European Network of Centres for Pharmacoepidemiology

ENCePP Guide on Methodological Standards in Pharmacoepidemiology → 12th Revision and publication strategy

ENCePP Plenary - 22 November 2024, Amsterdam

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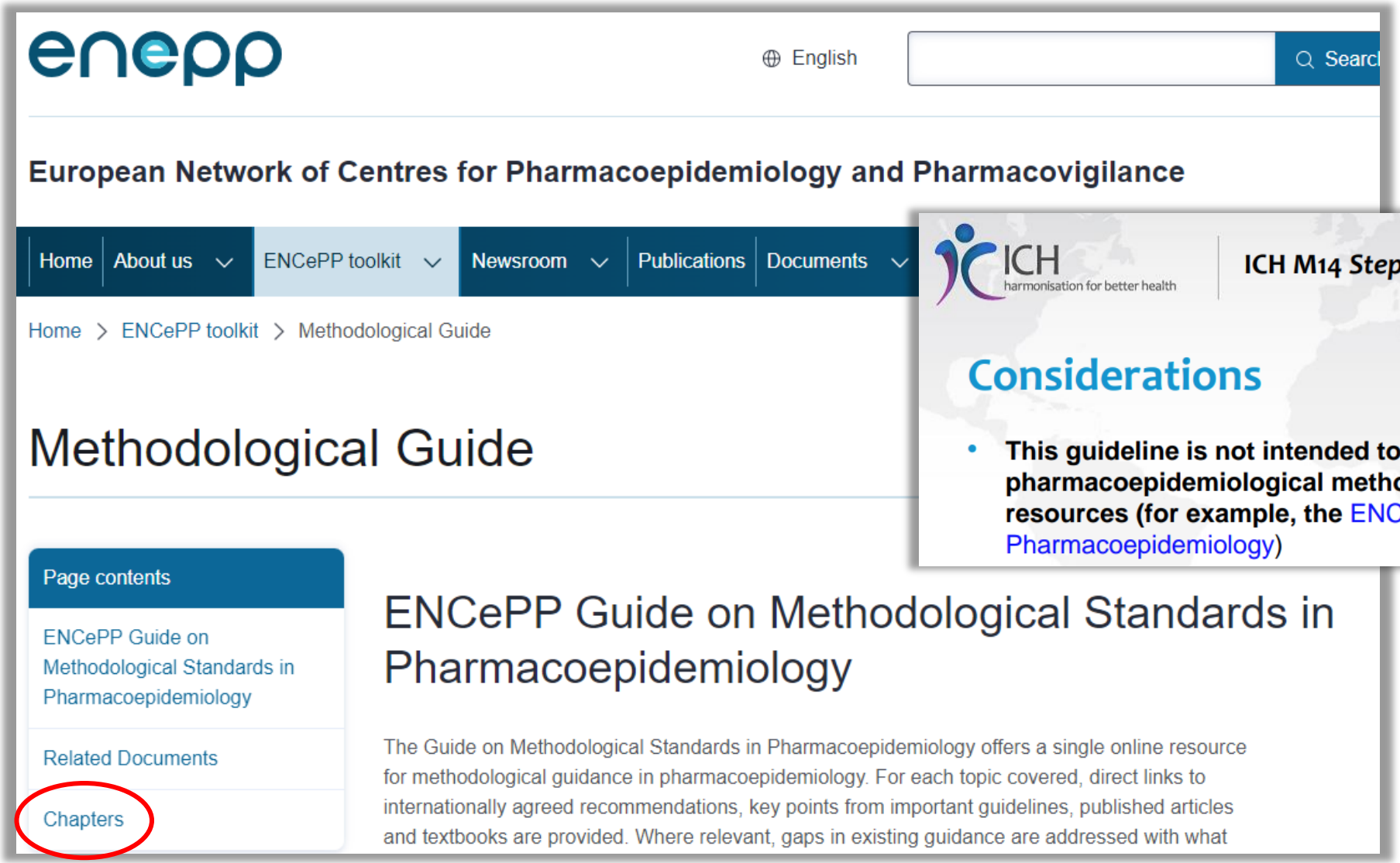
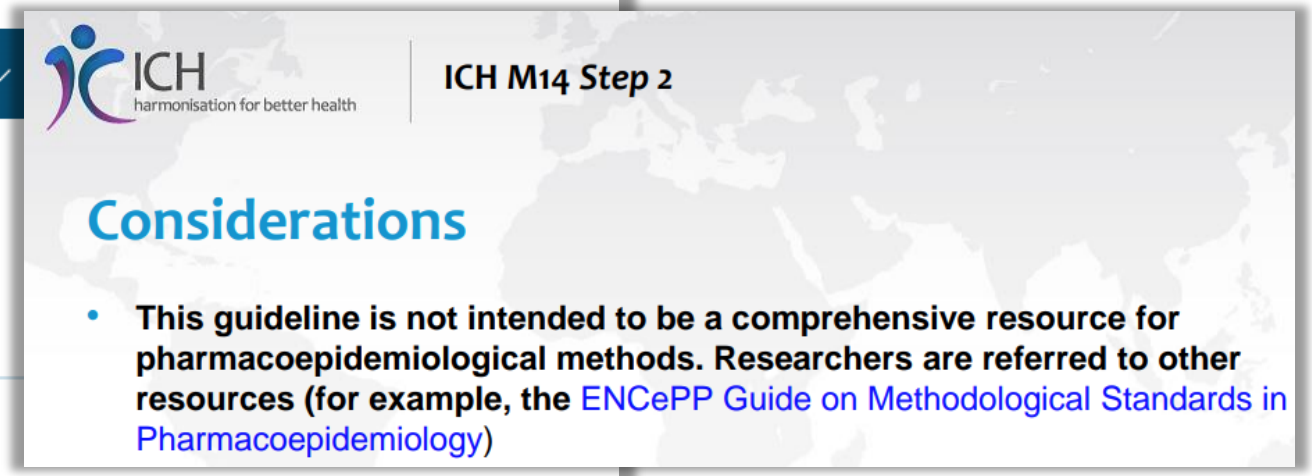
EMA
EUROPEAN MEDICINES AGENCY





