EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Guide on Methodological Research Standards

ENCePP Plenary 11th December 2009

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Acknowledgements

- Xavier Kurz, Stefanie Prilla
- Members of ENCePP Working Group “Research standards & guidance”

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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 2009

- Develop the Checklist of MRS – *public consultation*
- Further develop the Inventory of PE Guidelines (general application as well as more specific) & first steps to develop Guide on Methodological Research Standards

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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

Review of guidelines by individual members of the group

Next steps: Further structure and populate the Inventory

Inventory of existing PE Guidelines

	Organization & Guideline short title	Document/Link
1	**ISPE - Good PEpi Practices**	Good Pharmacoepidemiology Practices http://www.pharmacoepi.org/resources/guidelines_08027.cfm
2	**IEA - Good Epi Practice**	Good Epidemiology Practice http://www.dundee.ac.uk/iea/download/GEPNov07.pdf
3	**CIOMS - Ethical GL for PEpi Studies**	International Ethical Guidelines for Epidemiological Studies http://www.cioms.ch/080221feb_2008.pdf
4	**STROBE - Reporting of Observational Studies**	von Elm E. et al. - The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies. Ann Intern Med. 2007;147:573-577 Vandenbroucke J.P. et al. - Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration. Ann Intern Med. 2007;147:W-163–W-194.
5	**AHRQ - Patient Registries**	Registries for Evaluating Patient Outcomes: A User's Guide http://effectivehealthcare.ahrq.gov/repFiles/PatOutcomes.pdf
6	**ISPOR - Checklist for Retrospective DB studies**	Motheral B, Brooks J, Clark MA, Crown WH, Davey P. A Checklist for Retrospective Database Studies - Report of the ISPOR Task Force on Retrospective Databases. Value Health 2003; 6(2): 90-97 www.ispor.org/TaskForces/RetrospectiveDBPractices.asp
7	**DGEpi - Good Practices for Secondary Data Analysis**	*Gute Praxis Sekundaerdatenanalyse* (Good Practices for Secondary Data Analysis) of the German Society for Epidemiology (DGEpi) www.dgepi.de/pdf/infoboard/stellungnahme/gps-version2-final.pdf

