EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ENCePP webinar for Academia - Real world research on medicines

European Medicines Agency, 8 March 2021

What is ENCePP and why is it relevant to Academia?

Xavier Kurz

Network of centres active in the fields of pharmacoepidemiology and phamacovigilance in Europe

- **Brings together expertise and resources** in pharmacoepidemiology and pharmacovigilance across Europe and **supports collaborations**
- Facilitates the conduct of **high quality, multi-centre, independent post-authorisation studies with a focus on observational research**;
- Develops and maintains **methodological standards and governance principles for research** in pharmacovigilance and pharmacoepidemiology.
- **Does not assess specific safety or effectiveness issues of authorised medicinal products** – does not replace regulatory authorities – **BUT** discusses **methods for studies**

ENCePP network of research centres (as of March 2021)

Centres (198)

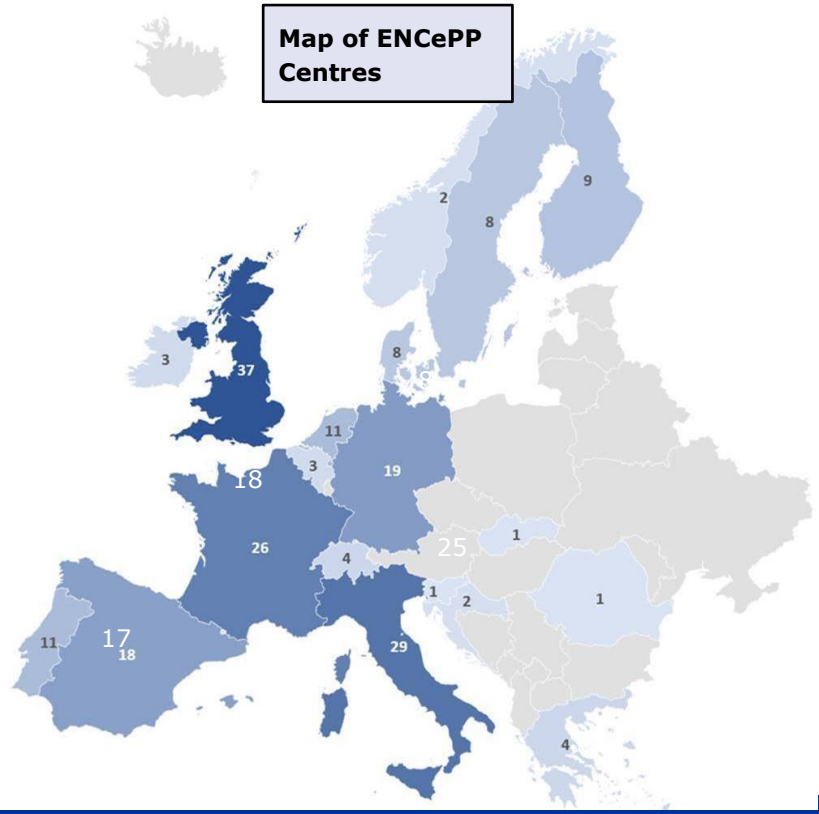
- Public (university, hospital, government, charities)
- Others (CROs, consultants)

Networks (31)

- International
- National

Data sources (153)

