ENCePP Plenary meeting 2024 Report

Friday, 22 November 2024

EMA, Amsterdam (hybrid)

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This report summarises the main topics and outcomes of the 2024 ENCePP Plenary hybrid meeting. For more details, the presentations are available on the ENCePP website alongside the report.

Meeting objectives

- To reflect on the work of ENCePP since the December 2023 Plenary, and inform the ENCePP community on recent progress;
- To provide an update on milestones and deliverables of the ENCePP workplan, and seek feedback and contribution from ENCePP Partners on governance aspects and future activities and deliverables;
- To continue placing the work of ENCePP in the context of an ever-changing regulatory environment;
- To learn about, and discuss, the strategy for the 2025 revision and dissemination of the ENCePP Methods Guide, as well as methodological topics of current interest.

Agenda

Chairs: Helga Gardarsdottir (Utrecht University), Catherine Cohet (EMA)

Item	Topic	Speaker(s)	Time
1.	Arrival, connection to virtual room and technical checks		08:30-9:00
2.	Welcome	Peter Arlett (EMA)	09:00-9:10
3.	Meeting objectives	Helga Gardarsdottir (Utrecht University) Catherine Cohet (EMA)	09:10-9:15
SESSION 1: ENCePP today, and the near future ***Chairs: Vera Ehrenstein (Aarhus University), Christos Kontogiorgis (University of Thrace)***			
4.	ENCePP workplan: 2024 achievements	Catherine Cohet (EMA) and Working Group leads (Alejandro Arana, Rosa Gini, Gianluca Trifiro)	9:15-9:45
5.	• Terms of Reference for the Working Groups and Special Interest Groups • Proposal for new groups	Helga Gardarsdottir (Utrecht University), Laura Pizzi (ISPOR), Gianmario Candore (Bayer AG)	9:45-10:30
Coffee break – 10:30 to 11:00			
6.	Qualitative research on the role and impact of ENCePP: key findings	Sharanya (Shar) Rao (Utrecht University)	11:00-11:40
SESSION 2: Role of ENCePP in an ever-changing regulatory environment ***Chairs: Katja Hakkarainen (Parexel), Patrice Verpillat (EMA)***			
7.	• Methodology Working Party (MWP) workplan • Learnings from public consultations on the MWP RWE Reflection Paper and ICH M14	Olaf Klungel (Utrecht University)	11:40-12:00
8.	Recent news from EMA • RWE to support EU regulatory decision-making: 2nd annual report • DARWIN EU®® update: focus on studies	María Clara Restrepo-Méndez, Andrej Segec (EMA)	12:00-12:30
Lunch – 12:30 to 13:15			

Item	Topic	Speaker(s)	Time
SESSION 3: Methodological topics of current interest ***Chairs: Hedvig Nordeng (University of Oslo), Tania Schink (Leibniz Institute for Prevention Research and Epidemiology – BIPS)***			
9.	ENCePP Guide on Methodological Standards: 12th Revision and publication strategy	Helga Gardarsdottir (Utrecht University) Alejandro Arana (RTI)	13:15-14:00
10.	Quantitative Bias Analysis	Ian Douglas (LSHTM)	14:00-14:45
11.	Prevalent new user design	Michael Webster-Clark (McGill University)	15:45-15:30
Wrap-up			
12.	• Feedback from Plenary participants on agenda topics and next steps (Slido and discussion) • Closing and next steps	Helga Gardarsdottir (Utrecht University) Catherine Cohet (EMA)	15:30-16:00
Adjournment – 16:00			

Meeting notes

Opening

Catherine Cohet, the co-chair of the ENCePP Steering Group (SG), welcomed the participants, and Peter Arlett (Head of the Data Analytics and Methods Task Force, EMA) opened the meeting.

Peter looked back at the journey since the establishment of ENCePP in 2007, reflecting on the discussion started at the 2022 Plenary on possible new directions for the network, in the wake of EMA's relocation to Amsterdam and the COVID-19 pandemic. The discussion was pursued at the 2023 Plenary, in the context of lessons learned from the COVID-19 and mpox public health crises, and the expansion of DARWIN EU®. The SG for the 2024-2026 mandate was introduced at the 2023 Plenary, with its first task to develop a new workplan focusing on concrete and measurable deliverables, and an updated governance. Peter thanked the SG for their work in its first year of operation, as well as the ENCePP partners who contributed to the rollout of the workplan, and highlighted the need for continued, increased contribution from all partners.

