



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



Guide on Methodological Research Standards

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Susana Perez-Gutthann/Kevin Blake

An agency of the European Union





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- Members of ENCePP WG “Research standards & guidance”
Chair (retired): Calvo Rojas, Gonzalo
Subgroup chairs: Perez-Gutthann, Susana; Leufkens, Hubert

Silva, Ivana
Vander Stichele, Robert
Jadrijevic-Mladar Takac, Milena
Le Louet, Herve
Moore, Nicholas
Moride, Yola
Bajrami, Rabi
Alejandro Arana

MacKenzie, Gilbert
Klungel, Olaf
Pedrós, Consuelo
Scalise, Andrea
Bergman, Ulf
Hallas, Jesper
Mayahi, Lila
Parkinson, John



ENCePP WG “Research standards & guidance”

Subgroup 1: Methodological Research Standards (MRS)

Chair: Bert Leufkens

Subgroup 2: Existing Recommendations & Guidelines

Chair: Susana Perez-Gutthann

Main activities in 2010:

- ‘**Checklist of MRS for ENCePP Protocols**’ finalised
- Draft ‘**Guide on MRS in Pharmacoepidemiology**’ based on ‘**Inventory of existing PE Guidelines**’



“Inventory of existing PE Guidelines”

Objective

- identify and compile existing guidance in the field of PE & PhV which could be used to provide recommendations on specific aspects of study development and conduct
- include information about the origin of the guidelines, its availability, and a short description

Result

- 11 guidance documents identified by the group as relevant
- Guidelines reviewed by individual members of the group
- Published on ENCePP website: **‘List of available Guidances’**

