Utrecht University

European Network of Centres for Pharmacoepidemiology

Investigating the role and impact of ENCePP in an evolving Real-World Data landscape – a qualitative study

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Layman's Summary

Once a medicine has been approved for sale on the market, it continues to be monitored for use, benefits, and risks in the relevant population. The European Medicines Agency (EMA) is the main body responsible for the scientific evaluation, supervision, and safety monitoring of medicines in Europe. The fields of scientific research related to these topics are called pharmacoepidemiology (PE) and pharmacovigilance (PV). There are several different types of centres that conduct PE/PV research, including academic institutions, regulatory bodies, and contract research organisations. In 2007, the EMA set up an initiative called the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), with the main aim of strengthening PE/PV research in Europe. One of the ways in which ENCePP does this is by bringing together researchers across Europe. ENCePP has also developed several helpful tools to provide common standards for research practices and ethics, in a way that encourages the independence and transparency of research.

In the last five years, there have been significant changes in the PE/PV research field. One aspect of this is the rapidly developing use of Real-World Data (RWD) and Real-World Evidence (RWE). RWD refers to patient data obtained outside of clinical trials. For example, health care data from physician visits, or information on medication dispensed in pharmacies. RWE is then the evidence generated based on RWD. The use of RWD/RWE in PE/PV research has increased significantly, especially since the COVID-19 pandemic, and several new initiatives related to this have come up. This warranted the question of where ENCePP stands today, and where it will be in the future.

The main aim of this study was therefore to investigate the role and impact of ENCePP in an evolving PE/PV research landscape. Through a series of interviews and a survey involving researchers across Europe, this study provides valuable insights into the opinions of and experiences with ENCePP. The interviews consisted of questions about the use and experience of ENCePP in general, while the survey focused more on the use of ENCePP tools. The results confirm that ENCePP plays several important roles. It is seen as an important network, which also develops and maintains useful tools. Many see ENCePP as a long-standing, respected body that makes valuable contributions to increasing the quality of PE/PV research in Europe. Participants also had several suggestions for the future, including ideas for new tools that could be developed and new roles that ENCePP could take on. This study provides a solid foundation upon which ENCePP can make important decisions about its future steps, including what its primary objective will be and where it would position itself in a fast-evolving RWD landscape.

Declaration on Generative AI use

In this research project, I utilised GenAI, specifically ChatGPT 4.0, to assist in a few writing and planning tasks. The AI tool was used to check the tone and flow of the invitational emails sent to interview contacts. It was also used to provide suggestions for structuring the results section and making a task list for completing it. No sensitive or confidential information was used in the prompts, and all questions were kept general. I critically reviewed all AI-generated content, and I assure that the text is accurate and of high academic integrity. Using GenAI improved my efficiency, but I remained vigilant to validate all information to maintain the rigour and originality of the work.

Abstract

Background: The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) was set up by the European Medicines Agency (EMA) in 2007, with the main aim of strengthening PE/PV research in Europe. In the last few years there have been significant developments in the PE/PV landscape, such as the increased use of Real-World Data (RWD) in PE/PV research and regulatory decision making, especially since the COVID-19 pandemic.

Objective: To investigate the current and future role and impact of ENCePP in a fast-evolving RWD/RWE landscape.

Methods: This was a qualitative study conducted between May – October 2024, consisting of a series of semi-structured interviews and a survey. Participants included relevant stakeholders from the PE/PV research field, with a mix of ENCePP Partners and non-Partners. The interviews covered opinions of and experiences with ENCePP overall, while the survey focused mainly on use of the ENCePP tools. The interviews were approximately 30 minutes long and were conducted via Microsoft Teams. They were transcribed verbatim using Amberscript and coded using NVivo. The survey consisted of 33 multiple-choice and open answer questions. It was created and distributed using Qualtrics, and the results were analysed using SPSS.

Results: 18 interviews were conducted, and there were 52 complete responses to the survey. The results confirm the current role of ENCePP as a network, a source of guidance, a bridge between institutions, and as a pioneer in establishing common research standards. Many participants received a strong benefit from the use of the ENCePP Network and tools, though there were some barriers and areas for improvement identified. Suggestions for the future included ideas for new tools and new roles ENCePP could take on, as well as what its primary objective and positioning could be. Majority of participants emphasised increasing visibility, both within and outside of the European Union (EU), as an important focus area.

Conclusion: The results of this study confirm that there are many who are invested in ENCePP's progress and output. Through an in-depth analysis of the opinions and experiences of relevant stakeholders in the PE/PV research field, combined with an overview of how the tools are used, this study provides a strong foundation for the decisions ENCePP has to make regarding its future steps.

Introduction

The need for ENCePP

Once a medicine or medicinal product has been approved for market authorisation, it continues to be monitored for use, safety, benefits, and risks. The field of research dedicated to studying the use of a medicine in a large population is known as pharmacoepidemiology (PE), which applies epidemiological methods to pharmaceutical products[1]. Risk assessments and safety evaluations, which are often the aim of post-authorisation safety studies (PASSs), fall under the field of pharmacovigilance (PV). Both PE and PV research are integral to the post-authorization monitoring of medicines and medicinal products. Along with the European Commission (EC), one of the main bodies responsible for the evaluation and supervision of medicines and medicinal products in the European Union (EU) is the European Medicines Agency (EMA). In the early 2000s, awareness of the number of annual deaths caused by adverse drug reactions to medicines on the market increased. In response, the EC led an extensive review of the EU pharmacovigilance system[2]. PASSs were more frequently requested to proactively monitor the safety of medicines and medicinal products on the market[3]. While PASSs can be in the form of standard clinical trials, they can also be observational, or non-interventional studies (NIS), for which the capacity to conduct multi-centre studies is critical. At the time, the heterogeneity in the PE/PV landscape in the EU was difficult to overcome, as there was no overview of available data sources or existing collaborations, and no common standards for research practices or quality[4]. There was extensive public consultation between 2006-2007 to determine how the EU pharmacovigilance system could be strengthened[2], during which discussions were held between representatives from the EC, EMA, academic centres, research organisations, existing clinical networks, and the pharmaceutical industry[4].

Thus, in 2007, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) was established by the EMA[3], with the aim of strengthening PE/PV research in Europe. One of the reasons for establishment, and a persisting aim of ENCePP, is to facilitate high-quality, multi-centre, independent NIS across Europe through the formation of an

active research network. The participating centres, known as the ENCePP Partners, consist of regulators, researchers, funders, and other related stakeholders. The ENCePP network facilitates their interaction, collaboration, and exchange of knowledge, resources, and expertise. To that extent, an annual Plenary meeting with all the ENCePP partners is held, fostering connection and providing an opportunity to meet in person when possible. ENCePP also provides the tools required to make multi-centre collaborations successful, such as defining a common set of methodological standards and providing a framework for the ethical conduct of collaborative studies.

The pillars of ENCePP

The three pillars of ENCePP's work include promoting (i) transparency and (ii) independence in scientific research and collaboration, and (iii) maintaining a set of common methodological standards for good research practice.

A. Transparency

By providing a platform for collaboration and making it possible to leverage available expertise and resources across the EU, ENCePP encourages transparent and open sharing of data and research. As a part of this, ENCePP established the EU Electronic Register of Post-authorization Studies (the EU PAS Register®)[4]. The register changed the research landscape significantly, as for the first time, there existed a large pan-European database for PE/PV studies, methodologies, and even funding sources. Building on the work of ENCePP with the EU PAS Register®, information from the Register was migrated to the HMA-EMA Catalogues of RWD Studies in February 2024, which is now hosted on the EMA website[5]. Similarly, the ENCePP Resource Database is now the HMA-EMA Catalogues RWD Sources.

B. Independence

The second pillar of ENCePP's work is promoting the scientific integrity of studies by encouraging independence. This means that no one with a personal, financial, commercial, or institutional interest in the outcome of the research should be involved with it. Keeping this in

mind, ENCePP has developed a set of rules and principles for the independent conduct of PE/PV studies, called the ENCePP Code of Conduct[6]. The Code spans the lifetime of a research study – from the planning, funding, and conducting of a study, to the final reporting of the results.

C. Standards

Establishing a set of common standards for good research practices has been an important aim for ENCePP since its conception. There have been two tools developed to meet this aim. the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, and the ENCePP Checklist for Study Protocols. The Methodological Guide is a comprehensive document that consists of international standards, previously established guidelines, and references to published articles and textbooks. Any gaps in available resources on good research practice are filled in by ENCePP itself. It is reviewed and updated regularly, the most recent iteration (version 11) having been published in July 2023[7]. The Checklist for Study Protocols[8] promotes the quality and transparency of PE/PV studies by encouraging researchers to consider important epidemiological principles when designing their study protocols. The inclusion of the Checklist in study protocols is also recommended in the HMA-EMA guideline on Good Pharmacovigilance Practices (GVP) Module VIII[9].

Another tool developed by ENCePP is the ENCePP Seal[10], which is a mark of quality and compliance with the pillars of ENCePP. It is a certification confirming that the study was designed and conducted in concordance with (i) the ENCePP Methodological Guide, Code of Conduct, and Checklist for Study Protocols and (ii) International research guidelines such as the Declaration of Helsinki and the European Code of Conduct for Research Integrity. It also requires that the study protocol be registered in the HMA-EMA Catalogues before its initiation.

Organisation of ENCePP

The internal composition and governance of ENCePP reflects its nature as a network of centres hosted by the EMA. The ENCePP Steering Group (SG), formed in 2010, is composed of approximately twenty representatives from a variety of institutions both within and outside of the EU. This includes the Heads of Medicines Agencies (HMA), the Pharmacovigilance Risk

Assessment Committee (PRAC), the International Society for Pharmacoepidemiology (ISPE), the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Food and Drug Administration (FDA). The SG has two co-chairs, one from the EMA and one representing the ENCePP Partners. The EMA also provides administrative support through the ENCePP Secretariat. Apart from the SG, ENCePP also has three Working Groups (WGs) that address the different aims of ENCePP (Figure 1).

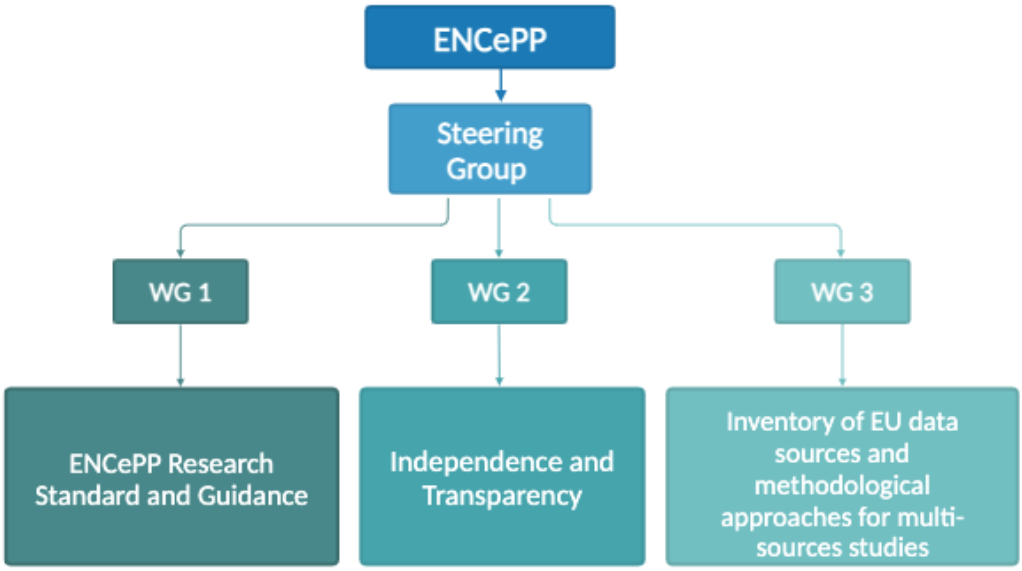

Figure 1. Overview of the current internal composition of ENCePP.

