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Report - 14th ENCePP Plenary Meeting

24 November 2015 - chaired by: Peter Arlett (AM) & Xavier Kurz (PM)

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1. General Matters

The Chair welcomed all delegates, including observers from EFPIA and EUnetHTA. An observer from Health Canada joined the afternoon session of the meeting via TC.

A special welcome was extended to Dinah Duarte, attending her first plenary in her role as the new representative from the Committee for Orphan Medicinal Products (COMP) on the ENCePP Steering Group, and also to Hubert Leufkens who attended his last plenary meeting as representative of the Committee for Medicinal Products for Human Use (CHMP).

2. Report from the Steering Group

In her role as Deputy Chair of the ENCePP Steering Group (SG), Susana Perez-Gutthann [presented](#) a summary of key achievements in 2015, including key messages for communication on ENCePP, and highlighting the revised [working group](#) and [plenary mandates](#). Her report concluded with a look ahead and a selection of high-level objectives and deliverables from the [ENCePP work plan](#) for the year 2016.

Delegates were informed that a general ENCePP slide set, including the key messages for communication as agreed by the SG, will be made available to them which they are encouraged to use in their communication about the network. The slide set will be circulated to all partners and published on the ENCePP website in due course.

3. Report from Working Groups

3.1. Report from WG1 'Research Standards and Guidances'

Alejandro Arana, Chair of the working group, provided a briefing on the group's meeting which had taken place during the afternoon preceding the Plenary.

He informed the delegates that following the inclusion of topics from the former working group on Health Technology Assessment (HTA), the [mandate of the group](#) has been revised to reflect the need for work around assessing opportunities for methods and common protocols for research that combines outcomes relevant to medicines regulation and HTA. To this end, three members of the former HTA group have joined WG1.

In this context the importance of a close cooperation with [EUnetHTA](#) was reiterated, and representatives from the HTA bodies will be invited to join the working group, not least to provide a link to the guideline developed by EUnetHTA. The practical details and exact scope of this cooperation between the two networks are under discussion.

François Meyer (EUnetHTA) informed the Plenary about the new EUnetHTA joint action, co-financed by the EC and participating bodies from nearly all EU Member States, which is due to start in early 2016. One of the work packages will be dedicated to evidence generation, dealing with the question of early dialogue on initial data collection for new products. Particular focus will be on observational data collection and registries. Close cooperation with ENCePP is envisaged particularly in relation to the development of methodologies and the EMA project on registries.

With this new joint action in mind, it was agreed that this is an opportune time for putting in place a framework for a mutually beneficial cooperation between ENCePP and EUnetHTA.

Alejandro continued his report of issues discussed by the working group, including the question of dissemination/citation of the [ENCePP Guide on Methodological Standards in Pharmacoepidemiology](#). In terms of evaluating the real use of the Guide, a survey of users is under consideration.

For the next revision of the Methods Guide the inclusion of specific topics, i.e. HTA topics and pharmacoepidemiology studies in paediatrics, is under consideration.

Finally, the group also considered the need for review of the [ENCePP Checklist for Study Protocols](#), for which only minor editorial amendments are envisaged in the short term.

3.2. Report from WG2 'Independence and Transparency'

On behalf of Laura Yates, Chair of the Working Group on Independence and Transparency, Thomas Goedecke reported on the outcome of the WG meeting which had taken place on 2 November 2015. He informed the plenary that the group has further revised the concept paper on a common funding route for pharmaceutical companies for pharmacovigilance and medication safety in pregnancy following Steering Group comment (see 4.3) and started a revision of the ENCePP Q&A with implementing the key messages of the communication plan adopted by the Steering Group and the results of the ENCePP Centres survey conducted in 2014. This revision will be shared with ENCePP partners via the ENCePP website. In addition, the working group has submitted comments in response to the public consultation on the ADVANCE Code of Conduct, with particular focus on potential overlap with the ENCePP Code.

Agnes Kant – member of WG2 – provided feedback on the group's discussions on the need for promotion of the [ENCePP Code of Conduct](#) and the [ENCePP Study Seal](#) concept. A communication proposal is under discussion which includes publication of an article, and raising the issue at next year's ICPE in Dublin.