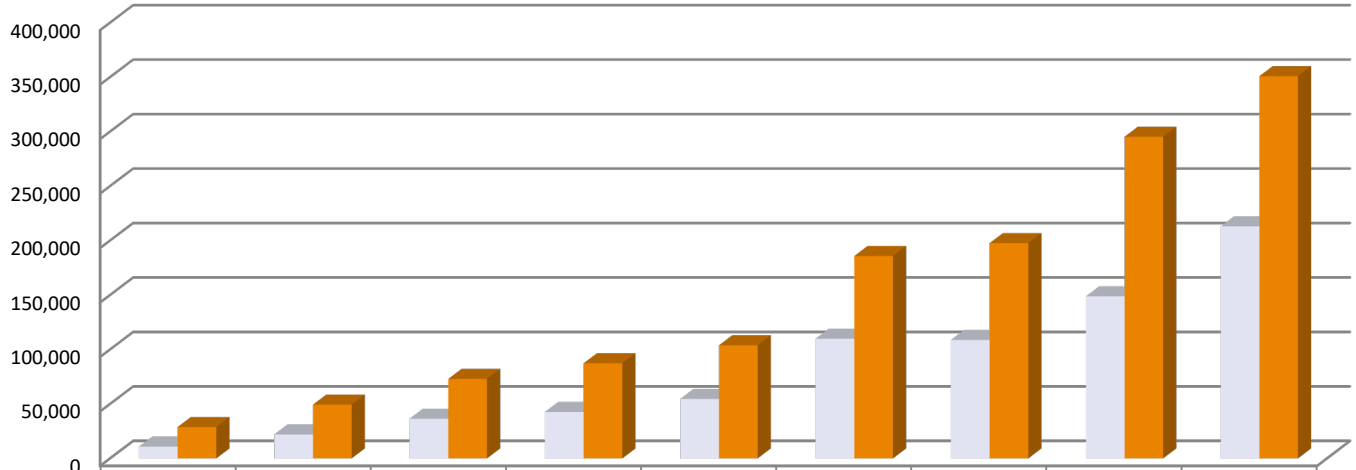
Network is steadily growing



Forum for exchange of information

ENCePP website visits – 2012 - 2020

Unique visitors and visits of ENCePP website
2012-2020



	2012	2013	2014	2015	2016	2017	2018	2019	2020
Unique visitors	10,765	21,980	36,372	42,594	54,588	109,859	108,730	148,812	213,021
Number of visits	28,824	49,348	73,005	87,335	103,836	185,760	197,606	295,277	350,856

Why should you register as an ENCePP Centre ?

Join ENCePP

- To be part of an **active community of scientists** discussing methodological and operational issues in pharmacoepidemiology that are not discussed elsewhere, e.g. in working groups and special interest groups
- To be directly informed of **research projects**, potential funding opportunities, calls for collaborations, and EMA announcements
- To contribute to the **development and dissemination of the best methodological standards** in pharmacoepidemiology and pharmacovigilance
- To contribute to develop **good governance of pharmacoepidemiological studies** in Europe, e.g. independence of academic investigators from the influence of study funders (such as pharmaceutical companies), publication rules or contractual agreements

What does it mean to be an ENCePP partner?

- All ENCePP partners are registered in the ENCePP Resources Database.
- Being an ENCePP partner means a commitment to:
  - **adhere** to the principles of the **ENCePP Code of Conduct** and **ENCePP Guide on Methodological Standards in Pharmacoepidemiology**,
  - **register** their post-authorisation studies in the EU PAS Register,
  - participate in the **development of research and good practice standards** by contributing to, or commenting on, draft proposals prepared by working groups or the ENCePP secretariat,
  - **collaborate with other ENCePP partners**, e.g. in multi-centres studies, and share their research experience.

Example of collaborative work from a ENCePP working group

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], Gianluca Trifirò [8],
Working Group 3 of ENCePP (Inventory of EU data sources and methodological approaches for multisource studies)

Affiliations + expand

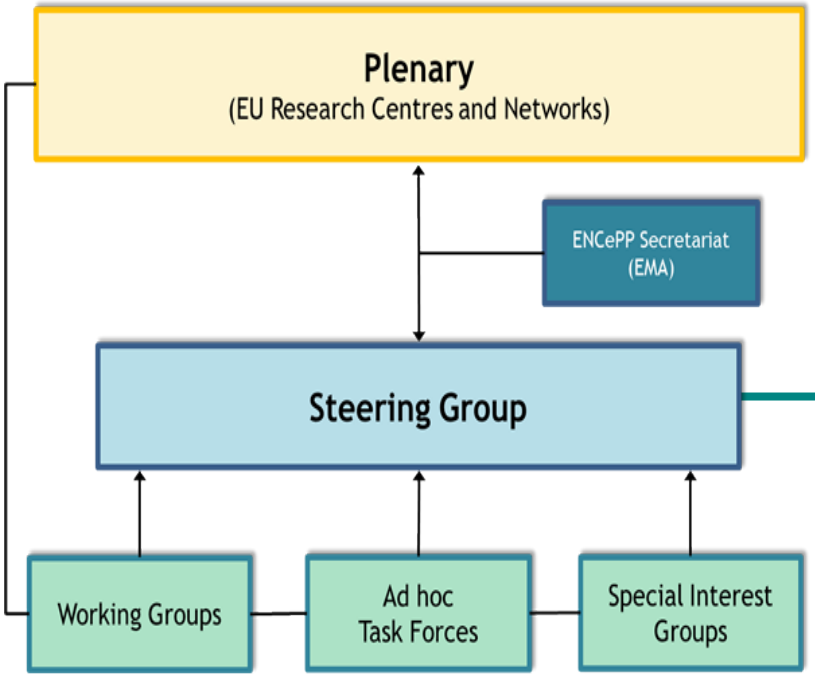
PMID: 32243569 PMCID: PMC7484985 DOI: 10.1002/cpt.1833