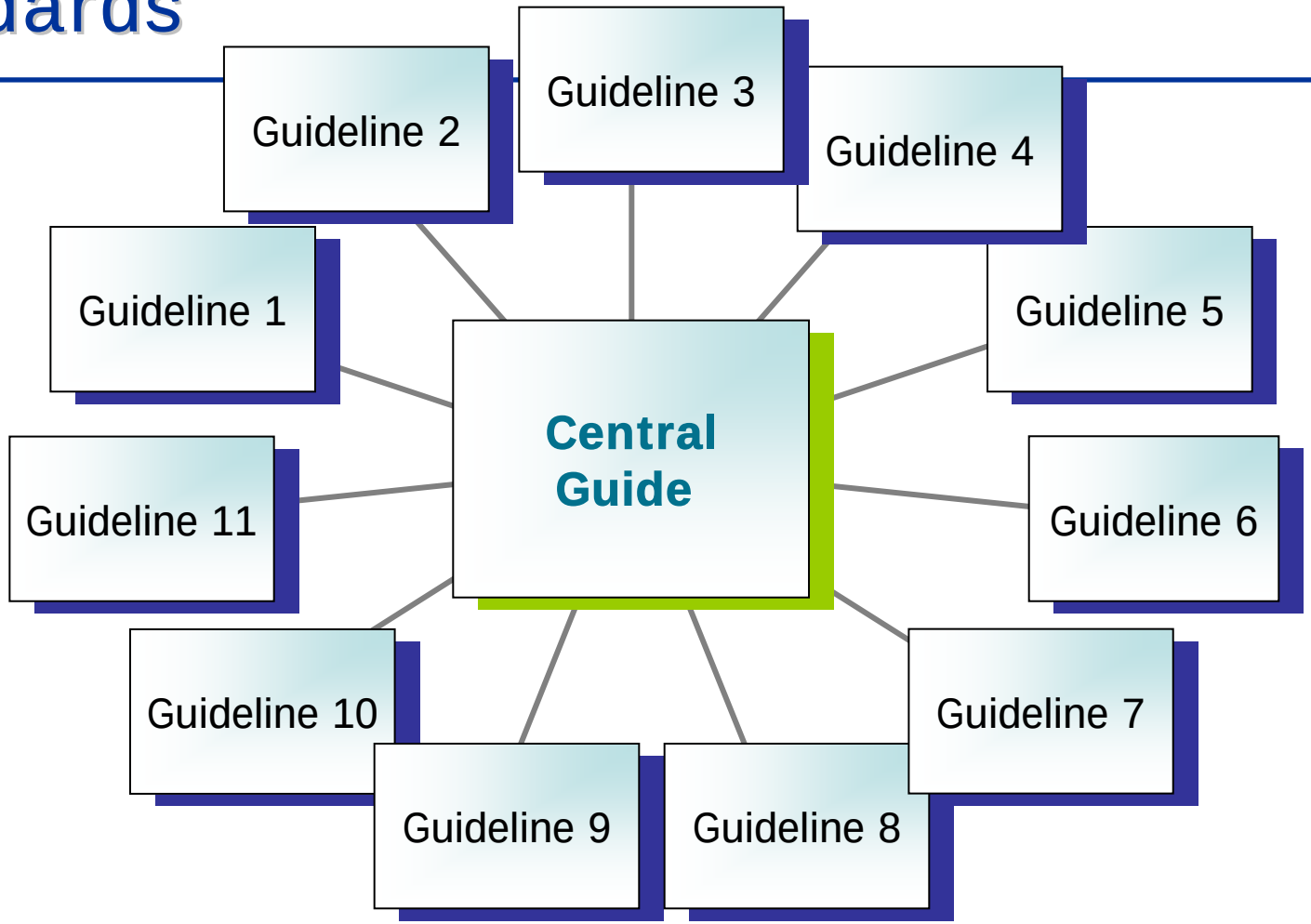
Inventory of existing PE Guidelines

	Organization & Guideline short title	Document/Link
8	**ISPE/ISoP - GL for Publication of AE Reports**	Kelly WN, Arellano FM, Barnes J, Bergman U, Edwards RI, Fernandez AM, et al. Guidelines for Submitting Adverse Event Reports for Publication. Pharmacoepidemiology and Drug Safety 2007(16):581-587. also published in Drug Safety 2007;30(5).
9	**EuroDURG - Drug Utilisation Research Quality Indicators**	Hoven JL, Haaijer-Ruskamp FM, Vander Stichele RH; DURQUIM Scientific Committee. Indicators of prescribing quality in drug utilization research: report of a European meeting (DURQUIM, 13-15 May 2004). Eur J Clin Pharmacol. 2005 Jan;60(11):831-4. http://www.eurodurg.com/durquim.htm: Recommendations of an European Expert Meeting on indicators of prescribing quality in drug utilization research (Recommendations on Methodology)
10	**MOOSE - Reporting of Epi Meta-analyses**	Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283(15):2008-12.
11	**FDA - Good PhV Practices**	Guidance for Industry - Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment
	EC/EMEA - GL on PV	Volume 9A of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-9/pdf/vol9a_09-2008.pdf
	FDA/EMEA - other specific GL	

Review of 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 Guidance and Guidelines for PE & PhV research

"Overarching" existing guidance; no need to reinvent the wheel

Note: keep in mind much guidance is found in standard reference epidemiology textbooks

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

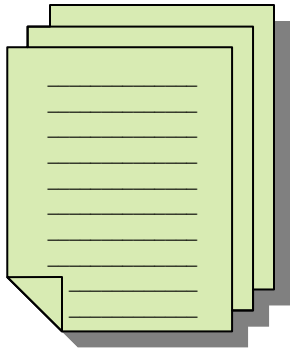
Structure of the Guide

Introduction

OR

New Guidance

…



Link to relevant existing guidance

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

Development of the Guidance

- 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

Meeting of WG on 10 December

- Identify different sections of the Guide (areas of operational/methodological research)
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Identify authors !

