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Report - ENCePP Plenary virtual meeting 2021

18 November 2021 – chairs: Gianmario Candore (EMA), Susana Perez-Gutthann (RTI Health Solutions)

This report is a summary of the ENCePP Plenary virtual meeting. More details are available in the presentations of the meeting here.

1. Introduction: Update on COVID-19 vaccines

1.1. Welcome and objectives of the webinar

Susana Perez-Gutthann and Gianmario Candore welcomed the participants (over 100 representatives of various organisations) of the webinar, including ENCePP partners and Steering Group members, then outlined the agenda and the objectives of the event:

- To learn about key results from observational studies on COVID-19, methodological challenges that remain to be addressed, and how ENCePP could further promote best practice for COVID-19 research
- To present the recently finalised CHMP Guideline on registry-based studies
- To update on the work programme of the HMA-EMA Big Data Task Force and discuss the interface with ENCePP activities
- To present the result of the surveys on the metadata and functionalities of the EU PAS Register and ENCePP Resources Database and discuss the amendments needed
- To exchange views on the activities of the ENCePP Steering Group and Working Groups (WGs), the renewal of the WGs, and the proposed new ENCePP activities (e.g. new SIGs)

1.2. Update on COVID-19 therapeutics and vaccines

Marco Cavaleri (EMA) gave an update on authorised and under review COVID-19 therapeutics and vaccines.[1] There are three COVID-19 therapeutics approved in the EU:

[1] Note from the ENCePP Secretariat: the information below was applicable at the date of the meeting (18 November 2021). It has evolved at the date of this report, based on the epidemiological and regulatory situation.

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- Veklury (redemsivir), approved for the treatment of COVID-19 in people over the age of 12 with pneumonia requiring extra oxygen
- Regkirona (regdanvimab), approved for the treatment of COVID-19 in adults at increased risk of severe disease
- Ronapreve (casirivimab / imdevimab), approved for the prevention of COVID-19 in people from 12 years of age, and the treatment in people from 12 years of age at increased risk of severe disease.

Other treatments under evaluation are Oluminant, Kineret and Ro-Actemra, all repurposed therapeutics and an EU decision is awaiting soon. Sotrovimab, Tixagevimab/cilgavimab and Molnupiravir are new treatments under rolling review by EMA.

Paxlovid is currently under development and EMA is discussing potential opinion to Member States on early use for emergency settings, ahead of a rolling review and a marketing authorisation application.

With regards to vaccines, four vaccines are already authorised, and a fifth one (from Novavax) might be approved soon; this more 'traditional' vaccine type is protein-based (nanoparticles), cultivated in insect cells.

A study from the UK published in the Lancet, showed that vaccination reduces the risk of delta variant infection and accelerates viral clearance. Nonetheless, fully vaccinated individuals with breakthrough infections have peak viral load similar to unvaccinated cases and can efficiently transmit infection in household settings.

Combination of different vaccines appears to increase effectiveness; however, it depends on the type of vaccines which are mixed. With regards to paediatric COVID-19, even if this age category is less at risk of severe outcomes, the number of cases in less than 12 years-old is growing as this population is not vaccinated. The hospitalization rates in children are increasing. Multi inflammatory syndrome (MIS-C) is also recognized to be a risk for infected children.

2. Session 1: CHMP Guideline on registry-based studies; EU PAS Register

Chairs: Alejandro Arana (RTI), Xavier Kurz (EMA)

2.1. Update on CHMP Guideline on registry-based studies

Kelly Plueschke (EMA) gave an update on the CHMP Guideline on registry-based studies published on the EMA website in October 2021. The presentation covered a summary on the EMA Patient Registry Initiative; timelines for development of the guideline, an overview of questions received during the consultation phase, and an insight into the guideline's sections.

The scope of the guidance is studies based on patients' registries (including disease or specific conditions registries). Its objective is to provide recommendations on key methodological aspects of registry-based studies and to highlight relevant legal bases and regulatory requirements. The main target audience is the MAAs/MAHs but the document is also relevant to other stakeholders.

The presenter highlighted that a registry-based study is the investigation of a research question using the data collection infrastructure or patient population of one or several patient registries. A registry-based study is a clinical trial or a non-interventional study as defined in Article 2 of Regulation (EU) No 536/2014. Important aspects to consider when planning a registry-based study (identify the scientific question(s), feasibility analysis to identify the suitable registry/ies to answer the study question(s), and early consultation with national competent authorities and EMA) were also introduced.