The Chair concluded the discussions by saying that the ENCePP work plan does foresee, as one of its objectives, the optimisation of the Code of Conduct. Raising the debate at ISPE in Dublin is seen as a useful proposal. He also invited ENCePP partners to review and use the communication messages adopted by the Steering Group. Any comments or proposals on the wording will be taken into consideration for future revisions.

3.3. Report from SIG 'Drug Research in Pregnancy'

On behalf of Laura Yates, Chair of the [Special Interest Group \(SIG\) on Drug Research in Pregnancy](#), Corinne de Vries provided a brief summary of items discussed by the group at its meeting which had taken place during the preceding afternoon. The group had discussed the update of the document "[Overview of data sources for drug safety in pregnancy research](#)"; the document has been completed further and updated with a more recent literature search. The SIG recommends that the document be placed more prominently on the ENCePP website.

The EUROmediCAT recommendations on 'European Pharmacovigilance concerning Safety of Medication Use in Pregnancy' were endorsed by the group and it was agreed to produce a document or flowchart to illustrate the workflow for implementation of the recommendations.

The SIG was supportive of the scope proposal by EMA of the Good Pharmacovigilance Practices (GVP) guidance on special populations (pregnant women and breastfeeding women). More substantive discussions on this topic will be held at the next meeting of the SIG.

The group also discussed the topic of pregnant women in clinical trials, and specifically the question of follow up, and in- and exclusion criteria. The SIG concluded that there is room for improvement in the current system and the suggestion is to – as a first step - take stock of current practice in the EU Member States.

4. Looking towards the future: Brainstorming on funding mechanisms for PAS

This session was chaired by Alison Bourke and Miriam Sturkenboom.

4.1. Introduction

Xavier Kurz set the scene by presenting a brief [introduction](#) highlighting ENCePP's potential role and contribution so far to the regulatory need for continuous monitoring and investigation of benefit/risk profiles of medicines.

4.2. Scenario 1: Central mechanism for industry-funded studies

Tom MacDonald presented his [proposal for a central mechanism for industry-funded studies](#).

4.3. Scenario 2: Medication safety in pregnancy

Helen Dolk presented a proposal from WG2 for a common funding route for pharmaceutical companies to [fund pharmacovigilance related to medication safety in pregnancy](#).

4.4. Scenario 3: Collaborative studies on vaccines

Xavier Kurz presented [different governance models for collaborative vaccine studies](#) based on the work of the ADVANCE project.

4.5. Discussion & way forward

Miriam Sturkenboom opened the discussion by stating that industry has not been as receptive to the Code as had been hoped, and that the perception is that industry feel excluded. She invited delegates to reflect on to what degree they felt the principle of independence should be applied.

Helen Dolk reminded the plenary that the Code does in no way exclude industry and foresees involvement until the stage of protocol agreement. This was agreed from the start and is a well-established principle of the Code. Although industry may not take part in the study beyond the protocol agreement, they are considered one of the stakeholders. She urged to focus today's discussion on a better way forward for funding mechanisms.

Peter Arlett clarified that, under current legislation the EMA and its committees are not in a position to directly impose the application of the ENCePP Code of Conduct and ENCePP Seal. However, EMA can certainly encourage industry to follow the principles of the ENCePP Code in its research. Regarding EMA's potential role in central funding he stated that the Agency is, in the first instance, very interested in hearing the ideas coming out of today's discussions. The feedback from ENCePP will be the basis for further reflection and feasibility discussions at both ENCePP SG and Agency level.

In line with Tom MacDonald's presentation, the plenary supports that an independent scientific peer review is key, and one suggestion was to approach existing research funding bodies and invite them to manage peer review of proposals to address research questions. The role of PRAC in the review of study protocols was raised in this context.

The emerging consensus was that in the interest of public health it would not be appropriate to exclude industry from the process of observational research. However, the public need to be re-assured that the academics doing the study are in control, and are independent.

It was agreed that industry should be involved in the funding discussions and asked to put forward its ideas on the topic in order to find a mutually agreeable solution. It was also proposed to perform a feasibility trial by identifying examples of joint studies performed by different pharma companies.