A detailed overview of the mandates, tasks, and people responsible for each WG can be found on the ENCePP website[11]. This is due to be updated in 2024-2025, as part of the most recent SG meeting was to revisit the division between the WGs and their mandates. Additionally, there are Special Interest Groups (SIGs) that are set up to achieve certain goals, after which they are disbanded – for example, there was a SIG on Drug Safety in Pregnancy in 2023[12]. Any registered ENCePP Partner can apply to become a member of a WG or a SIG. Participation in the SG, WGs, or SIGs, is completely voluntary and free of charge, as is becoming a registered ENCePP Partner.

Any public or non-profit organisation based in the EU and working in PE/PV research can become an ENCePP Partner. Some for-profit institutions such as certain Contract Research Organisation (CROs) are also allowed to become members. Although pharmaceutical companies cannot become ENCePP Partners, their expertise and value in conducting studies is

recognised by ENCePP Partners such as academic institutions and CROs, who often work with industry representatives. Since 2024, in the context of EMA's support to EU candidate countries, institutions from national medicines regulatory authorities in (potential) EU candidate countries may join the network as an ENCePP Partner, allowing them to benefit from ENCePP's joint expertise, contribute to WGs, attend the annual Plenary meeting, and participate in potential ad hoc trainings. As of February 2024, there are 226 institutions and 36 networks registered as ENCePP Partners across over 23 European countries (Supplementary 1).

Evolution of the Real-World Data and Real-World Evidence landscape

One of the most recent areas of rapid development is the use of Real-World Data (RWD). The EMA defines RWD as 'data that describe patient characteristics (including treatment utilisation and outcomes) in routine clinical practice'[06]/01/2025 07:30:00. The evidence generated from on RWD is known as Real-World Evidence (RWE). While the use of data collected from patients outside a clinic setting is not uncommon, especially for non-interventional PASSs, in more recent years the use of RWD in earlier stages of medicines development has increased[13,14]. There have also been investigations into the benefits of combining RWE with data from standard Randomised Clinical Trials (RCTs)[15,16]. During the COVID-19 pandemic, RWE played an important role in assessing the safety and effectiveness of vaccines, and contributed significantly to regulatory decision making[17].

The use of RWE in regulatory decision making has been considered by regulators in the EU and North America since as early as 2015, and several guidelines and frameworks have been developed[18]. Since then, and especially after the COVID-19 pandemic, similar documents have been developed in several other countries including China, Taiwan, Singapore, South Korea, Japan, Australia, and New Zealand[18]. The use of RWD/RWE in medicines regulation and decision making remains an important topic of discussion, as the RWD/RWE landscape continues to evolve[19,20]. There have also been initiatives set up to generate and analyse RWE, such as the Sentinel Initiative launched by the FDA in the U.S.[21], which is used to analyse electronic

healthcare data. More recently, the EMA launched the Data Analysis and Real-World Interrogation Network (DARWIN EU®) in 2022, which 'delivers RWE from across Europe'[22].

With all these developments in the RWD/RWE landscape on an international scale, the standardisation of methods, principles, and regulations become even more important. There are several documents, guidelines, and recommendations that have been developed keeping this in mind, some of which have incorporated aspects of the ENCePP tools. For example, the International Council for Harmonisation of Technical Requirements for Pharmaceutical for Human Use (ICH) M14 guideline on general principles for PE studies that use RWD[23], and the GVP Module VIII[9]. The RWD/RWE landscape is continuing to develop rapidly, especially with advancements in the use of Artificial Intelligence (AI), which could be used in RWD studies[24,25]. Considering ongoing changes and developments, it is relevant to assess the impact of ENCePP has today and explore the role it could assume in the future.

Aims and objectives of this study

The main aim of this study is to arrive at an understanding of the current and future role of ENCePP in an evolving RWD/RWE landscape. The study also aims to highlight the benefit and impact of ENCePP on the PE/PV research field, while illustrating areas for improvement and important points of consideration for the future.

A two-part qualitative research study to meet these aims. The first part consisted of a series of semi-structured interviews focusing on the opinions of and experiences with ENCePP, and the second part was a qualitative survey focusing on the use and experience of ENCePP tools. By speaking to stakeholders at varying degrees of involvement with ENCePP, we aimed to gain an in-depth insight into the challenges and opportunities for the network to stay relevant and adaptable to the changing environment.

Methodology

Interview Study

Study population

Data was collected through in-depth, semi-structured interviews with members from three layers of involvement (Figure 2) with ENCePP. Layer 1 (L1) was 'very active' members, defined as being part of the SG or WGs. Layer 2 (L2) was 'active' members who are ENCePP Partners but not part of the SG or WGs. Layer 3 (L3) was 'non-active' members, defined as not being directly involved in any ENCePP activities. This was mainly regulators and international stakeholders.

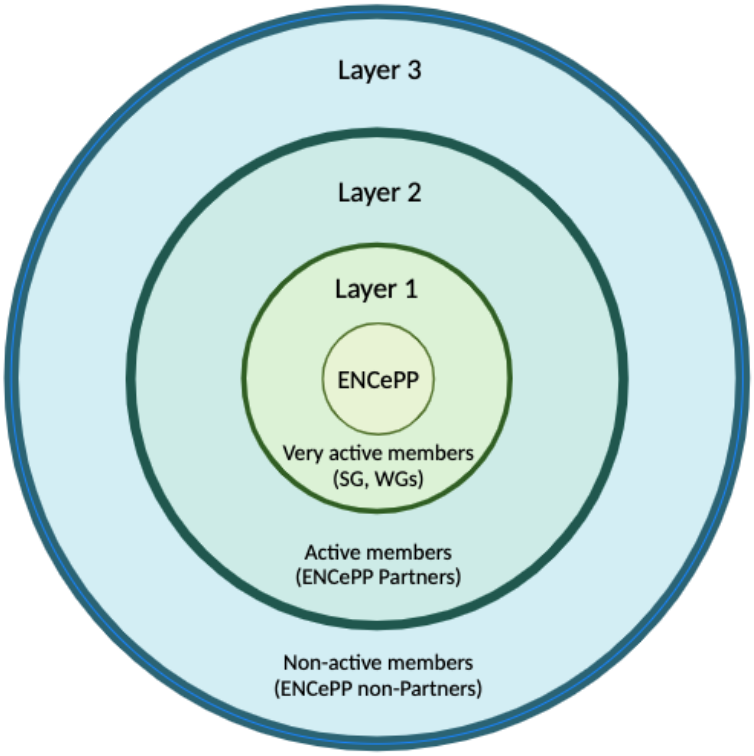

Figure 2. Three layers of involvement surrounding ENCePP from which interviewees were invited

In addition to the layer of involvement with ENCePP, potential interviewees were selected based on type of institution (Box 1) and geographical location. The aim was to have approximately 20 interviewees representing a diverse set of institutions and countries (N-E-W-S Europe, and a few beyond Europe).

L1 contacts, very active members, were found through the SG and WGs. L2 active members were found by searching through the HMA-EMA Catalogues for ENCePP Partner institutions. L3 non-active members were identified through suggestions from other contacts and looking at (international and European) regulatory bodies.

Box 1: Type of institution

i) Academic institution
ii) Regulatory body
iii) Contract research organization (CRO), for profit
iv) CRO, not-for-profit
v) Hospital/clinic
vi) Pharmaceutical industry
vii) Other (including learned societies)

Study design

The interview guide covered five major themes (Box 2), designed to get an in-depth insight into use, opinions, and experiences with ENCePP. The interviews were semi-structured, so follow-up questions were asked in addition to those present under each theme (Supplementary 2.1). The estimated duration for the interview was 30 minutes. To leave room for any additional comments, interviews were scheduled in 45 minute time slots.

Box 2: Themes in the interview guide

i) Knowledge and familiarity
ii) Use of ENCePP tools
iii) Experience (benefits and barriers)
iv) Role of ENCePP (currently)
v) Future of ENCePP

The interview guide was developed based on preliminary meetings with three ENCePP SG members (H.G., C.C., T.G.). Adjustments to the guide were made based on a pilot interview conducted before the official data collection phase of the study began.

Data collection and analysis

Contacts received an invitation letter (Supplementary 2.2) via e-mail from S.R., containing information about the study and a link to an online consent form (Supplementary 2.3). The form also contained questions regarding their availability, based on which a follow-up e-mail with scheduling options for the interview was sent.

The interviews were audio-recorded using Microsoft Teams[26], upon prior consent of the participant. The interviews were first transcribed verbatim using Amberscript[27], edited for accuracy (S.R.), and then qualitatively analyzed by thematic analysis using NVivo[28] (S.R). All sensitive participant data was anonymized or censored. For validation purposes, three interview transcripts coded by S.R. were reviewed by H.G. The codes were grouped together to form themes and sub themes, from which a thematic map was drawn (Figure 3.).

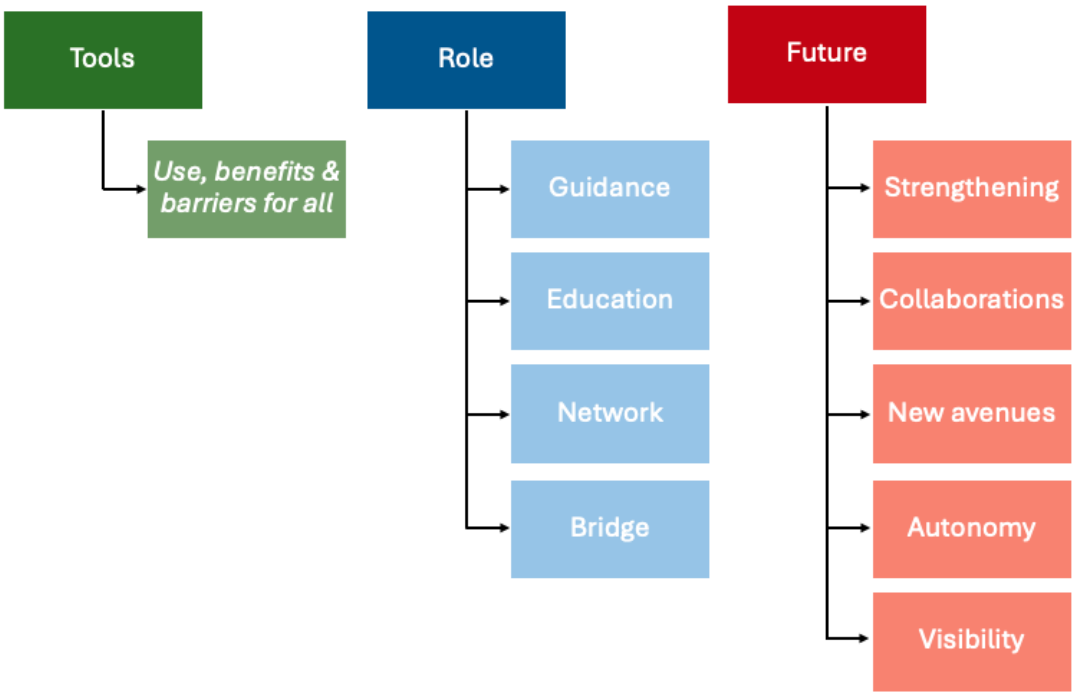

Figure 3. Coding framework used for thematic analysis, representing major and subthemes.

