EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Report from the ENCePP Steering Group, 2017-2020

ENCePP Plenary Meeting, 20 November 2020

Presented by Tom MacDonald
Deputy Chair, ENCePP Steering Group

Key points

- Steering Group in the last four years
- EU PAS Register
- ENCePP documents and publications
- Last words

Composition of the ENCePP Steering Group 2017-2020

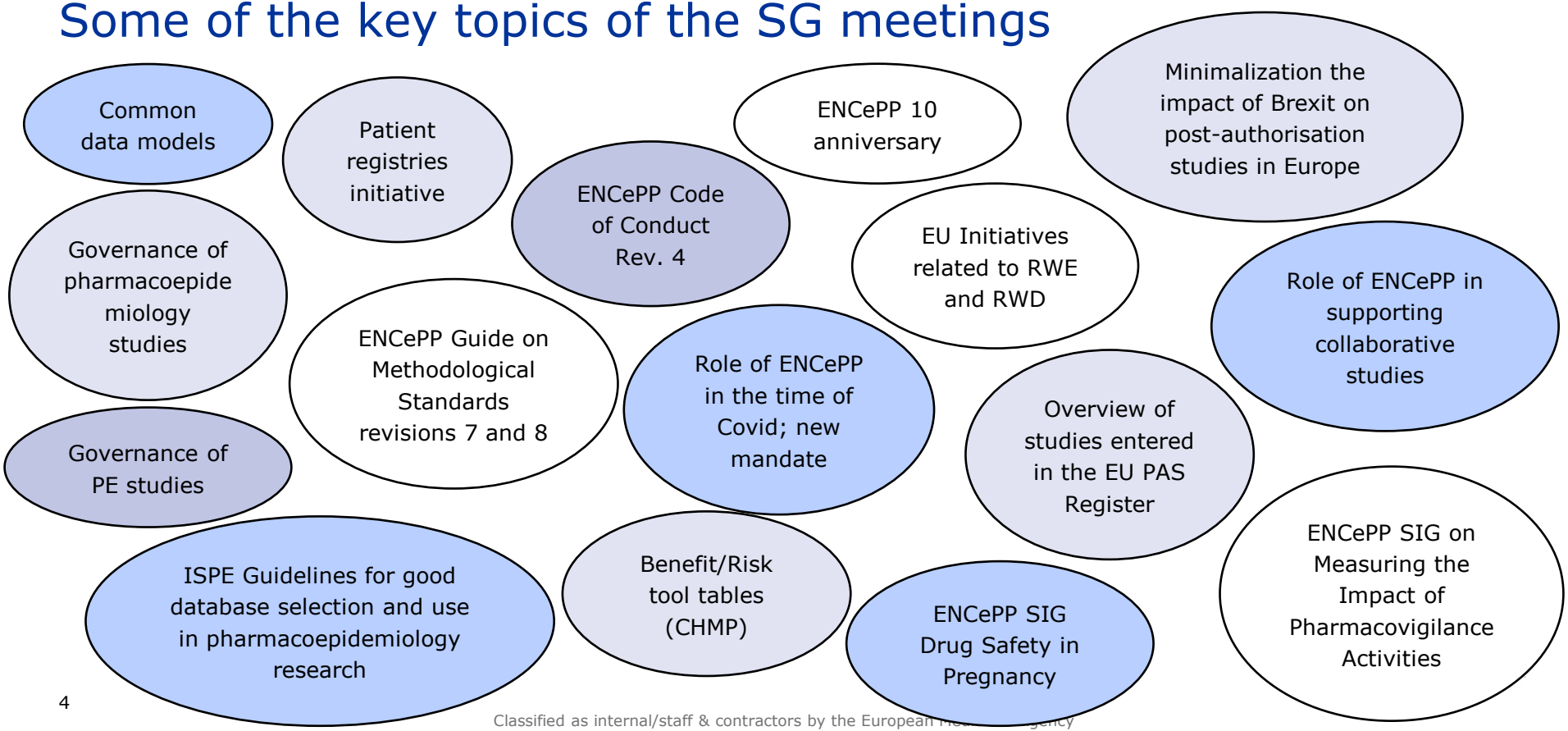
- One year extension of membership due to Brexit preparedness Business Continuity Plan
- 6 ENCePP members
- 9 appointed representatives
- 1 observer