2.2. Update on the rebuilding of the real world data sources catalogue and observational studies catalogue

Xavier Kurz (EMA) gave an update on the EMA project on Metadata, Data Quality framework and Catalogues.

Three drivers lead to the creation of the project: i) the increasing need to be able to identify appropriate RWD sources, ii) the more complex needs of data, and iii) the lack of standardised information and statistics on RWD sources.

This project aims to bring enhanced transparency and discoverability with regards to observational studies and data sources in the regulatory context and to increase their quality. This will also enhance the ability to evaluate the level of evidence provided by observational studies and RWD sources.

The ENCePP Resource Database was created 10 years ago, it provides an unprecedented level of knowledge and transparency on sources of data for pharmacoepidemiology in Europe, but some improvements are needed to match the expansion of the pharmacoepidemiology field in the last decade. The EU PAS Register was created by ENCePP primarily to exchange information between centres and provide transparency on studies. The ENCePP eRegister of studies was the first public register of observational studies, adopted as the EU PAS Register following the 2012 pharmacovigilance legislation.

The project is divided into three phases:

- Identification of the metadata for the catalogues (MINERVA study- EUPAS 39322)
- Creation of a Data Quality Framework and collection of metadata from eligible data sources
- Rebuilding of both the data sources and study catalogues

2.3. Survey results on the EU PAS Register and Slido Q&A session

Ana Cochino (EMA) gave an overview of the survey that had been circulated to the whole ENCePP network (18 responses received) on 25 October 2021. The aim was to understand how the catalogues can be improved for the user community, get feedback on the usefulness and feasibility of some data elements proposed in the current 'metadata list' of the MINERVA study, and collect requirements related to functionalities and common use scenarios.

The questionnaire was structured in three sections:

- Data sources catalogue, from the point of view of the data user
- Data sources catalogue, as a 'data owner'
- Studies catalogue

Responses for the third section were presented, including comments on the study type, study design, scope of the study, source of funding, coding of fields (dictionaries), automatic checks for data accuracy, and fields proposed to be added.

A **Slido session** followed Ana Cochino's presentation, to seek input from the webinar participants on specific questions.

The main results were the following:

- Study type: 90% of the 42 responders agreed to have only two options: interventional and non-interventional.

- Study design: 56% of the 43 responders found the classification 'retrospective' vs 'prospective' secondary use of data not useful.
- Scope of the study: based on 39 responses, three values were suggested to be added: a) validation of studies (92%), methodological studies (90%), feasibility studies (87%).
- Collection of data on medical conditions: based on 44 answers, the participants would find the following terminology useful: ICD (73%), MedDRA (43%), SNOMED (32%).

The need to have a systematic understanding of key terms was highlighted, and adding definitions of key concept on the ENCePP website was suggested (e.g. glossary in catalogue data entry point, guideline).

There was a mention of the ISPE/ISPOR transparency initiative that has a RWE registry similar to the EU PAS register, with fewer items to complete and larger international focus (link: OSF Registries | Search). Linkage between these registers could be considered.

Next steps: a dedicated meeting of ENCePP WG1 and WG3 will be held on 7 January 2022 to look at the suggestions presented and to agree on a proposal for the categories of fields.

The survey will be also sent to the pharmaceutical industry. Questions may be refined following this Plenary discussion. There was a suggestion from the Plenary participants to send it to CROs, as often these organisations advise industry on studies, although CROs that are members of ENCePP already received the survey.

3. Session 2: Update on Big Data SG and ENCePP SG

Chairs: Daniel Morales (Dundee University), Peter Arlett (EMA)

3.1. HMA-EMA Big Data workplan and update on DARWIN EU

Francois Domergue (EMA) presented the HMA-EMA Big Data Steering Group workplan, its key achievements, and an update on DARWIN EU.

In January 2020, the Big Data Task Force proposed Ten recommendations to unlock the potential of big data for public health in the EU. In September 2020 the Big Data Steering Group workplan for 2020-21, and in August 2021 the Big Data Steering Group Workplan 2021-2023 were published.

One of the main recommendations was the creation of DARWIN EU, a federated network of data, expertise and services, with EMA providing leadership, setting standards, contracting studies and overseeing.

The Coordination Centre will manage the network and execution of the studies on behalf of EMA; its appointment is expected in early 2022, and the first pilot/studies from 2022.

The implementation of the Big Data recommendations will require strong engagement and collaboration with stakeholders in 2022.