The Guide by Sections

- Chapter (Author_1/Author_2/…)
  - Sub-section

  Reference to guidance / gaps / other remarks

The Guide by Sections (I)

- Introduction (Perez/Leufkens/Prilla/Kurz)
  - Background, aim/scope
- Research question (Hallas)
  - Guidance: ENCePP checklist, GPS
  - Background to research: lit review (Moride)
    - Guidance on lit review (systematic, Cochrane, vs targeted, narrative…) pending to identify

The Guide by Sections (II)

- General aspects of study planning and conduct

(Perez/Leufkens/Prilla/Kurz)

  - Reference to ENCePP Code of Conduct (transparency & independence)
  - Reference to ENCePP Checklist of Operational Research Standards
  - Key references in non-guidance format
    - Dictionary of epidemiology / pharmacoepidemiology
    - Standard textbooks in epidemiology and pharmacoepidemiology
  - General guidance to conduct epidemiology ad pharmacoepidemiology research

The Guide by Sections (III)

- Governance (Parkinson/Klungel/UStbc)
  - Scientific standards, review and approval
  - Ethical conduct, review and approval
    - CIOMS (issue informed consent DB)
  - Patient & data protection
    - Keep in mind legislation: EU Directive, 1993 legislation, local rules and implementation of EU Directive]
  - ISPE, IEA, CIOMS, AHRQ, ...

The Guide by Sections (IV)

- Study protocol – ISPE, ENCePP checklist (Le Louet/Moore)
  - Keep in mind patient role: add patient targeted summary
  - [Concern: protocol driven by research question versus adapted to available data / resources (ethical & scientific implications)]
- Study Design & Methods (Klungel/Moore/Leufkens/)
  - Internal and external validity, relevance of design for research question… TEXTBOOKS
  - Challenges and lessons learned over time (history & present) – link to papers/chapters
    - Immortal time bias
    - Exposure/outcome definition and validation
    - Selective prescribing / channeling / confounding by indication
    - Unmeasured confounding
    - Use of technology, e.g. enrollment through websites, pros and cons
    - Special methods (emerging/not covered in textbooks): Propensity scores, Instrumental variables, Disease Risk Scores, Marginal Structural Models,…
    - Data mining / signal detection methodology & application
    - Limitations of observational research (also clinical trials)
    - Avoid interference by conducting de novo research related assessment (diagnostic, etc.)
    - …
  - Research networks - missing guidance (literature) (Sturkenboom)
    - Distributed network, shared protocol, sharing rich/lower level of data
  - Pooled analysis & Meta-analysis
    - Guidance pending to be identified . Cochrane…(Moride)

The Guide by Sections (V)

- Data Sources (Perez-Gutthann/Bergman/Vander Stichele)
  - Available (secondary) data use
    - GPS, ISPE, ISPOR
  - De novo data collection
    - Field (general): IEA
    - Registries: AHRQ
    - Large simple/pragmatic/streamlined trials – missing guidance
    - Chart abstraction – missing/pending to identify guidance
    - Questionnaires – survey epidemiology textbooks
    - Surveys: utilisation, patient & HCP surveys (risk management)
    - Scales & instrument development – PRO guidance to be identified
  - Hybrid
    - LST (randomized + DB follow-up) – missing guidance
  - Achieving size: Multi-center/database initiatives

The Guide by Sections (VI)

- Statistical Analysis Plan – missing guidance (Evans/tbc)
  - Interim analysis (& communication)
- Quality Control Plan / Quality Assurance (Jadrijevic-Mladar Takac / tbc)
  - AHRQ, more guidance welcome
- Safety reporting (AE) – volume 9a (Kurz)

The Guide by Sections (VII)

- Communication: results and study
  (Hallas/ Jadrijevic-Mladar Takac)
  - Reports to health authorities, sponsors (RMP, PSUR driven)
  - Presentations scientific fora
  - Publication:
    - Who: Authorship – ICMJE
    - What/How: STROBE, MOOSE
  - Patient focused
  - General: websites encouraged

The Guide by Sections (last)

- Other
- Gaps and priorities (All authors)
  - Multicenter studies operational aspects and list of challenges

Next steps

- Review of outline, guidance, and authors
  - By February 15, 2010
- Review by ENCePP (call for authors)
  - By March 15, 2010
- Final outline and authors document
  - By April 10, 2010
- First draft summary of sections
  - By May 15, 2010
- WG meeting in London