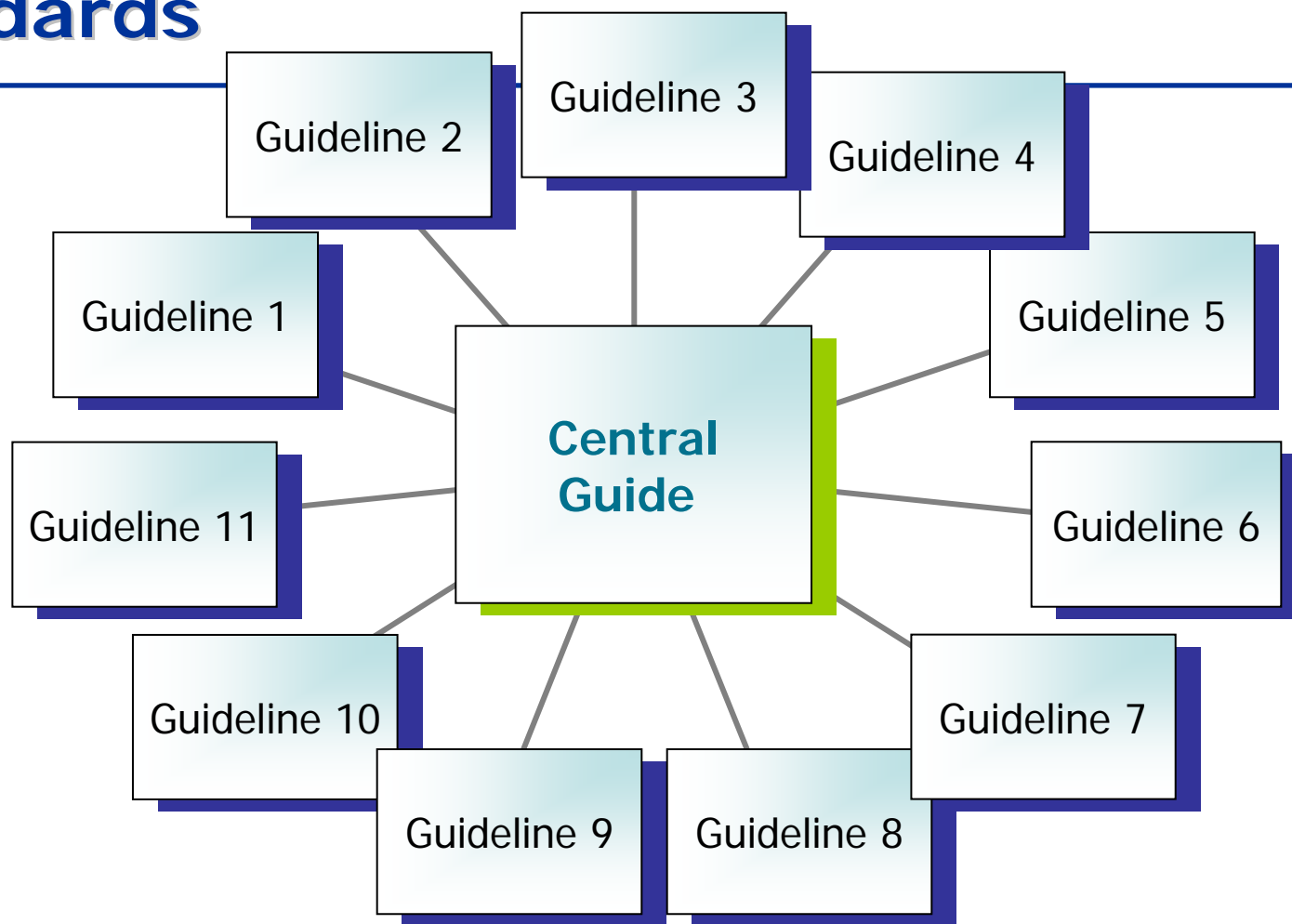


Review of existing Guidelines

- **Objective and scope of the guidance**
- **Target audience**
- **Table of Content**
- **Type of studies covered** (e.g. RCTs, observational studies, drug utilisation data, spontaneous reports)
- **Consideration of**
 - Multi-site studies
 - Data quality issues and data processing/transformation
 - Operational aspects of study development, conduct and analysis
 - Ethical issues, data ownership, privacy
- **Evaluation whether to be considered for developing ENCePP standards – in full or selected parts**
- **Comment on extent, completeness, quality and usefulness of information provided**



Guide on Methodological Research Standards





Scope of the Guide

- Based on “**Inventory of existing Guidelines**” for PE & PhV research
- “Overarching” existing guidance; no need to reinvent the wheel
- Provide new guidance for areas where no or not sufficient guidance is available
- *Note: keep in mind much guidance is found in standard reference epidemiology textbooks*

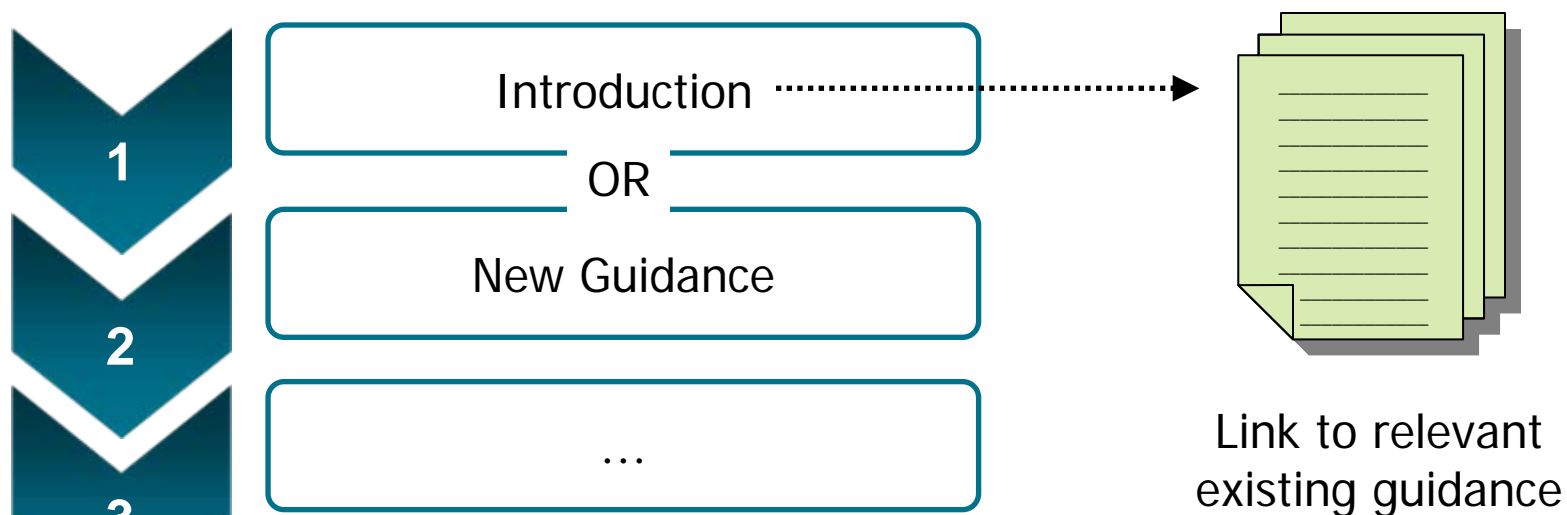


Development of the Guide

- Identify different sections of the Guide (areas of operational/methodological research)
- Match existing guidelines with the need for Guidance = Sections of the Guide
- Development of summary recommendations for each domain of study development and conduct
 - If guidance available: short introduction & link to appropriate existing guidance
 - If no guidance available: development of new guidance according to the needs



