17 Octubre 2017

Uso de datos basados en la historia clínica informatizada (“real world data”) en los estudios fármaco-epidemiologicos

IDIAP Jordi Gol, Barcelona

Buenas Prácticas en farmacoepidemiología: ENCePP

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The power of knowledge.
The value of understanding.

Buenas Practicas en Fármaco-epidemiología

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- ISPE guidelines for GPP
  - http://www.pharmacoepi.org/resources/guidelines_08027.cfm
- Guidelines for good database selection and use in pharmacoepidemiology research
  - http://onlinelibrary.wiley.com/doi/10.1002/pds.2229/full
- ENCePP guidelines
  - http://www.encepp.eu/standards_and_guidances/index.shtml
- STROBE
  - http://www.strobe-statement.org/index.php?id=strobe-home

ENCePP

- A project led by the EMA to strengthen the post-authorisation monitoring of medicinal products in Europe by facilitating the conduct of multi-centre, independent, post-authorisation safety studies
  - ENCePP will provide a unique opportunity to improve pharmacoepidemiological research and post-authorisation safety surveillance of medicinal products in Europe by offering access to a robust network of resources working in a transparent and independent manner according to the highest scientific standards.

http://www.encepp.eu/

ENCePP: Key Developments

- Kick-off meeting of centers, 2007
- Working Groups
  - Methods, Conduct, Centers and Databases, Study Registry
- First call for research through DG Health FP7
  - NSAID safety, www.sos-nsaids-project.org
- Website
  - Plenary Meeting Reports
  - Steering Group Meeting Reports
  - ENCePP Work Plans and other Documents

www.encepp.eu

Documents in the Public Domain

http://www.encepp.eu/publications/index.shtml

Who are the ENCePP partners?

Research **centres** located in one of the EU or EFTA countries, with no formal accreditation to join, but centres are requested to provide recent publications to confirm research focus:

- Universities, hospitals; owners of healthcare databases and/or electronic registries;
- Other public/non-profit research centres specialised in PhEpi and PhV;
- Existing European **networks** covering rare diseases, therapeutic fields and adverse drug events of interest, if at least one member is registered as an ENCePP centre;
- For-profit organisations such as CROs, provided that they perform studies commissioned by third parties and their main focus is PhEpi and PhV research;

Who are the ENCePP partners? (as of 11 Oct 2017)

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- **168 centres**
  - 124 public (university, hospital, government, charities)
- **24 networks**
  - 17 International
  - 7 National (France, Italy, Spain, Belgium, Austria, Sweden)

    Special interests: Psychiatry, rheumatology, respiratory effectiveness, teratology, pharmacogenetics, congenital abnormalities, women's health, paediatrics, psoriasis, severe cutaneous adverse reactions to drugs
- **107 data sources**

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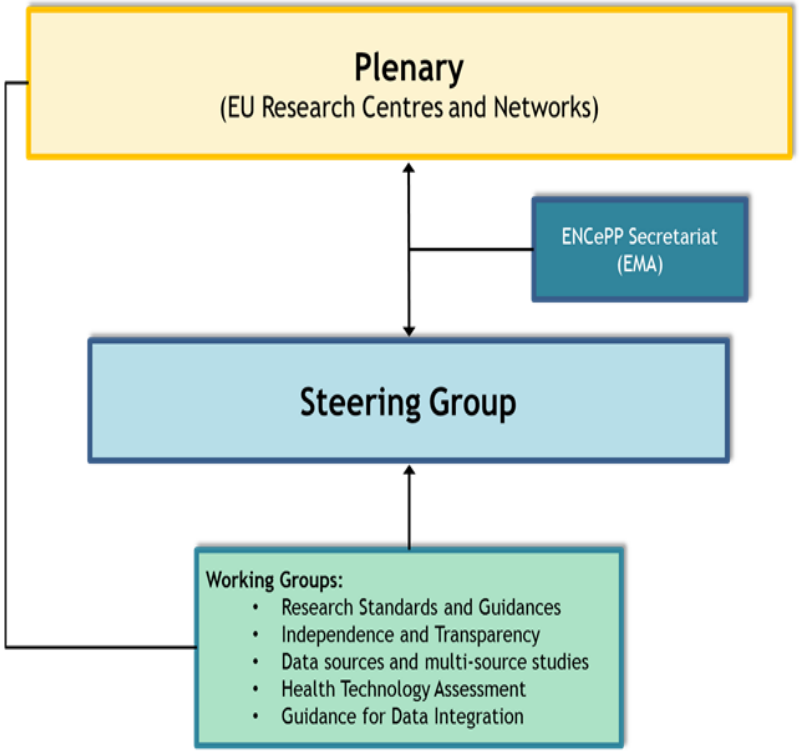
The value of understanding.