Qualitative Survey

Study population

The survey was distributed via the ENCePP Secretariat to all ENCePP Partners. It was also shared via LinkedIn and posted on the ENCePP website. The study population was therefore mainly ENCePP Partners, but it was also left open to any other interested stakeholders.

Similarly to the interview contacts, survey respondents were asked to mention the type of institution (Box 1) they worked at and the country in which they were based.

Study design

The survey focused mainly on the use of ENCePP tools, with a few additional questions about the network and future. There were 33 questions in total (Supplementary 3), divided into five sections (Box 3). The survey consisted of a mix of multiple-choice and open questions and was designed to take approximately 10-15 minutes to complete.

A draft of the survey was reviewed by ENCePP SG members and adjusted based on their comments. The section regarding the Code of Conduct was developed in accordance with discussions with WG2.

Box 3: Survey sections

i) Participant information
ii) ENCePP in general (use, benefits, barriers, and future)
iii) ENCePP tools (use, benefits, barriers, and improvements)
    a. Code of Conduct
    b. ENCePP Seal
    c. Checklist for Study Protocols
    d. Methodological Guide
iv) Regulatory perspective*
v) Additional comments

**Note: this was an extra section only visible to respondents from regulatory bodies. They were asked how they perceive studies conducted according to the Code of Conduct or having the ENCePP Seal as compared to those that don't.*

Data collection and analysis

The survey was designed and distributed using Qualtrics[29]. The software was also used to collected and record responses. All answers were anonymized, with identifying information automatically censored by the software. Respondents were given a total of five weeks to complete the survey, after which it was closed. The dataset of the responses generated by Qualtrics was then transformed such that results could be analysed using SPSS[30]. The responses could then be easily filtered through for analysis based on relevant characteristics, such as type of institution or level of involvement with ENCePP. Quotes from open text questions were used to compare opinions and experience of survey respondents with those of the interviewees.

Results

Participant information

The terms 'participants' is used to indicate all who provided input to the study. Those who completed the interview are referred to as 'interviewees', and those who answered the survey are referred to as 'respondents'.

In total, 80 invitations for interviews were sent out (Table 1). L2 active members (ENCePP Partners), had the lowest response rate, with only 6.67% of contacts following through to an interview. For the survey, only 58.4% the 89 of respondents completed the survey. The results discussed here are representative of the completed responses only.

Table 1. Overview of interviews and survey

	Interviews				**Survey**
Timeline	June – August 2024				September - October 2024
Average duration	30min				10min
	L1	*L2*	*L3*	*Total*	-
No. of invitations sent	20	45	15	80	
Initial no. of responses	15	9	8	32	89
Final no. of participants	11	3	4	18	52

The highest percentage of participants were from regulatory bodies (27.8% of interviewees and 38.5% of survey respondents), followed by academic institutions (Table 2).

Table 2. Participant characteristics: type of institution

Type of institution	**Count (%)**	
	Interviewees	*Respondents*
Regulatory body	5 (27.8)	20 (38.5)
Academic institution	4 (22.2)	14 (26.9)
CRO (for profit)	4 (22.2)	5 (9.6)
CRO (not-for-profit)	2 (11.1)	4 (7.7)
Hospital/Clinic	0 (0.0)	5 (9.6)
Pharmaceutical company	2 (11.1)	2 (3.8)
Other	1 (0.6)	2 (3.8)

65% of survey respondents identified as ENCePP Partners. Additionally, the survey respondents were asked to indicate their country of residence (Table S4.1), number of years of experience they had with NIS (Table S4.2), and years of involvement with ENCePP (Table S4.3). The highest percentage (40.4%) had between 6-15 years of experience with NIS. For years of involvement with ENCePP, which was defined as being part of the network or using ENCePP tools, the highest percentage (36.5%) was 1-5 years.

Theme-wise analysis

The major themes divide the results into the ENCePP tools, its current role, and possible future positioning. There were several subthemes that will be addressed in the following sections. Quotes from interviewees are cited using an anonymised code denoting layer of involvement (eg. L1xx – very active, L2xx – active (Partner), L3xx – non-active). Quotes from respondents are cited as 'svr'.

Tools

Questions were posed to the interviewees and respondents regarding the use, benefits, barriers, and areas of improvement for each tool. These are discussed in further detail in the following subsections.

A. ENCePP Toolkit

Several interviewees spoke of their experience with the ENCePP tools in general. One common theme here was education. *"I always encourage my students to check these documents [ENCePP tools in general] before starting a study. I think it's a really important road map to organize pharmacoepi studies." [L109]* Another was communication, for example when collaborating with pharmaceutical industry partners. *"We have in our contracts [that] we have to follow the methods, guides, and the code of conduct, because that's the standard we want to comply with... it's always very convincing if you say 'but this is said in the standard in the methods guide, so we have to do it like this, or 'you cannot be involved in the discussion anymore, because of the code of conduct.'"* [L103]

The ENCePP tools are often used as reference documents. This refers to individual use by researchers, and for larger institutions developing their own material using ENCePP as an inspiration. *"ENCePP, I think has been very valuable in the sense that it's very well resourced and a lot has been produced out of ENCePP. So for smaller regulators, where we don't necessarily have the same level of capacity, it has been very valuable to be able to look to that and to kind of inform our activities, our guidance." [L302]*

The main area for improvement identified was the frequency of use of the tools within the ENCePP community. "*It's not that all researchers being a member of ENCEPP use [the tools] themselves, and I think it's quite strange. So, you make some [measures of] quality, but your own members are not the ones who stick to it."* [L102] This sentiment was echoed by other L1 (very active) interviewees, who felt that the use of the tools within the ENCePP community could be increased in the future. "*I think it's time to use [the tools] as a network – not only present them, but also to use them."* [L109]

B. Code of Conduct

The ENCePP Code of Conduct is one of the most well-known ENCePP tools, mentioned by a majority of interviewees. L2 active members seemed to be more familiar with the Code of Conduct than with the Methodological Guide or any other tool, while L3 non-active members were not very familiar with the Code of Conduct. It was mentioned that seniority in position was more likely to warrant familiarity. *"I'm not the right person to ask. That would be the honest answer, because I'm not the principal investigator of studies, so it's not something that I deal with directly."* [L110] Other interviewees expressed a similar sentiment – *"Now that you mention [the Code of Conduct], it does sound familiar. I think our medical or scientific leads have read those and probably adhere to them in a large part."* [L201]

For those that were familiar with the Code, its main uses and benefits were in facilitating collaboration with the pharmaceutical industry and promoting the independence and transparency of research (Figure 4). Several respondents from regulatory bodies reported not using the Code of Conduct, which overlaps with the low levels of familiarity expressed by L3 non-active interviewees with a similar background.

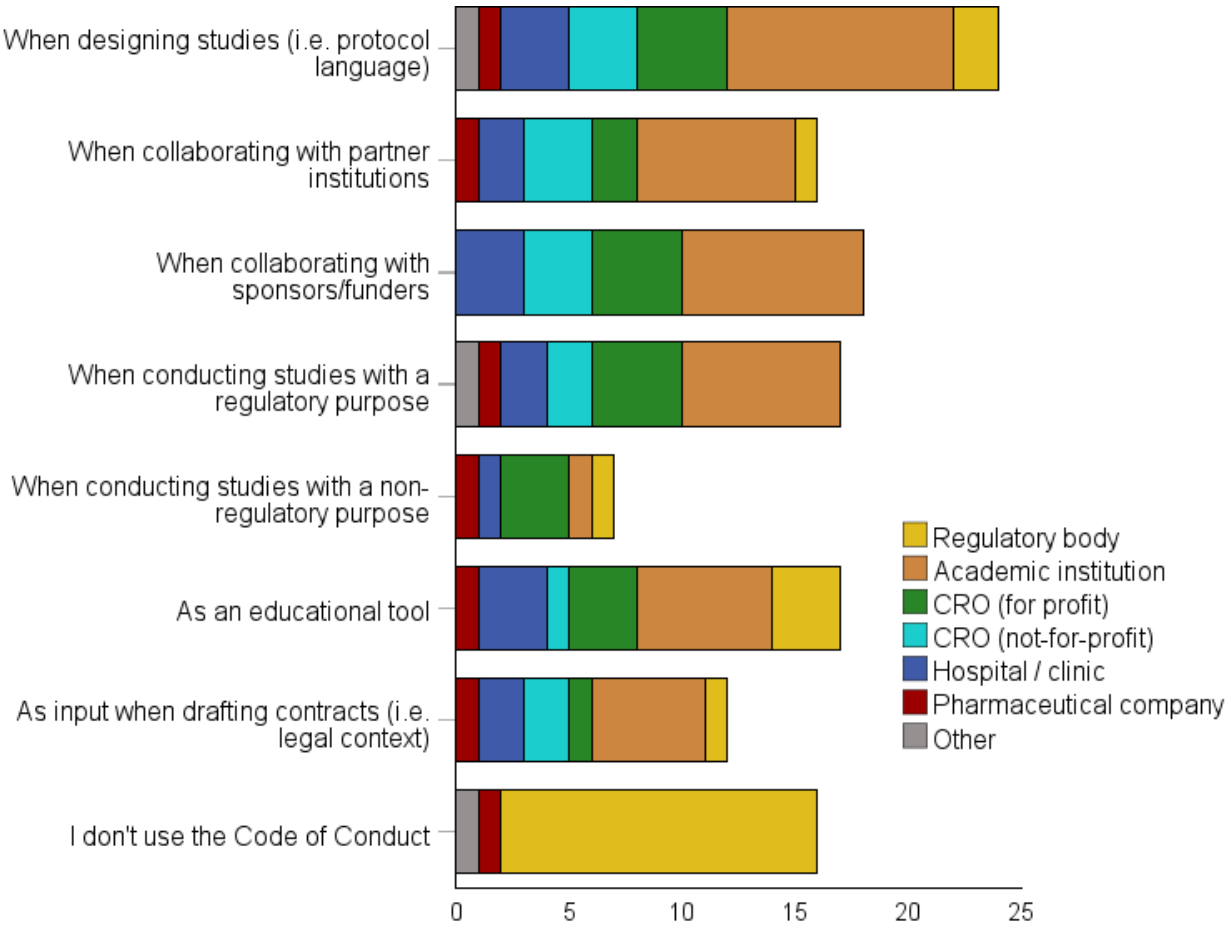

Figure 4. Use of the Code of Conduct as expressed by survey respondents (n = 50/52), marked by type of institution.

For benefits, barriers, and improvements related to the Code of Conduct (Table S5.1), respondents were asked to provide their answers in an open text box. One benefit of the Code is that it facilitates ethical collaboration between CRO and sponsors/pharmaceutical industry. This was also brought up by interviewees. *"[The Code of Conduct is] something that we continuously need to revisit when we get research ideas, and for instance proposals that originally come from the industry, [to see] whether we can collaborate and what are the terms and conditions in which we could do collaboration research studies."* [L202]. A second benefit mentioned was the protection of transparency and quality of research. This was also mentioned by interviewees, who also saw the Code of Conduct as necessary foundation for publicly owned research centres – *"[We] could not participate in pharmacoepi studies if there was no code of conduct...post authorization safety studies funded by pharmaceutical companies would be*

incomprehensible to the public and to our stakeholders if we didn't have the code of conduct." [L104]. Lastly, survey respondents expressed that the Code provides clear regulation and guidance on study design, including a legal model that is beneficial to their work.

