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4 ENCePP Guide on Methodological Standards in 5 Pharmacoepidemiology

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ENCePP Guide on Methodological Standards in Pharmacoepidemiology

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1. Introduction

The present guide seeks to provide an overview of internationally acknowledged recommendations, key points from other existing guidelines and standards in pharmacoepidemiology and directions for learning on study design and methods. The main aim is to provide a structured architecture for thinking and learning. The point on the horizon is to assure high quality pharmacoepidemiological European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) studies to fuel learned regulatory decision making and to stimulate innovation that benefits patients and public health at large. The intention is not to duplicate the text from existing guidelines and textbooks, but rather to offer the researcher a single overview document and web resource that refers to specific existing guidances after a brief introduction or overview of the relevant guidance text.

The identification and compilation of existing guidelines in the fields of pharmacoepidemiology and pharmacovigilance is a goal of ENCePP, with the purpose of supporting the development and strengthening of a functional pharmacoepidemiology research network in the field. In acknowledgement of the diverse nature and levels of expertise among present researchers in Europe, ENCEPP aims at encouraging participation across the spectrum of researchers and considers the current overview document appropriate to serve both experienced and relatively new researchers in pharmacoepidemiology.

Interested parties are also referred to the ENCEPP Checklist of Methodological Standards for ENCePP Study Protocols, which objective is to increase the 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 pharmacoepidemiological and pharmacovigilance studies

In order to develop this inventory, the first step was to identify and review existing English-language guidance. The review consisted of documenting the objective, scope, target audience, content and relevance to ENCePP, for each guidance. Gaps in guidance in areas important to collaborative pharmacoepidemiology research were also identified.

The scope of the inventory is to be dynamic in that it will be updated and expanded by structured review and also on an ad-hoc basis in response to comments received. New guidance may appear and new sections may be developed specifically targeted to the needs of collaborative research in ENCePP, or other research networks, that are not covered by current guidance. Researchers are kindly requested to refer any additional guidance document (with an electronic link, where possible) they may be aware of, and that is considered relevant, to the ENCePP Secretariat to assist in future updates. 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 references addressing a number of methodological challenges and lessons learned (see Section 5.2).

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. 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. It must describe everything precisely that will be done in the study, so that the study can be exactly 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 Guidelines for Good Pharmacoepidemiology Practices (GPP) provides guidance on what is expected of a 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. 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. The GPP does not provide detailed recommendations regarding these issues but instead more general statements. It should be borne in mind that, as stated in the GPP, adherence to guidelines will not guarantee valid research. The Checklist of Methodological Standards for ENCePP 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 all of the following aspects:

- The research question the study is designed to answer, which might be purely descriptive, exploratory or explanatory (hypothesis driven). The protocol will 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 derived from the research question and the specific study objectives. The protocol should describe whether this population is already included 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 non-case or non-exposed study groups.

- Exposures of interest that need to be pre-specified, defined and described unambiguously, including durations 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, defined and described unambiguously, 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 retrieved and measured.
- The statistical analysis of the resulting data, including statistical methods and software, adjustment strategies, and how the results are going to be addressed.
- 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 ENCePP Code of Conduct.
- The contract between the investigating team and the sponsor, which may be a part of the protocol (or the protocol a part of the contract).
- The various data collection forms including the Case Report Form (CRF) or descriptions of the data elements to be appended to the protocol, allowing having an exact representation of the data collection. For field studies, physician or patient forms would be included depending on data collection methodology. Other forms might be included as needed, such as patient information, patient-oriented summaries, copies of submissions (e.g. to ClinicalTrials.gov, ENCePP or other repositories), publications etc.

3. Research question

The research question and the associated objectives describe the knowledge or information to be gained from the study. The definition of the research question typically corresponds to the introduction section of a research report. Within the definition, it is important that current knowledge gaps are properly identified. Existing guidance on this aspect includes the ISPE Guidelines for Good Pharmacoepidemiology Practices (GPP) and the Checklist of Methodological Standards for ENCePP 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, or to assess a new or emerging safety issue). It should also be clear whether the results that will be reported represent *a priori* (pre-formed) hypotheses or data driven research. If there is no *a priori* hypothesis, this should be clearly stated. The Checklist of Methodological Standards for ENCePP Study Protocols also suggests that the research objective should briefly state the target population, primary endpoints, questions of dose-dependency and the main statistical measures.

