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Strengthening Pharmacoepidemiology in a Changing Research Environment: The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)

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ABSTRACT

Key changes in the pharmacoepidemiological research environment had a significant influence on the activities of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) over the last decade. These changes included the SARS-CoV-2 pandemic, the increased access to anonymized real-world data (RWD) sources, the integration of real-world evidence (RWE) into regulatory and public health decision-making, and the emergence of new technologies and methods. This paper describes how ENCePP has evolved in this changing environment to strengthen pharmacoepidemiological methods and practice in Europe and globally. It also provides future perspectives for the network. Through a collaborative approach in non-interventional research, ENCePP will collectively continue to promote excellence for RWE generation, supporting the safe and effective use of medicines.

1 | Introduction

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) was launched in 2008 by the European Medicines Agency (EMA) with the aim of establishing a network of researchers and experts willing to collaborate for conducting large non-interventional studies and provide guidance on best practices in pharmacoepidemiology and pharmacovigilance. Its achievements over the first 10 years have been described: the creation of a strong network of research consortia, the creation of public registers of research institutions and networks, data sources and non-interventional studies, and the development of three core guidance documents, namely the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, the ENCePP Checklist for Study Protocols and the ENCePP Code of Conduct [1]. These outputs have provided a strong set of recognized standards and tools with global outreach and impact (Figure 1). Collaborations with Special Interest Groups of the International Society for Pharmacoepidemiology (ISPE) have provided opportunities to promote common principles and standards internationally [2].

ENCePP has continued its development. On 20 October 2025, 803 institutions, 185 networks, 266 data sources and 3195 studies

Summary

- ENCePP has been influenced by changes in the pharmacoepidemiological research environment over the last decade: the SARS-CoV-2 pandemic, the integration of real-world evidence (RWE) into regulatory and public health decision-making, better access to more anonymized data sources, such as large electronic health care data and patient registries, and the emergence of new technologies and methods.
- These changes required evolution of ENCePP's scientific guidance and governance.
- A major change has been the transition from the public ENCePP Resource database of centres and data sources and the EU PAS Register to the HMA-EMA Catalogues of real-world data (RWD) sources and studies.
- Through long-term presence and leadership in pharmacoepidemiology and pharmacovigilance, the ENCePP research community is well positioned to remain at the forefront of supporting valid and fit-for-purpose RWE generation globally.

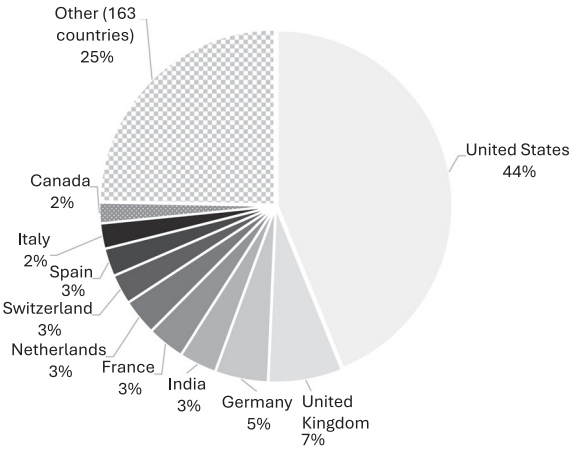

FIGURE 1 | Distribution of ENCePP website visits per country, March 2024 to June 2025 ($n = 55449$ visits).

had been registered in the HMA-EMA Catalogues of real-world data sources and studies (formerly the ENCePP Resource database and the EU PAS Register), providing a unique source of knowledge [3–5]. The ENCePP Guide is currently undergoing its 12th revision, and updates of the Checklist for study protocols, the Code of Conduct and other methodological documents have been published on the ENCePP website [6]. ENCePP guidance is referred to in international guidance documents, such as, recently, the ICH M14 General Principles on Planning, Designing, Analyzing, and Reporting of Non-interventional Studies That Utilize Real-World Data for Safety Assessment of Medicines [7], and is the basis for training at academic, industry and other research institutions.

Over the last decade, key changes in the pharmacoepidemiological research environment had to be addressed by ENCePP: the SARS-CoV-2 pandemic, the increased integration of real-world evidence (RWE) into regulatory and public health decision-making, the increase in the number of data sources (such as electronic health care data and patient registries) made accessible for research and supporting multi-database studies, and the emergence of new technologies and methods. In this paper, we describe these events, their impact on ENCePP, and how the network has evolved and is still evolving to keep abreast of this rapidly changing environment. This is summarised in Table 1. We also delineate possible future outlooks for ENCePP.