There were also few barriers and areas for improvement that came up. The first was a lack of clarity on the regulatory benefit, which could deter sponsors from wanting to comply with the Code of Conduct. *"Particularly I see an area for improvement [in] the relationship with regulators and correspondence of the understanding of the relevance of the ENCePP Code of conduct...having some feedback or support from the regulatory agencies regarding the practical benefit of following the ENCePP guidelines, the ENCePP Code of Conduct, and how they make sure that this is valued and accounted for when they review protocols, statistical analysis plans, and more so when they review study reports."* [L111] Another area mentioned by the respondents was that there is sometimes a *"misinterpretation about authorships of industry partners when code is used."* [svr] Finally, some participants felt that the Code is not visible enough, especially considering that there are possibly other documents. *"There's not just the EMA out there with various codes of conduct or guidances. There's many agencies, particularly in the world of Real-World Evidence - it's an explosion." [L304]* Given the number of documents pertaining to observational studies, it is possible that the Code is *"not the first choice."*

Some suggestions for the future include increasing visibility Code of Conduct in more *"stakeholder groups for observational research (local governmental institutions, MAH and academics)"* [svr]. The other aspect of this would be *"that EMA, PRAC, HMAs give value/recognition to its use, [for example] through asking about the transparency and independence practice at the time of protocol and report reviews."* [svr]. Some participants felt that making it mandatory to use the Code could be beneficial. *"Why doesn't EMA [make it obligatory]? If you do research and EMA is going to pay you for the research, then this research is definitely independent from industry, and follows the Code of Conduct, but they're not doing that. And if it's not [obligatory] then, well, it's voluntary and then it's not used."* [L102]

C. ENCePP Seal

The ENCePP Seal is the least used ENCePP tool, with many participants being unaware of its existence. 67.3% of respondents reported never having applied for the ENCePP Seal. Those that had applied did so mainly when conducting studies with a regulatory purpose. A couple of participants reported using it to show their adherence to the ENCePP core principles, and to demonstrate the quality of their protocols. *"Going through all the requirements [for the Seal] improved our thoroughness... I would personally apply for it in the next project again."* [svr]

One of the main reasons for low use was the lengthy process and extensive criteria required to obtain the Seal, which can deter sponsors from going through the process of applying for it. The requirement to make data available is also a strong deterrent as in many cases it is not possible. Similarly to the Code of Conduct, another barrier mentioned was the lack of awareness regarding the regulatory benefit.

There were a few suggestions for the future, should the Seal continue to be active. The first would be to clarify the regulatory benefit. *"When it comes to the Seal, to be honest, the process is not transparent to assess what [it is] and the burden [is]...If we want to pursue the ENCePP Seal we should be clearer with the message - and what are the advantage? Because I'm not sure what are the advantages to have an ENCePP Seal."* [L303] In terms of visibility of regulatory benefit, a survey respondent stated that "*acknowledgement/recognition by EMA, PRAC, NCA of the value of application of transparency and independence principles though the Seal*" [svr] would increase use. Some also felt that increased visibility of ENCePP itself would increase the impact of the Seal, leading to increased use. Finally, there were some suggestions to make application for the Seal a mandatory part of conducting studies for a regulatory purpose.

D. Regulator responses

One of the barriers mentioned for both the Code of Conduct and the ENCePP Seal were lack of clarity on the regulatory benefit. Questions regarding this were posed to respondents from regulatory bodies (n = 20) to investigate this (Table 3). They were asked if they see ENCePP tools in their work as a regulator, to which 75% of respondents answered 'yes'. They were also

asked if they perceive studies conducted according to the Code of Conduct, or with the ENCePP Seal, to be of a higher quality that those that don't.

Table 3. Regulator responses.

Responses	Count (%)	
	Code of Conduct	*ENCePP Seal**
Yes	11 (55)	12 (60)
No	3 (15)	4 (20)
Other (open text)	4 (20)	3 (15)
	"Perhaps, depending on the type of study."	*"It may give greater trust, but not entirely."*
No answer	2 (10)	1 (5)

**Note: studies with the ENCePP Seal are required to comply with the Code of Conduct.*

E. Checklist for Study Protocols

The Checklist for Study Protocols was mainly discussed by L3 non-active members, though some L1 very active interviewees mentioned being familiar with it. This could be related to the type of institution, as regulators and CROs are more likely to encounter the Checklist based on the nature of their work. A similar trend could be seen in the survey responses (Figure 5).

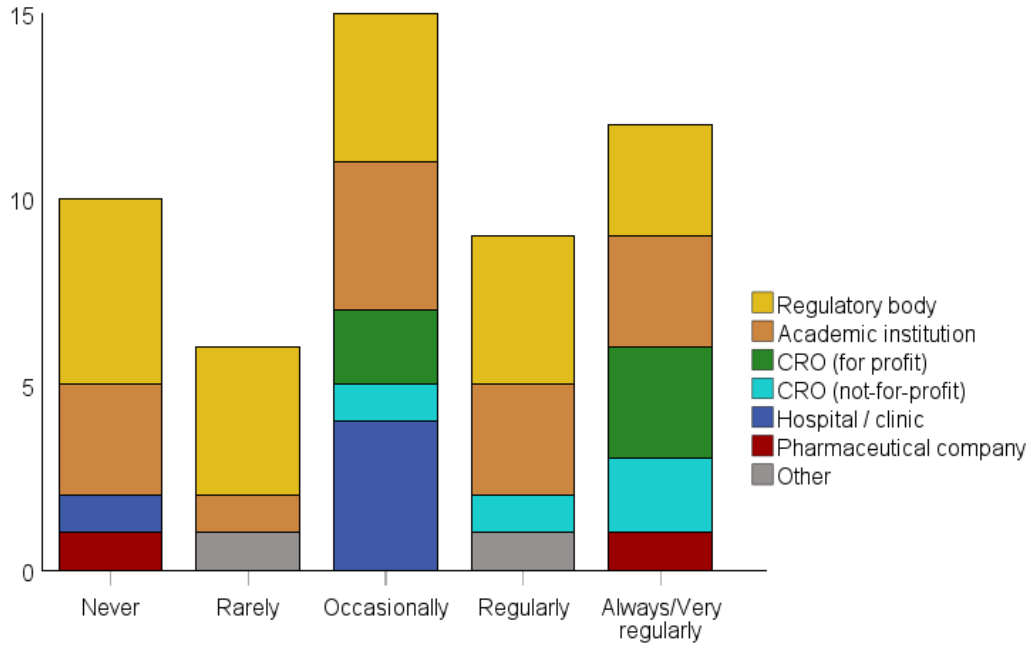

Figure 5. Frequency of use of the Checklist for Study Protocols by survey respondents (n = 44/52), categorized by type of institution.

The interviewees and survey respondents had similar responses in terms of use, benefits, and areas for improvement. 61.4% of survey respondents reported using the Checklist when designing studies, stating that doing so provides "*confidence that all aspects have been considered.*" [svr]. Several survey respondents, mainly those from regulatory bodies, also reported using the Checklist when assessing studies for PRAC and evaluating PASS study protocols, *"to check if the company responsible for the PASS have answered the checklist appropriately as an indicator of good study conduct."* [svr] They also reported that it "*aids in structuring the review of a study protocol."* [svr]

Interviewees mentioned using the Checklist as a reference template during the development of other documents. *"We participated in the development of a guidance document on reporting in studies that use Real-World Evidence. And so [the Checklist] was definitely considered through the development of that.*" [L302]

The Checklist is also used widely as an educational tool. *"The Checklist for Protocols I sometimes use, but actually mostly for teaching purposes, because for publications we normally use the ones which are more present with reviewers.*" [L103] This quote also highlights one of the main barriers mentioned, which was the presence of other checklists. This included internal checklists and ones requested by journals such as RECORD-PE and STROBE. While for some participants, this meant lower use of the ENCePP Checklist, others expressed a preference. "*[The ENCePP Checklist] is very complete and easy to use. I also trust its content and the fact that it gets updated, so I prefer going there directly instead of searching for other popular checklists for protocol evaluation."* [svr]. For some, the differences between the available checklists proved to be quite challenging. "*In case the protocol is not structured according to the ENCePP Checklist, and the information is scattered in different parts in different order it is a challenge for the assessor. Companies outside EU follow different structure of the protocol. Then we have to ask the company to resubmit the protocol to be in line with the EU requirements."* [svr] One of the main areas for improvement, suggested by several participants, was a higher degree of alignment between these checklists.

Some respondents also felt that the Checklist needed to be update on other fronts, for example, to clarify some items and update the page numbers. A few participants felt that the criteria were too extensive. *"Sometimes when you listen to some people who are not actually conducting these studies, they have too ambitious demands for what should be documented, for example, in the protocol phase."* [L107] One respondent suggested the creation of a manual or training to make it easier to use. Several participants mentioned visibility as an area for improvement. Suggestions for this included making it mandatory and increasing accessibility via the EMA, for example through inclusion in EMA templates for format/content for PASS protocols, and in future guidance/updates.

It is relevant to note that while there were several comments regarding barriers and areas for improvement, 58.1% of respondents reported facing no barriers in their use of the Checklist for Study Protocols.

F. Methodological Guide

The ENCePP Guide on Methodological Standards in Pharmacoepidemiology is one of the most well-known resources developed by ENCePP. *"The methodological guide is an everyday, go-to resource, [and] I think for everybody in the world, frankly, not for me only."* [L104]. There was a slight difference in the reported frequency of use between interviewees and respondents. A majority of interviewees, mainly L1 very active members and L3 non-active members, brought up the Methodological Guide and discussed several benefits. However, only about half of the survey respondents reported using it 'occasionally' to 'very regularly', with other half using it 'never' or 'rarely'.

The uses and benefits (Figure 6) mentioned were similar, with majority of participants using the Methodological Guide for educational purposes. *"The ENCePP Guide, I know is used a bit everywhere, because this is one of the only guides of this type that exists, and with so many references that are directly accessible by researchers. So I know it is used, for example, for training, by many universities around the world." [L105]* The Methodological Guide is used frequently as a reference document during the design and conduction of studies. *"So before I knew ENCePP I would go to epidemiology textbooks, but now I can go to guidelines, and they*

are actually updated more than usual textbooks." [L301] It is also used during communication with collaborators, for example *"to address queries from sponsors whether this is a regulatory acknowledged approach."* [svr] Similarly to the Checklist, survey respondents from regulatory bodies stating using the Methodological Guide in their assessment of PASS protocols.