Helga Gardarsdottir, co-chair of the SG, presented the objectives and agenda of the Plenary meeting.

Session 1: ENCePP today, and the near future

Chairs: Vera Ehrenstein (Aarhus University), Christos Kontogiorgis (University of Thrace)

1.1 ENCePP workplan: 2024 achievements

Catherine Cohet discussed the progress made during 2024 to start delivering the workplan, focusing on three milestones: governance, visibility, and impact, as reflected in several deliverables.

- Objective 1 - *Update the governance and ways of working of ENCePP*: draft Terms of reference for establishment and maintenance of the Working Groups (WGs) and Special Interest Groups (SIGs); update and posting of the ENCePP and ENCePP Steering Group mandates.
- Objective 2 - *Increase the visibility of ENCePP in Europe and globally*: development of ENCePP overview slides for use by partners (upon request to the Secretariat); podcast series launched by WG2; exploring means of leveraging social media to promote ENCePP; increasing reach out to the larger PV/PE community through the RSS feed[1] on the ENCePP website; publication strategy (for selected chapters of the ENCePP Guide on Methodological Standards in Pharmacoepidemiology).
- Objective 3 - *Increase the impact of ENCePP in Europe and globally*: qualitative research by Utrecht University; events with learned societies (at ICPE 2024 and ISPOR EU 2024); opening of ENCePP to public bodies in EU candidate countries/potential candidates (first applications accepted); revisiting the WGs/SIGs and their governance to best address the workplan.

The co-chairs of the three current WGs presented their 2024 achievements (see presentations):

- WG1: focus on ENCePP Checklist for Study Protocols.
- WG2: start of the 'Conduct your study' podcast series – 2 episodes so far, and more in preparation.
- WG3: ongoing studies exploring studies registered in the HMA-EMA Catalogues of real-world data studies (previously in the EU PAS Register).

1.2. Terms of Reference (ToRs) for the Working Groups and Special Interest Groups (SIGs); proposal for new groups

Gianmario Candore presented the rationale for the development of ToRs for the WGs/SIGs, highlighting the importance of transparency on how the groups are created and operate, and the need for measurable deliverables with prespecified timelines.

WGs/SIGs should be updated and/or established in accordance with the workplan and be better aligned with EMA strategy and needs. The new ToRs, and the re-structuring of the current groups, and/or the creation of new WGs/SIGs in compliance with the ToRs, will be discussed by the SG at their first meeting in 2025.

SG members and ENCePP partners are encouraged to propose new WGs/SIGs. Proposal should include a draft objectives, deliverables, and timelines. The SG will review the proposals. Once a WG/SIG has achieved all deliverables, it will be closed. Members will be expected to contribute actively, and membership will be revised by the co-chairs annually based on contribution.

When asked via Slido, the large majority of meeting participants agreed with the ToRs presented.

[1] ENCePP website visitors may subscribe to updates through the RSS feed on the News page (requires RSS Feed Reader plugin in browsers)

Q&A/discussion

- Further clarity was provided following questions on time limitation; the aim is not to stop activities, but increase clarity and transparency on the work of the WGs by having start/end dates, also to better engage group members. It was acknowledged that some topics require prolonged time periods, e.g., revision of the Methods Guide.
- Link between ENCePP and DARWIN EU® and conduct of studies by ENCePP partners: it was clarified that DARWIN EU® is an EMA contract, therefore there is no "role" for ENCePP in DARWIN EU® per se, however, ENCePP members may apply to become DARWIN EU® data partners. ENCePP has a key role in methods development, which directly benefits studies delivered via DARWIN EU®.

Proposals from meeting participants for topics to be addressed by WGs/SIGs (via Slido):

- Update of the ENCePP Checklist for Study Protocols
- ENCePP Communications (promoting and increasing the visibility of ENCePP)
- Regular revision of the Methods Guide, including 2025 12th revision
- Update and maintenance of the ENCePP Code of Conduct
- Target Trial Emulation
- Artificial intelligence (focus to be defined, may be linked to the ENCePP Guide AI chapter)
- Integrating randomised controlled trials into routine clinical practice
- Digital pharmacovigilance e.g. use of social media or other digital platforms for ADR reporting
- Data protection and privacy, education of the public on how data is used
- Interplay between PV and PE for use of data sources (related to ISOP)
- Rare diseases – focus on methodologies (rare disease, rare no. of events) and data sources
- Measuring the impact of pharmacovigilance activities (former SIG now closed, need to be defined)
- Diversity and fairness in pharmacoepidemiological research to advance health equity in Europe
- Central European countries – encourage ENCePP participation, in particular to bring data sources.

