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European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Report - 15th ENCePP Plenary Meeting

22 November 2016 – chaired by Xavier Kurz & Susana Perez-Gutthann

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30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
E-mail: encepp_secretariat@ema.europa.eu **Website** www.encepp.eu

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1. General Matters

1.1. Welcome and adoption of agenda

The two Chairs opened the meeting by welcoming all delegates, including observers from EFPIA and EUnetHTA.

The agenda was put together in consultation with the Steering Group (SG) and it was highlighted that the time dedicated to reports from Working Groups and Special Interest Groups had been reduced in order to give more time to scientific discussions.

2. Report from the Steering Group

2.1. Report from the ENCePP Steering Group

Susana Perez-Gutthann provided the report from the ENCePP Steering Group which included a list of key achievements since the previous plenary, and a high-level introduction to the new ENCePP work plan which is due for adoption by the SG in December 2016.

With the mandate of the current Steering Group coming to an end, this was Susana's last plenary meeting in her role as Vice Chair of the Steering Group. She therefore concluded her presentation with some personal reflections on ENCePP's impact to date, and possible enhancements going forward.

In terms of impact, in her opinion, European research on pharmacovigilance and pharmacoepidemiology is robust scientifically, transparent and independent, and ENCePP has been a major contributor to this. There has been tremendous improvement with increased numbers of European centres and researchers collaborating more than ever before.

She expressed concerns about the lack of sustainable public funding for pharmacoepidemiology research and the currently low number of ENCePP Seal studies.

She invited the plenary to share their insights on the past ten years of pharmacoepidemiology in Europe, including achievements and successes, major challenges and areas for improvement.

The overall consensus was that the availability of ENCePP methodological guidance has strengthened pharmacoepidemiology research in Europe by increasing transparency and independence.

Patrice Verpillat shared the concern over the low number of ENCePP Seal studies, but pledged his support to the new SG in trying to increase the appeal of the study seal through his role as industry observer. He stressed the need for optimal collaboration between industry and ENCePP.

3. Report from Working Groups

3.1. Report from WG1 'Research Standards and Guidances'

Alejandro Arana, the group's Chair, thanked all members of WG1 for their hard work and extended his gratitude to everybody who had provided comments on the *Methods Guide* and *Checklist for Study Protocols*. He presented a summary of achievements over the past year and provided feedback from the WG meeting that had taken place on the day preceding the Plenary.

In terms of HTA, François Meyer, the observer from EUnetHTA, stated that the network will conduct a limited number of pilots of cross-border data collection under a project co-funded by DG SANTE. It has been agreed that ENCePP WG1 would assess the need for the integration of HTA aspects in the ENCePP Methods Guide, taking into consideration the EUnetHTA position papers on study design and research standards.

Following a call for collaboration, EUnetHTA will identify relevant documents for circulation by the ENCePP Secretariat to WG1 and the ENCePP network.

3.2. Report from Special Interest Group (SIG) 'Drug Research in Pregnancy'

Corinne de Vries reported that discussions had taken place with the Chair of the SIG, Laura Yates, on how to leverage the expertise present in the group in order to maximise its outputs. Given the broad scope of the group's mandate the SIG membership includes a range of backgrounds and expertise. It is therefore proposed that the most effective way of taking the SIG forward will be to identify smaller sub-groups that will be charged with working on specific issues.

One of the SIG's deliverables under the new work plan will be an annex to the ENCePP Methods Guide relating to pregnancy research. In closing, Corinne expressed her gratitude to Rachel Charlton for periodically reviewing the *Overview of data sources for drug safety in pregnancy research* which has been collated in collaboration with all SIG members, and is published on the ENCePP website.

3.3. Report from Special Interest Group (SIG) 'Impact of pharmacovigilance activities'

A meeting of the SIG coordinators took place during the day preceding the plenary meeting. Agnes Kant, Chair of the SIG, presented a brief summary from that meeting, including next steps.

It was highlighted that the SIG's work is hugely important, but at the same time very challenging. The ENCePP SIG works in close cooperation with the PRAC Interest Group (IG) on impact, and members from both groups will be represented at the Workshop on measuring the impact of pharmacovigilance activities which will be taking place at the EMA on 5 & 6 December 2016 and which has attracted a lot of interest from stakeholders. The output from the workshop will feed into a revision of the SIG's work plan in 2017.

In support of its work, ENCePP partners are invited to provide the SIG with examples of identified safety risks where major regulatory actions have been taken in order to look at the methodologies used to measure impact and to identify gaps in the knowledge base.

4. Election of ENCePP partners to the Steering Group

Thomas Goedecke briefly explained the procedure for election of ENCePP partners to the Steering Group. This introduction was followed by a secret ballot as a result of which the following six candidates were elected to the Steering Group 2017-2019 (in alphabetical order):

- Vera Ehrenstein, Department of Clinical Epidemiology, Aarhus University, Denmark
- Rosa Gini, Agenzia regionale di sanità della Toscana, Florence, Italy
- Teresa Herdeiro, iBiMED, University of Aveiro, Portugal
- Olaf Klungel, Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, The Netherlands
- Tom MacDonald, Department of Clinical Pharmacology & Pharmacoepidemiology, Medicines Monitoring Unit (MEMO) and Hypertension Research Centre (HRC), University of Dundee, United Kingdom
- Gianluca Trifirò, University of Messina, Italy

The Chairs warmly welcomed the new SG which will serve a three year mandate.