enepp

From 15 Feb (launch of new website) to ICPE Aug 2024:

- >7,568 unique views
- 1,117 unique downloads

Context

- Last update of the Guide: 11th Revision, published July 2023
- Continued wide use and recognition by multiple stakeholders/regions (EU and beyond)

Today's objective

- Present and discuss **strategy** and **planning** for **12th Revision** (Pillar 1) and increased dissemination and visibility through **publication** in peer-reviewed journals (Pillar 2)
- To engage the ENCePP community (chapter selection for both pillars, contents/structure for Pillar 1, authorship)

Desired impact

- Strong focus on methodological standards/good practice to continue enhance **confidence** in **non-interventional** research
- Guide to continue being a **reference** for new/innovative methodologies

12th Revision

Revision process – WG1 perspective

- Guide open for public comments: call for interest to ENCePP members by e-mail (+ reminders)
- Review of (selected) chapters by authors/experts

12th Revision

- Minimise burden of editorial and administrative work while focusing on key updates on current topics of high methodological and regulatory interest

  - Step 1 - Identify chapters that need significant update and revision: WG (or SIG) discussion, Survey, Plenary discussion
  - Step 2 – Contents and editorial update of the selected chapters

Revision process – EMA editorial team perspective

- Organise **kick-off** with WG1 (discuss update of table of contents, authorship…)
- Contact previous **authors** for updates, identify and contact potential new authors
- Introductory **meetings**
- Several **reminders** to authors, and **liaison** between authors as needed
- Continuous **progress tracking** (responses, reviews done, editorial checks done, etc.)
- **Editorial work** on all chapters, including alignment meetings editor/authors, and editorial work of the Guide as a whole
- Creation of list of references for all chapters, creation of list of authors
- Share new/selected chapters for **review** by **WG1** (and key chapters for **SG**) and **implement** comments
- **Finalise** all chapters
- **Publication** on ENCePP website (>3 full days - new system)

A collaborative effort over >6 months

Survey among ENCePP Partners

- **Objective** - seek feedback from the ENCePP community and users of the Guide to inform selection of chapters
- **Structure** - (i) identification of chapters for update (ii) questions about user experience, authorship interest, responder background
- **Limitations**
  - Short survey period <2 weeks, not sufficient for snowballing
  - Response rate (N=23)

Output of the survey to support discussion at the end of this session!