No.	Representing	Name	Affiliation
1	ENCePP	**Vera Ehrenstein**	Department of Clinical Epidemiology, Aarhus University, Denmark
2	ENCePP	**Rosa Gini**	Agenzia regionale di sanità della Toscana, Florence, Italy
3	ENCePP	**Teresa Herdeiro**	iBiMED, University of Aveiro, Portugal
4	ENCePP	**Olaf Klungel**	Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Netherlands
5	ENCePP	**Tom MacDonald** (Deputy Chair)	Medicines Monitoring Unit (MEMO) and Hypertension Research Centre (HRC), University of Dundee, UK
6	ENCePP	**Gianluca Trifirò**	University of Messina, Italy
7	EMA	**Xavier Kurz** (Chair)	European Medicines Agency
8	EMA	**Corinne de Vries**	European Medicines Agency
9	EMA	**Hans-Georg Eichler**	European Medicines Agency
10	HMA	***vacant***	
11	CHMP	**Johann Lodewijk Hillege**	College ter Beoordeling van Geneesmiddelen, Netherlands
12	COMP	**Frauke Naumann-Winter**	Bundesinstitut für Arzneimittel und Medizinprodukte, Germany
13	PRAC	**Daniel Morales**	University of Dundee, UK
14	PCWP	**Kathi Apostolidis**	ECPC - European Cancer Patient Coalition
15	ISPE	**Yola Moride**	Faculty of Pharmacy, Université de Montréal, Canada
16	ISoP	**Herve Le Louet**	Centre de Pharmacovigilance & Information sur le médicament, Hôpital Henri Mondor, Paris, France
Observer	EFPIA	**Patrice Verpillat**	Merck Group, Germany
Statistical Advisor	EMA	**Jim Slattery**	European Medicines Agency
Observer	EMA	**Gianmario Candore**	European Medicines Agency

SG meetings in the last four years

- **14** meetings organised by the ENCePP Secretariat - Reduced activities due to Brexit Business Continuity Plan (BCP), followed by the Covid Business Continuity Plan
- Between November 2018 and April 2020 – **8** general informal SG meetings organised by Rosa Gini (Agenzia regionale di sanità della Toscana), and **3** meetings to discuss the preparation of the general 2019 web meeting

