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Report - ENCePP Plenary meeting, 30 November 2022

Chairs: Catherine Cohet (EMA) and Susana Perez-Gutthann (RTI Health Solutions)

This report summarises the main topics and discussions of the 2022 ENCePP Plenary meeting. The presentations are published on the ENCePP website (Link).

Welcome and introduction - Meeting objectives

Susana and Catherine welcomed the participants, introduced the meeting and presented the meeting objectives:

- To present and discuss the activities of the ENCePP Steering Group and Working Groups and exchange ideas to populate the ENCePP workplan for 2023 and beyond;

- To update and seek input from ENCePP partners on upcoming developments including the new ENCePP website and the upgrading of the EU PAS Register and ENCePP Resources Database catalogues into the new RWD sources and RWD studies catalogues;

- To exchange views on the future of ENCePP and how to improve visibility, enhance collaborations with learned societies, and consider current and future guidance initiatives in the ENCePP work plan;

- To inform the ENCePP community about latest developments on COVID-19 and monkeypox vaccines and therapeutics and the contribution of pharmacoepidemiology to EMA's decision-making;

- To update on DARWIN EU® and discuss the interface with ENCePP activities;

- To learn about, and discuss, current methodological hot topics.

This is the first in-person (hybrid) plenary since 2017, the EMA Business Continuity Plan and the COVID-19 pandemic. Susana thanked Xavier Kurz on behalf of the ENCePP community for his outstanding contribution over the years.

Update on COVID-19 and mpox vaccines and therapeutics – how can ENCePP support public health crisis management

Marco Cavaleri (EMA) provided an update on approved COVID-19 vaccines, their use in immunisation campaigns, and the current target populations. His presentation included an overview of efficacy and safety of mRNA COVID-19 vaccines in children; immunogenicity results against Omicron BA.4-5 with Vidprevtyn Beta (newly approved Sanofi vaccine); and immunogenicity and effectiveness data for the newly adapted vaccines against recently emerging sub-variants. An overview of available treatments and data with antivirals were also presented. Regarding mpox, the results of an effectiveness study from the UK were presented, as well as an overview of European initiatives by EMA and ECDC.

Evidence from independent pharmacoepidemiological vaccine studies has contributed to EMA decision-making in public health crisis management for COVID-19. ENCePP can contribute to this effort by fostering good practices, methods, and selection of suitable data sources. Research questions important for regulatory decision-making can be addressed by the ENCePP community.

DARWIN EU®: update and interface with ENCePP

Daniel Prieto-Alhambra (University of Oxford, DARWIN EU Coordination Centre) introduced the topic by reminding challenges and solutions (CDM) for the generation of RWE for regulatory purposes. An overview of the vision, objectives and governance, and the Coordination Centre of DARWIN EU were presented, as well as the data sources recently onboarded, the types of studies that DARWIN EU will produce, the draft catalogue of standard analyses inspired by the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, and the process flow for conducting studies (starting from NCA/EMA committee request). The Coordination Centre is registered as an ENCEPP Network and ENCePP Centres/data sources are contributing. The DARWIN EU Declaration of Interests policy is based on the ENCePP Code of Conduct.

Discussion

- Possibility to apply for the ENCePP Seal for DARWIN EU studies: as DARWIN EUs ambition is to generate a large number of rapid studies, it would be challenging to apply the ENCePP Seal to all of them.

- DARWIN EU is funded by the European Commission, there is no access for industry so far.

- Expertise of centres who have conducted studies in the past with local data will continue to have a role, as the analyses will run locally, and it will be possible to check and review the findings.

SESSION 1: Looking back at 2022

Chairs: Xavier Kurz (EMA) / Massoud Toussi (IQVIA)

1.1. Update from the Steering Group

Susana and Catherine introduced the session by sharing highlights of the past year, including DARWIN EU, the return to "normal" while work on COVID and mpox continues, the multiple outputs from the Working Groups, the work of EMA on the transition of the ENCePP website and catalogues, and the importance of the continued engagement of the ENCePP community.

1.2. Update from the Working Groups

Working Group 1 - Research Standards and Guidances

Alejandro Arana (RTI Health Solutions) presented the mandate, objectives, and activities of WG1 such as the 10th Revision of the ENCePP Guide (with two new chapters, a new annex, and several improved chapters). A proposal for the 11th Revision was presented, including the estimand framework for observational studies, target trials, use of external comparators, and a more structured presentation of study designs. Statistics on the access to the Guide and lessons learned were presented. Next year activities will also consist of the update of the Checklist for Study protocols based on recent methodological developments, and the consideration in the Guide of the HARPER protocol template.

Working Group 2 - Independence and Transparency

Rosa Gini (ARS Toscana) presented the group mandate, its members, and main activities to continue in the next year, including a comparison between the ENCePP Code of Conduct (CoC) and the new EMA CoI policy; a proposal to add questions to the EU PAS register on the details of the primary investigator and compliance of the study with the CoC, and a SHARING scoping review to characterise

levels of transparency in the execution of pharmacoepidemiological studies. The workplan 2023-2025 will include promotion of, and support compliance with the ENCePP CoC.