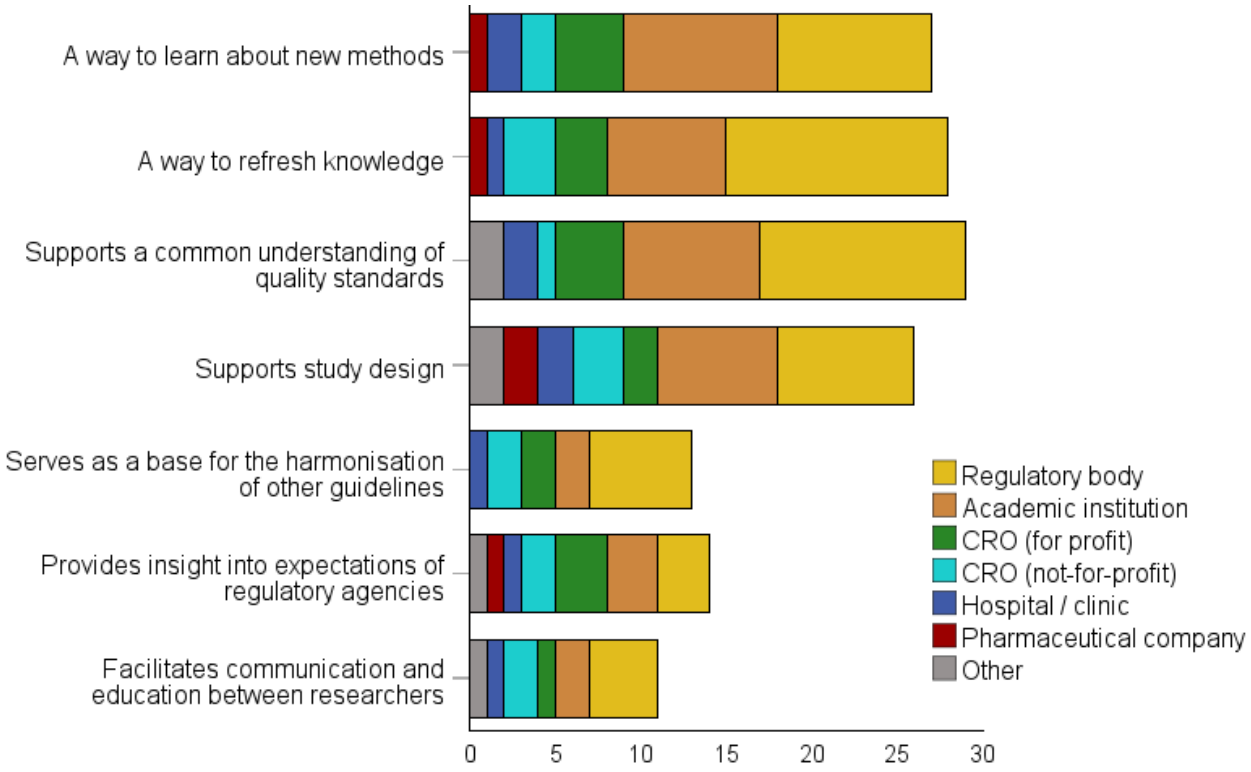

Figure 6. Benefits of the Methodological Guide by survey respondents (n = 52/52)

Additional benefits mentioned by the respondents included facilitation of communication and education between assessors, and increasing quality of PASS assessments.

While 78.9% of respondents reported not facing any barriers in using the Methodological Guide, there were a few points that came up. One of these was the length of the document. *"Some of these toolkits are quite long documents. I can fully understand that it's not easy, and they need to cover many different cases. And they need to protect researchers from any difficulties that they might face in in each case... But we need to give the most important information at a glance, and then whoever is interested can go to each point and see more details there."* [L109] Some suggestions for this include creating an "*executive summary of the guide"* [svr] and making it a "*digital tool that can be updated more frequently and is fully*

searchable, including cross-links." [svr] At the same time, several respondents said the format of the Methodological Guide, based on literature references, was useful, as it "*keeps the content concise and I can choose whether I want more information on the topic or not, and if I do the reference is already there."* [svr] Another suggestion was to include more input from the ENCePP community and be open for discussion on additions. *"It seems to be a tool to insert methods, where not all community actually agrees (e.g. issue on negative controls, and calibration) not transparent how things that may be controversial end up in the Guide."* [svr]

Another area for improvement was the inclusion of more diverse topics. Some suggestions for these topics can be seen in Box 5.

Box 5: Suggestions for topics to be included in the Methodological Guide

i) Drug utilization studies
ii) Disease burden, incidence, and prevalence studies
iii) Natural history studies
iv) AI in RWE
v) (More) Target Trial Emulation
vi) Genetic and familial confounding / paternal exposure
vii) Section on how the regulatory agencies should use these studies for making a decision (e.g., would further studies be required if the one submitted doesn't meet the quality standards? If bias cannot be mitigated but that's the best evidence we have, should we make a decision or wait for more data?).

Finally, as with most of the other tools, increasing visibility was mentioned as an important future step. *"Sponsors do not always see the necessity to follow the methods described and want to use 'old', 'standard' methodology."* [svr] There was also a comment about difficulties in citing the Methodological Guide. A suggestion to improve visibility was to *"disseminate widely - EMA, PRAC, NCA to query about adherence to guidance when reviewing protocols and reports."* [svr]

Role

Participants were asked how they made use of ENCePP, and what their experience of it is. A high percentage of survey respondents (86.5%) reported using ENCePP tools, followed by attending the Plenary meetings (40.4%) and participating in the WGs, SG, or former SIG (30.8%). The interviewees had similar responses in terms of use and familiarity, and were later

asked what they saw as the key role of ENCePP today. The identified subthemes were network (including WGs), guidance, bridge, and education through establishing common standards. These themes also overlap with the benefits survey respondents stated that they get from ENCePP (Figure 7). Additional details that came up during the interviews are discussed in the following sections.

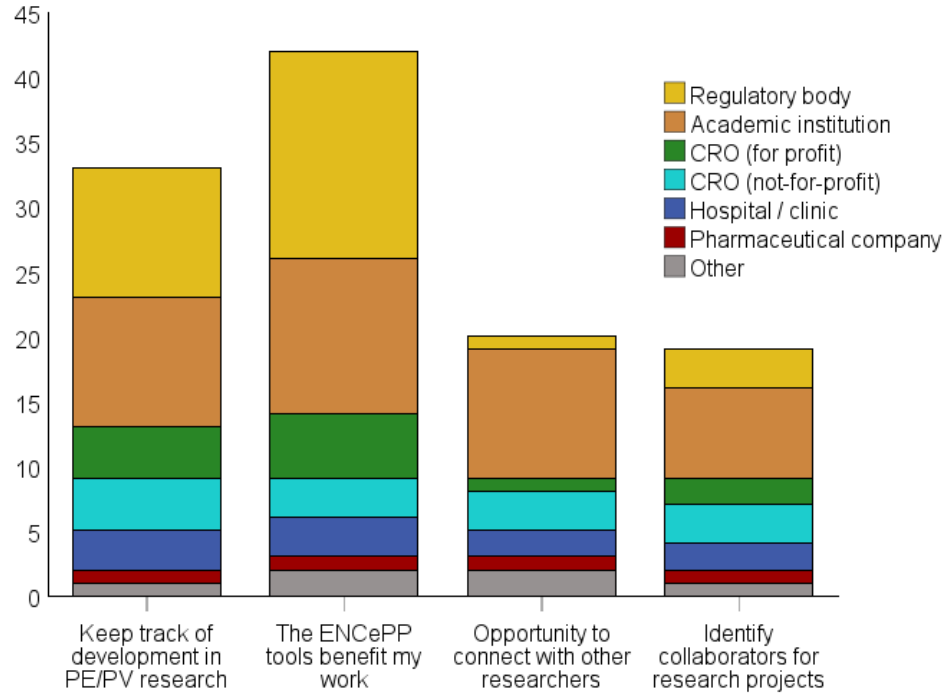

Figure 7. Benefits from ENCePP from survey respondents (n = 52/52)

A. Network

The benefits related to the ENCePP Network and WGs included connecting with other researchers, identifying collaborators for projects, and keeping up to date on developments in the PE/PV research. Many interviewees also saw this as the key role of ENCePP today. *"For me, ENCePP is, let's say, like a church or a meeting point, a library and cafeteria for pharmacoepidemiologists. A place where we know that there are colleagues with the same interests where we can ask for methods, for guidelines, for templates, for examples – in which we can express our ideas and get comments from others." [L106]* An overview of the key quotes from interviewees regarding benefits and barriers of the networks and WGs are presented in Table 4.

Table 4. Overview of benefits and barriers of Network and WGs from interviewees.

Main themes	Relevant quotes
Benefits	
Keeping up to date on developments	*"Being part of the SG is a great benefit to understand the hot topics of discussion in the pharmacoepi world, in Europe, and also from an EMA point of view, so how EMA is thinking on certain topics or what direction they're going to take." [L110]*
Connecting with other researchers	*"For me, it's like an opportunity to learn and grow professionally since in this working group we are conducting several studies... I actually have the opportunity to know the most important researchers in Europe, because most of them are involved in ENCePP." [L101]*
Cross-institution collaboration	*"Sometimes I feel like we are too siloed - people who are pharma industry do their thing, and people who are in academia do their thing. So [ENCePP] is a good forum for collaboration." [L107]*
Cross-country collaboration	*"There are no other research groups in Greece involved in PE. But in PE it's more than important to build a network of collaboration, and I think that ENCePP gives us this tool to start collaborating with each other." [L109]*
Barriers	
Time constraints and visibility	*"It's more agenda problems, it's not that I don't want to go." [L102]*
	"All of us are very busy and do not have time to check the ENCePP website...more newsletters or some general information about activities [would be beneficial]." [L203]
Administration of WGs	*"[WG meetings are often] scheduled in the last minute... but it's easier if there are more heads up and the meeting minutes come close to the meeting - if you get the minutes two months later then nobody remembers what the discussion was like." [L107]*
Scheduling of events	*"I've seen the preliminary invitations, but I think that autumn is always very busy? Because of the ISPE meeting, and then we have the Nordic Pharmacoepidemiology network meeting always in November. So I think that this ENCePP Plenary is always at the wrong time." [L202]*
Reduced in-person meetings	*"We are now used to all these teleconferences, which are more distant, and all the charm of ENCePP – which was like talking to people all over Europe who were experts in their field and now very reachable – that was a bit lost...it was a sad time because first during Brexit we were not able to have these meetings, and then came the pandemic. For some meetings that was okay, for other things, but especially for ENCePP, I think it was a big loss." [L103]*
Lack of resources	*"One of the difficult things [in voluntary work] is to survive...of course, you get your name in participating and you can influence what is done, but it's really difficult to have people constantly developing new things without being considered." [L106]*
Representation of stakeholders - pharmaceutical industry, CROs,	*"I think ENCePP could leverage more industry... I think we could get more out of it if we had more pharmacoepi representatives discussing methods and providing updates from their side... and really [having] discussion – not product related, [but] really scientific discussion so there is no conflict of interest. I think this could be a way to try to have more resources in ENCePP." [L110]*

international regulators, patient organisations	*"We on the CRO side, who are really the users of the ENCePP materials - I mean certainly the checklist and registering the studies and so on - I think that it's necessary that we are represented in these forums...my ultimate point is that – the people who actually do these studies, in practice, that their voice [should be] on the table as well." [L107]*
	"If we can get that greater involvement... less of an observer type role in the steering committee and more actually being an active contributor, I think that would definitely be helpful so that we can leverage the collective power across the different jurisdictions of all the experts that we have." [L303]
	"I think that we can build an interprofessional collaboration with patients in terms of ENCePP, which is very crucial. And since we're not sure if EMA can build such network with patients, I think ENCEPP it's much more easy for us to build this network to collaborate with them. Also to build a stronger network with industry." [L109]

Similar barriers and areas for improvement were mentioned by interviewees and survey respondents (Figure 8). Some additional suggestions included webinars from expert researchers in the field, trainings, and increased recognition of the ENCePP community from the EMA.

