EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Guide on Methodological Research Standards

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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

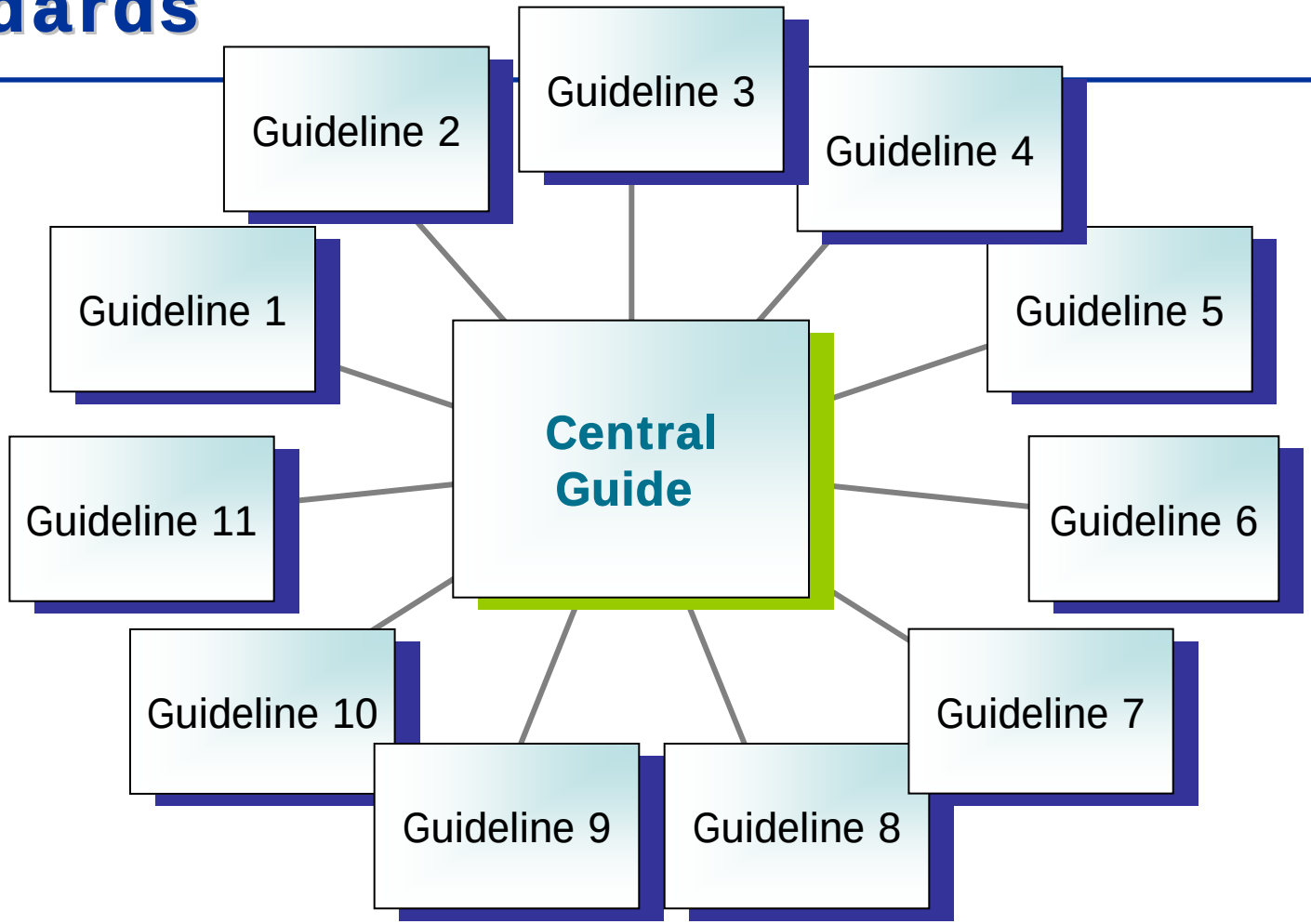