3.2. Curricula in Data Science, Pharmacoepidemiology and Biostatistics

The training curriculum on Big Data for regulators was presented by Stefania Simou (EMA). The HMA-EMA joint Big Data Task Force introduced Recommendation IV "*To develop EU network skills in Big Data*" in its workplan, with the aim to develop a big data training curriculum based on a skills analysis across the network, and roll-out the training.

By increasing the level of expertise within the EU regulatory network, it is expected that there will be more contribution from regulators to the definition of research questions, study protocols and interpretation of study results, as well as informed advice on strengths and weaknesses of using certain types of data sources for post-authorisation studies; the general level of expertise on pharmacoepidemiological methods will be increased; and the EU Network will act as a reference for data-driven regulation.

There was an update given on the Biostatistics, Pharmacoepidemiology and Data Science curriculum.

At a later stage, there will be discussions on whether the training curriculum can be made available more widely, e.g. to the ENCePP community, though many aspects will need to be considered before.

3.3. Artificial Intelligence in Medicine Regulation

Luis Pinheiro (EMA) gave an overview on Artificial Intelligence, focusing on the promises, the initiatives undertaken by the regulatory network and concrete examples.

HMA/EMA organised a workshop on artificial intelligence in medicines regulation on 19-20 April 2021. There were six AI recommendations previously identified by the HMA/EMA Big Data Taskforce, the Regulatory Science Strategy 2025 and the European Medicines Agencies Network Strategy 2025, of which the stakeholder input in the workshop was to prioritise methods & guidelines, partnerships, and learning & skills.

Examples of the use of AI in the network were presented in three areas: i) process, ii) regulatory submission and iii) data analytics.

3.4. Update on the activities of the ENCePP Steering Group (SG) and Working Groups (WGs)

The co-chairs of the ENCePP Steering Group - Susana Perez Gutthann (RTI HS) and Gianmario Candore (EMA) - updated the network on the first year of the new SG. There were three meetings in 2021, where the group had discussions on the ENCePP mandate, the 9th revision of the ENCePP Guide on Methodological Standards, the reactivation of the WGs and the rebuilding of catalogues (ENCePP Resource Database and EU PAS Register).

A webinar was organised for Academia in March to promote a better understanding of what ENCePP is and how it contributes to improving pharmacoepidemiological research.

The future areas of focus were highlighted: strengthening the network, access to data, high quality studies, methods and governance, new data sources and approaches.

After the SG overview, the ENCePP WG chairs (WG1: Research Standards and Guidance – Alejandro Arana (RTI); WG2: Independence and Transparency – Rosa Gini (ARS Toscana); WG3: Inventory of EU data sources and methodological approaches for multi-source studies - Gianluca Trifirò (University of Verona) – gave a status report on the work of the WGs.

4. Session 3: ENCePP Resource Database

Chairs: Gianluca Trifirò (University of Verona), Paolo Alcini (EMA)

4.1. Survey results on the resource database and Slido Q&A session

Ana Cochino (EMA) gave an overview on the survey results related to ENCePP Resource Database.

The presentation was followed by a Slido Q&A session with four questions to the audience:

- Data source/data bank concept: the majority of the respondents preferred the terms 'data source – database' (49%), followed by 'data source – dataset' (26%), 'data source – databank' (23%).
- 'Terminology aside – do you find the conceptual split [between data sources and data banks]…': 39% out of the 33 people responded 'very useful (implement catalogue structure focusing around these concepts)', 45% 'useful (collect minimal information on data sources)' and 15% answered 'too granular (think alternative solutions)'.
- The third question related to the need to have information about the vocabulary used for specific fields in the new database catalogue: almost unanimous agreement was shown for fields like '*Cause of death*' and '*Prescriptions*'.
- The last question was about what fields the users would consider the most useful in the new catalogue. Within the proposed fields, '*population size by age group*', and '*detailed information on data access* (e.g. reason for requesting access,…)' were considered the most useful; while '*Median age of population in data source*', and '*Distribution of population by gender*' the least.