How is ENCePP organised?

- **ENCePP Steering Group**
- 16 members in total:
  - 6 elected: from network
  - 7 appointed:
  -
    - Heads of Medicines Agencies (HMA),
    - Committee for Medicinal Products for Human Use (CHMP),
    - Committee for Orphan Medicinal Products (COMP)
    - Pharmacovigilance Risk Assessment Committee (PRAC),
    - CHMP's Patient and Consumers Working Party (PCWP),
    - International Society of Pharmacoepidemiology (ISPE),
    - International Society of Pharmacovigilance (ISoP)
  - 3 members from EMA



- 2 observers: European Federation of the Pharmaceutical Industries & Associations (EFPIA) and EMA
- 2 Scientific advisors from EMA

The ENCePP Plenary Mandate

Annual meeting of all ENCePP partners and platform for the exchange of scientific and operational information for collaboration between the ENCePP centres and networks, i.e.:

- Exchange information and experience;
- Elaborate standards and best practices for research;
- Share best practice and support capacity building;
- Foster further collaboration between partners;
- Provide advice to the EMA's Scientific Committees on scientific and operational aspects on PhEpi and PhV on an ad hoc basis;
- Disseminate information on research funding opportunities;

Development of ENCePP deliverables

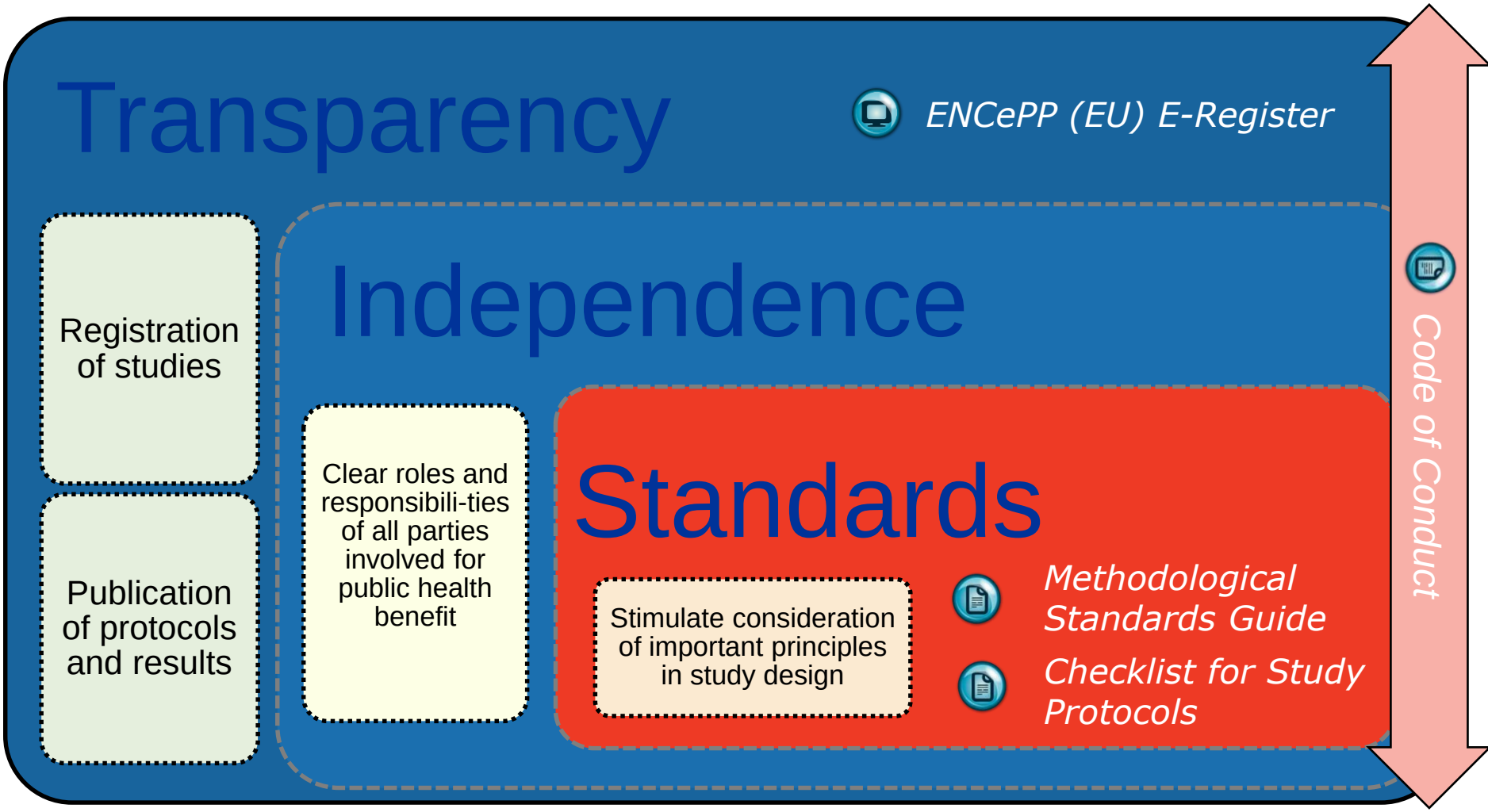
5 Working Groups (WG) composed of ENCePP Centres' representatives and EMA staff focus on producing specific outputs in line with the **bi-annual ENCePP Work Plan**:

- Research Standards and Guidance (WG 1)
- Independence and Transparency (WG 2)
- Data sources and multi-source studies (WG 3)
- Health Technology Assessment (WG HTA)
- Guidance for Data Integration (WG DI)

Complementary initiatives:

- Joint ENCePP-EnprEMA network for paediatrics
- Special Interest Group in Drug Research in Pregnancy

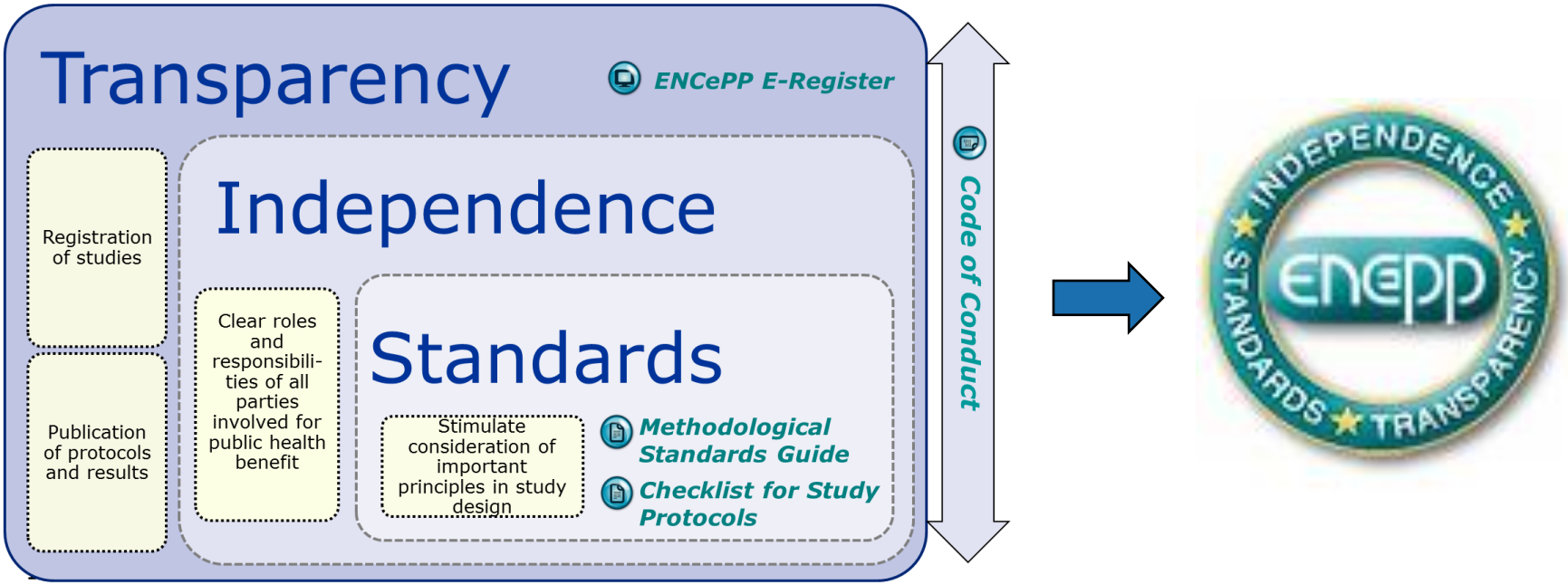
ENCePP guiding principles and tools



ENCePP guiding principles and ENCePP seal

Code of Conduct

The ENCePP Seal publicly recognises studies following the ENCePP principles as a form of quality hallmark:



EU PAS Register (ENCePP E-Register of Studies)

- Public register for research. Currently >1175 studies with focus on PASS;
- Purpose is to reduce publication bias, increase transparency;
- Promotes information exchange and facilitates collaborations within the scientific community;
- Regulatory: Hosts EU PAS Register: protocol registration in EU PAS Register is mandatory for imposed PASS

ENCePP

- ENCePP achievements:
  - ENCePP Code of Conduct
    - Designed to provide a set of rules and principles for studies to encourage transparency and scientific independence
  - ENCePP Guide on Methodological Standards in Pharmacoepidemiology
    - Identification and compilation of existing guidelines in the fields of pharmacoepidemiology and pharmacovigilance
  - Checklist of Methodological Standards for ENCePP Study Protocols
    - The goal is to increase awareness about scientific and methodological developments in the field of pharmacoepidemiology

ENCePP Checklist

- Checklist of Methodological Standards for ENCePP Study Protocols (requirement for ENCePP protocols)
  - To improve the quality of studies and facilitate the work of protocol reviewers
- Title
- Milestones
  - Start of data collection
  - End of data collection
  - Final report results

ENCePP Checklist

- Research Question
  - Clear explanation of why the study is to be conducted (new safety issues, health concerns, etc).
  - Whether results will be reported for an a priori hypothesis or as an exploratory analysis
  - Brief discussion of the target population, primary endpoints, and main outcome measures
  - Background description of the research question using a thorough review of available literature; this should include the relevant animal and human data
  - Gaps in knowledge that the study is supposed to address

ENCePP Checklist

- Research question
- Study design
- Source and study populations
- Exposure definition and measurement
- Endpoint definition and measurement
- Confounders and effect modifiers
- Data sources

ENCePP Checklist

- Study size and power
- Analysis plan
- Data management and quality control
- Limitations
- Ethical issues
- Amendments and deviations
- Plans for communication of study results