Free PMC article

Abstract

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.

Organigramme



ENCePP Steering Group

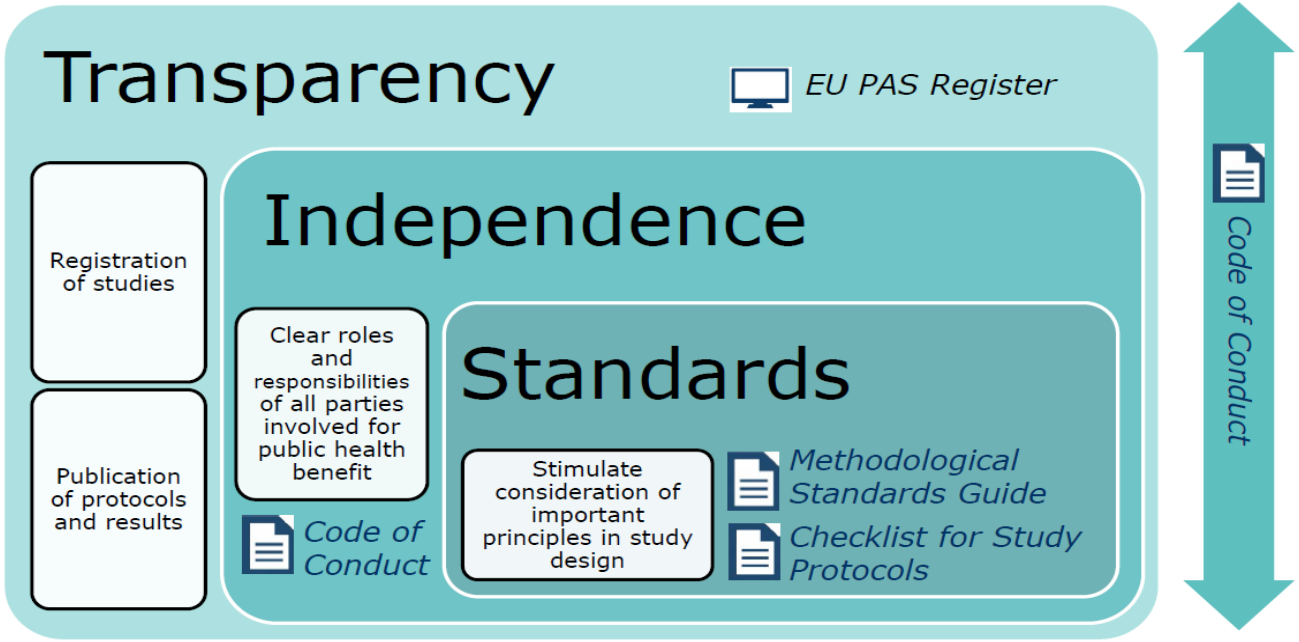
17 members in total:

- **6** elected: from network
- **8** appointed:
  - Heads of Medicines Agencies (HMA),
  - Committee for Medicinal Products for Human Use (CHMP),
  - Committee for Orphan Medicinal Products (COMP)
  - Pharmacovigilance Risk Assessment Committee (PRAC),
  - CHMP's Patient and Consumers Working Party (PCWP),
  - International Society of Pharmacoepidemiology (ISPE),
  - International Society of Pharmacovigilance (ISoP)
  - International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
- **3** members from EMA
- 4 observers: European Federation of the Pharmaceutical Industries & Associations (EFPIA), Food and Drug Administration (FDA), Health Canada
- EMA statistical and scientific advisers