5. The role of pharmacoepidemiology in medicines regulation

This session aimed at stimulating discussion in the context of the current general approach within regulatory bodies to increase the use of pharmacoepidemiology ("real-world evidence") in benefit-risk evaluation and decision-making, i.e. to be less dependent on studies done by industry.

5.1. 50 years of pharmacovigilance: unfinished job

Use of pharmacoepidemiology in regulatory decision-making is not a new concept, and there have been examples where pharmacoepidemiological studies have had an important impact on decisions on drugs. Joan-Ramon Laporte (Fundació Institut Català de Farmacologia) was invited to address the plenary on this subject, based on his recent article on 50 years of pharmacovigilance.

Xavier Kurz reminded that much progress has been made since the coming into force of the new pharmacovigilance legislation, e.g. through the publication of clinical trial data, improved interaction with patients and healthcare professionals via public hearings with PRAC; established contact with patient safety organisations, and use of observational data. However, further improvements are needed and ENCePP is best placed to contribute to the further improvement of pharmacovigilance activities.

It was agreed that the new ENCePP Steering Group would be tasked with identifying any aspects of Joan-Ramon's conclusions that could be addressed by ENCePP, and to report back to the Plenary on its findings.

5.2. Identifying opportunities for 'Big data' in medicines development and regulatory science

Jim Slattery gave a presentation on discussions that have taken place around the concept of big data, also in the context of the EMA workshop which took place in London on 14-15 November 2016.

5.3. Meta-analysis of safety – thoughts from CIOMS X

The presentation by Stephen Evans (LSHTM) provided an overview of the contents of the CIOMS X book "Evidence synthesis and meta-analysis for drug safety", highlighted key issues in meta-analysis for drug safety, and meta-analysis of observational data.

6. Methods in Pharmacoepidemiology

Susana Perez-Gutthann introduced the session by saying that ENCePP is a platform for sharing and discussing interesting and new methodological approaches and issues arising in multi-source research

The following two studies were presented on this occasion:

6.1. EURO-SALT - a study of drug exposed acute liver injury in European transplant centres

Presented by Sinem Ezgi Gulmez, University of Bordeaux.

6.2. Pragmatic Trials - The Salford Lung Study

Presented by Tjeerd van Staa, University of Manchester.

Xavier Kurz mentioned that the ENCePP Methods Guide includes a section on pragmatic trials which requires further revision, he proposed to consult Tjeerd on this review.

7. Recent developments in EMA activities

The following interventions aimed at informing ENCePP partners about current EMA activities that are relevant to their work.

7.1. Draft framework of collaboration between EMA and Academia

Isabelle Moulon, EMA's Head of Public Engagement, presented the background to this EMA initiative aimed at implementing the strategic priority of establishing a greater collaboration with academia. Her presentation included a summary of the consultation with academia which was performed via an online survey.

She concluded by saying that at this stage not all details have been defined yet, but it is the intention to consult ENCePP at a later stage with a view to identifying the role the network might play in this initiative. A potential area of involvement could be the strategic research agenda where ENCePP might help in identifying research areas requiring particular attention.

7.2. Scientific guidance on post-authorisation efficacy studies (PAES)

Kevin Blake informed the Plenary that, following adoption by all EMA committees, the scientific guidance on PAES is due to be published on the EMA website shortly. Full implementation of the guidance is scheduled to commence six months after publication (i.e. July 2017).

ENCePP partners will be informed when the guidance has been published.

7.3. Update on the new General Data Protection Regulation (GDPR)

The new data protection law reform has been adopted in May 2016; together with Regulation (EU) 679/2016 ('GDPR') it will have a big impact on processing of health data.

Alessandro Spina, EMA's Data Protection Office, provided a high-level overview covering changes introduced by the GDPR, in particular with regard to the practical impact on activities in health data/research. He stressed that, whilst the original proposal has undergone some substantial changes, the key principles of data protection have been left unchanged and even strengthened to a certain extent.

7.4. ENCePP Seal studies and imposed PASS: new compliance and disclosure measures

Xavier Kurz explained the new compliance and disclosure measures related to ENCePP Seal Studies and imposed non-interventional post-authorisation safety studies (PASS) in context of GVP VIII regulatory requirements.

A recent check has revealed that a number of ENCePP Seal studies do not comply with the requirement of publication of the study report following finalisation of the study. This is considered a critical issue of credibility for the Seal, ENCePP and EMA, and reminder letters will be sent to the PLI's concerned. In case of continued non-compliance the Seal will be removed from the studies concerned.

From now on marketing authorisation holders (MAHs) will be strongly encouraged to upload in the EU PAS Register the protocols and results of imposed non-interventional PASS after the PRAC recommendation. After a defined deadline the Agency will upload the protocols and public abstracts of results to the EU PAS Register on its own initiative in order to fulfil its legal obligations according to Article 26(1)(h) of Regulation (EC) No 726/2004. Xavier confirmed that industry associations and companies will receive official notification of these new obligations and a reminder will be sent to update EU PAS Register study records to provide the EU RMP study category.