1.3. Qualitative research on the role and impact of ENCePP: key findings

Shar Rao, MSs student at Utrecht University, presented the results of a qualitative study aimed at informing the continued ENCePP strategy and providing insights into relevance, usefulness and positioning of ENCePP in the RWE and PE/PV environment. This research was conducted under the guidance of the ENCePP co-chair, Helga Gardarsdottir.

Methods included interviews and a survey among SG/WG members, ENCePP Partners, EMA staff, and other stakeholders.

- Topics: perceived benefits of ENCePP; barriers and improvements; use and impact of the ENCePP tools (Code of Conduct, Seal, Methods Guide, Protocol checklist); perception of the current and insight into the future role of ENCePP, included in the RWD/RWE landscape.
- Strengths: the design allowed an in-depth analysis and a high-level overview, with input from a wide range of stakeholders. Limitations: overrepresentation of active ENCePP members in interviews, most responders from Western Europe, incomplete survey responses.

Q&A/discussion

- Results confirmed the relevance and benefits of ENCePP in the PE/PV landscape, in particular the value of the Code of Conduct and the Methods Guide; however, the Seal remains under-utilised (EMA confirmed very few Seal applications are received); this will be discussed at SG level.
- In the interviews, it was confirmed that the Checklist is used by regulators. This is important in the context of the ongoing update of GVP module VIII (to be published in 2025), and reinforces the usefulness of the update of the checklist (started under current WG1).
- Most results were expected by the SG, e.g., need for more visibility and communications, need for increased contribution from ENCePP partners.
- Dissemination of the results: analyses planned to be completed in December 2024 and the report subsequently communicated to the SG, for discussion in its first meeting in 2025, and potentially resulting in an update of the workplan and a publication.
- In conclusion, this research will provide valuable additional insights into how ENCePP can move forward.

Session 2: Role of ENCePP in an ever-changing regulatory environment

Chairs: Katja Hakkarainen (Parexel), Patrice Verpillat (EMA)

2.1. Methodology Working Party (MWP) workplan; Learnings from public consultations on the MWP RWE Reflection Paper and ICH M14

Olaf Klungel presented the MWP workplan and its goals in relation to RWE.

2022–2024 workplan

- Roadmap for the development of RWE guidance by regulators and HTA bodies worldwide: an overview was presented, including areas covered and areas of potential interest.
- Reflection paper on the use of Real-World Data to generate Real-World Evidence in non-interventional studies: many of the principles of the ENCePP Methods Guide are incorporated in the reflection paper. Close to 700 comments received during public consultation from 39 organisations, including industry, CROs, regulatory authorities, HTAs, professional associations, patient associations.

2025–2027 workplan

- Concept paper on external controls (joint activity with Biostatistics)
- Concept Paper on the use of pragmatic trials in regulatory decision making (joint activity with Biostatistics)

ICH M14

- ICH M14 on '*General principles on plan, design and analysis of pharmacoepidemiological studies that utilize real-world data for safety assessment of medicines*': one of the key contents relates to study feasibility, as reflected in the 'Framework for generating adequate evidence using fit-for-purpose RWD to address regulatory questions' presented in the guidleine. Public consultation closed end of Oct. 2024, and comments are currently being addressed by the ICH Expert WG in view of guideline establishment in June 2025.

Other updates relevant for ENCePP

- GVP Module VIII revision - public consultation tentatively planned Q1 2025 (to be announced on the ENCePP website). Updates: study feasibility, selection of fit-for-purpose data sources for PASS.
- Update of the ENCePP Checklist for Study Protocols – Q2 2025
- ICH new topic on '*Considerations for the Use of Real-World Evidence (RWE) to Inform Regulatory Decision Making with a focus on Effectiveness of Medicines*' (led by EMA, FDA, and Health Canada). High-level contents: harmonised operational definitions of RWD/RWE; use of metadata; assessment principles.