2 | The Changing Pharmacoepidemiological Research Environment and Its Influence on ENCePP

2.1 | The SARS-CoV-2 Pandemic

The SARS-CoV-2 pandemic, which began in December 2019 with an outbreak in Wuhan, China, had a profound impact on the practice of pharmacoepidemiology. An unprecedent response from medicinal product developers and the pharmaceutical industry resulted in COVID-19 vaccines being developed at unprecedented speed and approved in an accelerated manner by regulatory authorities worldwide. The urgent need for evidence on the use, safety and effectiveness of vaccines and therapeutics gave high visibility to researchers. It also generated high expectations for the rapid conduct of studies and swift appraisal of a very large amount of scientific literature for a new disease and for new vaccines for which data on benefits and risks accumulated at a fast pace. Many researchers were faced with methodological challenges such as the design of comparative studies in circumstances of targeted vaccine exposure and ultimately high vaccine coverage driven by national vaccination policies. The limited availability of vaccine exposure data, including variant-specific data, the heterogeneity of published background incidence rates for adverse events of special interest (AESIs) and the readiness of health care data sources (such as low frequency of updates and lag time to access recent data) impacted the feasibility and speed of studies.

ENCePP addressed this challenge. At the beginning of the pandemic, nearly daily calls between ENCePP centers were organized by the ENCePP Secretariat to exchange information on study plans, collaborative research networks, suitable data sources and study designs. An inventory of this information was established and shared with all ENCePP centers. Identification of COVID-19-related study protocols and study reports in the EU PAS Register was facilitated. Research consortia, including many ENCePP centers, were contracted by the EMA to proactively collect background incidence rates of a large number of AESIs, design templates for study protocols and perform studies on vaccine safety, effectiveness and benefit–risk [8–10]. Methodological expertise was made available and guidance was rapidly published [11]. It was integrated into updates of the ENCePP Guide, resulting in a peak in its consultation in 2020, the first year of the pandemic (Figure 2).

Lessons have continued to be drawn by ENCePP. This evaluation considered the value of the extensive exchange of information stimulated by the pandemic, the facilitation of research networks and international collaborations [12], the rich methodological work done during this period, as well as challenges related to data availability and study design. Lessons applicable to routine pharmacoepidemiological practice were translated

TABLE 1 | Changes in the pharmacoepidemiological research environment and their impact on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

Changes in the pharmacoepidemiological research environment	Influence on ENCePP	How ENCePP has evolved
SARS-CoV-2 pandemic	• Need for fast multi-database collaborative studies integrating multiple expertise • Faster communications based on fast-track publications and social media • Expedited appraisal of published data • Need to address low frequency of data source updates and lag-time to recent data • Recommendations on good practice in vaccine monitoring • Strengthening of international collaborations	During the pandemic • Unprecedented communication between ENCePP centres • Enabling of exchange of methodological expertise • Capacity building with collaborative networks opened to larger research community based on expertise • Data sources made more accessible for research After the pandemic • Lessons learned reflected in updates of the ENCePP Guide • Review of the ENCePP mandate and governance
Increased integration of real-world evidence into regulatory decision-making	• Multiple regulatory guidance on the planning, design, conduct and reporting of real-world data studies • Focus on data quality (reliability and relevance) of real-world data sources • Need to address relevance of ENCePP tools used by regulatory and public health authorities, such as Heads of Medicines Agencies (HMA), EMA (e.g., guidance documents, HMA-EMA catalogues of real-world data sources and studies), ICH	• Updates of the ENCePP Guide addressing quality of RWD and expanding methods for RWD studies to support interpretation and replicability of studies • Update of ENCePP Checklist for study protocols • Evolution of ENCePP as an open multidisciplinary network able to provide leadership in the various set of domains related to RWD studies • Qualitative study with insights on role of ENCePP in the RWE landscape
Increase in number of anonymized data sources, such as large electronic health care data and registries, made accessible for research	• Landscape of data sources providing data quality, scientific value and up-to-date data protection • Need for data quality frameworks applicable to all data sources involved in a study • Evaluation of different models of multi-database studies	• Description in the ENCePP Guide of models of multi-database studies using data linkage and suitable models of integration • Additions and updates in the ENCePP Guide on systematic review and meta-analyses • ENCePP partnership opened to data source owners from EU candidate countries and potential candidates • Better information sharing through new searchable website (www.encepp.europa.eu) • Update of the ENCePP Code of Conduct.
Emergence of technologies and methods applicable to pharmacoepidemiology, e.g., artificial intelligence, target trial emulation, feasibility assessments, estimand framework, HARPER protocol	• Need to develop or enhance good practice on place and appropriate use of new methods in pharmacoepidemiology and pharmacovigilance	• Update of the ENCePP Guide providing methodological standards and highlighting illustrative studies • Revised Working Groups and Special Interest Groups