A critical and thorough review of the literature usually forms the basis for the background description of the research question and a description of the theoretical framework of the study should be included in a protocol. Such review aims at evaluating the pertinent information and at identifying gaps in knowledge. According to the ISPE Guidelines for Good Pharmacoepidemiology Practices, 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 (which would correspond to the expected contribution of the study found in the *Relevance/Significance* section of the protocol) should be described.

In addition, previous findings are useful for the methodological planning of the current study as 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). In some circumstances systematic review and meta-analysis are appropriate (see Section 5.4) and guidance is available in the Cochrane Handbook for Systematic Reviews of Interventions. The key source for identifying systematic reviews is via the Cochrane Collaboration, an international network of researchers working on systematic reviews.

4. Governance

In Europe, EU and national laws and guidelines are the keys to what can and cannot 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 minimum requirements will naturally fit within the overall need to meet all applicable EU and national laws and guidelines for the actual study, including in situations where multicountry 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, to be approved for conduct accordingly.

Of note, some approval systems only want to see a summary or shortened form of the protocol, but at least one of the approvals generally needs to be based upon the full protocol. In addition, ethics approval does not cover science approval and within the concept of ENCePP both need to be fully satisfied.

4.1. General principles

The objective of the ENCePP Code of Conduct is to provide a set of rules and principles for best practice of the investigator-study funder relationship as well as research transparency in pharmacoepidemiology and pharmacovigilance studies, thereby promoting scientific independence.

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 and pharmacovigilance research. To this end, the Code addresses critical areas in the planning, conduct and reporting of studies and the interaction of investigators and study funders. At its core is the requirement to register studies before they start (see ENCePP E-Register of Studies) and the obligation to publish all study findings irrespective of positive or negative results.

The Code is an integral part of the 'ENCePP Study' concept. 'ENCePP studies' need to comply with the provisions of the Code in their entirety and investigators seeking the ENCePP study seal need to confirm their intention to do so by submitting a completed and signed Checklist and Declaration on compliance as part of their application.

4.2. Scientific standards, review and approval

The standards for designing a pharmacoepidemiological and pharmacovigilance study are captured in the Checklist of Methodological Standards for ENCePP Study Protocols.

Many research organisations and 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 independent experts to review the study results as well as the protocol and any publications and/or communications thereof, regardless of whether a study steering group has been established. The role of scientific committees in governance is also emphasised as being of particular importance.

4.3. 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 45/2001 of the European Parliament and of the Council need to be followed in terms of the ethical conduct of studies. For interventional research, the 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. Specifically, Marketing Authorisation Holders will need to comply with Directive 2001/83/EC and Regulation (EC) No 726/2004 of the European Parliament and of the Council. The guidance in Volume 9A on Pharmacovigilance of the Rules Governing Medicinal Products in the EU and 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 ISPE Guidelines for Good Pharmacoepidemiology Practices (GPP), section IV, including a sub-section (IV.A) on protection of human subjects, which includes a reference to the ISPE guidelines on Data Privacy, Medical Record Confidentiality, and Research in the Interest of Public Health for additional information. The GPP also recommends a stand-alone section within the protocol containing a description of plans for protecting human subjects that includes consideration of the need for submitting the protocol to an Institutional Review Board/Independent Ethics Committee (IRB/IEC) and the requirement of informed consent in accordance with local law.

The main scope of the 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 CIOMS 2009 International Ethical Guidelines for Epidemiological Studies have as their objective the preparation of guidelines to indicate how the ethical principles that should govern the conduct of biomedical research involving human subjects could be effectively applied. The Guidelines set forth ethical guidance on how epidemiologists - 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 the process of producing this information.

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, which is a reference for establishing, maintaining and evaluating the success of registries created to collect data about patient outcomes. In Section 1: 'Creating a registry' is a specific chapter dedicated to ethics, data ownership, and privacy. The concepts are useful although the authors indicate that this section focuses solely on US Law.

The Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors 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.

5. Study Design and Methods

5.1. 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 [GI] 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.