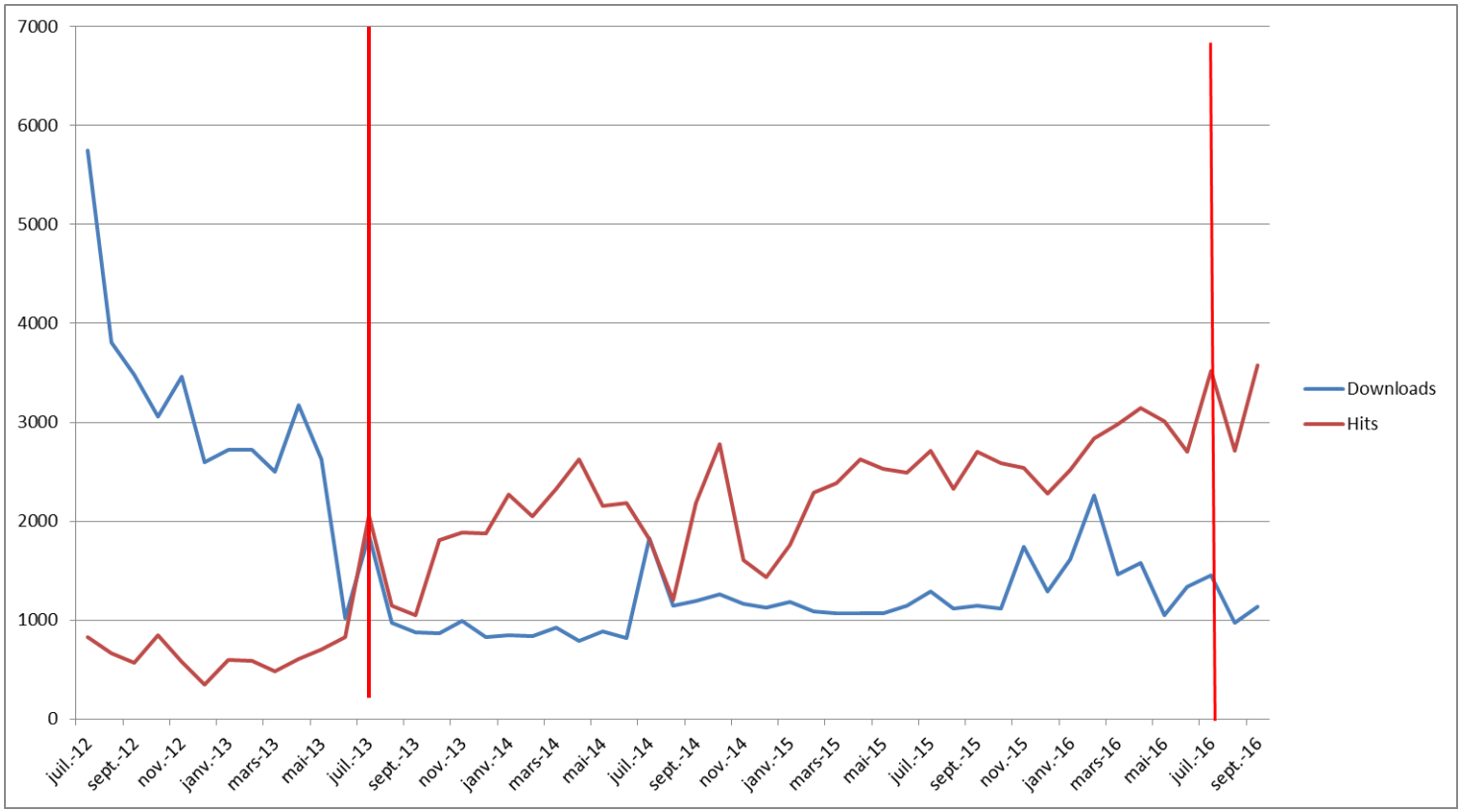
Research Standards & Guidance

- Methods Checklist for Study Protocols:
  - To stimulate researchers to consider important epidemiological principles when designing a pharmacoepidemiological study and writing a study protocol
  - To promote transparency regarding methodologies and design used in pharmacoepidemiological studies performed in the EU
  - To increase awareness about developments in science and methodology in the field of pharmacoepidemiology
- Research Guidance Overview:
  - To facilitate a one-stop access to existing guidances to conduct research