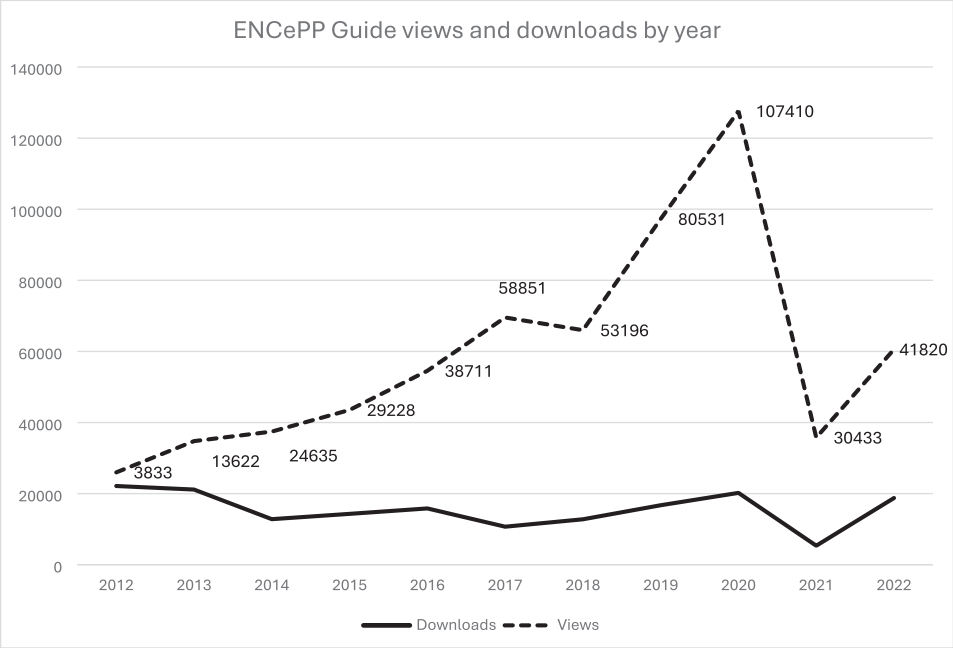

FIGURE 2 | ENCePP Guide views and downloads per year, 2012–2022 (no data available for the year 2021).

into the 10th and 11th revisions of the ENCePP Guide and will continue to be integrated into further guidance.

2.2 | Increased Integration of Real-World Evidence Into Regulatory Decision-Making

The increasing ability to electronically capture and store a large amount of data from healthcare systems has opened new opportunities for regulatory authorities to access real-world data (RWD) from routine clinical practice and use the evidence derived from such data across the lifecycle of medicines. In Europe, the HMA-EMA Big Data strategy was initiated to address the role of "big data" for the evaluation and supervision of medicines in the EU and provide recommendations for their use [13]. This has led to a change of paradigm for regulatory evidence generation that requires access to health care data sources and assurances of data quality and relevance for non-interventional studies [14–17].

The introduction of the RWE concept has been associated with the publication of several guidance documents by different regulatory authorities, albeit without a common theoretical scientific foundation and definitions [18, 19]. Although harmonization is in progress [20], this multiplicity requires researchers to consider different methodological recommendations when designing RWD studies for regulatory submissions. In addition, the regulatory focus on data quality based on the concepts of reliability and relevance requires researchers to develop expertise in using formal data quality frameworks and the interpretation of results of algorithms analyzing the quality of a data source and its value for a specific study [21].

Another important consequence for ENCePP has been a redesign, integration and renaming by EMA of the public ENCePP resource database and EU PAS Register into repositories of metadata collected from RWD sources and studies (namely the HMA-EMA Catalogues of RWD sources and studies) [22]. This development was piloted by a research consortium of ENCePP centers [23]. It helped improve the technical features, interoperability and transparency of the Catalogues and ensures their long-term continuation, while supporting the discoverability and assessment of RWD sources, transparency and reproducibility of research [24].