The research question drives essentially three keys and sequentially structured phases in the conduct of an epidemiological study: (1) the design of the occurrence relation (theoretical design, for instance use of NSAIDs resulting in GI bleeds), (2) the design of the data collection to document empirically the occurrence relation (collection from a database of exposure [use of NSAIDs] and outcomes data [GI bleeding] in a cohort of patients that are/have been NSAIDs users), and (3) the design of the data analysis (from raw data to quantification of associations). These three phases are not independent. A hypothesised occurrence relation may lead to a certain array of designs for data collection given, in this example, the multi-source availability of data on use of NSAIDs (exposure) and on occurrences of GI bleeds in patients (outcomes). Finally, each design for data collection, given a well-defined occurrence relation, will be followed by only a few appropriate designs of data analysis.

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 sample of textbooks recommended for consultation. Researchers may find other textbooks more appropriate to their specific needs.

- B. MacMahon, D. Trichopoulos. *Epidemiology: Principles and Methods 2nd Edition* (Lippincott Williams & Wilkins, 1996) offers an introductory understanding of

epidemiological methods and processes, including on study designs and control for confounding.

- K. Rothman, S. Greenland, T. Lash. *Modern Epidemiology 3rd Edition* (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.
- B. Strom. *Pharmacoepidemiology 4th Edition* (Wiley, 2005) provides a complete review of epidemiological methods applied to the study of drugs. In Chapters 45 – 46, it emphasises that, whatever the source of the data, the veracity of a study's conclusion rests on the validity of the data.
- A.G. Hartzema, H.H. Tilson and K.A. Chan, Editors. *Pharmacoepidemiology and Therapeutic Risk Management 1st Edition* (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.
- M.H. Gail, J. Benichou, Editors. *Encyclopedia of Epidemiologic Methods* (Wiley, 2000). This compilation of articles complements existing textbooks by providing a large coverage of specialised topics in epidemiological and statistical methods.
- D. Altman. *Practical Statistics for Medical Research* (Chapman & Hall, 1990) presents a problem-based statistical text for medical researchers.

5.2. Challenges and lessons learned

Experience has shown that 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, particularly in terms of how to deal with them. The following section details a number of sources of biases and confounding. It also provides references on possible methods for controlling for confounding, both measured and unmeasured.

- Drug exposure/outcome definition and validation

Physicians rely on patient-supplied information on past drug use and illness to assist with the diagnosis of current disease. Chapter 45 of *Pharmacoepidemiology* (B. Strom, 4th Edition. Wiley, 2005) presents 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. It 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.

- Use of automated health databases

The use of technology including administrative databases for pharmacoepidemiological research has limitations. For example, as explored 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), researchers using claims data rarely have

the opportunity to carry out quality assurance of the whole data set. 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.

The biases in assessment of drug exposure from an administrative database and their relevance for quality control in more clinical databases are 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 (ATC); errors in calculations of defined daily doses (DDD) per package; bias by over-the-counter sales and parallel trade; and bias in ambulatory care (AC)/hospital care (HC) mix. The authors conclude that methodological rigour is needed to assure data validity and to ensure reliable cross-national comparison.

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 included 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. The authors make recommendations for methodology and reporting to further strengthen the use of the GPRD in research that are potentially applicable to other databases.

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

- **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) focuses on its possible reduction in studies of intended effects.

- **Channelling**

Channelling is a form of allocation bias, where drugs with similar therapeutic indications are prescribed to groups of patients with prognostic differences. 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. 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). This study shows that when the newer NSAIDs were introduced they were channelled to particular groups of patients. In situations where indication or contraindication biases exist, and complex channelling effects can be expected, only randomised trials can be relied upon to provide unbiased treatment comparisons. Conventional randomised controlled clinical trials are expensive, involve relatively small numbers of patients, and the potential to generalise their results can be limited. 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 health care 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.

- **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 and is defined in the book *Modern Epidemiology* (K. Rothman, S. Greenland, T. Lash. 3rd Edition, Lippincott Williams & Wilkins, 2008 p. 106-107).

Bias from immortal time was first identified in the 1970s in epidemiology in the context of cohort studies of the survival benefit of heart transplantation. It recently resurfaced in pharmacoepidemiology, with several observational studies reporting that various medications can be extremely effective at reducing morbidity and mortality. These studies, while using different cohort designs, all involved some form of immortal time and the corresponding bias.