Discussion

- There is a lack of clarity among industry partners about the Seal and how it should be applied. It was confirmed that teaching materials will be developed by WG1.

Working Group 3 - Data sources and multi-source studies

Gianluca Trifirò (University of Verona) presented recent achievements of the group, including a publication on strategies to execute multi-database studies, an overview of studies in the EU PAS Register between 2010-2018, and a list of 16 recommendations on how to improve the EU PAS Register. Ongoing activities based on the EU PAS Register include: exploring differences across countries in the conduct of various types of observational studies; regulatory outcomes of registered PASs using distributed database networks; and overview of studies on paediatric populations. Proposed activities for the 2023-2025 work plan include: support to revision and structure of functionalities of the EU PAS Register; comparison with other observational study registers (e.g. clinicaltrials.gov); liaison with scientific societies such as ISOP Big Data and ISPE RWE SIG to explore the role of distributed networks in the context of signal management/signal detection.

Discussion

- Comparison between the EU PAS Register and other registers: the first step will be a mapping activity; suggestion are welcome in terms of comparison to specific registers. Similar discussions are underway at ISPOR level.

1.3. ENCePP website update

Andrej Segec (EMA) presented ongoing work on the development of the ENCePP website, including background information, statistics on the current traffic and some proposals and options for the new website that will be hosted on the EMA website. The update to the website had been supported by the ENCePP Steering Group during its meeting of May 2022. ENCePP branding, the www.encepp.eu address, and existing content (ENCePP Guide, CoC, mandate, meeting documents) are expected to be maintained.

Discussion

- For the time being, there is no plan to create an ENCePP LinkedIn account. In the future, visitors to the website will have the opportunity to share the content on their social media, including LinkedIn, and updates can also be shared on the EMA LinkedIn account.

1.4. Update on the RWD sources and RWD studies catalogues

Katerina-Christina Deli presented ongoing EMA work on the RWD sources and RWD studies catalogues. The following topics were covered: data discoverability, achievements and outlook for 2023 and beyond, metadata list, overview & comments from public consultation on the Good Practice Guide, status update on development of the catalogues, and the EU Metadata catalogue.

Discussion

- Some centres will be requested to update the information about a data source registered some years ago. Although the same data source may be accessed by multiple institutions, there will be only one user that will be responsible to update the content.

- Technical solutions to allow access to a study for more than one user (e.g., project manager and study principal investigator) are being considered.

- In the new catalogues, when a study is registered, it will be linked to the data source(s).

SESSION 2: A new era for ENCePP?

Chairs: Peter Arlett (EMA) / Susana Perez-Gutthann (RTI Health Solutions)

1.5. Collaboration between ENCePP and learned societies / guidance initiatives

Arnold Chan (National Taiwan University and NTU Health Data Research Center, ISPE representative in ENCePP steering group) discussed possible links with the International Society for Pharmacoepidemiology (ISPE), such as an ENCePP symposium during the annual or mid-year meeting.

Gianluca Trifirò presented potential collaborations between ENCePP and the International Society of Pharmacovigilance (ISOP) Big Data and RWE Special Interest Group, such as developing methodological papers on how SRS and RWE could complement each other, the role of RWE/big data in signal management/detection, and the mapping exercise of ongoing initiatives on signal detection using large scale distributed database networks.

Susana Perez-Gutthann (RTI Health Solutions) presented the HARPER (HARmonized Protocol to Enhance Reproducibility) template. The table of content was presented in comparison with the template for PASS protocols.

Catherine Cohet (EMA) informed on the revision of GVP Module VIII: adapted definitions, alignment with new/updated guidelines and international standards, inclusion of language on feasibility, etc. HARPER is fully compatible with GVP VIII in terms of legal aspects and content. She then presented the ICH M14 guideline on planning and designing pharmacoepidemiological studies using RWD for the safety assessment of medicines, for which work is ongoing, with a target date for establishment in January 2025.

Discussion

- It was reminded by WG2 that from an ENCePP CoC perspective, protocols should be registered before data processing starts, which is not highlighted in HARPER – it was noted that HARPER focuses on aspects of study development and is aimed at a broader community.

- The co-existence of several guidelines was discussed. The ENCePP Guide was initially developed as a guidance encompassing different available guidelines. Harmonisation of these guidelines is considered under ICH M14. In general, once an ICH document is published, it supersedes other guidelines ("hierarchy"). The ENCePP community should reflect on the place of the ENCePP Guide in this environment.

1.6. Open discussion on new directions for ENCePP, and impact on the work plan development

Xavier Kurz (EMA) presented the main achievements of ENCePP since its inception and reflected on possible future directions, including membership, coordination, interactions with learned societies, visibility, declarations of interests (DoI), and the ENCePP Seal.