Some of the key topics of the SG meetings

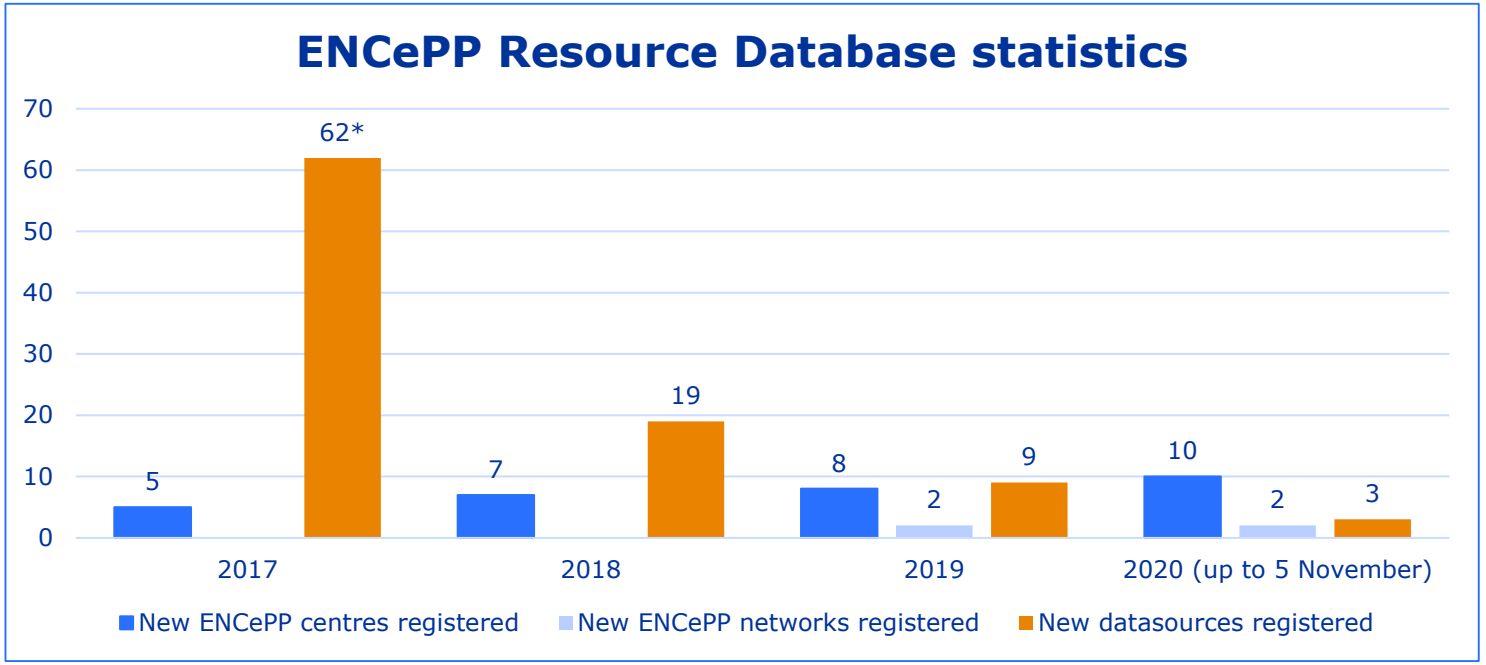


EU PAS Register – Statistics

	2017	2018	2019	2020 (until 5 Nov)	TOTAL 2011-2020
All new studies (ENCePP partner + others)	**251**	**199**	**251**	**264**	**2155**
ENCePP Partner studies*	53	32	52	58	566
Seal studies**	4	8	6	3	63
Covid-related studies	-	-	-	63	63

*Also included in "All new studies"
**Also included in "All new studies" and "ENCePP Partner studies"

ENCePP Resource Database



* Disease registries were introduced by EMA in the database in 2017

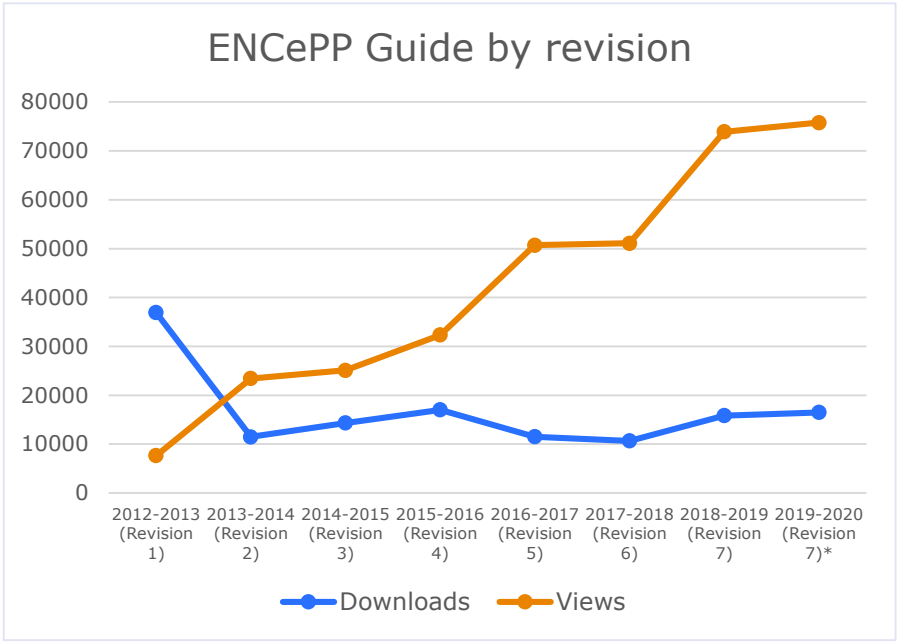
EU PAS Register – Upgrade in January 2020