2.2. Recent news from EMA

RWE to support EU regulatory decision-making: 2nd annual report

María Clara Restrepo-Méndez presented the 2nd EMA RWE report on regulator-led RWD studies to support decision-making, covering the period February 2023 to February 2024, building on the 1st report on the previous period starting in 2021. During the new reporting period, DARWIN EU® expanded to 20 data partners, with access to data from around 130 million patients from 13 European countries.

DARWIN EU® is now the main pathway for RWE generation by EMA. 40 studies were ongoing or finalised during the period, including 13 to inform vaccine safety and effectiveness related to public health emergencies. For the first time, studies were initiated to monitor supply and demand of critical medicines; to investigate herbal substances; to address HTA and payer organisations research questions; and to support EMA's geriatric medicines strategy.

DARWIN EU® update: focus on studies

Andrej Segec gave an update on operational aspects of DARWIN EU® and provided several examples of studies. DARWIN EU® completed its establishment and scale-up enabled it: focus on Data Partners, studies, pilot use cases and developing standard analytical pipelines. As of 2024: bigger network, higher study volume, and shorter timelines for studies are foreseen.

Q&A/discussion

- The choice of the OMOP common data model was driven by its availability at the time of DARWIN EU® development, it has been an enabler for the programme scale-up. A large amount of the data has already been mapped and transformed, which helps analysing counts. Standardised counts can be computed quickly as they are available at the coordination centre portal.
- Average time from the request of the research topic to study completion: off-the-shelf studies, 3-4 months; complex studies >6 months (see darwin-eu.org - Studies).
- Topics requested by CHMP are related to disease management, in the domain of pulmonary hypertension and asthma.
- Combination products within the scope of DARWIN EU® are in scope, but limited by how well they are captured in the data. Device studies have not yet been conducted, but will happen in the future.
- Alignment between MAH responsibility on risk management plan, safety and risk minimisation and DARWIN EU® studies: while obligation on MAHs remain unchanged, DARWIN EU® is able to perform further analyses, for example, for the assessment of a safety signal, as PASS conducted by MAHs may take time. The type of studies can be multi-products (e.g. opioids) or single products (e.g. doxycycline).

- Plan to conduct a survey among DARWIN EU® data partners on lessons learned, positive and negative experiences. There are plans also in 2025 to engage with existing and new data partners to share learnings, how the evidence is used by EMA committees, and what is its impact.

Session 3: Methodological topics of current interest

Chairs: Hedvig Nordeng (University of Oslo), Tania Schink (Leibniz Institute for Prevention Research and Epidemiology – BIPS)

3.1. ENCePP Guide on Methodological Standards: 12th Revision and publication strategy

Catherine Cohet highlighted the continued wide use and EU/international recognition by multiple stakeholders of the Guide, and presented the objectives of this sub-session:

- Discuss the strategy for the 12th Revision of the Guide (Pillar 1) and increase dissemination and visibility through publication in peer-reviewed journals (Pillar 2).
- Engage the ENCePP community (chapter selection for both pillars, contents/structure for Pillar 1, authorship).

To reduce editorial and administrative work and focus on updates of topics of current high methodological and regulatory interest, only selected chapters will be revised.

Before the Plenary, ENCePP partners were sent a survey to collect feedback on identification of chapters for update. The survey had limitations due to the short response time and hence low response rate (N=23), but it still provided insight into which chapters may be revised: AI, Development of study protocol, Real-world evidence and pharmacoepidemiology, Formulating the research question and objectives and assessing feasibility, Quality management, Vaccine safety and effectiveness, Study design.

Q&A/discussion

- Chapters that need update: AI, external control arms and pragmatic trials, study design (making causal studies more visible), statistical analyses (highlighting the need to prevent misuse of statistical significance).
- Need for review of the table of contents and agreement on which topics to include as chapters vs. annexes. The vaccine chapter for example is very extensive – should it be an annex? Should it be shortened?
- Suggestion to include natural history studies, prevalence and incidence studies conducted early in the development cycle. However, even if such studies are important for regulatory purposes, 'traditional' epidemiology is already covered in many textbooks, and the Guide needs to remain focused.
- Suggestion to reflect on approaches for rare/genetic diseases.
- No need for a pre-defined strategy on frequency of revisions, but important to track key/relevant publications for inclusion. Annual updates have a high resource burden; a 2-year update frequency is more realistic, with revision of specific chapters only, as needed.