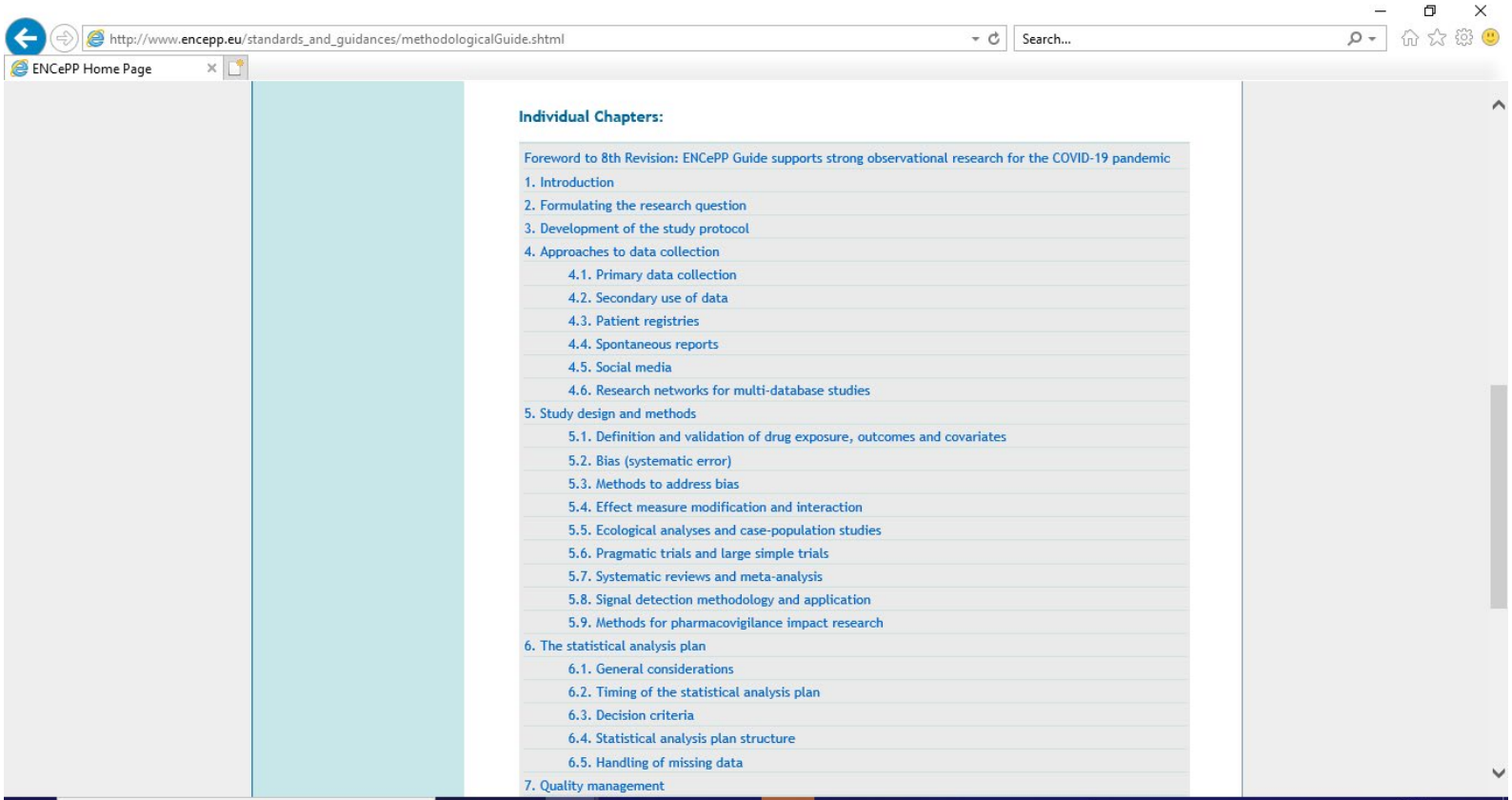
How does ENCePP supports academia?