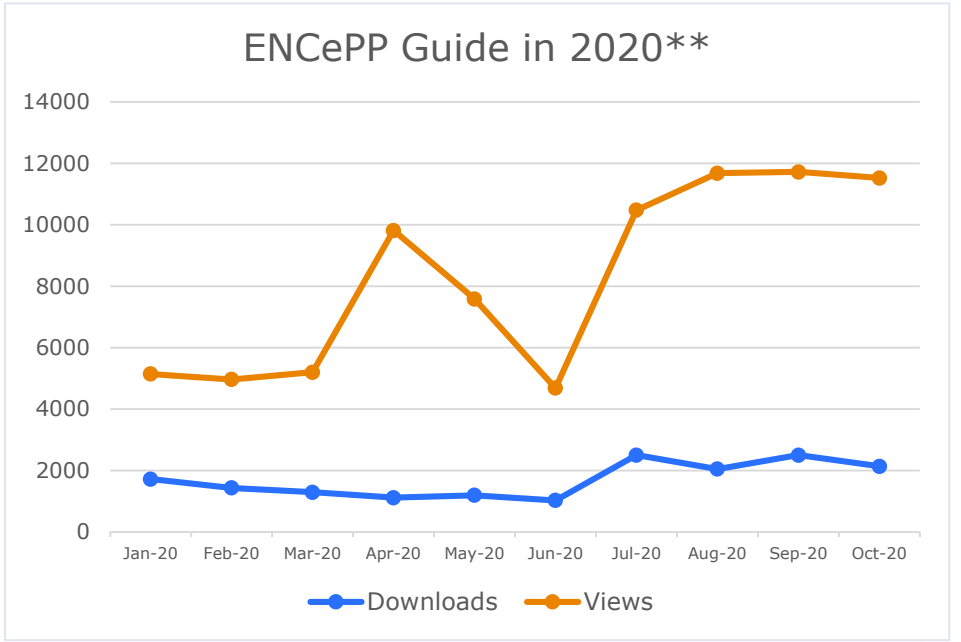
Functionality	Comment
Date of first registration	The date of first registration of a study in the EU PAS Register® is displayed on screen and printout
Delayed protocol publication	After protocol upload users may choose to make the protocol public only at the study end date, or immediately
Search by country	Allows searching for studies conducted in a specific country
Search by (primary) lead investigator	Allows searching for studies conducted by a specific (primary) lead investigator
Regulatory procedure number	New data field to facilitate compliance with regulatory requirements for RMP category 1 and 2 post-authorisation safety studies (PASS) and facilitate regulatory oversight
Medical conditions studied	New free text data field to provide medical conditions in addition to the maximum of ten conditions available from a drop-down list
EU PAS Register® study number in search results	The unique EU PAS Register® number instead of the (primary) lead investigator name is displayed for search results on screen

ENCePP documents published

- Code of Conduct Rev. 4 in March 2018
- ENCePP Checklist for Study Protocols Rev. 4 in October 2018
- ENCePP Guide on Methodological Standards in Pharmacoepidemiology revisions in July 2017 (Rev 6.), July 2018 (Rev. 7) and July 2020 (Rev. 8)
  - Rev. 8 - foreword highlights the importance of the Guide for pharmacoepidemiological studies carried-out in the context of the COVID-19 pandemic in order to provide valid results useful for clinicians and regulators

ENCePP Guide on Methodological Standards in Pharmacoepidemiology – website statistics





*No revision of the Guide took place in July 2019

9** Revision 8 was published in July 2020

Publications

Xavier Kurz, Susana Perez-Gutthann, ENCePP Steering Group. Strengthening standards, transparency, and collaboration to support medicine evaluation: Ten years of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Pharmacoepidemiol Drug Saf. 2018;27(3):245-252.