Helga Gardarsdottir presented a plan for publication of selected chapters in *Pharmacoepidemiology and Drug Safety (PDS)*. The idea emerged in the SG in 2024 and was discussed with the PDS Editorial Board during ICPE 2024. The publication process will comply with the conventional PDS peer-review policy. *Value in Health* is interested in co-publishing. The list of proposed chapters for this special issue

has been drafted. Next steps are to share the proposal with PDS, discuss co-publishing with PDS and Value in Health, and agree on authorship.

Q&A/discussion

- Suggestions of chapters for the PDS issue: Interpretation of results; Networks and multi-database studies; Similarities and differences between pharmacoepidemiology and real-world evidence.
- The PDS issue should be aligned with the next revision of the Guide, with cross-referencing.
- There was a proposal to have a SIG dedicated to the PDS Special issue and a WG to coordinate and organise Revision 12 of the Guide. Once these groups are established, ENCePP partners will be encouraged to express their interest to contribute to selected chapters.

3.2. Quantitative Bias Analysis

Ian Douglas presented on methods for quantifying potential bias in epidemiological studies, including insights about Quantitative Bias Analysis (QBA) application in epidemiology and examples of methods applied to addressing confounding, misclassification and selection bias.

Q&A/discussion

- The examples provided seem to show that it doesn't really matter to perform a QBA, as you would have interpreted the results from the examples in the same way had you not performed QBA?
  - The examples shown are just some known examples, QBA does not always lead to the same conclusion as the main analysis. Nevertheless, even if the conclusion is consistent, performing a QBA is beneficial as it increases reliability of the results.
- QBA is currently underused: should we have some reasons not to use it, should we use it only in specific situations, or should it be systematically used?
  - It should be performed in selected use cases: for example, when important confounders are missing, a pre-specified QBA should be conducted.
- Recommendations on how to find the best parameters needed for QBA: this can either be external information (e.g., literature) or information collected from experts (e.g., clinicians).
- Examples on when QBA is misused or misinterpreted: e-values are often misunderstood and can give a false reassurance on the confidence in the results.
- Since very diverse data sources are available within the EU network, information can be drawn from this diversity, which can potentially help the application of QBA by selecting the more appropriate data source for obtaining information on the needed variable(s).

3.3. Prevalent new user design

In his presentation on the Prevalent New User (PNU) design, Michael Webster-Clark focused on 5 core questions:

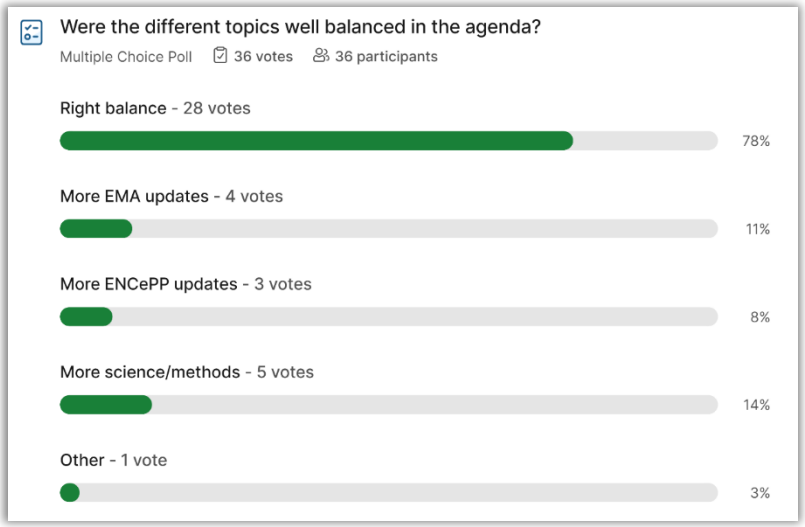
- Why avoid the inclusion of prevalent users in cohort studies of drug safety and effectiveness?
- What are prevalent new users (vs prevalent users) and how can we identify them?
- What does the PNU design estimate?
- What are some analytic strategies for PNU design studies?
- How is the PNU design evolving?

