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Annual ENCePP Plenary hybrid meeting 2023 - Report

Co-chairs: Susana Perez-Gutthann (RTI Health Solutions); Catherine Cohet (EMA)

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This report summarises the main topics and discussions of the 2023 ENCePP Plenary meeting. The presentations are published on the ENCePP website along with the report.

1. Welcome and introduction

The co-chairs 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. He addressed the current rapid changes in the pharmacovigilance, pharmacoepidemiology and real-world evidence (RWE) environment, where private and public organisations, and governments, are investing in the digitalisation of healthcare records, providing the opportunity to leverage real-world data (RWD) for better decision-making. He highlighted the importance of observational research and the role of RWE in complementing clinical trials to support the development and supervision of medicines, linking these considerations to the work of the ENCePP community.

The policy environment is also rapidly changing, as reflected in the EMA extended mandate based on COVID-19 lessons learned, fostering the analysis of healthcare data for preparedness and response to public health emergencies. Peter also emphasised the significant impact on EMA, but also on ENCePP, of the European Health Data Space (EHDS) and the EU Artificial Intelligence (AI) Act. He gave an update on other key EMA initiatives, such as the first release of the Data Quality Framework for EU medicines regulation; the new HMA-EMA Catalogues of RWD and studies (to be launched in early 2024[1]); EMA's expanded access to data sources (through DARWIN EU®, EMA framework contracts with large research consortia, and in-house databases); the launch of the training curricula in pharmacoepidemiology and RWE for the European medicines regulatory network (EMRN); and the establishment of the Methodology European Specialised Expert Community (ESEC) to support the EMA Methodology Working Party in terms of guideline development and trainings.

[1]*Post-meeting note* - Link to the catalogues: HMA-EMA Catalogues of real-world data sources and studies

2. Meeting objectives

Catherine Cohet and Susana Perez-Gutthann, the co-chairs of the ENCePP Steering Group, introduced the objectives of the Plenary:

- To reflect on the work of ENCePP in recent years, and present and agree on proposed changes to the ENCePP mandate;
- To present and agree on proposed changes to the Steering Group mandate, and introduce the newly elected SG members for the 2024-2026 term;
- To present the ENCePP Workplan for 2024, including activities of the Working Groups, and seek feedback and contribution from ENCePP Partners on planned activities and deliverables;
- To update on, and seek feedback from ENCePP Partners, on the new ENCePP website and the EMA catalogues on RWD sources and on non-interventional (NIS) studies (former ENCePP Resource Database and EU PAS Register);
- To learn about, and discuss, current key data- and method-related initiatives;
- To place the work of ENCePP in the broader context of a changing regulatory environment.

3. Session 1: Looking back at 2023

Chairs: Catherine Cohet, Susana Perez-Gutthann

3.1. ENCePP: history and achievements

As this was the last Plenary meeting of the current ENCePP SG (2021-2023 mandate), Catherine Cohet interviewed Susana Perez-Gutthann, her co-chair on the SG, and invited her to share her reflections on the early days of ENCePP, the uniqueness of the network and community, and potential new directions. Susana served three terms in the SG (2012-13; 2014-16; 2020-23), two of them as co-chair. She recalled that the establishment of ENCePP in 2007 was an exciting period, which gave the opportunity to the members to learn about the work of the Agency. One of the uniqueness of ENCePP is the direct communication between experts, and the opportunity to collaboratively develop guidance documents supporting study development and conduct. The international impact now includes professional societies (ISPE, ISOP, ISPOR), but also regulatory agencies outside the EU (FDA, Health Canada) and patient representatives. ENCePP allows EU researchers to have a voice, and regarding the future, Susana expressed the sustained importance for the ENCePP community to continue supporting the improvement of data quality and study design/methods.

3.2. Achievements of the Working Groups and a view to 2024 activities

The chairs of the three Working Groups (WG) shared the achievements of their WG in 2023 and their planned future activities for 2024, which will be embedded in the workplan.