Pharmacoepidemiol Drug Saf. 2018 Mar; 27(3): 245–252.
Published online 2018 Jan 11. doi: 10.1002/pds.4381
PMCID: PMC5873428
PMID: 29327451

Strengthening standards, transparency, and collaboration to support medicine evaluation: Ten years of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)

Xavier Kurz,[1] Susana Perez-Gutthann,[2] and the ENCePP Steering Group [†]

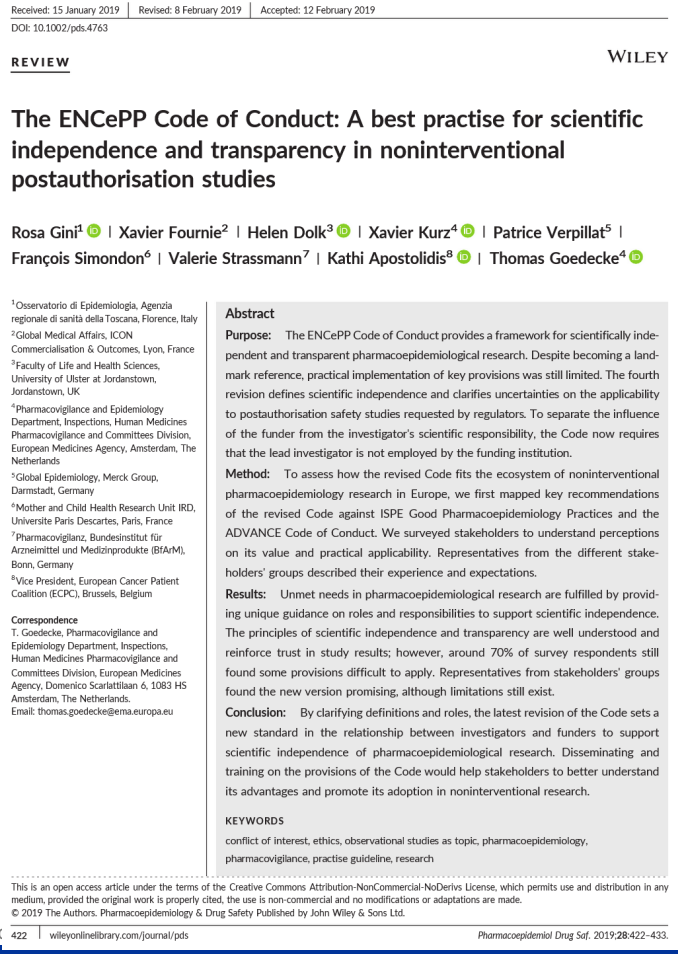
1. BACKGROUND

Go to:

The European Medicines Agency (EMA) has the responsibility for the scientific evaluation, supervision, and safety monitoring of medicines in the European Union (EU) to ensure that their benefits outweigh thei risks. While the roots of medicines' safety monitoring lie in the development of mechanisms for spontaneous reporting of suspected adverse reactions by health-care professionals and patients, the importance of using the full spectrum of evidence including observational studies has long been acknowledged.[1, 2, 3] The risk management system introduced in the EU in 2006 highlighted the need to build capacity and to facilitate the conduct of multicenter independent postauthorization studies to investigate important risks or missing information in European populations.[4] In March 2006, the EMA contacted more than 90 academic centers in Europe identified through the International Society for Pharmacoepidemiology (ISPE) and national drug regulatory authorities to request information on their expertise and activities in pharmacoepidemiology and pharmacovigilance. Over the following 12 months, possible models for collaboration on independent observational studies were discussed with representative of academic and other research centers, pharmaceutical industry, other existing clinical networks, EMA scientific committees, and the European Commission.[5] The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP; www.encepp.eu) was launched on June 28, 2007 with 79 participants who agreed to develop an active research network based on principles of transparency, scientific independence, and common quality standards. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance was presented in a symposium at the 24th Internationa Conference on Pharmacoepidemiology and Therapeutic Risk Management in August 2008.[6] Ten years on, we review ENCePP's main achievements, discuss its impact on the benefit-risk evaluation of medicinal products in Europe, and outline future perspectives.