http://www.encepp.eu/standards_and_guidances/index.html

WG1. Research Standards and Guidances

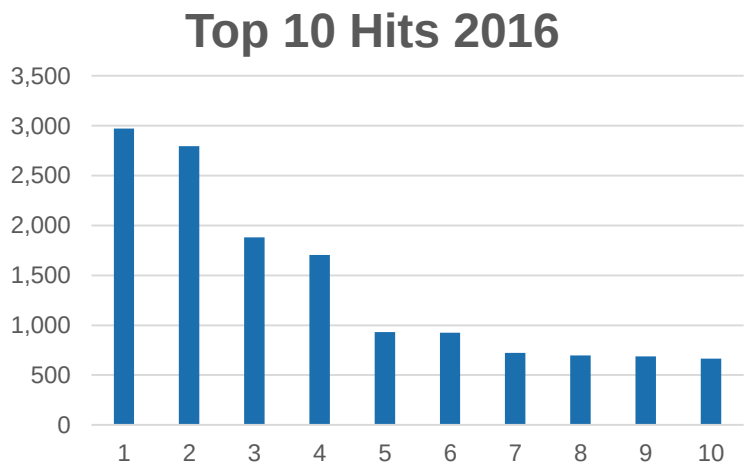
- **Results from hits: most popular deliverable**



WG1. Research Standards and Guidances

Hits by chapters

as of 16 NOV 2016



1*: Statistical plan (5)

2*: Bias and confounding (4.2.2)

3*: Signal detection methodology and application (4.6)

4*: Immortal time bias (4.2.2.2.1)

5**: Confounding by indication (4.2.2.2.3)

6: Randomised clinical trials Vs observational studies (9.1.3.1)

7: General aspects of study protocols (1)

8: Guidance on conducting systematic reviews and meta-analyses (Annex1)

9: Study design and methods (4)

10: Case-only designs (4.2.3.2)

*: same ranking in 2015
**: Quality management was ranking #5 in 2015 (Vs 12 in 2016)

- ISPE GPP – Provides guidance on what is expected of a pharmacoepidemiology study protocol:
  - Description of the research methods
  - Description of data quality and integrity
  - Certifications/qualifications of any lab or research group
  - Validation steps taken or considered to standardize lab methods
  - 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

http://www.pharmacoepi.org/resources/guidelines_08027.cfm

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Data Sources

- There are two basic approaches for data collection:
  - Use of data collected previously as part of administrative records or patient health care records
  - De novo data collection – collection of primary data specifically for the study
- In some cases, a combination of both approaches is used.

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Data Sources

- Use of available data–use of already available electronic data (automated health databases) can have a large impact on pharmacoepidemiology studies. Database examples:
  - Electronic medical records
  - Record linkage of administrative health records
  - ENCePP inventory databases are a good resource of databases that are registered in the ENCePP network; guidance on the use of these databases can be found in the ISPE GPP
  - ISPOR has published a Checklist for Retrospective Database Studies which can help evaluate the quality of reporting in published studies

ISPE Database Guidance

- Aims to assist in:
  - selection and evaluation of a resource
  - use of a data resource
  - review of database studies
  - provide a check list of factors to consider

Motivation for ISPE guidance

- Variation in resources:
  - healthcare system
  - reason for data collection
    - Clinical – electronic medical record
    - Financial – claims / payment system
- analysis not always by specialist teams
- linkage between resources
- different concerns about confidentiality
- number and variety of resources

Guidance for Industry and FDA Staff

- Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data
  - U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) May 2013

  – http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformati on/Guidances/UCM243537.pdf
- 'Investigators should demonstrate a complete understanding of the electronic healthcare data source and its appropriateness to address specific hypotheses'

Guidance sections

- 1. Selection of a database
- 2. Use of multiple data resources
- 3. Extraction & analysis of the study population
- 4. Privacy and security
- 5. Quality and validation procedures
- 6. Documentation

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Data Sources

- De novo data collection: this type of data collection has allowed the evaluation of drug-disease associations for rare and complex conditions that require large populations
  - Case-control surveillance networks – used for selected studies and for signal detection/clarification
  - Registries – sometimes regulatory driven – AHRQ document on good registry practices
  - Pharmacoepidemiology surveys – potentially questionnaire based (validation important)
  - Randomised controlled trials (RCTs) – form of de novo data collection

Guide on Methodological Standards in Pharmacoepidemiology

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Data Sources

- Signal detection methodology and application – quantitative analysis of spontaneous drug reaction reports are increasingly used in drug safety research. Core methods:
  - Proportional reporting ratio (PRR)
  - Reporting odds ratio (ROR)
  - Information component (IC)
  - Empirical Bayes geometric mean (EBGM)
  - The CIOMS working group VIII provides a thorough resource on signal management
  - Ongoing initiatives to compliment existing methods of safety surveillance (IMI Protect, EU-ADR, etc.)