WG1 - Alejandro Arana highlighted the 11th Revision of the ENCePP Guide on Methodological Standards in Pharmacoepidemiology as the main task of the group. Revision 11 was released in July 2023, with new recommendations including the use of the causal inference target trial emulation approach; the use of the estimand framework to inform study design and analysis choices; and the use of the HARPER protocol template to foster transparency, reproducibility and harmonisation of non-interventional study protocols and facilitate their assessment. Future activities include the 12th Revision of the Guide in 2025, moving to bi-annual updates, with potential changes in format and/or contents, including considering publication in a peer-reviewed journal.

Q&A/discussion

- There are several ongoing activities independent of ENCePP on guidance for non-interventional studies that ENCePP should consider, e.g.: ongoing revision of GVP module VIII; reflection paper/guideline on RWE under development by the EMA Methodological Working Party; ICH M14 guideline on "*General principles on plan, design, and analysis of pharmacoepidemiological studies that utilize real-world data for safety assessment of medicines*".
- Feedback from the audience on how the ENCePP Guide is used and perceived: academia and industry regularly use the Guide; some CRO and companies are integrating contents in trainings for newcomers.

WG2 – Rosa Gini reflected on the mandate of the group, to be updated in light of the migration of the EU PAS Register and the ENCePP Resource Database to the new catalogues on the EMA website. Future activities include actions to promote and support compliance with the ENCePP Code of Conduct and the launch of a podcast series "*Conduct your study*", with 5 episodes planned in 2024.

WG3 - Gianluca Trifiro shared the achievements of the group, including three publications in 2023. Activities include a further review of the former databases/new EMA catalogues, analysis of the non-interventional studies, how to link information on the studies to other sources (e.g., regulatory documents), and comparison with other observational study registers. Future activities include a study on the relationship between countries economic indicators and use of data in observational studies; an analysis of regulatory outcomes of studies requested by regulators; and a study on the impact of recent regulatory initiatives in promoting clinical research in the paediatric population.

4. Session 2: 2024 and beyond

Chairs: Helga Gardarsdottir, Patrice Verpillat

4.1. Results of the Steering Group election and introduction of the new members

Susana Perez-Gutthann presented the results of the new ENCePP SG for the next term (2024-2026). The elected members are: Alejandro Arana, Annalisa Landi, Christos Kontogiorgis, Helga Gardarsdottir, Marco Tuccori and Vera Ehrenstein. The first meeting of the new SG will be organised in Q1 2024. The list of appointed representatives is under finalisation[2].

4.2. 2024 ENCePP workplan

Catherine Cohet presented the objectives of the 2024 ENCePP workplan, building on objectives set in 2023, some of which partly addressed already, while others will be updated by the new Steering Group.

Objective 1: to support the migration of the EU PAS register and ENCePP resource database to the new catalogues.

Objective 2: to support the re-building of the ENCePP website.

Objective 3: to inform the ENCePP community and other relevant stakeholders on the new catalogues and website.

Objective 4: to inform on the place and impact of ENCePP in a fast-evolving environment.

[2] *Post-meeting note* - Now available: Steering Group - European Union (europa.eu)

Objective 5: strategic review to re-define/finetune ENCePP's scope and initiatives.

Objective 6: to increase visibility of ENCePP activities and deliverables through collaboration with learned societies and study registration initiatives.

Q&A/discussion

- Question on type of stakeholders to be involved in addressing the workplan: broad contribution is needed in addition to the ENCePP members, such as from industry, learned/professional societies, international organisations.
- Volunteering/active participation of ENCePP partners in activities (workplan rollout) and information sharing is key.
- Other types of stakeholder participation may be necessary, such as including lawyers. Also question on whether individual registration may be an opportunity for e.g., retired partners, to maintain contribution (pros/cons to be explored).
- Webinars/symposia are efficient approaches to create synergies. Upcoming opportunities are the next annual ISPE meeting (August 2024) or the ISOP mid-year symposium (June 2024).