Publications

Gini R, Fournie X, Dolk H, Kurz X, Verpillat P, Simondon F, Strassmann V, Apostolidis K, Goedecke T. The ENCePP Code of Conduct: A best practise for scientific independence and transparency in noninterventional postauthorisation studies. Pharmacoepidemiol Drug Saf. 2019;28(4):422-433



Received: 15 January 2019 | Revised: 8 February 2019 | Accepted: 12 February 2019
DOI: 10.1002/pds.4763

REVIEW

WILEY

The ENCePP Code of Conduct: A best practise for scientific independence and transparency in noninterventional postauthorisation studies

Rosa Gini[1] | Xavier Fournie[2] | Helen Dolk[3] | Xavier Kurz[4] | Patrice Verpillat[5] | François Simondon[6] | Valerie Strassmann[7] | Kathi Apostolidis[8] | Thomas Goedecke[4]

[1]Osservatorio di Epidemiologia, Agenzia regionale di sanità della Toscana, Florence, Italy
[2]Global Medical Affairs, ICON Commercialisation & Outcomes, Lyon, France
[3]Faculty of Life and Health Sciences, University of Ulster at Jordanstown, Jordanstown, UK
[4]Pharmacovigilance and Epidemiology Department, Inspections, Human Medicines Pharmacovigilance and Committees Division, European Medicines Agency, Amsterdam, The Netherlands
[5]Global Epidemiology, Merck Group, Darmstadt, Germany
[6]Mother and Child Health Research Unit IRD, Universite Paris Descartes, Paris, France
[7]Pharmacovigilanz, Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), Bonn, Germany
[8]Vice President, European Cancer Patient Coalition (ECPC), Brussels, Belgium

Correspondence
T. Goedecke, Pharmacovigilance and Epidemiology Department, Inspections, Human Medicines Pharmacovigilance and Committees Division, European Medicines Agency, Domenico Scarlattilaan 6, 1083 HS Amsterdam, The Netherlands.
Email: thomas.goedecke@ema.europa.eu

Abstract

Purpose: The ENCePP Code of Conduct provides a framework for scientifically independent and transparent pharmacoepidemiological research. Despite becoming a landmark reference, practical implementation of key provisions was still limited. The fourth revision defines scientific independence and clarifies uncertainties on the applicability to postauthorisation safety studies requested by regulators. To separate the influence of the funder from the investigator's scientific responsibility, the Code now requires that the lead investigator is not employed by the funding institution.

Method: To assess how the revised Code fits the ecosystem of noninterventional pharmacoepidemiology research in Europe, we first mapped key recommendations of the revised Code against ISPE Good Pharmacoepidemiology Practices and the ADVANCE Code of Conduct. We surveyed stakeholders to understand perceptions on its value and practical applicability. Representatives from the different stakeholders' groups described their experience and expectations.