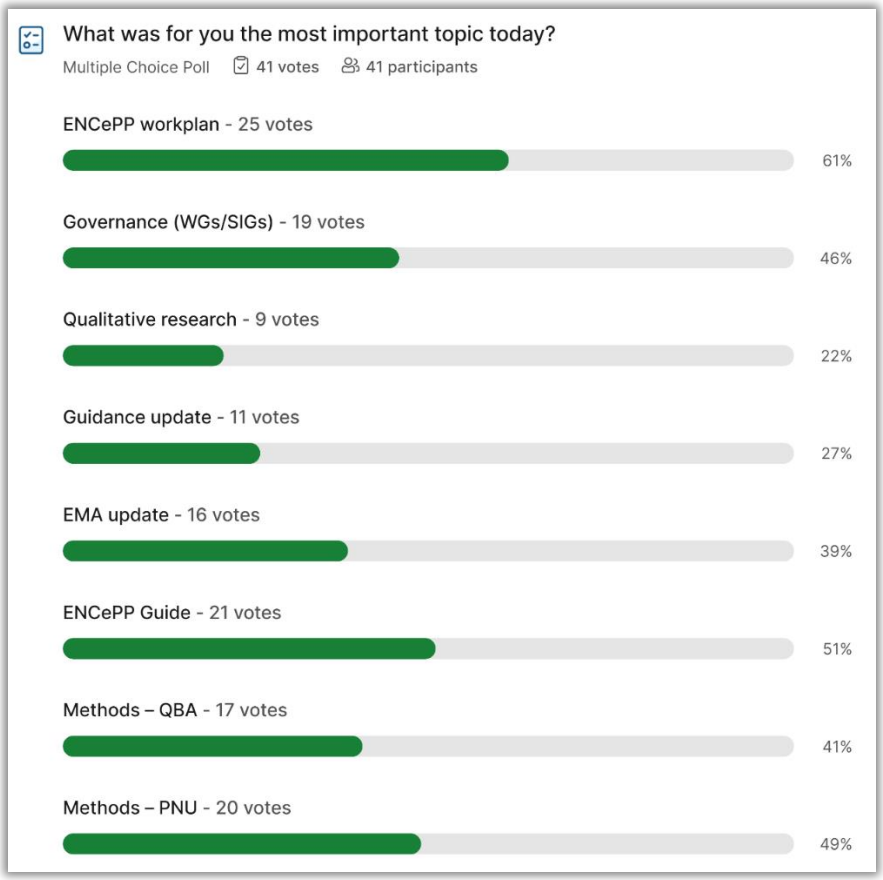
Q&A/discussion

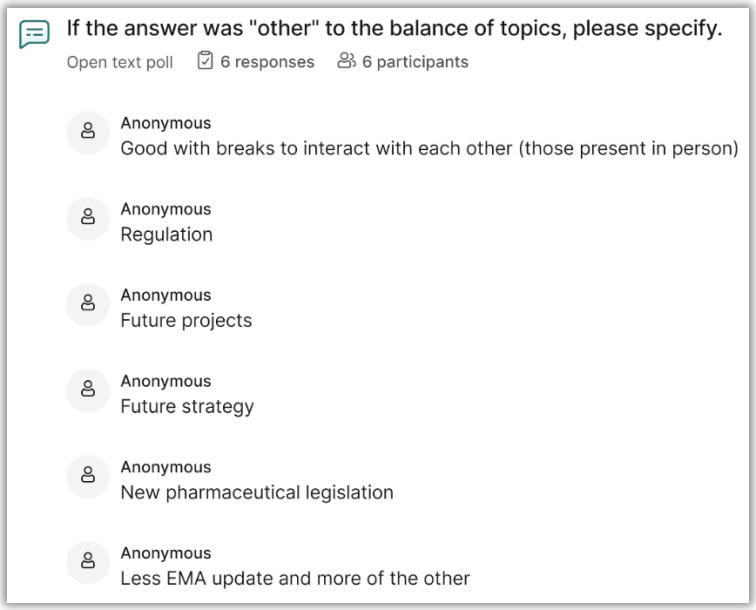
- PNU design is not meant to replace the new user design, as it answers a different question.
- What results simulations using the two methods on the same scenario have brought?
  - In the scenario with time fixed treatment effects, the two methods have shown to provide the same answers.
- The crucial point is the comparability between the two groups: would the comparator be a good comparator if the switching is due to a side effect?
  - This depends on what the outcome of the study is (e.g., if the outcome is efficacy and people are switching because the treatment is not working then the PNU design cannot be used). If the side effects are unrelated to the efficacy outcome, then the comparator group can still be a good comparator. The key point is whether there is an association between switching and the outcome.
- Use of the PNU design in pregnancy settings: the method could be more useful for analysing stopping of medicines in pregnancy rather than switching or adding medicines.