4.3. Proposal for revision of the ENCePP mandate and the mandate of the Steering Group

Patrice Verpillat highlighted the importance of revising the mandates of ENCePP and of the Steering Group (SG), due to important changes, such as the migration from the EU PAS Register and Resource database from ENCePP, and the fact that these mandates have not been significantly since the inception of ENCePP. Regarding the ENCEPP mandate, he suggested better leveraging SIGs (Special Interest Groups) to address specific topics. With regards to the SG mandate, one of the key suggested changes is membership, with considering additional members (e.g., from the Methodological Working Party) and updating the observer status to that of representative.

Q&A/discussion

- Question on whether the proportion of ENCePP centres should also increase in the SG, seeing that the number of appointed representatives is increasing, and whether there is a maximum number for re-election.
  - Answer: increasing the number of seats (for example to 8 or 10) will be considered. A maximum number of times that members can be re-elected will also be included.
- Comment that restriction of the mandate to non-interventional studies could limit opportunities, for example, external comparator studies.
  - Answer: Additional language could be added e.g. on hybrid designs and how RWD can complement trials including external comparators.
- Question on why 'data sources' was included in the list of non-public entities in the slide on ENCePP representativeness.
  - Answer: This covers the organisations which have access to a data source.
- Question on the process of opening new SIGs.
  - Answer: the decision of establishing a new SIG is made by the SG, and can be triggered by any ENCePP partner.

4.4. New EMA Catalogues of RWD sources and studies (former ENCePP Resource Database and EU PAS Register)

Ana Cochino gave an overview on the development and status of the upcoming catalogues, focusing on the improvements for a better user experience, and showcasing the new platform and functionalities. The expected launch of the catalogues is early 2024.

Q&A/discussion

- Question on analogy used for the metadata.
  - Answer: It is standardised to DICA.
- With regards to, EHDS many countries are developing catalogues at national level. Are activities planned to engage and harmonise terminology?
  - Answer: Actions to connect with Member States and national initiatives are underway.
- Question on linking studies and data sources, and validation of the data sources.
  - Answer: These activities have been performed.
- Question on guidance for understanding the definition of each of the metadata fields.
  - Answer: guidance will be provided.
- Comment: hidden protocols won't be migrated, and this could create transparency issues.
  - Answer: Action needs to be taken. (*Post-meeting note*: communication sent to all study owners to make their protocol public, if they wish them to be migrated, or upload them in the new system as soon as possible. In the future, for transparency reasons, all protocols will be published by default).

4.5. The new ENCePP website: overview and key improvements

Julianna Fogd presented the status of the new ENCePP website development, the new functionalities, the new design and the new ENCePP logo that was approved by the Steering Group in October 2023. The website will be launched on the same day as the catalogues in early 2024. The EU PAS Register will no longer be available on the ENCePP website. Users will be redirected from the former ENCePP URL to the new URL: https://encepp.europa.eu. Julianna encouraged the audience to explore the new website after its launch and share any proposals for improvement.

Q&A/discussion

- Question on monitoring the usage of the site.
  - Answer: This is foreseen.

5. Session 3: Key data- and method-related initiatives

Chairs: Vera Ehrenstein, Xavier Kurz

5.1. HealthData@EU: Update on the EHDS pilot

Denise Umuhire presented the EHDS pilot and its two components, on primary use of data and patients' rights to access their own data, and on secondary use of data. The new legislation proposes a new platform that would allow each researcher to access securely data for research purposes, via the national data access body. Several data access bodies are in the process of being established in various countries. Five use cases are currently running to test the system, led by various institutions such as by the European Centre for Disease Prevention and Control (ECDC), the Health Data Hub (France) and Sciensano (Belgium).

EMA is leading on a use case on coagulopathy in COVID-19 patients. The pilot is running for another year (2 years in total).

The EHDS offers an opportunity to scale up secondary use of data, with transparency and trust as key elements of success. The work ENCePP has paved the way in many areas of the user journey, with tools such as the checklist for protocols, the ENCePP Guide, etc., that can be leveraged.

Q&A/d*iscussion*

- Question on how the ENCePP centres, which have experience in using RWD to generate RWE, could benefit EHDS.
  - Answer: the organisation of EHDS will be at national level. ENCePP centres can contact the data access bodies which will be responsible to centralise the requests, and centres will have the opportunity to share their experience.