ENCePP played an important role in providing methodological recommendations supporting the validity of the evidence generated in RWD studies. The ENCePP Guide was updated to address the quality of RWD and methods for RWD studies, to support their interpretation and replicability. The Guide also includes a list of areas of expertise that ENCePP considered important to develop and disseminate in relation to RWE. The increased integration of RWE into regulatory decision-making has indeed highlighted that the expertise to conduct studies for regulatory purposes is no longer confined within the field of pharmacoepidemiology (traditionally found in academic institutions, regulatory authorities, contract research organisations and pharmaceutical companies) but needs to expand to other fields such as data sciences, computer sciences, health care systems, patient-reported outcomes, data protection and ethical issues. ENCePP would benefit from evolving into an open multidisciplinary network able to provide leadership in various domains related to the planning, design, conduct, reporting and interpretation of RWD studies. How to achieve this was one of the objectives of the qualitative study on the value of ENCePP in the RWD landscape described below.

2.3 | Increased Number of Anonymized Data Sources Made Accessible for Research

In the European Union (EU), research collaborations for multi-database studies have been strongly encouraged as part of the drug safety research funded by the European Commission (EC)

as well as public-private partnerships such as the Innovative Health Initiative (IHI) [25]. This funding resulted in the conduct of groundwork necessary to overcome the hurdles of data access and sharing across countries for non-interventional studies. The EC is also establishing the European Health Data Space (EHDS) with the development of joint European principles for the secondary use of health care data [26]. The public HMA-EMA Catalogue of RWD sources allows the identification of these sources by country, study, type of research and other relevant fields. This information supports networking between research groups and stakeholders, planning of studies, evaluation and contextualization of study results based on secondary use of anonymized data, and the conduct of multi-database studies.

Multi-database studies increase the size of the study population for rare events and medicines used in specialised settings or population subgroups. Besides this, they may provide additional knowledge on the generalizability of results and consistency of associations across countries and regions. This is particularly important in the context of the European centralized regulatory system for medicines based on an EU-wide assessment [27]. Where allowed by local legislation, record linkage between data sources containing different information (such as biological, laboratory, drug utilisation, genomics or hospital data) also provides access to more comprehensive data, such as confounders, exposures and outcomes. Multi-database studies often require prespecified agreements on governance, certification of data quality, common definitions, extraction of algorithms for study variables and analytical systems, and a rigorous interpretation of heterogeneous results between databases [28, 29]. These challenges were addressed by updating the ENCePP Guide in 2023 with a description of different models of studies using multiple data sources, from independent analyses using separate protocols and local data analysis, to studies using a general common data model with a common protocol and common data analysis. This description aimed to support researchers in running studies in multiple data sources using the most suitable model of integration.

Collaboration with data owners was strengthened to broaden the range of data sources and enlarge their representativeness of countries and health care systems, including from EU candidate countries and potential candidates. The multiple interactions between ENCePP centers and regulatory and public health authorities, contract research organisations, pharmaceutical companies and other organisations led in 2018 to an in-depth revision of the ENCePP Code of Conduct to maintain a high level of scientific independence and transparency guiding pharmacoepidemiological studies in Europe.

2.4 | New Technologies and Methods Applicable to Pharmacoepidemiology and Pharmacovigilance

An important change in the pharmacoepidemiological research environment concerned applications of artificial intelligence (AI), with its subsets of machine learning, deep learning and natural language processing [30]. The feasibility assessment to support protocol development [31], the causal inference target trial emulation approach [32], possibly augmented with components of the estimand framework [33], and the HARmonized Protocol Template to Enhance Reproducibility of hypothesis evaluating real-world evidence studies on treatment effects (HARPER) [34] are examples of methods and frameworks that are recognized as improving the validity, reproducibility and transparency of non-interventional studies. They are progressively integrated by regulatory authorities in their recommendations. These developments drove ENCePP towards reinforcing good practice and highlighting use cases. New chapters were introduced in the ENCePP Guide and selected chapters are further discussed in companion papers of this ENCePP Special Series.