Structure of the Guide



A SHORT DOCUMENT PUBLISHED ONLINE

- (but downloadable and can be referenced),
- with links to established guidance,
- that will be maintained over time, and
- expanded to cover gaps in current guidance



The Guide by Sections (I)

1. Introduction (Perez/Leufkens/Prilla/Kurz)

- Background, aims, scope

2. General aspects of study protocol (LeLouet/Moore/Calvo)

- Core document of a study
- Aspects to be covered

3. Research question (Hallas/Moride)

- Knowledge to be gained from a study



The Guide by Sections (II)

4. Governance (Parkinson/Klungel/Theodorakis, Sampaio)

- Introduction: EU and national laws are the keys

4.1 General principles (ENCePP CoC, 'ENCePP Studies')

4.2 Scientific standards, review and approval

4.3 Ethical conduct, patient and data protection

- Declaration of Helsinki
- Legislation: relevant EU Directives, Volume 9A, local rules and implementation of EU Directives
- ISPE, IEA, CIOMS, AHRQ, ICMJE



The Guide by Sections (III)

5. Study Design and Methods (Klungel/Moore/Leufkens)

5.1 General considerations

- NSAIDs and GI bleeds, textbooks

5.2 Challenges and lessons learned

5.3 Signal detection methodology and application

- PRR, EudraVigilance, CIOMS WG VIII

5.4 Integrating and pooling studies

- SR/MA, Cochrane



The Guide by Sections (III)

5.2 Challenges and lessons learned - Sources of bias and confounding + methods for controlling for (measured and unmeasured):

- Drug exposure/outcome definition and validation
- Use of automated health databases
- Confounding by indication
- Channelling
- Immortal time bias
- Unmeasured confounding
- Disease risk scores
- Propensity scores
- Instrumental variables
- Marginal Structural Models



The Guide by Sections (IV)

6. Data Sources (Perez-Gutthann/Bergman/Vander Stichele/Sturkenboom)

6.1 Available (secondary) data use

6.2 De novo data collection

6.3 Hybrid (bridging (non)+interventional study design)

- LST *Note 'simple' v's 'streamlined'*
- RDS

6.4 Research Networks



The Guide by Sections (V)

7. Statistical Analysis Plan (Slattery/Evans/VanGanse)

- particular 'missing guidance' for epi studies

8. Quality Control and Quality Assurance (Jadrijevic-Mladar Takac/Halles)

- AHRQ, ISPE, DURQUIM, CIOMS...

9. Safety reporting (Adverse Events) (Kurz)

- Volume 9A



The Guide by Sections (VI)

10. Communication (Hallas/Jadrijevic-Mladar Takac)

- Reports to health authorities, sponsors (RMP, PSUR driven) – guidelines for AE reports ISOP, ISPE
- presentations in scientific fora
- publication:
 - Who: Authorship – ICMJE
 - What/How: EQUATOR, STROBE, MOOSE, CONSORT
- Patient focused communication



The Guide by Sections (final)

11. Update

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.

12. References

Public Consultation



EUROPEAN MEDICINES AGENCY

on - Windows Internet Explorer

cepp.eu/public_consultation/index.html

Google

ENCePP Public Consultation

Home, Back, Forward, Stop, Print, P

News

About Us

ENCePP Documents

Public Consultation

Glossary of terms

Code of Conduct **NEW**

Standards & Guidances

ENCePP Studies **NEW**

Resources Database

Partners forum

ENCePP Public Consultation

Current Consultations

ENCePP Guide on Methodological Standards in Pharmacoepidemiology

On 5 November 2010, the European Medicines Agency (EMA) released for public consultation a draft **Guide on Methodological Standards in Pharmacoepidemiology**. This guideline has been developed by ENCePP, a collaboration between the EMA and the pharmacoepidemiology research community that aims to strengthen the post-authorisation monitoring of medicines by facilitating the conduct of multi-centre, independent and scientifically robust studies focusing on safety and the balance of benefits and risks. In line with this, the Guide seeks to assure high quality pharmacoepidemiological "ENCePP Studies" to fuel learned regulatory decision making and to stimulate innovation that benefits patients and public health at large.

The objective is to provide a structured architecture for thinking and learning through presenting:

- an overview of internationally acknowledged recommendations,
- key points from other existing English-language guidelines and standards in pharmacoepidemiology, and
- directions for learning on study design and methods.

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 scope of the guide is to be dynamic. Systematic updates of this electronic document will, therefore, be performed each year. More frequent amendments may be performed for important modifications.

The document has been developed over a period of several months by a dedicated ENCePP Working Group consisting of experts in pharmacoepidemiological and pharmacovigilance research and has been peer reviewed and adopted by the ENCePP Steering Group.

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.

Document details

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