for studies seeking an ['ENCePP Study'](#) seal.

The [ISPE GPP](#) contain a section on communication (section V) which includes a statement that there is an ethical obligation to disseminate findings of potential scientific or public health importance and that research sponsors (government agencies, private sector, etc.) shall be informed of study results in a manner that complies with local regulatory requirements.

The [Guidelines for Submitting Adverse Event Reports for Publication](#) (Kelly WN, Arellano FM, Barnes J, Bergman U, Edwards IR, Fernandez AM, Freedman SB, Goldsmith DI, Huang K, Jones JK, McLeay R, Moore N, Stather RH, Trenque T, Troutman WG, van Puijenbroek E, Williams F, Wise RP; ISPE, ISOP. *Pharmacoepidemiol Drug Saf* 2007; 16(5): 581 – 7) introduce readers to the key elements that have to be included when someone wishes to report and publish results about adverse drug events. The information is clearly and coherently presented and the data are divided based on three levels of requests: 'required', 'highly desirable' and 'if relevant'.

The [Enhancing the Quality and Transparency of Health Research \(EQUATOR\)](#) network is an international initiative that aims to enhance the reliability and value of the published health research literature. The article [A catalogue of reporting guidelines for health research](#) (Simera I, Moher D, Hoey J, Schulz KF, Altman DG. *Eur J Clin Invest* 2010; 40(1): 35-53) presents a collection of tools and guidelines available on the [EQUATOR website](#) relating to resources, education and training to facilitate good research reporting and the development, dissemination and implementation of robust reporting guidelines to increase the accuracy and transparency of health research reporting.

The [Strengthening the Reporting of Observational studies in Epidemiology \(STROBE\) Statement Guidelines for reporting observational studies](#) has established recommendations for improving the quality of reporting of observational studies and seeks to ensure a clear presentation of what was planned, done, and found. Of note, the aim of these guidelines was not to prescribe the reporting of observational research in a rigid format, but to address what should be the critical information that a publication on an observational study should contain. In this regard, the guidance provided is complete, with practical examples that facilitate interpretation and understanding of the recommendations, though it is of limited usefulness for the design and conduct of epidemiological research projects. The recommendations are limited to cohort, case-control, and cross-sectional studies, though other types of epidemiological studies might benefit from most of the recommendations at the time of drafting the manuscript. No recommendation on ethical considerations, ownership of data and criteria for establishing the authorship are given. This is a major limitation of these recommendations, since these aspects are highly relevant for the reporting and publishing of studies.

The [Meta-analysis of Observational Studies in Epidemiology \(MOOSE\)](#) group has developed [a consensus statement](#) and recommendations for reporting meta-analyses of observational studies in epidemiology. It is equivalent to the [STROBE Statement Guidelines for reporting observational studies](#) and the Consolidated Standards of Reporting Trials [Consolidated Standards for Reporting Trials \(CONSORT\) 2010 Statement](#) for RCTs, in that they have communication as their primary objective and take the form of a

list of minimum requirements for adequate reporting. The MOOSE article is quite similar to the others in its structure, scope, length and depth of detail and is useful for the declared audience of researchers, readers, reviewers and editors. The structure of the article is slightly confusing though, as the formal 'Results' includes subheadings such as 'background', 'search strategy', 'results' and 'discussion'. The authors recommend a broad inclusion of studies and to conduct post-hoc sensitivity on the dependence of the results on factors, such as quality of underlying papers, design, accounting for confounders etc. The authors comment on the particular problems in merging observational studies with highly variable sets of confounders that were or were not controlled for, but they do not suggest any solution or give any references to possible ways to address it.

The [Preferred Reporting Items for Systematic Reviews and Meta-analyses \(PRISMA\) Statement](#) is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses consisting of a 27-item checklist and a flow diagram. While focused on randomised trials, PRISMA can also be used as a basis for reporting systematic reviews of other types of research, particularly evaluations of interventions. PRISMA may also be useful for critical appraisal of published systematic reviews, although it is not a quality assessment instrument to gauge the quality of a systematic review. PRISMA is a successor to the [Quality of Reporting of Meta-analyses \(QUORUM\) Statement](#) and the associated QUORUM flow chart.

Additional guidance is provided in the ENCePP [Checklist for Study Protocols](#) and [Code of Conduct](#) and the [IEA GEP](#) guideline that have been reviewed elsewhere in the present document.

Some of the points that are emphasised by the cited guidelines are:

- Sources of research funding should always be disclosed whether in oral or written presentation.
- A dissemination and communication strategy should be predefined as part of the funding contract.
- All results with a scientific or public health impact must be made publicly available without undue delay.
- Quantitative measures of association should be reported rather than just results of testing.
- Authorship should conform to the guidelines established by the [International Committee of Medical Journal Editors \(ICJME\)](#) 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals'.
- For a case report (or series) on suspected adverse drug reactions, minimum requirements include an account of the patients medical history and disposition, a detailed account of the dispensed product (substances, brand, route of administration) and a detailed account of the adverse event (nature, timing, severity, outcome).

11. Update of the Guide

In line with the scope of the present inventory to be dynamic, researchers are kindly requested to refer any additional guidance document (with an electronic link, where possible) that is considered relevant, to encepp_comments@ema.europa.eu for possible inclusion in future updates.

Systematic updates of this electronic document will be performed every year. More frequent amendments may be performed for important modifications. Specific sections related to vaccines, pharmacogenetics and comparative effectiveness methods are planned to be incorporated in future revisions.

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