5. Session 4: Observational studies for COVID-19

Chairs: Olaf Klungel (University of Utrecht), Catherine Cohet (EMA)

5.1. Update on COVID-19 vaccine studies

Considerations on timely real-world evidence to monitor COVID-19 vaccines were presented by Miriam Sturkenboom (University of Utrecht and VAC4EU/PE&PV Research Network), who stated that more collaboration in RWE is needed especially in context of the pandemic. Different projects were presented:

- The ACCESS project laid the background for the COVID-19 vaccine monitoring in early 2020, calculating background incidence rates of AESI (Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines | Zenodo). These have been used for observed/expected analyses by the EMA and vaccine manufacturers. Publicly available templates for different types of study designs for vaccine safety (EUPAS39361) and effectiveness (EUPAS39289) were also developed.
- Monitoring event rates post vaccination (via prospective cohort monitoring and secondary data collection): in the first cohort, ending in November 2021, 117,000 patients were included. The main findings were that the number of ADRs seems to decrease with age, and the most reactogenic vaccine was ChAdOx1 nCoV-19 (Astra Zeneca). The second cohort will run from September 2021 to 2023 and will include more countries as well as special interest sub-populations and vaccine boosters.
- The monitoring study based on EHR used four data sources (BIFAP, Tuscany, Pharmo and CPRD UK) selected due to their short lag times.

  Incidence rates for AESI were calculated and provided regularly to EMA in the past year.
- Collection of incidence rates for signals following PRAC requests ('Rapid assessment study') was conducted in five data sources. So far two data requests were received from PRAC: multi-system inflammatory syndrome (MIS) and myocarditis.

In conclusion, the AESI list has been well predictive for serious issues that occurred with the new vaccines, while an infrastructure has been created and is ready to address additional COVID-19 related questions in a timely manner and covering different EU Member States.

5.2. Update on TTS and vaccine studies

Daniel Prieto-Alhambra (Erasmus University Medical Center, Oxford University, UK) gave a presentation on TTS and vaccine studies.

A federated network of data sources in OMOP CDM was used to calculate background rates of fifteen AESIs. Substantial heterogeneity was observed in the databases, but the data validated rates of commonly known events as AMI and anaphylaxis and their relationship with age, which was reassuring. SIDIAP and UK CPRD databases were used to calculate observed vs expected rates of VTE/ATE/TTS following vaccination and infection with SARS-COV-2. Four cohorts were used: vaccinated with ChAdOx1, vaccinated with BNT162b2, COVID-19 positive and background population.

Another ongoing study aims to quantify the association between the administration of a COVID-19 vaccine and the occurrence of TTS and other venous or arterial thromboembolic events (VTE or ATE) within pre-specified risk periods, and to compare the risk against different vaccine brands. A new user cohort design is used, with propensity scores used for adjustment. Same data sources as for the previous study, complemented with US hospital data have been used.

Upcoming work on vaccine effectiveness, namely an emulation of an RCT was also briefly introduced.

5.3. Steroids and the E-CORE network

Deborah Layton (IQVIA) presented about the E-CORE (European COVID-19 Observational Research Exchange) network and study.

In June 2020, at the initiative of the EMA, the E-CORE network was created with the aim to conduct multicentre cohort studies on the use of medicines for the treatment of COVID-19, accelerating the generation of valid and reliable RWE for COVID-19 treatments. E-CORE contains as of now fourteen databases from nine countries and is organised in working packages.

A study was run as a proof of concept for the network. The aim of the study were to describe the utilisation patterns of systemic glucocorticoids in patients with COVID-19 and investigate the risks of adverse outcomes in both ambulatory and hospital inpatient care settings.

Results were presented to the EMA on an online platform and are comprised of glucocorticoid prescribing patterns, demographics of the cohort, adverse events (AEs) and disease outcomes of interest. A meta-analysis was performed as well.

Many more patients were captured in ambulatory than in hospital setting. Eight AEs were investigated and by far the most frequent ones were those infection related. The frequency of events was higher in hospital.

Discussion

A discussion followed the presentations on the COVID-19 studies. It was said that COVID-19 offered an 'opportunity' for scientists to collaborate more extensively, but there is a risk of publications with less thorough review. ENCePP provides the opportunity to increase scrutiny and transparency by requirement to register studies. There was a suggestion that more people with expertise should volunteer for reviewing journals. Protocol templates are also of help.

ENCePP has focussed traditionally on safety but especially in the current situation with COVID-19 vaccines, effectiveness is becoming more important for research and more methodological guidance will be needed. It was suggested that the Standards & Methods Working Group (WG1) should look into this further. Viral transmission studies as well might be important.

The ENCePP SG chairs, Gianmario Candore and Susana Perez-Gutthann closed the ENCePP Plenary, thanking the participants for their contribution to the meeting and wishing to have a face to face plenary next year.