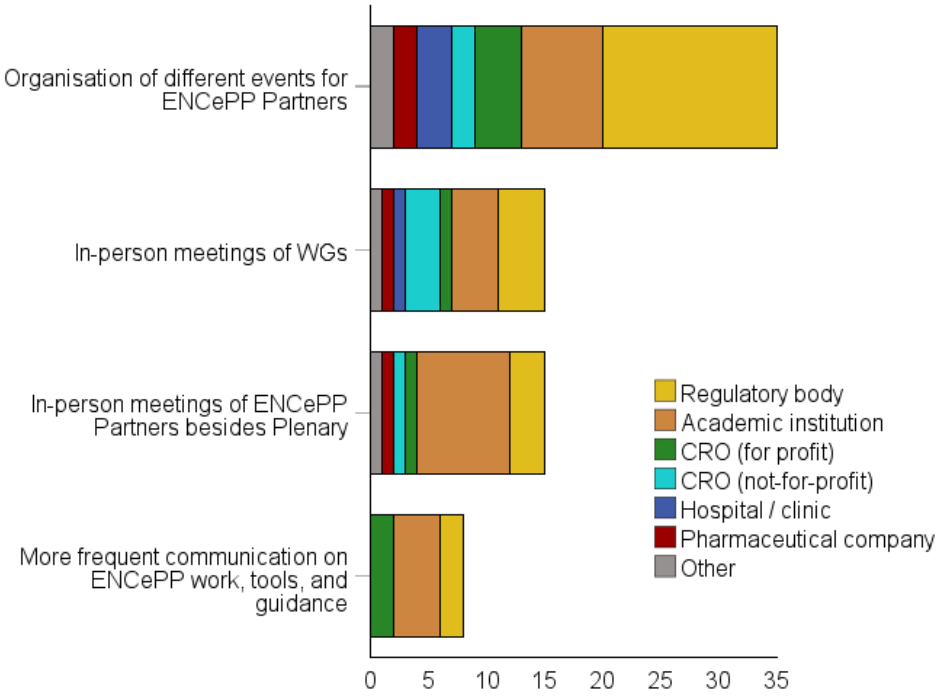

Figure 8. Areas for improvement of ENCePP Network and WGs from survey respondents (n = 49/52)

B. Guidance

ENCePP is revered as a source of guidance, both through the ENCePP tools, which directly offer guidance for good and ethical research practices, and through the long-standing name of ENCePP, in which trust has been built over the years. *"It's not only a regulatory perspective, but*

also a set of methodologies and guidelines that key experts are developing to help researchers conduct their studies... it's really important for the conduction of observational studies, not only in Europe but also worldwide." [L101] Another interviewee expressed a similar sentiment – "*The role of ENCePP is] to keep the balance of encouraging people using RWD, but also teaching them how to do it right."* [L103] The advice and recommendation given by ENCePP hold a lot of weight, not just in the PE/PV research space, but also in the emerging and evolving RWD landscape. When asked about the key role of ENCePP, one interviewee responded – *"To raise the level of methodological rigor that we see in studies that are going to be generating Real-World Evidence."* [L304] Another interviewee [L301] referred to ENCePP as a 'central hub for everything there is to know about RWE', further highlighting both the network and guidance aspects of its role.

C. Bridge

ENCePP also plays an important role in bridging different stakeholders in the PE/PV research field. *"[The role of ENCePP is] to bring together EMA, industry, researchers, and patients."* [L109] The interviewee clarified that including patients would be more of a future step for ENCePP, while the current role is in creating a platform through which regulatory (in the form of EMA), pharmaceutical industry, and researchers (both academic and non-academic) can meet. Interviewees from various institutional backgrounds mentioned the value of being able to connect with colleagues from different sectors through ENCePP.

D. Establishing common standards

Another important role of ENCePP was the establishment of common standards for research practices and conduct. *"I think that the standardisation of studies / the conduct is a very valuable thing... so as an industry, or niche industry, you're able to have more common standards. It's not that everyone has to do it on their own, and it may also prevent a big of the lower quality observational studies that have also been out there."* [L201] Many saw the role of ENCePP as providing tools that can be used to educate on the best practices for conducting high quality, ethical research studies. *"[The role of ENCePP is] providing guidance to the academic and industry collaboration and making sure that we will get important PV studies done." [*L202*]*

Participants also see the value of ENCePP's work in this beyond Europe. *"I see the key role of ENCePP as providing the tools and the guidance to try and increase that consistency and understanding across Europe, but also contributing more globally through the communication of their guidance, their principles, their code of conduct - so that other regulators are also informed and we can have better discussions, [and see] how we can better collaborate together."* [L302] In this way, ENCePP has a direct influence on the standardization of research practices and conduct, and the ENCePP tools are used to educate and aid collaboration globally.

There were also several participants that were quite unsure what the role of ENCePP was/is supposed to be and requested more clarity on the matter in the form of a clearly defined objective. *"My personal opinion is that [ENCePP's objectives] are still a bit vague, and then even the impact is a bit vague."* [L110] Interviewees all three layers of involvement with ENCePP expressed a similar sentiment, suggesting that proximity to ENCePP activities isn't necessarily the deciding factor for clarity on its goals.

Future

Participants were asked where they see ENCePP in the future. The subthemes that came up in the interviews (Figure 3) were strengthening, collaborations, new avenues, autonomy, and visibility. Similar themes can be seen in the answers given by survey respondents (Figure 9).

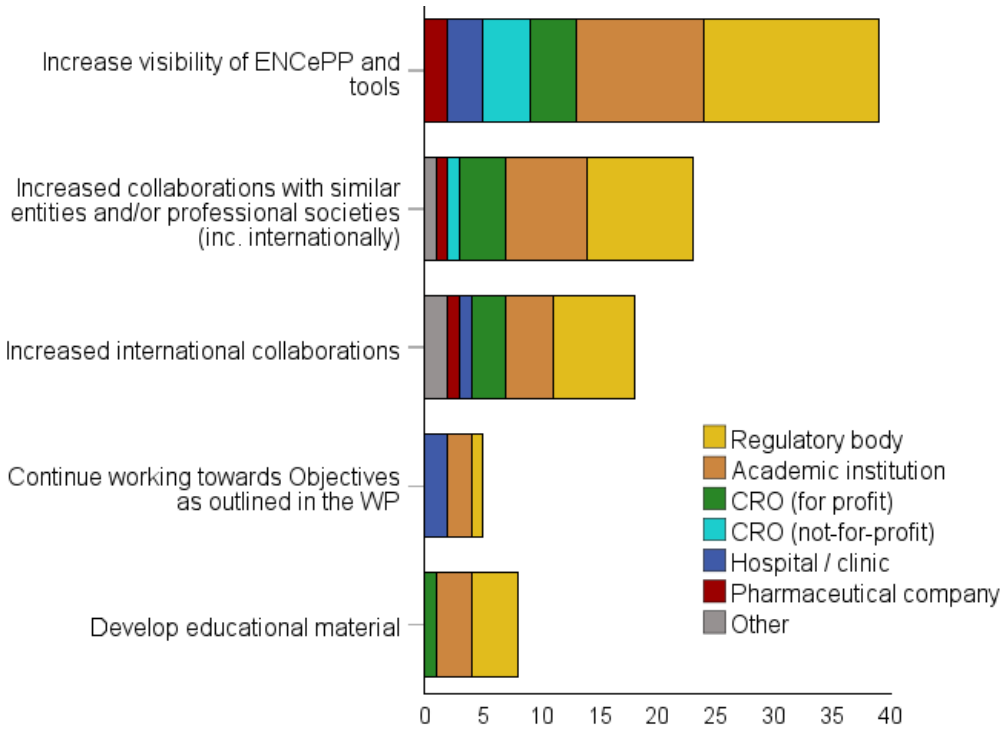

Figure 9. Areas to focus on in the future as given by survey respondents (n = 51/52)

A. Strengthening

Several participants felt that ENCePP already has a strong position, and the best course of action for its future would be to strengthen the tools and the network. *"[ENCePP is] a reference point for researchers in pharmacovigilance in pharmacoepidemiology. I think that there's a strong interest in maintaining this network, and maybe it could be stronger and stronger within five, ten years." [L101]* This was also reflected in the surveys, with 9.8% of respondents voting for ENCePP to continue working towards the objectives outlined in its current work plan. Other interviewees felt similarly, reflecting on the period of low activity in the last few years. *"I think ENCePP should just go on as they are doing and try to catch up with that was lost during the pandemic." [L103]*

B. Collaborations within the EU and internationally

39.4% of survey respondents indicated that increasing collaborations, both within the EU and internationally, would be an important future focus for ENCePP. This was mirrored by some interviewees who brought up a few different aspects of EU-collaborations. *"[Having] more connection with things like the EHDEN Foundation with those sorts of European data sources, I*

think [would be beneficial because] it still is a barrier and a challenge for people to figure out, 'how do I implement a study across Europe'? Can these databases, can they speak to each other? The transferability of data [is] an area where ENCePP could branch into more." [L304] Several interviewees brought up the relationship with DARWIN EU®. *"It would be interesting to know how DARWIN EU is related or using or connected with ENCePP as well, because DARWIN EU is a very specific EMA effort...industry is not really part of that and allowed to be part of that - however, from a methods point of view, we have lots of questions as to how DARWIN EU is implemented."* [L304] The collaboration between ENCePP and EMA committees was also mentioned. *"Maybe ENCePP could discuss how they can ensure that in all the committees the EMA has where RWD is there, that someone who has RWD experience is there – because at the moment it doesn't look like that. I think they should address it because we are the RWD experts and there's not much opportunity for RWD experts to be involved."* [L103] Another aspect of collaborations within the EU was an *"interprofessional collaboration with patients"* [L109], which could be *"crucial"* in ENCePP's future. L109 goes on to suggest that ENCePP could start by having meetings between ENCePP representatives and patient organization representatives, with possibly creating a fifth working group in the future specifically referring to patients to increase the collaboration there.

While ENCePP is first and foremost an EU based network, more than half the interviewees mentioned the possibility of ENCePP expanding its international presence in the future. "*The 'European' bit doesn't have to be anything restricting... [more] collaborations with others outside Europe, definitely."* [L110] The idea of expanding more into a global space was also brought up in the context of ENCePP's future position in a fast-evolving RWD landscape. *"I think Europe cannot be isolated in this effort ... [we need to make sure that] ENCePP collaborates and is also open to contributors and experts and hearing other voices regardless of location."* [L111] Some interviewees saw ENCePP taking on a leadership role here. *"ENCePP is long standing, it's been around a long time, and it is very comprehensive, so I could see it take a leadership role in creating a common threshold for methodological rigor globally*." [L304] They expressed support for the idea of ENCePP working internationally towards harmonization. *"Being cognizant of the landscape and developing what's needed based on the other gaps that are not being filled, and*

especially looking at it probably from the European context, but also considering more of that international context." [L302] Interviewee L302 acknowledged that part of ENCePP's uniqueness is that it focuses on the European perspective – however, they would be open to further discussions on perhaps having a greater degree of involvement in ENCePP. Collaborations with other active bodies in the PE and PV research space from non-EU countries were also mentioned. *"There's probably a US equivalent [of something like ENCePP], an Asia equivalent, or in larger countries. There potentially could be interest in that alignment, might be logical to explore that."* [L201] Another example of how this could look was highlighted by interviewee L301's experience of being involved in the development of guidance documents for a non-EU country, wherein they consulted the ENCePP documents for reference. This experience led them to reflect on a possible future role for ENCePP as "*the central hub for pharmacoepi for Europe, but perhaps also being a learning experience or an example for other countries as it becomes more and more known."* [L301] While many participants were in favour of ENCePP expanding globally, others expressed some doubt as to how successful this might be "*because there is also ISPE which attracts a lot of people and is more naturally an international network than ENCePP*." [L105]