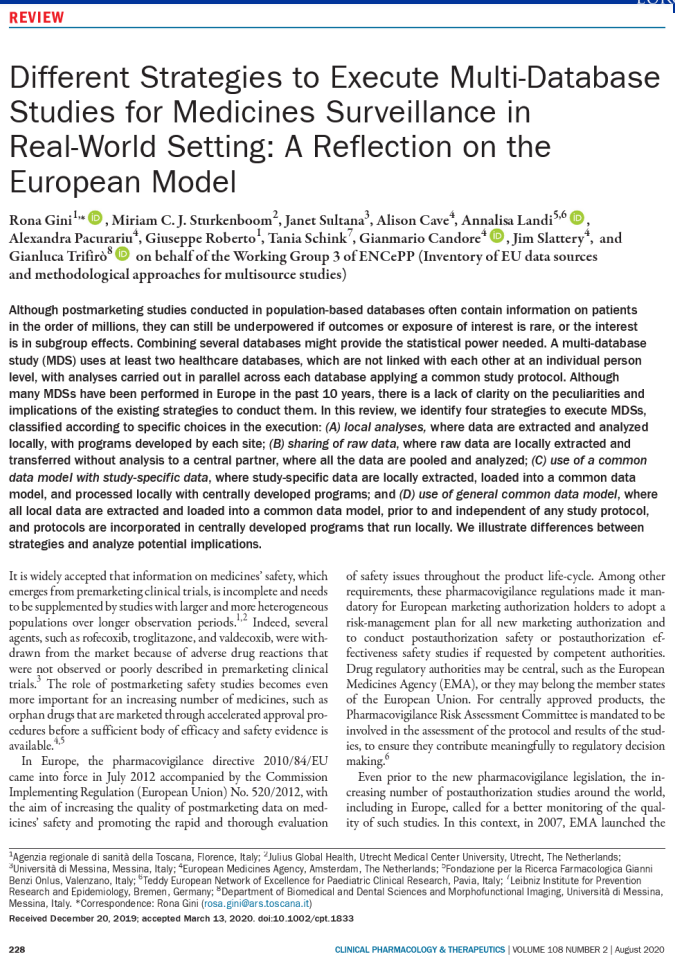
Results: Unmet needs in pharmacoepidemiological research are fulfilled by providing unique guidance on roles and responsibilities to support scientific independence. The principles of scientific independence and transparency are well understood and reinforce trust in study results; however, around 70% of survey respondents still found some provisions difficult to apply. Representatives from stakeholders' groups found the new version promising, although limitations still exist.

Conclusion: By clarifying definitions and roles, the latest revision of the Code sets a new standard in the relationship between investigators and funders to support scientific independence of pharmacoepidemiological research. Disseminating and training on the provisions of the Code would help stakeholders to better understand its advantages and promote its adoption in noninterventional research.

KEYWORDS
conflict of interest, ethics, observational studies as topic, pharmacoepidemiology, pharmacovigilance, practise guideline, research

Publications

Gini R, Sturkenboom MC, Sultana J, Cave A, Landi A, Pacurariu A, Roberto G, Schink T, Candore G, Slattery J, Trifirò G; Working Group 3 of ENCePP. Different strategies to execute multi-database studies for medicines surveillance in real world setting: a reflection on the European model. Clin Pharmacol Ther. 2020 Apr 3. doi: 10.1002/cpt.1833



REVIEW

Different Strategies to Execute Multi-Database Studies for Medicines Surveillance in Real-World Setting: A Reflection on the European Model

Rona Gini[1,*], Miriam C. J. Sturkenboom[2], Janet Sultana[3], Alison Cave[4], Annalisa Landi[5,6], Alexandra Pacurariu[4], Giuseppe Roberto[1], Tania Schink[7], Gianmario Candore[4], Jim Slattery[4], and Gianluca Trifirò[8] on behalf of the Working Group 3 of ENCePP (Inventory of EU data sources and methodological approaches for multisource studies)

Although postmarketing studies conducted in population-based databases often contain information on patients in the order of millions, they can still be underpowered if outcomes or exposure of interest is rare, or the interest is in subgroup effects. Combining several databases might provide the statistical power needed. A multi-database study (MDS) uses at least two healthcare databases, which are not linked with each other at an individual person level, with analyses carried out in parallel across each database applying a common study protocol. Although many MDSs have been performed in Europe in the past 10 years, there is a lack of clarity on the peculiarities and implications of the existing strategies to conduct them. In this review, we identify four strategies to execute MDSs, classified according to specific choices in the execution: *(A) local analyses*, where data are extracted and analyzed locally, with programs developed by each site; *(B) sharing of raw data*, where raw data are locally extracted and transferred without analysis to a central partner, where all the data are pooled and analyzed; *(C) use of a common data model with study-specific data*, where study-specific data are locally extracted, loaded into a common data model, and processed locally with centrally developed programs; and *(D) use of general common data model*, where all local data are extracted and loaded into a common data model, prior to and independent of any study protocol, and protocols are incorporated in centrally developed programs that run locally. We illustrate differences between strategies and analyze potential implications.