What's next for Revision 12?

- Chapter selection: for discussion today
- Repeat survey?
- Timelines: kick-off meeting with focused WG or SIG in early Feb. 2025

Publication in Pharmacoepidemiology and Drug Safety

Publication in PDS

- Idea from the ENCePP Steering group
- Proposal discussed with PDS Editorial Board at ICPE 2024
- Positive towards publication of ENCePP Methods Guide:
  - Selected chapters published alongside the Core concepts
    - Validation of health outcomes
    - Key biases
    - Violation of positivity assumption in causal analysis
    - Drug utilization measures
    - Confounding my indication & active comparators
  - PDS special issue
- Publication process will comply with the conventional PDS peer-review policy
- Value in Health would be interested in co-publishing (liaison via Laura Pizzi - ISPOR)

Proposed content

1. Introduction: History and evolvement of ENCePP (Writing by SG+ potentially Xavier)
2. Good epi practice: Research question and assessing feasibility (ENCePP Guide chapter 2)
3. Good epi practice: Data quality (ENCePP Guide chapter 13.2, 13.4)
4. Good epi practice: Dissemination of results (ENCePP Guide chapter 14)
5. Good epi practice: Data protection and ethical aspects (ENCePP Guide chapter 15)
6. Methods: Conducting systematic reviews and meta-analyses (ENCePP Guide chapter 10)
7. Methods: Target trial emulation + estimand framework (ENCePP Guide chapter 4.2.6)
8. Methods: Evaluating medicines in pregnancy and breastfeeding (ENCePP Guide Annex 2)
9. Methods: Pharmacovigilance impact research (including broader implementation research) (ENCePP Guide chapter 16.4)
1. Methods: AI in pharmacoepi (ENCePP Guide chapter 16.5)

Proposed process and timelines

- Share content proposal with PDS and inform them of Value in Health in co-publishing interests
- Discuss co-publishing with PDS and Value in Health following content review
- Contact authors of the specific chapters to verify involvement

Timelines

- November 2024 — Presentation at plenary and sharing with PDS
- December 2025 — Following reaction from PDS, reach out to the ENCePP authors
- December/ January — Meeting with PDS and Value in Health (depending on holidays + PDS review)

Open discussion

Responders asked to tick chapters they feel deserve update

- Chapter 16.5 - Artificial intelligence in pharmacoepidemiology (7)
- Chapter 3 - Development of the study protocol (6)
- Chapter 2 - Formulating the research question and objectives and assessing feasibility (5)
- Chapter 13 - Quality management (5)
- Chapter 16.6 - Real-world evidence and pharmacoepidemiology (5)
- Chapter 16.2 - Vaccine safety and effectiveness (5)
- Chapter 4 - Study design (5)
- Chapter 8 - Approaches to data collection (4)
- Chapter 16.4 - Methods for pharmacovigilance impact (4)
- Chapter 12 - Statistical analyses (4)
- Chapter 9 - Research networks for multi-database studies (4)
- Chapter 6 - Methods to address bias and confounding (3)
- Annex 2 - Guidance on methods for the evaluation of medicines in pregnancy and breastfeeding (3)
- Chapter 16.3 - Design, implementation and analysis of pharmacogenomic studies (3)
- Annex I - Guidance on conducting systematic reviews and meta-analyses (3)
- Chapter 5 - Definition and validation of drug exposure, outcomes and covariates (2)
- Chapter 14 - Dissemination and communication of study results (2)
- Chapter 15 - Data protection and ethical aspects (2)
- Chapter 16.1 - Comparative effectiveness research (2)
- Chapter 10 - Systematic reviews and meta-analysis (2)
- Chapter 11 - Signal detection methodology and application
- Chapter 12 - Statistical analyses
- Chapter 7 - Effect modification and interaction

Which specific aspects of the Chapter?