C. New avenues

Participants identified several areas where ENCePP could play a role in the future through the adoption of new roles or development of new tools. One of these was the facilitation of RWD and PASS studies. *"I see somewhat of the role now, but perhaps more of a future role – more clarity, more intentional opportunity for government, industry, academic to collaborate... meetings, private-public partnerships... co-authoring, co-working can really be a help here, with the intent that this is about methods, this is about science."* [L304] There was some difference in opinions regarding whether ENCePP should conduct studies itself or not. Some participants believed it would be an important step in terms of collaboration, while others thought it wasn't and shouldn't be the role of ENCePP. Some respondents felt that ENCePP should keep its focus on *"methodological best practice[s] in pharmcoepi studies,"* [svr] and to *"focus more on academic research/science, [as] in later years it has been [focused on] too many members outside the academic environment."* [svr]

Participants also saw ENCePP helping different countries develop their PE/PV research fields. *"Facilitating, maybe finding, [or] helping to find partners, or joining some projects... [in] some Central European countries, such kind of studies is a little bit underdeveloped. So helping folks like Lithuania and other Central European countries to develop such studies. [There are] very nice possibilities through collaboration to involve [these countries]."* [L203] Similarly, some interviewees saw ENCePP "*being this learning experience or an example for other [non-EU] countries, as it becomes more known."* [L301]

Providing reassurance on the use of RWD is another aspect that participants saw ENCePP having an important role in. *"That's probably something where ENCePP should find a position – how do we deal with bad studies, with new people doing bad studies? How do we, on one hand, keep people interested in doing their studies and being not the police of what to do?" [L103]* Interviewee L103 suggested education but also stressed the importance of ENCePP openly providing reassurance on the use of RWD in the form of a written statement that could be cited, such as "'*new data is emerging, a lot of people are doing [RWD studies], and some of these studies are not good because they do well-known things wrong. But if you do them right, RWD can be used.'"* [L103]. Along similar lines, participant L106 felt that currently, RWD has far less regulations than other safety studies. "*Until now, what we have seen is that they prefer to run quick studies, not so formal or 'tailored'."* They saw a possible role for ENCePP in the future where RWE is *"considered for approval and regulatory purposes",* and "*approach our standards."* [L106]

There were also several ideas for new tools that ENCePP could develop or be involved in developing (Box 6). When discussing the possible influence of ENCePP on reviewers of journals, participant L103 provided an example – *"I was a statistician before, and when I was starting there was the problem that a lot of papers were published which were really bad on the statistics side. And then the statistician societies made it clear that every editor*

Box 6: Suggestions for new tools

i)	Educational material; trainings, courses, webinars, collaborative projects
ii)	New WGs / SIGs; patients, AI in RWE
iii)	Tools for evaluating studies; guidance on RWE appraisal
iv)	Tools facilitating access to data
v)	Tools to improve / assess data quality measures

would need a statistician looking at the papers too. So maybe it would be helpful if ENCePP, or maybe the ISPE, or maybe both together could do something similar on pharmacoepi studies, saying that someone who's known to be good in methods [looks over the papers] - at least in the good journals, you probably cannot capture everything, but especially during Covid, we saw so many super bad pharmacoepi studies. So maybe that would be something that ENCePP could also do." [L103] Another way to go about this was suggested by a survey respondent. "*Perhaps ENCePP should consider developing a new tool for guidance specific for regulators making decisions based on pharmacoepi studies."* [svr]

While some participants saw ENCePP's role in education through developing material like trainings, other saw it through the facilitation of collaborative projects. *"When you have trainings for one, two, or three weeks, it's nice, you are listening. But if you are not using what you learned, using your own data...you will just forget after several months. But when you are participating in projects, you are working with your environment, with your data - you will have usually questions, and somebody is helping you."* [L203] A similar sentiment was expressed in the context of bringing together government, academia, and industry through "*not just workshops, but [also] actually co-working on particular projects."* [L304]

D. Autonomy

One of the important themes that came up when discussing the future position of ENCePP was autonomy. *"ENCePP could be also more active in consortiums and in conferences as an independent network."* [L108] Another aspect of this would be *"for example, to have training schools for young researchers, maybe some small conferences where researchers from ENCePP might present their work. And from that point, you can start further collaboration."* [L109] However, others felt that ENCePP *"wouldn't be a place where consortia or collaborators would meet... [as] there's a lot of other places for that already in terms of organization around conferences, consortia. [ENCePP wouldn't] have a logical role there."* [L201]

The idea of an autonomous ENCePP also included publishing their position papers, opinions on emerging methods and taking a public stance on developments in the RWD landscape. For example, "*a position statement maybe by the ENCePP researcher on the use of AI for Real-*

World Data analysis." [L101] This could also be something ENCePP does in collaboration. *"If we decide to do [a] position paper for instance on one topic [and] have one every year, maybe it's worth not doing them alone, but doing with ISPE or doing with some other society, [which] could increase the impact of this activity."* [L110]

An important point of discussion was the degree of involvement with the EMA. Opinions were divided, with several participants seeing the EMA's involvement as an integral part of ENCePP. "*ENCePP gives research centres an opportunity to interact directly with the EMA, give a voice and receive first-hand information from the Agency."* [svr] Others saw it as a distinct advantage. For example, when discussing studies conducting across countries, where they work with different languages, levels of healthcare, and healthcare systems overall, interviewee L304 expressed that *"[It's] a special, unique advantage of ENCePP as it relates to EMA, because it's across so many countries and so many geographies... So I think it, can really bring a more comprehensive view, looking at all those variations from a methods point of view."* [L304] Some interviewees felt that a closer collaborative relationship could be beneficial, though this does not necessarily indicate the degree of direct involvement. *"I would like to see ENCePP closer to EMA for more studies, to be involved in more issues that EMA faces regarding drug use in the European Union."* [L109] Some interviewees were in support of closer contact with EMA as a way to strengthen ENCePP's role in guidance representing the regulatory perspective. *"We would need the EMA staff keeping the core ENCePP working group members updated about what is what is happening in the regulatory space so that we can consider those optimally in the production of the guidance materials."* [L107]

On the other hand, there were participants who felt that it is time for ENCePP to develop as a body independent from EMA. *"I always thought it's a little bit strange that you have an European network of excellence and that it's hosted by the EMA... it doesn't interfere with the guidelines, it doesn't interfere with the code of conduct, but I think ENCePP should be an independent network – independent from industry, but also independent from the EMA."* [L102] An important aspect to consider is resources. While some felt that ENCePP *"should be self-sustaining...it's also depending on the infrastructure of EMA for the meetings, for the organization."* [L102] It was therefore acknowledged that becoming independent from EMA

would be difficult to accomplish immediately. *"I think EMA is coordinating a bit because EMA is interested in having ENCePP. Now, if EMA was not involved... who would take the role of coordinating ENCePP and make it work?"* [L105]. The question of whether reliance on EMA for resources is beneficial or not remains, especially considering that EMA often has other priorities, leading to periods of low activity for ENCePP. Interviewee L105 suggested a 'rebalancing' of the work away from the EMA and towards the academic centres involved in ENCePP as a possible solution.

It is relevant to note that it was mainly L1 very active interviewees who had an opinion on the degree of EMA involvement in ENCePP. A few L2 active members and L3 non-active interviewees were unclear on the relationship between ENCePP and EMA. *"Even though ENCePP isn't, I guess officially under EMA, there seems to be a lot of people who are coming back and forth. So from an outside perspective, it isn't always so distinguished - is it EMA? Is it not? I actually don't quite understand what the governance aspect is."* [L304] There were other interviewees who also questioned the relationship between ENCePP and EMA from a visibility perspective, which is discussed in more detail in the following section.

E. Visibility

Increasing visibility of ENCePP and its tools was mentioned by 76.5% of respondents and a majority of interviewees as an important area of focus for the future (Tables S5.2 and S6.1). One of the interview questions was about familiarity with ENCePP, to get an insight into how visible it current is. The degree of familiarity differed based on type of institution and research. *"I have many colleagues in the same area... the only ones that worked with ENCePP were the ones either working in regulatory agencies or industry. So, people in academia, they don't know about it – they should."* [L301] Other interviewees shared the experience of being less familiar with ENCePP while in academic institutions. They were also asked if their colleagues and collaborators were familiar with ENCePP. *"We are working with other companies more specialized in pharmacovigilance or pharmacoepi, so that's a route [through which] we've come across ENCePP."* [L201] Several interviewees mentioned that when it comes to pharmaceutical

companies, the larger ones tended to be more aware of ENCePP, sometimes also using the tools, while smaller companies were usually not familiar.

An important prerequisite to increasing visibility is the clarification of ENCePP's primary objective. Interviewees expressed not being *"entirely sure in the end of what ENCePP as an organization also is. So this is residing in a public setting. It's this group of enthusiasts. It's not a company, right? It's a semi-public setting... so I don't have a specific notion of what ENCePP should do [in the future] compared to, for instance, what's [already] out there or what commercial or academic institutions are already doing."* [L201] Some saw ENCePP being in a *"no-man zone, where on one hand we have what comes out of EMA that has regulatory guidance or regulatory implication. And on the other hand, we have organizations that go very much in detail on methods of publishing method paper[s]. ENCePP is a bit in the middle. Because the methodological guidance is not regulatory guidance and but is not even a detailed methods discussion paper, position paper - so where do we want to go?"* [L110]

Another aspect requiring clarification is ENCePP's positioning. There were questions on the relationship ENCePP has with other RWD initiatives "*because there are a lot of initiatives out there, and that gets confusing - especially when it's the same people.*" [L304] This also included its positioning within the EMA. "*Usually if you have an authority or authority-mandate, it creates visibility by itself – but I think [ENCePP] could have a more clear role under the EMA. So what's ENCePP, why it's needed, and how EMA endorses that."* [L202] Other interviewees also reflected on ENCePP's position within the EMA and associated committees. *"I think that there is somehow a disconnect that I would like to see somehow bridged again with the committees of the EMA... even though in ENCEPP there is a representative of PRAC, I have the impression that the committees are not fully aware of the benefits that come from studies that are conducted using ENCePP tools versus those that are not. And this is detrimental because at the end it weakens us as researchers."* [L104]

Many also saw *"recognition of ENCePP community as leading experts by EMA, when it matters*," as an important avenue for increasing awareness and external visibility. Several interviewees felt that it would be important to reach those who are not part of the network or using the

tools. *"I believe that there are many people outside ENCePP that might be involved in the similar studies, but they have never heard of ENCePP, and we need to gather them in our family."* [L109] This also extends to those outside of Europe. *"What would really help is to promote it a bit more over the borders... I know that the Methods Guide is seen worldwide, and it gets downloads and all that, but maybe also [promote] that there's a network of people knowing what they are doing and exchanging ideas."* [L103] This interviewee suggested promotion through other external bodies in addition to EMA as a way to increase visibility. *"What I would want is like every year, or at least every second year when the ISPE is in Europe, to have something on ENCePP, to be present because everyone is talking about Sentinel [and] all the US initiatives. But ENCePP, which is longer and probably a bit different, but at least it's productive is kind of lost in there."* [L103] A similar sentiment was also expressed by other interviewees. *"In this annual ISPE meeting, which is targeting quite a lot of researchers in this field, [ENCePP] could be one expert group meeting - or I'm not sure what it would be, but as of today, I think that ENCePP networking is not very active or hasn't at least reached me."* [L202]

Another aspect is making ENCePP more accessible to those who are already aware of the network. *"It would be really nice [to receive] some newsletters... just all activities that were performed during the last three months, and maybe some important announcements for the future."* [L202] This interviewee also mentions being able to communicate with other ENCePP Partners, by having the possibility to ask and answer questions from each other. Another suggestion was to curate more events and utilise different forms of communication. *"I think we should be a bit more active with the communication...what they are doing is great, but a bit more webinar, events, meetings somehow - because then we have created a bit more of enthusiasm."* [L110] Interviewees emphasised the importance of adapting to a more digitalized age as a way to improve visibility and accessibility. *"I think that although [ENCePP] has done a great job in these toolkits, they are quite long. I would rather have a schematic way of presenting these procedures... explained at different levels. But I need that, since we are in the age of Instagram and TikTok, we have to make information shorter."* [L109] Other ideas for more 'contemporary' methods of communication included increased use of social media, LinkedIn, videos and so on (Table S6.2).