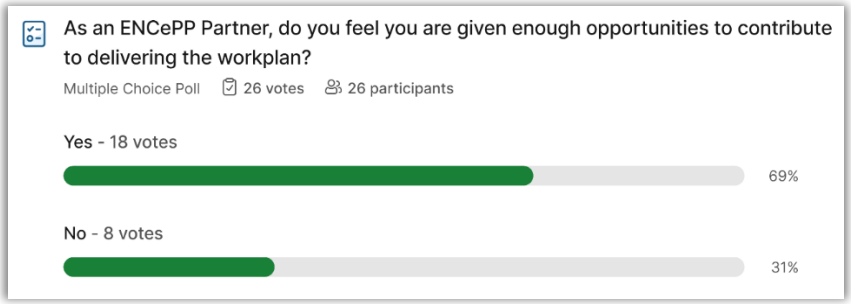
Wrap-up

Feedback from Plenary participants on agenda topics and next steps (Slido and discussion)




What was for you the most important topic today?
Multiple Choice Poll
41 votes
41 participants
ENCePP workplan - 25 votes
61%
Governance (WGs/SIGs) - 19 votes
46%
Qualitative research - 9 votes
22%
Guidance update - 11 votes
27%
EMA update - 16 votes
39%
ENCePP Guide - 21 votes
51%
Methods – QBA - 17 votes
41%
Methods – PNU - 20 votes
49%


If the answer was "other" to the balance of topics, please specify.
Open text poll
6 responses
6 participants
Anonymous
Good with breaks to interact with each other (those present in person)
Anonymous
Regulation
Anonymous
Future projects
Anonymous
Future strategy
Anonymous
New pharmaceutical legislation
Anonymous
Less EMA update and more of the other


As an ENCePP Partner, do you feel you are given enough opportunities to contribute to delivering the workplan?
Multiple Choice Poll
26 votes
26 participants
Yes - 18 votes
69%
No - 8 votes
31%

How can ENCePP improve? Any ideas for the future? Any last comments?

Open text poll | 17 responses | 15 participants

Anonymous
The qualitative research was maybe not so high on the list but at the same time workplan it is feeding into was highest on the list. Just noting, thank you to Shar! Big effort made for us!

Anonymous
Try to disseminate the importance of real world data in the academic/clinical setting where the education is still lacking

Anonymous
Meetings in warmer places

Anonymous
Some changes have now been suggested, good communication and guidance on further implementation important so that the targeted new engagement is achieved.

Anonymous
Training

Anonymous
Medicines in Pregnancy/Lactation WG. European Network of Teratology Information Services could contribute.

Anonymous
more activities for work groups

Anonymous
More joined activities

Anonymous
Attracting more members and meeting them in person in the plenary. The live attendance has decreased a lot

Anonymous
More f2f meetings

Anonymous
Get important items like data access and public education on political agenda

Anonymous
More face-to-face collaboration opportunities.

Anonymous
I really enjoyed the discussions and take home several ideas to act on 😊

Anonymous
Continue plenaries F2F and remote. Great steering group and cochairs

Anonymous
More meetings between WG members More contribution of young researchers

Anonymous
How can one join a WG or SIG?

Anonymous
More interesting mix and time for discussion than the previous years 👍

Reflecting on the Slido comments (all meeting participants)

- How to join the WGs:
  - This will be discussed at the next SG meeting, as per ToRs. Communication to all ENCePP partners will follow.
  - ENCePP Partners are encouraged to send proposals for WGs/SIGs, including volunteering for contribution, to the Secretariat, which will consolidate for the SG.
- More face-to-face meetings are challenging as EMA only has capability to organise one face-to-face event/year.
- More young researchers needed: ENCePP partners are asked to cascade information on ENCePP and its activities to their teams (including PhDs, post-docs).
- More meetings between WG members: this is a task for the WG leads, which is not driven by EMA.
- Trainings
  - The ENCePP tools are already used for training purposes in academia (e.g. Utrecht University).
  - Recorded presentations could be developed on different topics, for publication on the ENCePP website.

Adjournment

The co-chairs thanked everyone for their active participation and summarised the key outcomes of the meeting. Next steps will be discussed at the first meeting of the SG (post-meeting note: to be held 22 January 2025).