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Data Sources

- Research networks – collaboration networks. Benefits:
  - Can increase the size of the study population, which can shorten the time needed for obtaining the desired sample size
  - Can facilitate research of rare events
  - 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 differences in those countries
  - Involvement of experts can provide opportunities to increase consistency of observational studies
  - Requirement to share data forces harmonisation of data elaboration, transparency in analysis, and benchmarking of data management

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Study Design and Methods

- General considerations – The research question will drive three fundamental phases of an epidemiological study:
  - The design of the "occurrence relation" as defined in Theoretical Epidemiology
    - The relation of a parameter of occurrence to a detriment or set of detriments (e.g., incidence rate ratio of GI bleeds among users and nonusers of NSAIDS)
  - The design of data collection to document the occurrence relation empirically
  - The design of data analysis (from raw data to quantification of associations)

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Definition and validation of exposure, covariates and outcomes

- Bias in assessment of drug exposure from an administrative database
- Validity of the data and definitions used
- The quality of pharmacoepidemiological studies that rely heavily of clinical databases from medical practice could be greatly enhanced by stimulating the quality of medical registration in electronic health records

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Bias and confounding

- Methods to handle bias and confounding
  - Choice of time windows
  - Immortal time bias
  - Depletion of susceptibles
  - Confounding by indication or channeling bias
  - Protopathic bias
  - Unmeasured confounding

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- Methods to handle bias and confounding
  - New-user designs –the inclusion of many prevalent users can lead to two types of bias:
    - Risk varying with time for users who are survivors
    - Covariates for drug users at study entry are affected by the drug itself
      - Restricting the analysis to persons under observation at the start of the current course of treatment can avoid these biases
  - Self-controlled designs
  - Disease risk scores (DRS)
  - Propensity score

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- Methods to handle bias and confounding
  - Instrumental variables (IV) are used to estimate causal relationships when controlled experiments are not feasible. IV corrections can be valuable in many situations even when IV assumptions are questionable.
  - G-estimation – a method for estimating the joint effects of time-varying treatments using ideas from IV methods; can allow for appropriate adjustment of the effect of a time-varying exposure in the presence of time-dependent confounders
  - Marginal structural modes – a class of casual models that allow for improved adjustments in confounding in observational studies with exposures or treatments that vary with time

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- Hybrid studies
  - Simple large trials
  - Randomised database studies

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Study Design and Methods

- Integrating and pooling studies
  - Systematic review: a review of the literature to answer a specific research question using appropriate measures to identify, select, and appraise relevant research to collect and analyze data from the studies that are included in the review
  - Meta-analysis: used to analyze and summarize the findings of a systematic review by quantitative pooling of data from individual studies that address the same question included in the systematic review.
- Both systematic review and meta-analysis can be conducted with different sources of information, including clinical trials and epidemiological studies
- Both analyses also have limitations based on the sources they use

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Statistical Analysis Plan

- The statistical model used to address each primary and secondary analysis
- Formal definitions of any outcomes
- Formal definitions for other variables
- Sample size considerations, which define the data source from which the expected variation of relevant quantities and the clinically relevant differences are derived
- Blinding to exposure variables of evaluators making subjective judgments about the study
- Methods of adjusting confounding
- Handling of missing data (how reported, methods of imputation, sensitivity analysis, etc.)
- Fit of the model
- Interim analysis
- Description of achieved patient population

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Quality Control and Quality Assurance

- QA is typically less defined for observational studies than traditional randomised, controlled trials due to the use of other data sources
- Database owners have the responsibility to provide researchers with the minimal level of validity and sensitivity of the coded data.
- The following steps can be used to implement QA in the research plan:
  - Determining the standards
  - Identifying the expectations
  - Measuring and comparing performances
  - Analyzing
  - Planning and controlling