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. 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 Secret of Immortal Time Bias in Epidemiologic Studies (Shariff SZ, Cuerden MS, Jain AK, Garg AX. J Am Soc Nephrol 2008; 19: 841-843) proposes two methods to account for immortal time with an example in nephrology i.e. comparing patients who had chronic kidney disease (CKD) and attended multidisciplinary care (MDC) clinics with those who received usual care. The first solution is *matching.* At the design stage, an extra criterion is added to the matching procedure; a non-MDC clinic patient must be alive at the time when their matched patient attends the MDC clinic. In this situation, cohort entry becomes the date of the MDC clinic visit, and any time between a baseline serum creatinine test and the MDC clinic visit is not counted for in either of the groups. The other solution is to perform an analysis using *time-dependent covariates*. A time-dependent covariate is a predictor whose value may change over time. Immortal time bias can be avoided by acknowledging a change in exposure status using a time-dependent covariate. For example, a MDC clinic patient would be considered unexposed from the date of study entry until he or she visits the MDC clinic and exposed from that point forward. Many statistical software packages can incorporate time-dependent covariates into survival analysis.

- **Unmeasured confounding**

Large health care 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. 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 health care 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 techniques, 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. The conclusion was that the validity of an epidemiological study may be threatened by both residual and unmeasured confounding. 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.

- **Disease risk scores**

An approach to controlling for confounding 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. Use of disease risk scores in pharmacoepidemiologic studies (Arbogast P. Stat Methods Med Res 2009; 18: 67-80) includes a brief discussion of the DRS history, a more 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.

- **Propensity scores**

Databases used in pharmacoepidemiologic studies often include records of prescribed medications and encounters with medical care providers, from which one can construct very detailed 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 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 control subjects on EPS tends to balance all of the observed covariates. However, unlike random assignment of treatments, the propensity score may not also 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.

Analytic Strategies to Adjust Confounding using Exposure Propensity Scores and Disease Risk Scores (Stürmer T, Schneeweiss S, Brookhart MA, Rothman KJ, Avorn J, Glynn RJ. Am J Epidemiol 2005; 161(9): 891-898) illustrates the different ways that both EPS and DRS methods can be used to control for confounding in a large cohort study. The authors conclude that in the setting of claims data on an elderly population, various ways to apply EPSs and DRSs to control for confounding were not generally superior to ‘‘conventional’’ multivariable outcome modeling, and differences in effect estimates between analytic strategies became more pronounced with smaller study size. Several of the same authors more recently 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 introduced 'propensity score calibration' (PSC). This technique combines propensity score matching methods with measurement error regression models to address confounding by variables unobserved in the main study by using variables observed in a validation study. Their analyses demonstrated that PSC greatly improves inference when the critical assumption of surrogacy holds, but when surrogacy does not hold, PSC estimation can exacerbate bias relative to uncorrected propensity score models.

- **Instrumental variables**

Instrumental variable (IV) methods were invented over 70 years ago, but remained uncommon in epidemiology for a long time. 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 RCT results showing that COX-2 inhibitors lead to a reduced risk of GI 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 another interesting potential source of bias in the instrumental variable method results with 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 (PPIs) for additional gastro-protection. In such a situation, the protective effect due to COX-2 exposure is partly attributable to the use of a PPI.

- **Marginal Structural Models**

In observational studies with exposures or treatments that vary over time, standard approaches for adjustment of confounding are biased when there exist time-dependent confounders that are also affected by previous treatment. Marginal Structural Models and Causal Inference in Epidemiology (Robins JM, Hernán MA, Brumback B. Epidemiology 2000;

11(5): 550-560) introduces marginal structural models, a class of causal models that allow for improved adjustment of confounding in those situations.

5.3. Signal detection methodology and application

Quantitative analysis of spontaneous adverse drug reaction reports is increasingly used in drug safety research. The article 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.