5.2. DARWIN EU® update

Andrej Segec gave an update on the DARWIN EU® programme. This is the second year of DARWIN EU, and 18 studies have been conducted. Examples of ongoing or recently completed studies, illustrating a wide range of study types, and the publicly available catalogue of standard data analyses, were presented.

Q&A/discussion

- Question about breakdown of studies using OMOP Common Data Model vs. native data.
  - Answer: all studies are analysed using the Common Data Model.

5.3. Use of estimands in target trial emulation

Juan Jose Abellan discussed the use of estimands in target trial emulation (TTE). Research questions around comparative effectiveness or safety would ideally be addressed with a randomised clinical trial (RCT). Addressing the same question with a non-interventional study using observational databases can be viewed as an attempt to emulate an RCT: the target trial. Juan Jose mentioned the Hernán and Robins publication from 2014 that outlines the TTE framework for comparative studies.

When emulating a target trial, key elements of the trial should be specified; Hernán and Robins suggest: eligibility criteria, treatment strategy, assignment procedures, follow-up period, outcome, comparators and analysis plan. This is similar to the well-established PICO(T) framework for non-interventional studies. Juan Jose noted that the TTE approach has already been used to support regulatory decisions.

In RCTs, the estimands framework outlined in ICH E9(R1) is used to specify the research question of interest, instead of the PICO(T) framework. ICH E9(R1) is driven by causal inference principles. Defining an estimand requires specification of its attributes: population, treatment conditions, outcome to be collected from each individual, group-level summary measure, and intercurrent events and strategies to deal with those. Juan Jose briefly outlined the several strategies discussed in ICH E9(R1). When using the estimands framework, the study objective, estimand, main analysis and sensitivity analysis should all be aligned. The concept of sensitivity analysis in ICH E9(R1) is different from the one used in non-interventional studies. For example, changing the population is not a sensitivity analysis according to the estimands framework, but a different estimand. PICO(T) and the estimand framework have many features in common, although intercurrent events are not in PICO(T). The estimand framework (published in 2019) can be seen as an evolution of the PICO(T) (published in 1995). Juan Jose presented a few examples of research questions and how they can be addressed according to the estimand framework principles.

In conclusion, PICO(T) in used in non-interventional studies, while the estimand framework is used to clearly define the research question addressed with an RCT. TTE offers a bridge between RCTs and non-interventional studies, but the estimand framework should still be applied for the target trial to enable better emulation with the non-interventional study.

Q&A/discussion

- Question on whether it's foreseen that TTE comes as a requirement for post-authorisation studies.
  - Answer: Maybe as a recommendation, but not a requirement. TTE is already in the mind of regulators, as they are used to RCTs. The bridge to clinical trials is therefore needed for increased acceptance of non-interventional studies.
- Sensitivity analysis in this framework became important. Question if there will be any guidelines and (meta)models that could be used for producing the results.
  - Answer: Sensitivity analysis in the estimand framework is just assessing how robust the results are to assumptions made in the primary analysis. Changing e.g. the definition of 'exposure' or the definition of 'outcome' changes the research question and will not be a sensitivity analysis but a different estimand. Therefore, the (meta)models are probably not of help in that case.
- Comment: Emulation of RCTs in non-interventional studies is not a new concept. But maybe sometime could be the other way round, when the type of treated population changes as time passes.

5.4. Artificial Intelligence (AI) applications in pharmacoepidemiology: opportunities for the European regulatory network

Luis Pinheiro gave a brief introduction about AI. AI is a catch-all term for a collection of novel digital technologies and methods, it allows machines to extract rules from data (i.e., learn) and predict, classify or cluster similar patterns using those rules or execute autonomous actions. There are two types of AIs, analytic AI (group and trying to be accurate) and generative AI (main aim is to mimic and generate content).

AI in medicines regulations can lead to greater efficiency and productivity, reduce error and cognitive load, expose and prepare data and expand insights. For example, exposing data (name entity recognition) is a task performed to identify and extract entities (e.g. ADRs extracted from SmPCs, identifying negative controls).