Guide on Methodological Standards in Pharmacoepidemiology

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Safety Reporting

- 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
- ISPE recommendations

Guide on Methodological Standards in Pharmacoepidemiology

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Communication

- The ISPE GPP – Ethical obligation to report findings of potential scientific or public health importance. Sponsors should be informed of study results in a manner that complies with local regulatory requirements. Guide on Methodological Stardards in Pharmacoepidemiology
- A number of cited guidelines are available that discuss communication in more detail. Highlights of these are as follows:
  - Sources or research funding should always be disclosed whether in oral or written presentation
  - A dissemination or communication strategy should be predefined as part of the funding contract
  - All results with a scientific or public health impact must be made publically available without delay

Specific topics

- Comparative effectiveness research
- Vaccine safety and effectiveness
- Design and analysis of pharmacogenetic studies

STROBE Statement

Strengthening the reporting of observational studies in epidemiology

- “STROBE stands for an international, collaborative initiative of epidemiologists, methodologists, statisticians, researchers, and journal editors involved in the conduct and dissemination of observational studies, with the common aim of STrengthening the Reporting of OBservational studies in Epidemiology”

Title and Abstract

- Indicate the study's design with a commonly used term in the title or the abstract
- Provide in the abstract an informative and balanced summary of what was done and what was found

Introduction

- Background/rationale
  - Explain the scientific background and rationale for the investigation being reported
- Objectives
  - State specific objectives, including any prespecified hypotheses

Methods

- Study design; key elements
- Setting
  - Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection

Methods

- Participants
  - Cohort study
    - Give the eligibility criteria and the sources and methods of selection of participants
    - Describe methods of follow-up
  - Case-control study
    - Give the eligibility criteria and the sources and methods of case ascertainment and control selection
    - Give the rationale for the choice of cases and controls
  - Cross-sectional study
    - Give the eligibility criteria and the sources and methods of selection of participants

Methods

- Matching participants
  - Cohort study
    - For matched studies, give matching criteria and number of exposed and unexposed
  - Case-control study
    - For matched studies, give matching criteria and the number of controls per case

Methods

- Variables
  - Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers
    - Give diagnostic criteria, if applicable
  - For each variable of interest, give sources of data and details of methods of assessment (measurement)
    - Describe comparability of assessment methods if there is more than one group
- Describe any efforts to address potential sources of bias
- Explain how the study size was determined

Methods

- Statistical methods
  - Describe all statistical methods, including those used to control for confounding
  - Describe any methods used to examine subgroups and interactions
  - Explain how missing data were addressed
  - Cohort study—if applicable, explain how loss to follow-up was addressed
  - Case-control study—if applicable, explain how matching of cases and controls was addressed
  - Cross-sectional study—if applicable, describe analytical methods taking account of sampling strategy
  - Describe any sensitivity analyses

Results

- Participants
  - Report numbers of individuals at each stage of study
    - For example, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
  - Give reasons for nonparticipation at each stage
  - Consider use of a flow diagram

Results

- Descriptive data
  - Report numbers of individuals at each stage of study
    - For example, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
  - Indicate number of participants with missing data for each variable of interest
  - Cohort study—summarise follow-up time (e.g., average and total amount)

Results

- Outcome data
  - Cohort study
    - Report numbers of outcome events or summary measures over time
  - Case-control study
    - Report numbers in each exposure category, or summary measures of exposure
  - Cross-sectional study
    - Report numbers of outcome events or summary measures

Results

- Main results
  - Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval)
    - Make clear which confounders were adjusted for and why they were included
  - If possible, give estimates of absolute risk for a meaningful time period
- Other analyses
  - Report other analyses done
    - For example, analyses of subgroups and interactions, and sensitivity analyses

Discussion

- Summarise key results with reference to study objectives
- Discuss limitations of the study, taking into account sources of potential bias or imprecision.
  - Discuss both direction and magnitude of any potential bias
- Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
- Discuss the generalisability (external validity) of the study results

Funding

- Give the source of funding
  - The role of the funders for the present study
  - If applicable, the role of the funders for the original study on which the present article is based