Even for initial studies aimed at signal detection, a primary aim ought to be to estimate the magnitude of the adverse effect with minimum possible bias. The PRR is the proportion of spontaneous reports for a given drug that are linked to a specific adverse outcome, divided by the corresponding proportion for all or several other drugs. In the article The reporting odds ratio and its advantages over the proportional reporting ratio (Rothman KJ, Lanes S, Sacks ST. Pharmacoepidemiol Drug Saf 2004; 13: 519-523) the PRR is reviewed. It is shown that, if a spontaneous report database is viewed as source data for a case-control study, the reporting odds ratio (ROR) can be used to estimate relative risk and how, therefore, the corresponding odds ratio represents an improvement over the PRR.

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 European Medicines Agency 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 health care 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.

The 2010 report of 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.

5.4. Integrating and pooling studies

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 (SR) is a review of the literature aiming to answer a specific and clearly formulated research question. SR 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 GI toxicity and to explore multi-factorial determinants in the risk of GI bleeding among NSAID users including clinical background, use of concomitant medications or a possible genetic susceptibility.

Frequently, a statistical technique known as meta-analysis (MA) is used to analyse and summarise the findings of a SR by quantitative pooling of the data from individual studies addressing the same question included in the SR. How MA can provide more precise estimates of the effects of health care than those derived from the individual studies included within a SR is demonstrated in Quantitative synthesis in systematic reviews (Lau J, Ioannidis JP, Schmid CH. Ann Intern Med 1997; 127: 820-826). In addition MA 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.

SR and MA 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. Any SR and MA will, however, have the same limitations as the sources of information they use.

For example, randomised controlled trials (RCTs) are considered the gold standard for establishing causal association for therapeutic interventions. However, RCTs frequently have limitations relating to sample size, narrow population characteristics and indications, and short follow-up duration. Therefore RCTs alone and subsequent SR/MA of RCTs alone 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. On the other hand, epidemiological observational studies cannot establish causality because of methodological concerns such as inherent confounding and bias that arise in their designs. SR and MA of observational studies and other epidemiological sources are becoming as common as SR 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. It is emphasised that the limitations of data sources will not be compensated for by a SR and/or MA.

Section 6.4 further describes different approaches to integrating studies and pooling data.

6. Data Sources

There are two basic approaches for data collection. One is to use data already collected as part of administrative records or patient health care. The second option is *de novo* data

collection, which is collection of primary data specifically for the study. Increasingly often, a combination of both approaches is used.

6.1. Available (secondary) data use

The use of already available electronic patient health care data in automated health databases 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 General Practice Research Database 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 by their owners or managers 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, 4th Edition, Wiley, August 2005, Chap. 13-22). As an increasing number of databases are now being made available for pharmacoepidemiological research, this list is inherently incomplete.

General guidance for studies including those conducted in databases can be found in the ISPE Good Pharmacoepidemiology Practice, in particular sections IV-B (Study conduct, Data collection). This guidance emphasises the paramount importance of patient data protection.

The Working Group for the Survey and Utilisation of Secondary Data (AGENS) with representatives from the German Society for Social Medicine and Prevention (DGSMP) 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 Pharmacoeconomics and Outcome Research (ISPOR) working group on databases has published a Checklist for Retrospective Database Studies to assist decision makers in evaluating the quality of reporting in published studies that use health-related databases. It should be noted that the checklist focuses (in discussed problems and examples) on claims and encounter-based databases. It is meant to serve as a supplement to already available checklists for economic evaluations and will be most useful for health insurers (public or private). Some important aspects for pharmacoepidemiological studies are not covered, such as outcome definition and validity, evaluation of biases, sensitivity analyses, ethical issues, data ownership and privacy.

6.2. De novo data collection

General guidance on proper conduct of prospective patient-based studies can be found in the ISPE Guideline for Good Pharmacoepidemiology Practices (GPP) and the IEA Good Epidemiological Practice (GEP) Guideline. 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 health care 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 as an observational study where entry is defined either by diagnosis of a disease (disease registry) or prescription of a drug (exposure registry). The AHRQ of the United States has published Registries to Evaluate Patient Outcomes: a User's guide, Second Edition. The purpose of this comprehensive and useful document on 'good registry practices' is to serve as a guide to the planning, design, implementation, analysis, interpretation, and evaluation of the registry's quality. A section also covers linking of registries to other data sources. This section is, however, focused on the United States. References to research review, funding and regulatory bodies are, therefore, 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 *de novo* 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 Guideline for Good Clinical Practice, which specifies obligations for the conduct of clinical trials to ensure that the data generated in the trial is valid.