Francesco Salvo

ENCePP guiding principles and tools



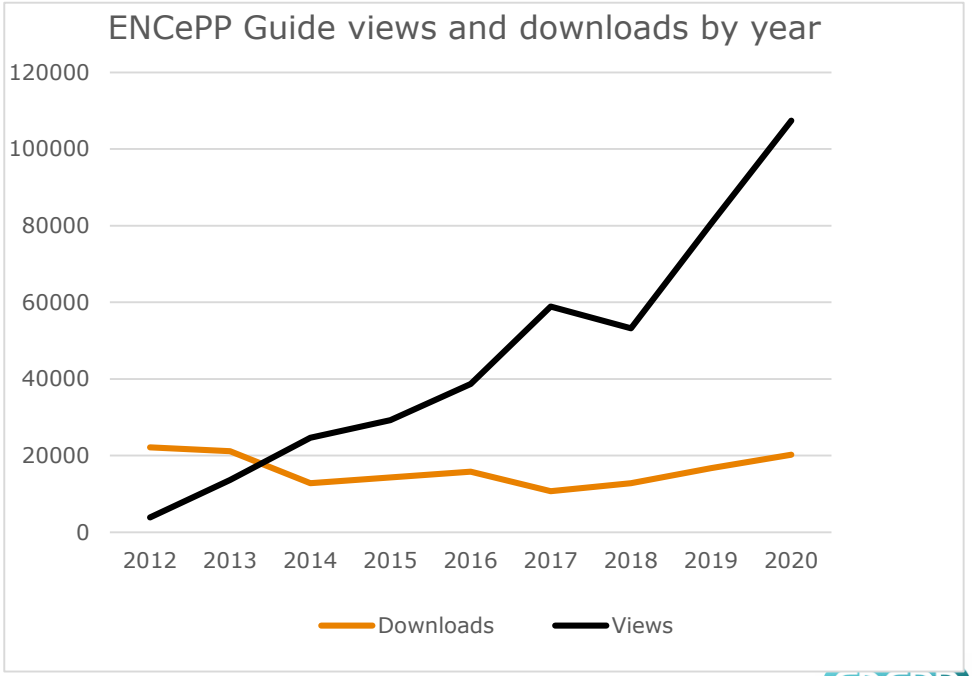
ENCePP Guide on Methodological Standards in Pharmacoepidemiology



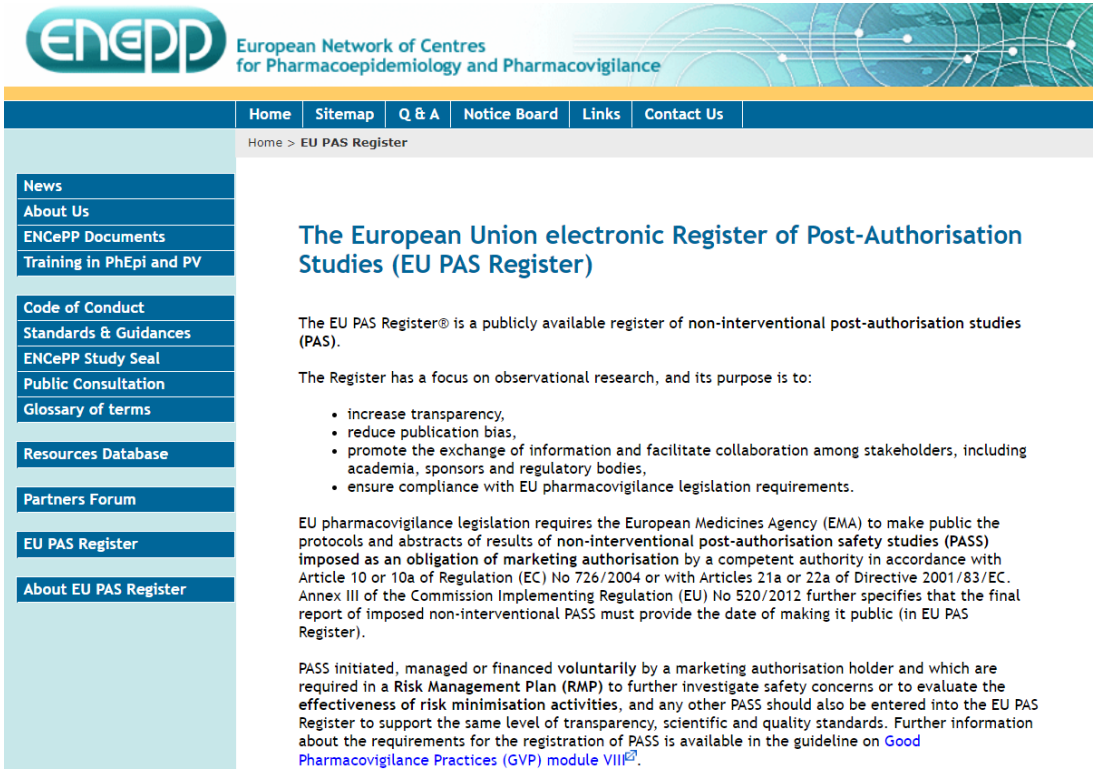
Individual Chapters:

ENCePP Guide on Methodological Standards in Pharmacoepidemiology

- A single web resource for methodological English language guidance (8th revision published in July 2020)
- Provides links to selected articles and, for some topics, what ENCePP considers the best methodological guidance
- Used for training worldwide
- Yearly update in every July (no revision took place in 2019)
- > **107.000** views in 2020
- > **20.000** downloads in 2020
- **33 authors** and a total of **551 references** for revision 8



EU PAS Register – public register – allows publication of study protocols, results and other study documents



ENCePP European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

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The European Union electronic Register of Post-Authorisation Studies (EU PAS Register)

The EU PAS Register® is a publicly available register of **non-interventional post-authorisation studies (PAS)**.

The Register has a focus on observational research, and its purpose is to:

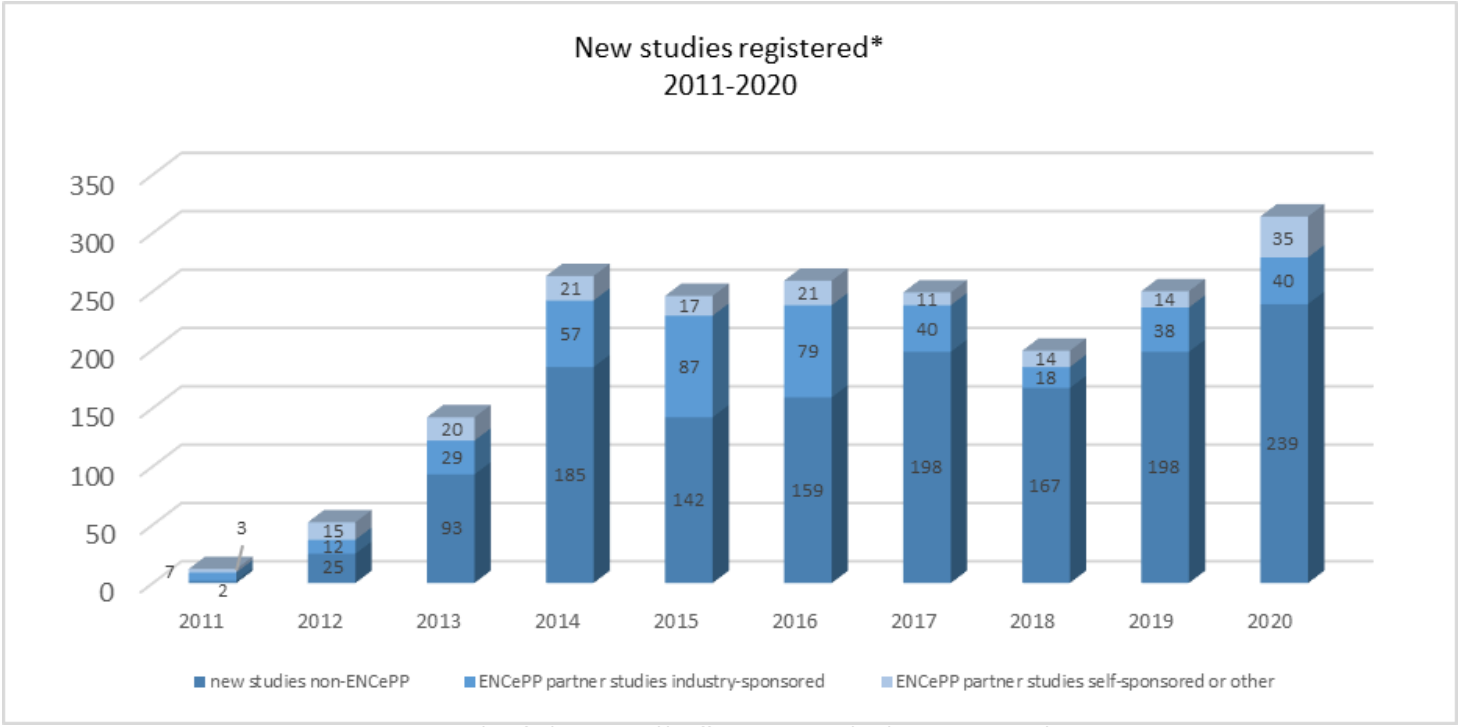
- increase transparency,
- reduce publication bias,
- promote the exchange of information and facilitate collaboration among stakeholders, including academia, sponsors and regulatory bodies,
- ensure compliance with EU pharmacovigilance legislation requirements.