Helga Gardarsdottir (Utrecht University) presented a proposal for the ENCePP workplan for 2023, including support to EMA through surveys/webinars/consultations, aspects on leveraging ENCePP activities and deliverables through collaboration with learned societies, and heightened visibility, particularly removing barriers and possibilities to reach a broader community. Discussion at Steering Group level will continue in 2023 for longer term topics of the work plan. A recap of the objectives on the WGs in the short-term was presented.

Discussion

- On the compatibility of the EMA DoI and the ENCePP CoC, proposals of WG2 for amendments of the ENCePP CoC will be considered by EMA.

- Different opinions regarding the expansion of membership to industry were expressed. Should industry be included, roles should be clarified.

- On whether, for example, ENCePP could become a 'classic' scientific society, feedback from the community is against a major change on the current model, especially given the EMA unique contribution in terms of independence, credibility and visibility.

- Nevertheless, work is needed on the promotion of ENCePP, and on barriers to the Seal: since it is little used, there should be a reflection on its actual need.

- This dialogue should continue, e.g., with a survey among members and a series of webinar discussions.

2. Session 3: Methodology

Chairs: Daniel Morales (EMA) / Helga Gardarsdottir (Utrecht University)

2.1. *Using primary data collection in pharmacoepidemiology: the SEMVAc mpox vaccine study*

Pierre Engel (Aetion) presented the SEMVAc study on the safety and effectiveness of the mpox vaccine in Germany that uses primary data collection, and the USMVAc study (same research questions with secondary use of data). Pierre discussed the advantages and disadvantages of the two types of data collection. Of note, WHO has recently recommended "mpox" as the new name for monkeypox disease, that will also be reflected in the ICD coding system.

2.2. *Results from RTC DUPLICATE and lessons for Europe*

Shirley Wang (Harvard Medical School, Boston, USA) presented the RCT DUPLICATE project (link), a series of studies with the objective to understand and improve the validity of RWE studies for regulatory decision-making. The first case study was a database study, where main challenges were about collecting information on start of follow-up, mixing effect of randomization and discontinuation of baseline maintenance therapy, delayed effect over long follow-up, differences in population distribution coupled with effect modification, inadequate emulation of exposure or outcome. Differences with the RCT were discussed in terms of biases and correcting emulation differences. Three other case studies were presented: Time varying effects, Discontinuation of prior Tx at randomization and Chance or other factors. Main learnings were the requirements to evaluate replicability of trial results with RWE studies, which requires nuance on residual bias, random error, efficacy vs effectiveness and single trial as reference standard, and the importance of thinking about the target trial that would match the question for end users when evaluating when and how RWE studies complement RCTs. If data are fit-for-purpose and if design and analysis are done properly, non-randomized RWE studies come to similar conclusions as randomized trials.

Sebastian Schneeweiss (Harvard Medical School) reiterated key conclusions. An important point often misunderstood is why emulating RCTs is needed if there is already an RCT: RWE is complementary to RCTs, answering questions that often are not seen in routine clinical practice. An RWE-based 2-stage approach to increase confidence in RWE was presented, where the first step consists in an RWE emulation of a completed RCT to confirm the validity of the RWE approach, and the second step consists in an RWE study with boosted confidence from successful Stage 1 RCT emulations.

Discussion

- It was highlighted that one of the challenges of the target trial approach is that included patients in the trial are generally healthier compared to patients in RWD. Some differences were observed in terms of age (with the trial population being younger on average) and sex (fewer female participants in trials compared to clinical practice). It is indeed important to have the information

on baseline characteristics of patients both from RCTs and RWD when conducting RCT emulation analyses.

2.3. Target Trial Emulation With and Without Cloning

Xabier García de Albéniz (RTI Health Solutions) presented examples of observational studies emulating target trials of COVID-19 vaccines. Emulating a target trial was presented as a fundamental approach for causal inference using observational data. While the most challenging component is treatment assignment (sometimes requiring cloning), main benefits include facilitating discussion of the design (as clinicians are often more confident with RCT than RWE studies), bias mitigation, evaluation of clinically relevant treatment strategies, and use of methods to study treatment strategies that are sustained over time. Two case studies were presented (with and without cloning): results highlighted the need of cloning when exposures are not well defined at time zero, and the absence of need of cloning when they are defined.

Wrap-up

Patient views on use of their data in pharmacoepidemiological studies

Iryna Vlasenko (European Chapter of the International Diabetes Federation, ENCePP Steering Group) presented aspects of pharmacoepidemiological studies from a patient perspective. Patients recognise the value of health research, however, they report a number of significant concerns. The ENCePP CoC can represent a useful tool to reinforce trust, and the ENCePP community can contribute to improve trust.

Summary and next steps

The ENCePP SG co-chairs, Catherine Cohet and Susana Perez-Gutthann, closed the Plenary, thanking the participants for their contribution to the meeting and looking forward to another face-to-face (hybrid) plenary in 2023.