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.

- 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 an 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. Large simple randomised trials (LST) are an attempt to overcome this problem by keeping 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. An example of a LST is the Assessment of the safety of paediatric ibuprofen: a practitioner based randomised clinical trial (Lesko SM, Mitchel AA. JAMA 1995; 279: 929-933).

The LST methodology is discussed in Chapter 39 of the book *Pharmacoepidemiology* (B. Strom, 4th Edition, Wiley, August 2005). It includes a list of conditions appropriate for the conduct of a LST and a list of conditions which make a LST feasible.

Note that the use of the term 'simple' in the expression 'LST' may not adequately reflect the complexity of the studies undertaken. Replacement of the term 'simple' with 'streamlined' is considered appropriate in that it better reflects the rationalised and efficient nature of these studies.

- **Randomised database studies**

Randomised database studies (RDS) can be considered a special form of a LST where patients included in the trial are enrolled in a health care system with electronic records. RDS attempt to combine the advantages of randomisation and observational database studies. In a RDS, 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 RDS are discussed in Chapter 17 of the book *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 RDS, but this design could become more common in the near future with the increasing computerisation of medical records.

6.4. Research networks

Networks of centres active in pharmacoepidemiology and pharmacovigilance are rapidly changing the landscape of drug safety research in Europe. 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, 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.

From a methodological point of view, research 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;
- Involvement of experts from various countries addressing case definitions, terminologies, coding in databases and research practices provides opportunities to increase consistency 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 SP, 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 12 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 (e.g. IMI PROTECT project).
- 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 person level analytical datasets of individual studies (person level meta-analysis).
- 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 health care data;
- Mapping of differing disease coding systems (ICD-9, ICD10, READ, ICPC) 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 can be maintained and used in the conduct of regulatory post-authorisation studies.

7. Statistical Analysis Plan

There is a considerable body of literature explaining statistical methods for observational studies but very little addressing the statistical analysis plan. Planning analyses for randomised clinical trials is covered in a number of publications and much of this applies equally to unrandomised design. A good reference in this respect is 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 deciding 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 manipulations 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.

A feature common to most studies is that some unprespecified analyses will be performed in response to chance observations in the data. It is important to distinguish between such data-driven analyses and the prespecified findings. 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 outcomes. This should be a consideration in the study design, particularly when feasibility studies are to be performed to inform the design phase.

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

1. The statistical model used to address each primary and secondary objective.
2. Formal definitions of any outcomes e.g. fatal Myocardial Infarction (MI) might be defined as death within 30 days of an MI.
3. Formal definitions for other variable – e.g. thresholds for abnormal levels of blood parameters.
4. Sample size consideration making the data source concerning the expected variation of relevant quantities and the study power explicit.
5. Blinding to exposure variables of evaluators making subjective judgements about the study.
6. Methods of adjusting for confounding, including
    - 6.1 Which confounders will be considered;
    - 6.2 Criteria for any selection of a subset of confounders.
7. Handling of missing data, including
    - 7.1 How missing data will be reported;
    - 7.2 Methods of imputation;
    - 7.3 Sensitivity analyses for handling missing data;
    - 7.4 How censored data will be treated, with rationale.
8. Fit of the model, including
    - 8.1 Criteria for assessing fit;
    - 8.2 Alternative models in the event of clear lack of fit.
9. Interim analyses – if considered:

9.1 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.

10. Description of achieved patient population

10.1 Departures from targeted population.

11. Treatment of multiplicity issues not elsewhere covered.

8. Quality Control and Quality Assurance

Although quality assurance is the rule for randomised clinical trials, the practice is less well established for observational studies, which may be used instead of clinical trials to assess the safety and effectiveness of specific pharmacologic interventions. They should, therefore, be held to the same standards of quality.

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.

Aspects of research quality control that require close attention include data collection, data recording, numbers of people making measurements and recording data, numbers and kinds of 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 Agency for Healthcare Research and Quality 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 (PLAS) 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 Guidelines for Good Pharmacoepidemiology Practices points out that copies of all quality assurance reports and audits should be included within the archived documents.