EU pharmacovigilance legislation requires the European Medicines Agency (EMA) to make public the protocols and abstracts of results of **non-interventional post-authorisation safety studies (PASS) imposed as an obligation of marketing authorisation** by a competent authority in accordance with Article 10 or 10a of Regulation (EC) No 726/2004 or with Articles 21a or 22a of Directive 2001/83/EC. Annex III of the Commission Implementing Regulation (EU) No 520/2012 further specifies that the final report of imposed non-interventional PASS must provide the date of making it public (in EU PAS Register).

PASS initiated, managed or financed **voluntarily** by a marketing authorisation holder and which are required in a **Risk Management Plan (RMP)** to further investigate safety concerns or to evaluate the **effectiveness of risk minimisation activities**, and any other PASS should also be entered into the EU PAS Register to support the same level of transparency, scientific and quality standards. Further information about the requirements for the registration of PASS is available in the guideline on Good Pharmacovigilance Practices (GVP) module VIII.

Total of 2040 studies registered on 5th March 2021

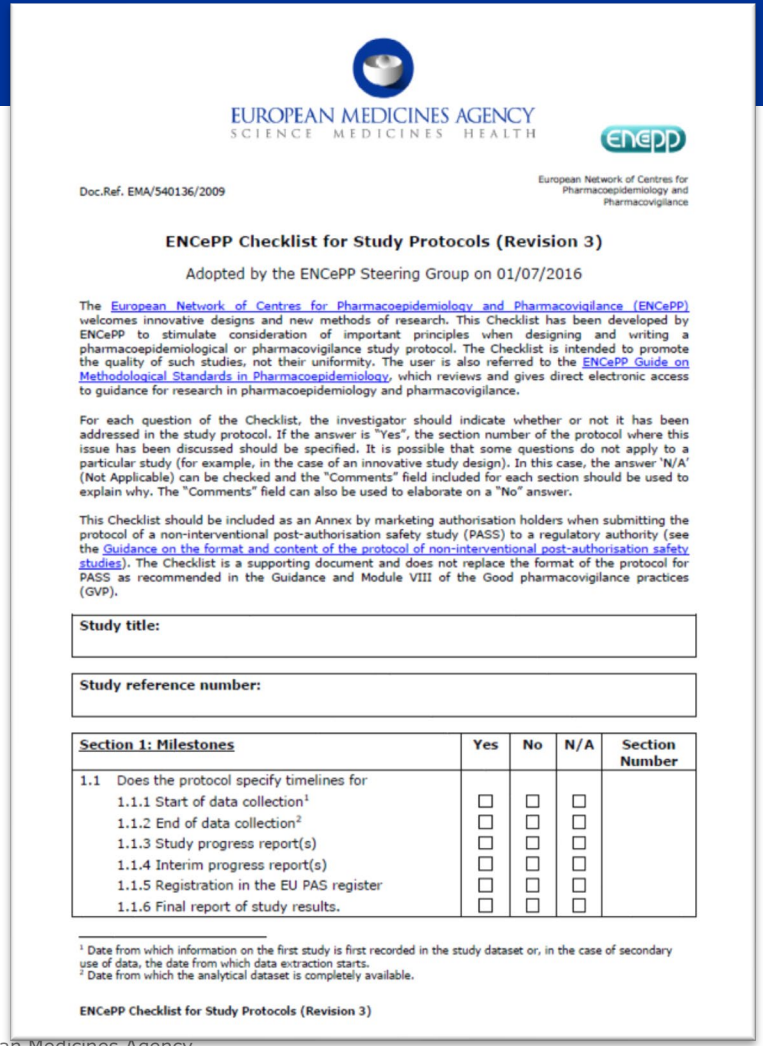
Studies in the EU PAS Register – 2011 - 2020