3 | How ENCePP Is Evolving

3.1 | Changes in Governance

The ENCePP Steering Group (SG) has been composed of 16 members elected among ENCePP partners representing the EMA and its committees, other regulatory bodies, and members from learned societies such as the International Society for Pharmacoepidemiology (ISPE) and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Following the update of its mandate in 2024, the SG was expanded to 20 members, including those from patient organisations and the pharmaceutical industry, who previously had observer status. The SG has two co-chairs, one from the EMA and one representing the ENCePP centers. The ENCePP Secretariat is provided by EMA. The SG is responsible for establishing a workplan and overseeing its implementation through the ENCePP working groups (WGs) or special interest groups (SIGs). Information on their focus and activities is published on the ENCePP website [35].

The mandate and workplan of ENCePP have evolved in line with the changing pharmacoepidemiology landscape and regulatory environment [36]. While the early focus was primarily on developing key standards and tools, the network's visibility and impact have recently been emphasized. While ENCePP tools have always been freely and openly accessible, a new searchable ENCePP website was launched in 2024. It was also considered important to assess the impact and role of ENCePP in the wider RWD/RWE community, as described below.

3.2 | Guidance on Methods

The choice of epidemiological methods to address a research question should be based on methodological standards supporting the validity of the study results. Textbooks describe these standards but cannot incorporate all new developments. The ENCePP Guide on Methodological Standards in Pharmacoepidemiology was therefore developed as a dynamic and publicly available web resource providing electronic links to illustrative examples of published studies and public documents selected by its authors. It aimed also at providing recommendations on the practical implementation of pharmacoepidemiological principles and innovative methods.

The Guide has been regularly updated to maintain its dynamic nature, which may explain that it has been widely used for more than 10 years, with a peak of consultations during the first

TABLE 2 | ENCePP guide on methodological standards in pharmacoepidemiology, top 10 chapters consulted in 2024.

Chapter of the ENCePP Guide	Number of page views	Number of individual viewers
Chapter 7: Effect modification and interaction	3052	2683
Chapter 11: Signal detection methodology and application	2210	1759
Chapter 6: Methods to address bias and confounding	2089	1813
Chapter 4: Study design	824	710
Chapter 2: Formulating the research question and objectives, and assessing study feasibility	657	553
Chapter 3: Development of the study protocol	284	212
Chapter 12: Statistical analyses	278	236
Chapter 1: Introduction	249	202
Chapter 5: Definition and validation of drug exposure, outcomes and covariates	233	197
Annex 2: Guidance on methods for evaluation of medicines in pregnancy and breastfeeding	223	185

SARS-CoV-2 pandemic year (Figure 2). The list of top 10 chapters consulted in 2024 highlights its important contribution to guidance on pharmacoepidemiological methods (Table 2). The need for updates is identified by a dedicated working group based on new research topics emerging from the published literature, the annual ISPE meeting, ENCePP plenary meetings and suggestions for additional guidance proposed by readers. Innovative topics have been covered, such as pharmacogenetics or the use of AI in pharmacoepidemiology. Updates to the Guide have led to the broadening of the authorship to non-ENCePP and non-European specialists to ensure relevant expertise. The increased number and complexity of the chapters made it challenging to maintain an annual revision cycle. As a result, a targeted revision approach has been adopted. Only a selection of chapters will be amended in regular updates, starting with the 12th revision.

3.3 | Transparency and Scientific Independence

The ENCePP Code of Conduct aims to strengthen the confidence of the general public, scientific community and all stakeholders in the integrity and value of the research. It promotes and supports scientific independence and transparency throughout the end-to-end research process by aiming to avoid the influence of commercial, financial, institutional or personal interests of study funders [37].

Many provisions of the Code could not apply to studies requested by regulatory authorities and contracted by the authority or the concerned pharmaceutical company to an academic centre. In this case, the study funder might require changes to the protocol considered necessary by the authority to answer the research question, which does not comply with the scientific independence principle. The last revision in 2018 therefore specified that all parties involved in the development of the protocol are responsible for ensuring compliance with regulatory requirements. This allows the competent regulatory authority to be involved, directly or indirectly, in the development of the protocol.