There are several and increasing opportunities to leverage AI in pharmacoepidemiology, and experimentation and collaboration will be essential. A European Medicines Regulatory Network (EMRN) workplan including experimentation and fora for interactions with, e.g., academia, is in preparation.

Q&A/discussion

- Question on how to deal with fake information, e.g., in literature reviews, evidence reviews.
  - Answer: this is part of individual experimentation, depending on the data. Concern is about what training data was used in the model, and there are ways to assess performance, including the possibility that the data is not correct. That is embedded in the process of experimentation in general. EMA also cooperates with other European agencies in a project looking at fake information.

5.5. Use of negative controls in pharmacoepidemiology

Daniel Morales discussed the use of negative controls in pharmacoepidemiological studies to mitigate bias. Negative control exposures share same biases with the exposure of interest, but are not causally

related to the outcome, whereas negative control outcomes share same biases with the outcome of interest but are not causally related to the exposure. A recent systematic review on use of negative controls found that most studies are cohort studies, negative control outcomes being the most frequently used.

There are four areas where negative controls can be of help: detection of bias, correction of bias, calibration of p-value and benchmark to assess performance of various pharmacoepidemiological methods. Examples were presented for each area and discussed the two strategies to validate negative control assumptions: lack of causality and shared bias structure.

Marc Suchard presented on the conceptual model for negative controls. A negative control is an exposure-outcome pair with *a priori* no causal relationship. Negative controls are typically defined relative to a causal question of interest. Marc spoke about 'one vs many negative control experiments', baseline characteristics (candidate confounders) in observational healthcare data, the value of using a large set of negative controls, and negative controls in a comparative cohort study. An example from the OHDSI community creating negative controls for cohort studies was presented.

Discussion, comments

- Comment that there may be a need as much for positive controls as for negative controls, however, the focus in the literature is mainly about negative controls and not positive controls.
  - Answer: Positive controls are important as negative controls only allow to learn about type 1 error and don't allow to provide information about type 2 error. The challenge with positive controls is that the 'real association' value is rarely known, and even if known, it will change over time, because knowing about a positive control will impact behaviour in terms of the exposure itself.
- Question on synthetic positive controls.
  - One approach is to use synthetic positive controls, which have residual confounding built into, and then scale the effect estimate up in a way that keeps repeating the confounding structure to a known relative risk. The difficulty is, that there is no learning about what additional unmeasured confounding might come into the process, given there is a true effect. There are some difficulties with the calibration as well. They might correlate with each other.

5.6. RWE and pharmacoepidemiology in the current regulatory environment

Emer Cooke, EMA's Executive Director, addressed the work of ENCePP in the context of a rapidly evolving regulatory, technological and data environment, and reflected on the work of EMA in 2023. Considering the increasing use of RWE for regulatory-decision making, ENCePP will continue to play an important role in supporting stakeholders involved in evidence generation by providing an exchange and learning forum. Emer reflected on the fact that the new EMA catalogues build on the work of ENCePP, on the importance of leveraging the Guide on methodological standards in European and international guidance, and on the role of ENCePP as an expert community in upcoming consultations on draft EMA guidance. She spoke to the new pharma legislation proposal aimed at reinforcing the role of the Agency in using RWD to support the development, authorisation, and supervision of medicines, and the reinforced legal basis for EMA to perform additional independent studies. She concluded with considerations on AI and EMA's recent AI reflection paper, and thanked the audience for their work to support the implementation of the ENCePP workplan.

5.7. Summary and next steps

Susana Perez-Gutthann and Catherine Cohet closed the Plenary, concluding that the morning had been about celebrating the history and the achievements of ENCePP, while the afternoon was about learning about methods and different perspectives and contributions that will impact the ENCePP workplan moving forward. They emphasised that feedback is welcome on what went well and what could have been done differently for this annual Plenary meeting, and that the Steering Group is counting on the entire ENCePP community to contribute to improve and roll out the ENCePP workplan.