It is widely accepted that information on medicines' safety, which emerges from premarketing clinical trials, is incomplete and needs to be supplemented by studies with larger and more heterogeneous populations over longer observation periods.[1,2] Indeed, several agents, such as rofecoxib, troglitazone, and valdecoxib, were withdrawn from the market because of adverse drug reactions that were not observed or poorly described in premarketing clinical trials.[3] The role of postmarketing safety studies becomes even more important for an increasing number of medicines, such as orphan drugs that are marketed through accelerated approval procedures before a sufficient body of efficacy and safety evidence is available.[4,5]

In Europe, the pharmacovigilance directive 2010/84/EU came into force in July 2012 accompanied by the Commission Implementing Regulation (European Union) No. 520/2012, with the aim of increasing the quality of postmarketing data on medicines' safety and promoting the rapid and thorough evaluation of safety issues throughout the product life-cycle. Among other requirements, these pharmacovigilance regulations made it mandatory for European marketing authorization holders to adopt a risk-management plan for all new marketing authorization and to conduct postauthorization safety or postauthorization effectiveness safety studies if requested by competent authorities. Drug regulatory authorities may be central, such as the European Medicines Agency (EMA), or they may belong the member states of the European Union. For centrally approved products, the Pharmacovigilance Risk Assessment Committee is mandated to be involved in the assessment of the protocol and results of the studies, to ensure they contribute meaningfully to regulatory decision making.[6]

Even prior to the new pharmacovigilance legislation, the increasing number of postauthorization studies around the world, including in Europe, called for a better monitoring of the quality of such studies. In this context, in 2007, EMA launched the

[1]Agenzia regionale di sanità della Toscana, Florence, Italy; [2]Julius Global Health, Utrecht Medical Center University, Utrecht, The Netherlands; [3]Università di Messina, Messina, Italy; [4]European Medicines Agency, Amsterdam, The Netherlands; [5]Fondazione per la Ricerca Farmacologica Gianni Benzi Onlus, Valenzano, Italy; [6]Teddy European Network of Excellence for Paediatric Clinical Research, Pavia, Italy; [7]Leibniz Institute for Prevention Research and Epidemiology, Bremen, Germany; [8]Department of Biomedical and Dental Sciences and Morphofunctional Imaging, Università di Messina, Messina, Italy. *Correspondence: Rona Gini (rosa.gini@ars.toscana.it)

Received December 20, 2019; accepted March 13, 2020. doi:10.1002/cpt.1833

Covid-related activities

- News item on the ENCePP website on registration of Covid-studies
- Weekly circulation of table of observational studies to ENCePP Partners, PRAC and researchers between March and October 2020
  - 218 studies included in the table
  - 63 studies registered in the EU PAS Register
- The Covid-related activities were discussed in four SG meetings between April and October 2020

Update from Working Groups and Special Interest Groups

- ENCePP WG1 - ENCePP research standards and guidances, Alejandro Arana, Xavier Kurz
- ENCePP WG2 - Independence and transparency, Rosa Gini
- ENCePP WG3 - Inventory of EU data sources and methodological approaches for multi-source studies, Gianluca Trifirò
- ENCePP SIG on Measuring the Impact of Pharmacovigilance Activities, Agnes Kant
- ENCePP SIG on Drug Safety in Pregnancy, Corinne de Vries

Conclusions & Last Words

- ENCePP Has fundamentally changed the landscape of regulatory science research in Europe
- Much has been achieved but innovation a continuous process
- We are all medicines regulators: we need better alignment with regulatory issues
- Better data : better regulation
- Rapid data : more rapid regulation
- Celebrate achievements
- Apologies UK leaving EU
- Scotland voted to stay in EU but….. Farewell!

Thank you for your attention!

- Further information:

  www.encepp.eu

  encepp_secretariat@ema.europa.eu