Chapter 2 – Research question and feasibility

- New guidance/reflection papers
- Distinction primary data collection / secondary use of data for feasibility assessment
- Use metadate catalogues/selection of data sources
- Refer to estimand framework already at stage of formulation of the research question for link to causal inference / TTE

Chapter 3 – Study protocol

- Align with GVP VIII
- Study design chapter to precede development of study protocol
- Multi-country/database studies: expected format of master vs local protocol
- Novel methodology to design validation study to estimate sensitivity of outcomes

Chapter 4 - Study design

- Overview, PCTs and large simple trials; positive/negative controls; use of active comparator
- New designs for studies with small sample size (paediatric/rare disease)
- Study size approach/recommendations
- Align with EMA RWE RP on descriptive vs causal inference studies, increase hierarchy of causal inference framework with focus on TTE

Which specific aspects of the Chapter?

Chapter 6 – Bias/confounding

- References for studies comparing different approaches to confounding by indication and impact on effect estimates
- Novel methodology to adjust bias from misclassification, and test for differential misclassification

Chapter 8 – Approaches to data collection

- Primary data collection, secondary use of data, patient registries (re. workshop)/too much about registries
- Use of digital health and PROs (re. revised GVP XVI)
- HMA/EMA Catalogues to be referenced.
- EHDS as data source / linkage in EHDS
- More on population-based databases (Nordic, Taiwan, others)

Chapter 9 - Systematic reviews and meta-analysis

- Dealing with aggregated data in meta-analyses, with zero events, masked numbers etc.

Chapter 12 - Statistical analyses

- Thresholds for elevated risk in comparative studies (95% CI/null value vs precision)
- Estimand framework upfront as informs design and analytical plan

Which specific aspects of the Chapter?

Chapter 13 – Quality management

- Practical recommendations for establishing fit for purpose QMS for secondary data use studies

Chapter 16.1 – CER

- 16.1.2.2. CER using observational data: more details on how to use estimand framework to design TT

Chapter 16.2 - Vaccines

- All topics should be updated
- May need separate Annex as becoming very large (following COVID...)

Chapter 16.5 – AI in pharmacoepidemiology

- Newer examples of actual use and clearer statements on scope for where AI can be used
- Synthetic data should be discussed
- New guidance and most important developments in this fast-evolving area

Chapter 16.6 – RWE and pharmacoepidemiology

- Update with new guidance

Annex 1 – Guidance on systematic reviews and meta-analyses

- Same comment as in corresponding chapter

Annex 2 – Guidance on evaluation of medicines in pregnancy and breastfeeding

- Further consideration on enhanced monitoring approach (PRIM)

Structure (links)

- I like this structure (N=14)
- I somewhat like this structure (N=8)

General comments

- Review conciseness, completeness, include recent references
- Some suggestions of additional literature references
- More discussion, further synthesize to provide more direct guidance
- Update to include future EHDS reality
- Unclear how selection of articles is done - ENCePP WG? Editorial team?
- Addition of templates, examples, working instructions
- Make more homogeneous to HARPER Protocol Template
- Align with EMA draft RWE guidance
- Willingness of ENCePP Partners to **contribute as author** - Yes (11), No (4)

Who are the responders?

Organisation

- Academia (3)
- CRO (6)
- CRO + Research network
- Regulatory / HTA / Public Health (4)
- Academia + Regulatory/HTA/PH (2)
- Other (4)
  - Pharmaceutical company
  - Public institution (non-academic)
  - Non-profit research organisation

Country

- UK
- Italy
- Greece
- Netherlands
- Lithuania
- Nordic
- Ethiopia
- Spain
- Global

Background

- Epidemiologist/pharmacoepi (10)
- Epidemiologist/pharmacoepi + healthcare professional (3)
- Statistician/biostatistician (3)
- Healthcare professional (1)
- Data scientist (1)
- Teaching position (1)