Result

- 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

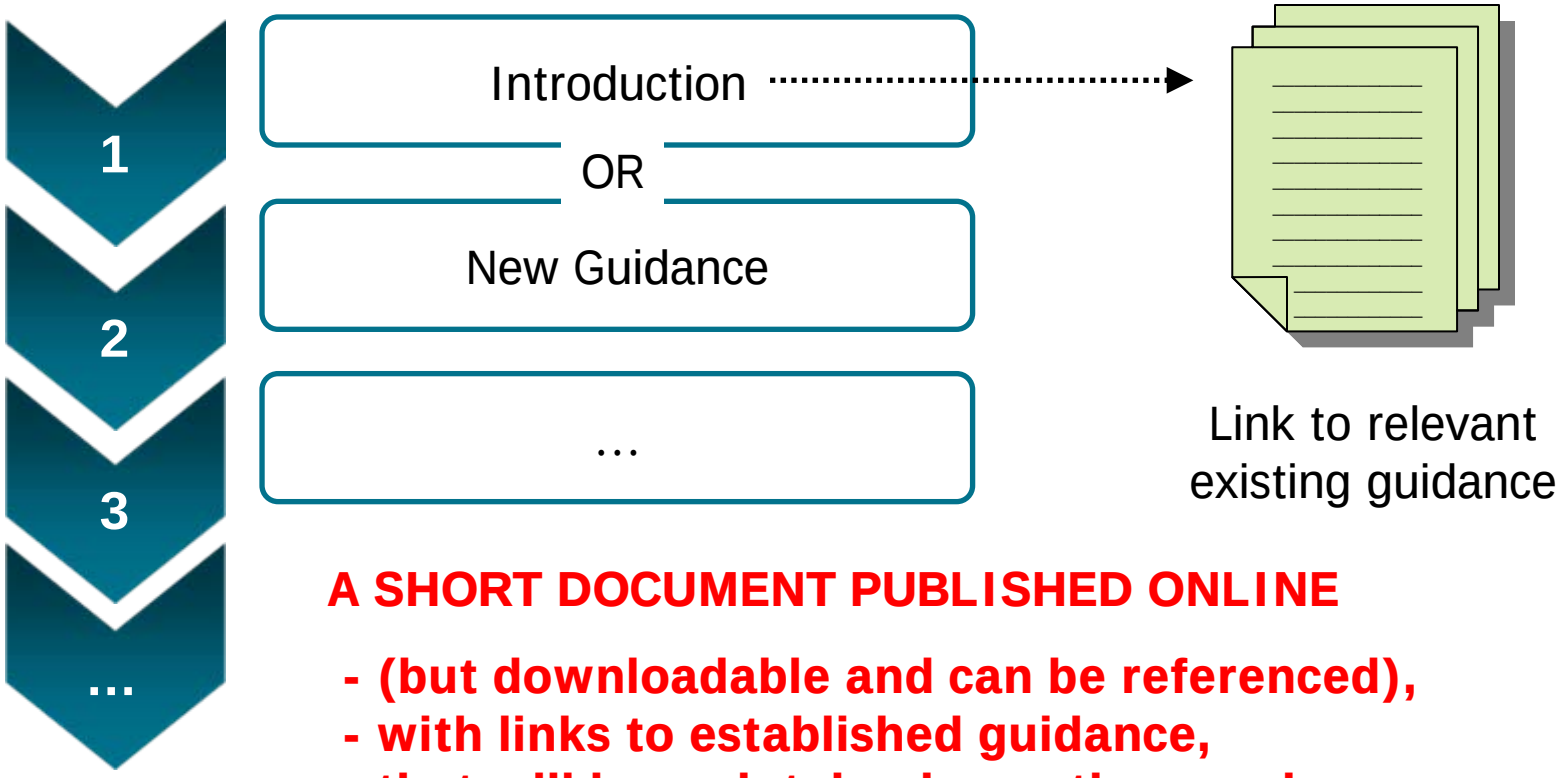
- Provide new guidance for areas where no or not sufficient guidance is available

- ***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