



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH



European Network of Centres for  
Pharmacoepidemiology and  
Pharmacovigilance

EMA/95098/2010 Rev.10

# The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology

Revision 10

## ENCePP Guide, Revision 10 - Authorship

### **Editor**

Catherine Cohet for the ENCePP Working Group *Research Standards and Guidance*

### **Coordination and publication**

Julianna Fogd

### **Main authors**

**Foreword:** Catherine Cohet, Susana Perez-Gutthann for the *ENCePP Steering Group*

**1. Introduction:** Xavier Kurz

**2. Formulating the research question and objectives and assessing study feasibility:** Yola Moride, Massoud Toussi, Catherine Cohet

**3. Development of the study protocol:** Catherine Cohet

### **4. Study design**

**4.1. Overview:** Alejandro Arana, Xavier Kurz

**4.2. Types of study designs:** Xavier Kurz, Jesper Hallas

**4.3. Definition and validation of drug exposure, outcomes and covariates:** Gillian Hall, Jesper Hallas, Tania Schink

#### **4.4. Specific aspects of study design**

**4.4.1. Pragmatic trials and large simple trials:** Juan J. Abellan, Catherine Cohet

**4.4.2. Target trial emulation:** Tania Schink, Gillian Hall, Finbarr Leacy, Jesper Hallas, Xavier Kurz

---

**Official address** Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

**Address for visits and deliveries** Refer to [www.ema.europa.eu/how-to-find-us](http://www.ema.europa.eu/how-to-find-us)

**Send us a question** Go to [www.ema.europa.eu/contact](http://www.ema.europa.eu/contact) **Telephone** +31 (0)88 781 6000

An agency of the European Union



**4.4.3. Self-controlled case series and self-controlled risk interval designs:**

Heather Withaker, Catherine Cohet

**4.4.4. Positive and negative control exposures and outcomes:**

Gillian Hall, Tania Schink, Xintong Li

**4.4.5. Use of an active comparator:**

Gillian Hall, Tania Schink, Xintong Li

**4.4.6. Interrupted time series analyses and Difference-in-Differences method:**

Gillian Hall, Albert Prats Uribe, Kim Lopez Guell

**4.4.7. Case-population studies:**

Ursula Kirchmayer

**5. Methods to address bias and confounding**

**5.1. Bias:** Alexandra Pacurariu, Ursula Kirchmayer, Alejandro Arana, Tania Schink

**5.2. Confounding:** Alejandro Arana, Alexandra Pacurariu, Vera Ehrenstein

**5.3. Missing data:** Chantal Quinten, Martin Russek

**5.4. Triangulation:** Gillian Hall, Tania Schink, Junging Xie

**6. Effect measure modification and interaction:** Chantal Quinten, Xavier Kurz

**7. Approaches to data collection**

**7.1. Primary data collection**

**7.1.1. General considerations:** Susana Perez-Gutthann

**7.1.2. Surveys:** Massoud Toussi, Xavier Fournie, Nawab Qizilbash

**7.1.3. Randomised controlled trials:** Susana Perez-Gutthann

**7.2. Secondary use of data:** Susana Perez-Gutthann, Gianluca Trifirò

**7.3. Patient registries:** Carla Jonker, Xavier Kurz, Liesbet Peeters

**7.4. Spontaneous reports:** Eugene van Puijenbroek, Niklas Norèn, Luis Pinheiro, Cosimo Zaccaria, Gianmario Candore

**7.5. Social media:** Massoud Toussi, Priya Bahri, Niklas Norèn

**8. Research networks for multi-database studies:** Alexandra Pacurariu, Deborah Layton, Karin Hedenmalm, Liesbet Peeters, Helga Gardarsdottir, Gianmario Candore

**9. Systematic reviews and meta-analysis:** Daniel Morales

**10. Signal detection methodology and application:** Niklas Norèn, Eugene van Puijenbroek, Luis Pinheiro, Cosimo Zaccaria, Gianmario Candore

**11. Statistical analysis plan:** Chantal Quinten

**12. Quality management:** Xavier Kurz, Juan J. Abellan

**13. Dissemination and communication of study results:** Susana Perez-Gutthann, Gillian Hall

**14. Data protection and ethical aspects**

**14.1. Personal data protection in the European Union:** Sabine Brosch, Orsolya Eotvos

**14.2. Scientific integrity and ethical conduct:** Xavier Kurz

## 15. Specific topics

**15.1. Comparative effectiveness research:** Thomas Debray, Xavier Kurz

**15.2. Vaccine safety and effectiveness:** Catherine Cohet, Luca Giraldi

**15.3. Design, implementation and analysis of pharmacogenetic studies:** Maria Gordillo-Marañón, Sonali Sanghvi, Aroon Hingorani, Reecha Sofat, Junging Xie

**15.4. Methods for pharmacovigilance impact research:** Thomas Goedecke, Helga Gardarsdottir, Alexandra Pacurariu, Daniel Morales for the *ENCePP Special Interest Group on Measuring the Impact of Pharmacovigilance Activities*

**15.5. Artificial intelligence in pharmacoepidemiology:** Luis Pinheiro

**15.6. Real-world evidence and pharmacoepidemiology:** Xavier Kurz, Robert Flynn, Massoud Toussi, Alejandro Arana, Chantal Quinten

**Annex 1 - Guidance on conducting systematic reviews and meta-analyses of completed comparative pharmacoepidemiological studies of safety outcomes:** Nawab Qizilbash, Daniel Morales

**Annex 2 - Guidance on methods for the evaluation of medicines in pregnancy and breastfeeding:** Vera Ehrenstein, Andrea Margulis, Tania Schink, Corinne De Vries, Irene Petersen, Nicolas Thurin, Hedvig Marie Egeland Nordeng

## **Acknowledgements**

From the 1<sup>st</sup> to the 10<sup>th</sup> revisions, peer review of one or several chapters was received from:

Alfonso Carvajal	Mark de Groot
Amalia Issa	Martin Daumer
Ana Marta Anes	Michael Theodorakis
Ann Daly	Mirko Di Martino
Annalisa Rubino	Munir Pirmohamed
Annie Fourrier-Réglat	Nada Božina
Brian Strom	Nancy Dreyer
Camilla Stephens	Olaf Klungel
Consuelo Pedros	Paddy Farrington
Daniel Prieto-Alhambra	Patrick Zuber
David Martin	Peter Arlett
Dimitri Bennett	Phillip Bryan
Elisabetta Poluzzi	Robert Vander Stichele
Federica Pisa	Rolf Groenwold
Frank DeStefano	Samy Suissa
Geoff Liu	Sarah McFarlane
Gillian Bartlet	Sebastian Botzenhardt
Gonzalo Calvo	Sebastian Schneeweiss
Gunilla Sjolin-Forsberg	Stefanie Prilla
Hervé Le Louet	Stephen Evans
Hubert Leufkens	Teresa Herdeiro
Ivana Silva	Ulf Bergman
Jan Bonhoeffer	Victoria Newbould
Jim Slattery	Viktor Kiri
John Parkinson	Wei Zhou
Kevin Blake	Yizhou Ye
Kenneth J. Rothman	Yvonne Lis
Lina Titievski	
Marina Davoli	