The DURQUIM Indicators of prescribing quality in drug utilisation research is a report of a European 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 following references are also useful guidance in terms of ensuring quality in pharmacoepidemiological research: the CIOMS International Ethical Guidelines for Epidemiological Studies, the AGENS, DGSMP and DGEpi Good Practice in Secondary Data Analysis Version 2 and the Checklist of Methodological Standards for ENCePP Study Protocols.

9. Safety reporting (Adverse Events)

Clinical trials carried out during drug development cannot detect all safety issues, especially those that are uncommon, occur in specific population groups or occur after a long delay. Spontaneous reports from health care professionals are the commonest source for the identification of safety concerns arising with marketed medicines. Studies or registers can also 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 provide the conditions to identify and characterise adverse reactions within the limits of study design, objectives, sample size and duration. Therefore, consideration should be given to the expedited reporting of adverse reactions to competent authorities when designing a study and writing a protocol.

Chapter VI of the ISPE Guidelines for Good Pharmacoepidemiology Practices (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. These recommendations do not take precedence over the obligations to companies sponsoring a post-authorisation study in the European Union specified in Volume 9A.

The following general recommendations should be followed for studies carried out in the European Union:

- For a company-sponsored non-interventional post-authorisation study, the provisions included in Part I (Guidelines for Marketing Authorisation Holders), Chapter 7.4.2. (Reporting of Adverse Reactions) of Volume 9A on Pharmacovigilance of the Rules

Governing Medicinal Products in the EU (page 93 for the version dated September 2008) should be followed. These provisions specify that the usual regulatory requirements for reporting of adverse reactions should be fulfilled. This means that Marketing Authorisation Holders should ensure that they are notified by the investigator of serious adverse reactions and, if specified in the protocol, of events. However, it is acknowledged that for certain study designs, such as case-control or retrospective cohort studies, it is not feasible or appropriate to make a causality assessment at the individual case level, and therefore expedited reporting is not required. In case of doubt, the reporting requirements for a specific study should be clarified with the competent authority. Marketing Authorisation Holders should check whether additional national requirements apply in countries where the study will be carried-out.

- For a non-interventional post-authorisation study which is not sponsored by a company, 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.

- If the study qualifies as an interventional trial, the reporting criteria laid down in Directive 2001/20/EC and related guidance (Volume 10 on Clinical trials of the Rules Governing Medicinal Products in the EU) should be followed.

Any update of the Rules Governing Medicinal Products in the EU can be found on the Eudralex website.

Chapter 12 of the AHRQ 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 United States. It also presents the enforceable new 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. For marketing authorisation holders, study results should also be reflected in regulatory documents such as the risk management plan and the periodic safety update report.

The ISPE Guidelines for Good Pharmacoepidemiology Practices 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 endorsed by ISOP and ISPE aim to introduce the audience/readers to the key elements that have to be included when someone wishes to report and publish results about adverse drug events (AEs). The information is clearly and coherently presented in the cited guideline. The required data are divided based on three levels of requests: 'required', 'highly desirable' and 'if relevant'. Of

note, these requirements only give clinical practitioners the opportunity to report and to publish AE findings, because the majority of these data are at their disposal.

The 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 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 topic under consideration (reporting and publishing of studies).

The MOOSE group has developed standards and a checklist for reporting meta-analyses of observational studies in epidemiology equivalent to the STROBE Statement (Guidelines for Reporting Observational Studies) and the CONSORT statement for trials, 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 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 QUORUM Statement and the associated QUORUM flow chart.

Additional guidance is provided in the ENCePP Checklist of Methodological Standards and Code of Conduct and the IEA Good Epidemiological Practice (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' '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 they may be aware of, and that is considered relevant, to the ENCePP Secretariat 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.

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Cochrane Handbook for Systematic Reviews of Interventions http://www.cochrane-handbook.org/

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IEA Good Epidemiological Practice Guideline http://www.ieaweb.org/iea/index.php?option=com_content&view=article&id=15&Itemid=43&showall=1

ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals http://www.icmje.org/urm_main.html

IMI PROTECT http://www.imi-protect.eu/wp2.html

ISPE Guidelines on Data Privacy, Medical Record Confidentiality, and Research in the Interest of Public Health http://www.pharmacoepi.org/resources/privacy.cfm

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