Through the ENCePP Seal, the ENCePP Secretariat could grant recognition of studies for which the lead investigator had signed a declaration of compliance with the Code of Conduct, the Checklist for Study Protocols and a Declaration of Interests and had registered the study and its protocol in the former EU PAS Register. However, the added value of the ENCePP Seal has been questioned given the difficulty to fully apply the principle of scientific independence to studies funded by pharmaceutical companies or regulatory authorities, and the reluctance of some investigators and/or funders to publish the study protocol and/or incorporate the Code of Conduct in study contracts. These reasons explain the low number of studies granted the ENCePP Seal since its inception, that is, a total of 84 studies. The ENCePP Seal was therefore discontinued in 2025. Its individual components (the Code of Conduct, the Guide and the Checklist for Study Protocols) remain nevertheless important tools reflecting the network's core principles, and researchers are strongly encouraged to continue using them when implementing studies.

4 | Future Outlooks for ENCePP

Following a decade of continuous development, it was deemed timely to reflect on the future directions of ENCePP. A qualitative study, comprising both semi-structured interviews and a questionnaire, was conducted in 2024 to gather perspectives from relevant stakeholders. Five key themes emerged from the study: strengthening ENCePP, increasing collaborations, new avenues, autonomy, and visibility. The network's strong positioning in the RWD/RWE landscape was widely acknowledged, and it was considered important that the network remains active and engaged. ENCePP was seen as a

TABLE 3 | List of revised ENCePP working groups (WGs) and special interest groups (SIGs).[a]

Working groups
- Communications and outreach
- Independence and transparency
- Revision of the ENCePP guide on methodological standards in pharmacoepidemiology
- Artificial Intelligence (AI) in pharmacoepidemiology
- Real-world data (RWD) sources in non-interventional studies
- Diversity and Health Equity

Special interest groups
- Update of the ENCePP Checklist for study protocols
- Pragmatic elements of clinical studies
- Supplement to the Good Practice Guide for the use of the HMA-EMA Catalogues of real-world data (RWD) sources and studies
- Publication of selected chapters of the ENCePP Guide in Pharmacoepidemiology and Drug Safety and in value in health

[a]The aim of the ENCePP WGs and SIGs is to address the objectives and deliverables of the ENCePP workplan. WGs are established based on emerging topics of interest. SIGs have a narrower focus, such as addressing one specific objective that cannot be addressed as a deliverable of a WG.

natural partner for European initiatives such as the EHDS. Stakeholders also emphasized the value of ENCePP in representing the European perspective at the international level. New avenues identified for ENCePP included outreach and capacity-building efforts in countries with less developed pharmacoepidemiology infrastructure—both within and outside Europe. It was also suggested that ENCePP could take a more proactive role in shaping the RWD/RWE landscape by answering public consultations on draft EMA guidance documents or issuing position or opinion papers on key developments. Finally, in line with the growing emphasis on public and patient engagement, enhancing the visibility of ENCePP was seen as essential to promoting greater use of its tools and resources, thereby increasing its overall impact [38]. Informed by results from the qualitative study, the ENCePP SG has revised the mandate of WGs and SIGs to further support the implementation of the ENCePP Workplan, while taking into account the themes identified. ENCePP now has a total of 10 active WGs and SIGs, focusing on various topics (Table 3). These groups are open to active contribution from members of ENCePP centers. Engagement of junior and mid-level members is specifically encouraged.

5 | Conclusions

The role of RWD and RWE in regulatory and public health decision making, health technology assessment, and medicine development, continues to expand. The role of ENCePP in fostering good practices for non-interventional studies is therefore becoming increasingly important. The ENCePP community, through both individual and collective efforts, will continue to strengthen methods, develop tools, and share lessons learned. These contributions are being advanced and disseminated through new WGs and SIGs under the leadership of the ENCePP SG. Applying its core principles, ENCePP will continue to promote excellence in pharmacoepidemiology and pharmacovigilance and support global networking, exchange of good practices, and discussions on cutting-edge science. Through a collaborative approach in non-interventional research, ENCePP will support RWE generation for the benefit of regulatory and public health decision-making.

5.1 | Plain Language Summary

Pharmacoepidemiology is a scientific discipline that uses epidemiological methods to evaluate the use, benefits, and risks of medical products and interventions in human populations. Over the last decade, key changes have impacted the research environment of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) such as the COVID-19 pandemic, the increased access to anonymized data, the increased integration into regulatory decision-making of information about how medical treatments and products work in real life (also called real-world evidence), and the emergence of new technologies and methods for pharmacoepidemiology and pharmacovigilance research. This paper describes how ENCePP has evolved in this changing environment and provides future perspectives for the network.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

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