



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



Guide on Methodological Research Standards

ENCePP Plenary 11th December 2009





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. <i>Ann Intern Med.</i> 2007;147:573-577 Vandenbroucke J.P. et al. - Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration. <i>Ann Intern Med.</i> 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. <i>Value Health</i> 2003; 6(2): 90-97 www.ispor.org/TaskForces/RetrospectiveDBPractices.asp
7	DGEpi - Good Practices for Secondary Data Analysis	<i>Gute Praxis Sekundaerdatenanalyse</i> (Good Practices for Secondary Data Analysis) of the German Society for Epidemiology (DGEpi) www.dgepi.de/pdf/infboard/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. <i>Pharmacoepidemiology and Drug Safety</i> 2007(16):581-587. also published in <i>Drug Safety</i> 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). <i>Eur J Clin Pharmacol.</i> 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. <i>JAMA</i> 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	

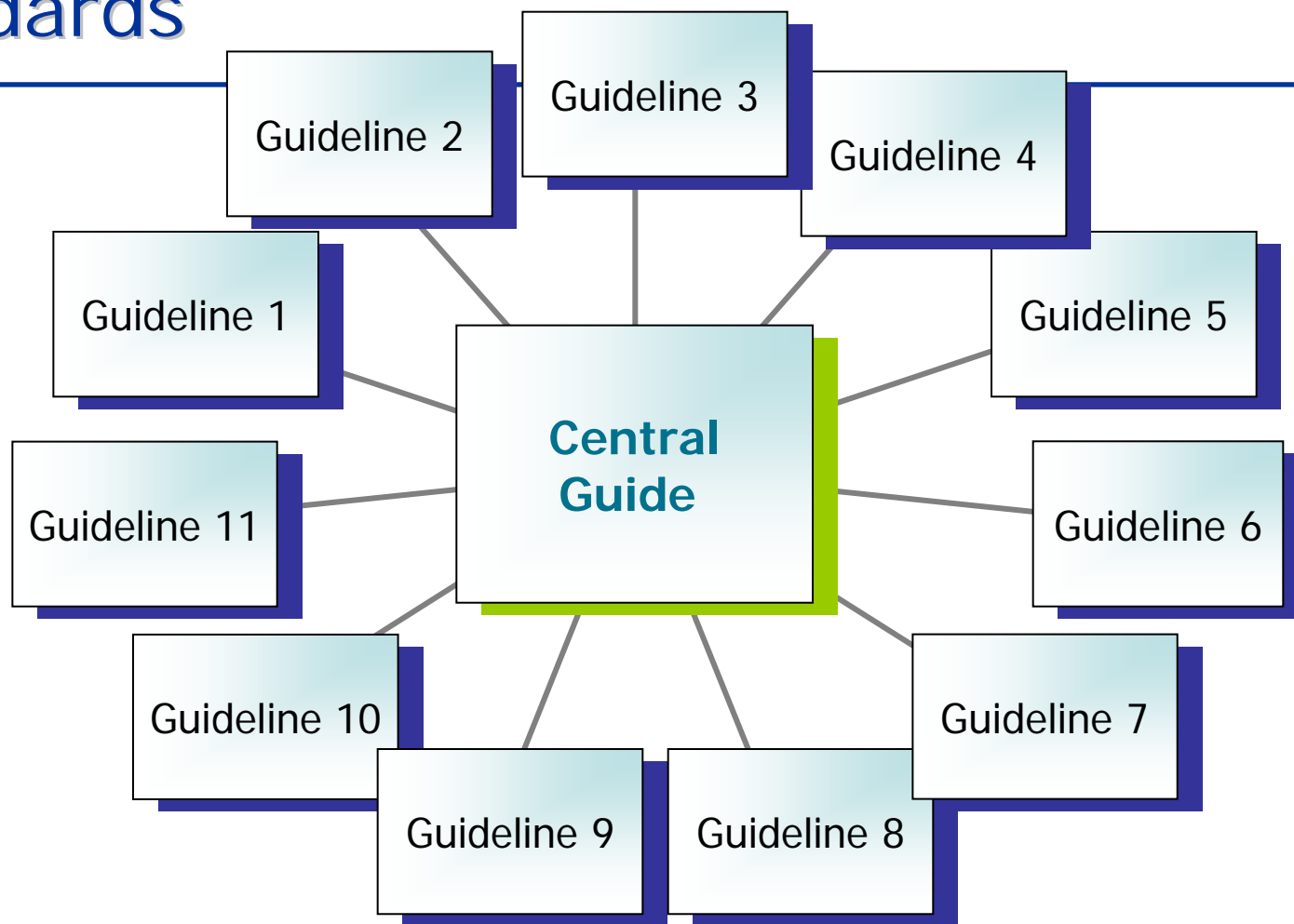


Review of Guidelines

- **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

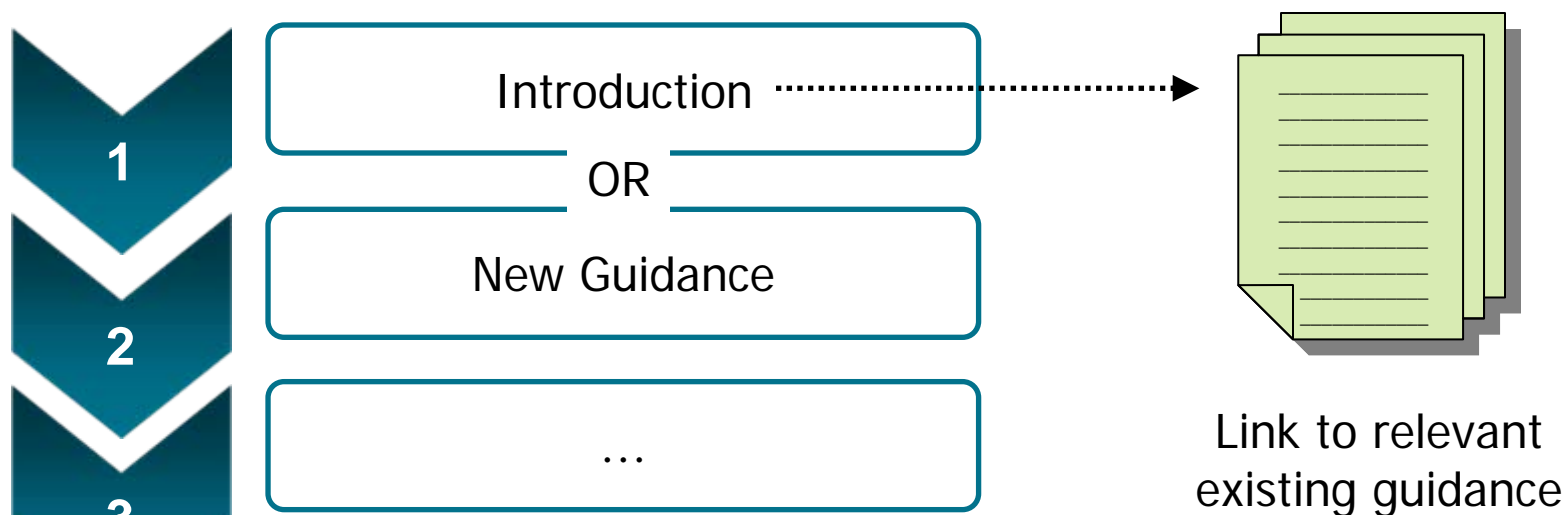
“Overarching” existing guidance; no need to reinvent the wheel

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



**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 and 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