Governance principles

ENCePP Checklist for Study Protocols

- ❑ Supporting best practice in study design
- ❑ Promoting transparency on study methods
- ❑ To be used by pharmaceutical companies when submitting study protocols to medicines regulators



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Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☐	☐	☐	
1.1.2 End of data collection[2]	☐	☐	☐	
1.1.3 Study progress report(s)	☐	☐	☐	
1.1.4 Interim progress report(s)	☐	☐	☐	
1.1.5 Registration in the EU PAS register	☐	☐	☐	
1.1.6 Final report of study results.	☐	☐	☐	

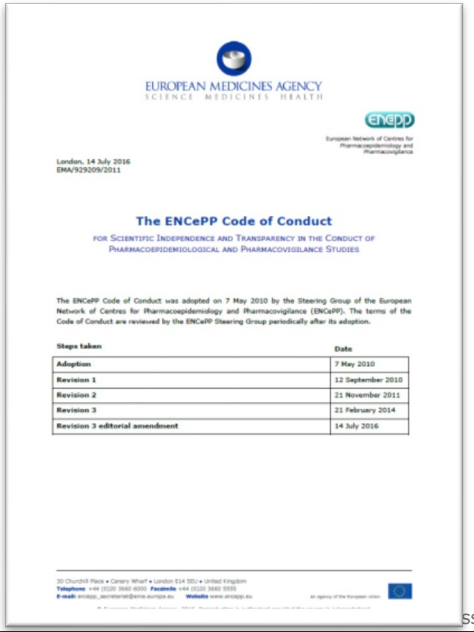
[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

ENCePP Checklist for Study Protocols (Revision 3)

Governance principles

ENCePP Code of Conduct

Promoting transparency and scientific independence throughout the research process



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London, 14 July 2016
EMA/929209/2011

The ENCePP Code of Conduct

FOR SCIENTIFIC INDEPENDENCE AND TRANSPARENCY IN THE CONDUCT OF PHARMACOEPIDEMIOLOGICAL AND PHARMACOVIGILANCE STUDIES

The ENCePP Code of Conduct was adopted on 7 May 2010 by the Steering Group of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The terms of the Code of Conduct are reviewed by the ENCePP Steering Group periodically after its adoption.

Steps taken	Date
Adoption	7 May 2010
Revision 1	12 September 2010
Revision 2	21 November 2011
Revision 3	21 February 2014
Revision 3 editorial amendment	14 July 2016

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

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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

ENCePP and regulatory decision-making / regulatory science

- ENCePP members provide data and publications occasionally to EMA that could support drug safety reviews
- EMA funded studies (through public procurement)
- European Commission FP7 Drug Safety programme
- IMI public-private partnerships
- Ad-hoc collaborations

What's next?

- Collaborate to strengthen the capacity for **multi-centre studies**
  - work on innovative methods to access and analyse data from e-databases, e.g. use of **common data models** and **artificial intelligence**
- **Interact** with new networks, such the Darwin EU community, the Big Data stakeholder forum, or coordinated registry networks
- Ensure the network :
  - remains **focussed on public health** and relevant to the decisions taken by regulators, Health Technology Assessment and other bodies
  - includes **new experts** and centres
  - embraces relevant **new areas** of activity e.g. use of patient registries, social media information and big data
- Reinforce collaboration with **non-European researchers** and health decision-makers

Thank you for your attention

Further information

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www.encepp.eu