Discussion

In a post-pandemic, post-Brexit time of rapid developments in both the EU PE/PV research landscape and the use of RWD globally, the role and positioning of ENCePP has been called into question. How has its relevance been affected by the changes in the last few years? Where does it stand amongst all the other emerging RWD initiatives?

Through valuable insights into the experiences of stakeholders in the PE/PV field, the results from this study provide a foundation from which these questions on the relevance and future role of ENCePP can be answered.

Role and impact of ENCePP today

Firstly, the results of this study confirm that ENCePP still plays a several important roles in the PE/PV landscape today. It hosts a network of expert researchers and facilitates communication and collaboration between them. As expressed by several interviewees, the inter-institutional conversation fostered by ENCePP is highly valuable for knowledge-sharing and building up the community of PE/PV researchers in Europe. Additionally, the existence of such a broad network with a common set of standards is immensely valuable in times of global crisis, as was seen during the COVID-19 pandemic[17]. One interviewee described how the common reference for research practices and ethical practices provided by ENCePP contributed significantly to the quality of PASS being conducted by European centres. The independence confirmed by compliance to Code of Conduct also made it possible to explain the safety and necessity of vaccines to the public.

In this way, ENCePP also plays an important role in providing the tools necessary to ensure that collaborations are successful, and the independence, transparency, and quality of research are upheld. For example, several interviewees described how the ENCePP Code of Conduct allows for high quality, ethical collaborations, especially when pharmaceutical companies are involved. The HMA-EMA Catalogues, though no longer under ENCePP's remit, are regarded as a milestone achievement that changed the PE/PV landscape and contributed significantly to increasing transparency.

It is clear that ENCePP has had - and continues to have - an important role in inspiring and guiding both new and experienced researchers through an evolving PE/PV landscape. Its voice on the quality and visibility of methodological practices is respected internationally. For example, the ICH M14 guideline[23] refers to the ENCePP Methodological Guide and Checklist for Study Protocols. This was also confirmed by interviewees involved in the development of the guideline. The ENCePP tools, including the Guide, Checklist, and Code of Conduct are also referred to in the GVP Module VIII guideline published in 2017 by the HMA and EMA[9]. The EMA draft reflection paper on RWE, published in 2024, also recommends the use of ENCePP tools[31]. Additionally, interviewees outside of Europe also shared their experience of referring to the ENCePP tools when developing guidelines. Its inclusion in several such important documents across the world provides further evidence for the foundational importance of the work ENCePP has done.

Future steps

Adapting the tools and network

The results of this study suggest several adaptations ENCePP could make to reflect the needs of stakeholders from the PE/PV research field. As the tools are an important part of ENCePP's mandate, deciding how to proceed with them are critical to defining the path forward. There are already steps being taken to update the ENCePP tools and incorporate aspects of other documents and guidelines as a step towards harmonization. At the same time, as one interviewee mentioned, the inclusion of ENCePP tools in the ICH M14 and GVP Module VIII guidelines would likely to lead to increased awareness of the value of ENCePP tools on a global scale. Several participants also had ideas for new tools that ENCePP could develop (Table S6.3).

Participation in ENCePP is completely voluntary, and some participants reported finding it hard to prioritise activities and deliverables in addition to their other work. With the lack of resources in mind, one possibility to consider is leveraging expertise from different sectors - for example, allowing for greater involvement of representatives from the pharmaceutical industry and CROs. Having more resources on hand could also help with some of the other areas for improvement mentioned, such as the administration of meetings and scheduling of events.

Defining primary objective and positioning

While many participants seemed to have an idea of what ENCePP is or should be, many also expressed not being clear on how ENCePP itself defines its objective and positioning. One of the important first steps for the future would therefore be to have clarity and visibility on these two aspects. The participants suggested several avenues to consider – focusing on methods, regulation, education, guidance, and so on. Some saw ENCePP becoming a kind of an academic centre that provides trainings and online courses. Others saw it taken on a more active role, by coordinating joint projects involving different institutions and countries. For example, interviewees from Central and Eastern European countries saw this as a way ENCePP could support the development of their PE/PV research fields. Several participants saw involvement with ENCePP as a way to stay informed of the current regulatory perspective. At the same time, participants also saw ENCePP developing a more independent voice and providing direct recommendations, which could be, for example, through publishing position papers. ENCePP has had, and continues to have, several important roles and functions, impacting the PE/PV landscape in various ways – clarifying its primary objective would not mean reducing to only one singular role, but rather as a way to inform on what its main focus is.

Similarly, an important step for ENCePP's future would be to clarify its positioning. Many participants, especially those who not directly involved in the SG or WGs of ENCePP, were unclear on where to place ENCePP amongst the other bodies (eg. EMA, ISPE) and initiatives (eg. DARWIN EU®) involved in PE/PV research in Europe. As mentioned by an interviewee, there is often an overlap in the people present and active in these different bodies or initiatives, further suggested a need for clarification. This includes its relationship with the EMA. The results show differing opinions on the degree of independence ENCePP should or could have from the EMA. The positioning also refers to how the two collaborate – what will be ENCePP's role in EMA's plan for the future of RWD? Several participants had questions about the relationship between ENCePP and DARWIN EU®, seeing it perhaps play a supportive role from a methodology perspective. ENCePP's positioning would likely be informed by its primary objective, as the two are related. By relaying the opinions of relevant stakeholders, the results from this study provide a foundation upon which these important decisions can be made.

ENCePP in an evolving RWD/RWE landscape

There are several identified aspects of the developing RWD/RWE landscape ENCePP could possibly address, based on the comments from participants in this study. For example, Arlett et al (2022) mentions two main priorities for the implementation of RWE in medicine regulation: enabling use and establishing value[19]. They mention the ENCePP Register (now HMA-EMA Catalogues), and the Methodological Guide when discussing enabling use. There could also be a role for ENCePP in terms of establishing value, as mentioned by some participants in the study who saw a future role for ENCePP in using its voice to encourage researchers to use RWD and regulators to accept its evidentiary value. Another area ENCePP could be active in is in the use of AI in RWD research. For example, Hines et al. (2023) mentions regular updates to the guidelines regarding post-authorization management of medicines if AI is involved[24], which is a project ENCePP could possibly be involved in. More recently, Pinhero et al. (2024) discussed the work the European Medicines Regulatory Network (EMRN) is doing in evaluating the safe use of AI in medicines regulation within the EU[25]. They mention guidance, policy, and effective cross-sector collaboration as some key areas in governing the ethical use of AI. These are areas that ENCePP is already active in, and many participants saw room for a greater role, especially in advising and recommending methods for the responsible use of AI in research. A task force or WG dedicated specifically to regulating use of AI was mentioned in both the interviews and survey and is already a topic of discussion with the ENCePP community. Prilla et al (2024) discuss EMRN's efforts to develop a framework for the integration of RWE into regulatory decision making[20], a part of which would include addressing feasibility and transferability of data. This was also a possible area of involvement for ENCePP identified by the interviewees. Considering the voice ENCePP has on advising methods and good practice, there could be a possible role for addressing RWE generation pathways and choosing appropriate data sources for studies. Many participants also saw ENCePP working together on papers, recommendations, and guidance with other institutions such as ISPE. Combining resources and networks could be quite beneficial, as broad collaborations have been identified to be integral in the development of RWE in regulatory decision making[18,25].

Visibility

Making ENCePP's efforts in adapting the network and tools to reflect the current, post-pandemic, highly digitalized time visible is critical. Participants had several ideas for this - for example, through utilising short forms of communication, expanding further into the social media space (eg. through an ENCePP LinkedIn page), publishing a newsletter, and curating online events. There have already been steps taking in this direction - for example, WG2 has developed the 'Conduct your study' podcast series, the first episode of which was released in June 2024. Developing short forms of communication, through videos or condensed versions of the documents, could also be a way to engage younger researchers and get them involved in ENCePP. As mentioned by Kurz et al (2018) in their paper reflected on 10 years of ENCePP[4], one of the key factors in determining the network's success will be its ability to attract new members that can assist in tackling upcoming challenges[4]. This was also brought up by several participants, who felt that finding ways involve younger researchers would be vital to keeping the network active, adaptable, and well-resourced. It is valuable to note that the suggestions for online communication and events are not intended to replace the in-person meetings appreciated by many. One of the key factors that contributed to ENCePP's development over the years was the opportunity to meet face-to-face[4]. The curation of online events could then be a way to bridge the gap between the annual Plenary sessions and provide an additional opportunity for ENCePP Partners to connect.

Another aspect of visibility is promotion through other bodies such as the EMA and PRAC. Several papers published in recent years reflecting on RWE and related developments mention the EMA and its work on developing guidelines and tools for the use of RWD, but not ENCePP directly[16,18]. There could therefore be some room here for increased promotion of ENCePP via the EMA, which was also suggested by several participants. Increasing visibility of the regulatory benefit of using ENCePP tools through PRAC is an important aspect as well, as several participants mentioned a current lack of awareness as a barrier to using the Code of Conduct or applying for the ENCePP Seal.

Several aspects of increasing ENCePP's visibility are linked to its relationship with the EMA. Some of the suggestions to increase visibility, such as increased communication on ENCePP activities, could be accomplished without becoming an autonomous network. Others would require a more independence from the EMA. ENCePP will therefore have to find a balance between making itself visible and accessible, and depending on the EMA for resources.

Strengths of the study

One of the strengths of this study lies in its design, which combined in-depth interviews with a high-level survey. This resulted in a comprehensive overview of the opinions and experience with ENCePP. The findings from the study therefore provide a solid foundation for the choices that ENCePP needs to make in the future, while confirming the importance of its role today. A second strength lies in the study population, which included a wide range of stakeholders from different institutions, countries, and levels of experience. The representation of different voices also allowed for valuable insights into the role and impact of ENCePP.

Limitations of the study

While the range of represented stakeholders was quite broad, there were certain groups that were overrepresented. For example, the low response rate for active (L2) and non-active members (L3) of ENCePP resulted in 11 out of 18 interviewees being very active members (L1), present in the ENCePP SG or WGs. Ideally, the study population would have been more evenly distributed across the layers of involvement. Similarly, majority of participants, both from the surveys and interviews, were from Western European countries, many of which have advanced PE/PV research fields. While the study population does include a few participants from Central and Eastern European countries and non-European countries, it would have been valuable to have heard more from the perspective of countries with less developed PE/PV research fields, and from non-EU countries outside of North America. The highest percentage of participants were from regulatory bodies, so it could be that the responses are slightly more tailored towards their perspective. Finally, a large percentage of initial survey respondents did not complete the survey (41.6%), which led to a significantly reduced study population.

Conclusion

Through the use of interviews and a survey, the results from this qualitative study provide valuable insights into what the current role and impact of ENCePP is, and where it could possibly go in the future. Through the years of work promoting transparency, independence, and standards, ENCePP has had – and continues to have – a foundational impact on the quality of PE/PV research worldwide. Whether ENCePP moves towards a more educational, regulatory, or independent role, it can do so knowing that there is plenty of interest and support for its progress and output.

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