The discussion moved on to the current lack of public funding at European level in the area of pharmacoepidemiology and pharmacovigilance. Horizon 2020 - the successor of the FP7 funding programme – includes no explicit reference to pharmacovigilance, and the European Commission's approach to funding in the area of pharmaceuticals appears to be embedded largely in IMI2. The next funding phase will start in 2020, but political decisions on priorities will be taking place earlier. Making

representations towards post-2020 funding of observational medicines research is therefore considered a necessity. Considering that ENCePP represents a large part of European pharmacoepidemiology and pharmacovigilance research, a coordinated ENCePP action could be helpful. For this purpose it was proposed to set up a virtual group within the network to look at a possible way forward in making the case for EU-level public funding.

In conclusion, Miriam Sturkenboom and Alison Bourke summarised the discussions as follows:

- The ENCePP Code of Conduct and its provisions regarding independence and industry stakeholder involvement remain current and helpful.
- It was agreed that funding should come from industry, but administered by an independent organisation; different options need to be explored further.
- In addition, in order to secure independent/public funding in the future, ENCePP should make use of its collective influence and make the case at European level. Setting up a virtual group is proposed.

Peter Arlett confirmed that the outcome of the discussions will be furthered at Steering Group level at its meeting on 16th December 2015.

5. Facilitating better use of existing data and joint studies

This session was chaired by Teresa Herdeiro, member of the ENCePP Steering Group.

5.1. OFSEP – The French Registry of Multiple Sclerosis

Eric van Ganse presented [slides](#) introducing the [Observatoire Français de la Sclérose en Plaques \(OFSEP\)](#), a registry whose objective it is to maintain and expand the cohort of patients with MS in France, to enrich existing clinical data with imaging and medical-economic data and with biological samples, and to allow access to the data and biological samples to researchers worldwide.

5.2. Lessons learned from PROTECT on common protocols for multi-database studies

Olaf Klungel's [presentation](#) provided an interesting insight into common protocol studies - including a list of recommendations - which were conducted in the framework of the [PROTECT](#) project.

5.3. Pilot phase on better use of existing patient registries

Peter Mol presented an overview of the pilot on better use of existing patient registries which is conducted under the auspices of a cross-committee task force set up by EMA in 2014.

5.4. Discussion: How can ENCePP facilitate better use of existing data?

The presentations were followed by a discussion on accessibility of databases to stakeholders.

In the discussion were addressed different approaches to combine data from several databases, including development of a common protocol for use in different databases, or a federated approach whereby anonymised data are extracted from databases and transferred to a central location for pooling and analysis. Strengths and limitations of both approaches were discussed, such as the time needed to develop a common protocol in the first approach or to agree on a common coding system in the second approach. Based on the experience from the PROTECT and CNODES approached it was suggested that the minimum time needed to develop a multicentre study protocol may be 3-6 months depending on the complexity of the questions to be answered. It was concurred that it is important in all approaches to first examine the database-specific results before pooling in order to identify

heterogeneity and its sources. It was agreed that the French multiple sclerosis registry (OFSEP), which makes its data available to researchers, is an excellent example of transparency.

6. Methods for measuring impact of regulatory activities

This session was chaired by Luisa Ibañez.

6.1. Why do we need methods to measure impact?

Jacoline Bouvy's [presentation](#) focussed on how pharmacovigilance activities generate health impacts and methods for measuring these health impacts.

6.2. A pilot experience on disseminating EMA alerts – Impact on medical prescribing at the Catalan Institute of Health

Joan Ramon Laporte [presented on the experience gained](#) at the [Catalan Institute of Health](#) following an EMA recommendation on the prescription of aliskiren-containing medicines.

6.3. Monitoring and Evaluating the Effect of Regulatory Action: Some Recent Case Studies

Andrew Thomson [presented on key outcomes and conclusions of two studies](#) conducted at [MHRA](#), one of which was the introduction of risk minimisation measures for dosulepin, and the second one relating to a change in prescribing for piroxicam.

6.4. Discussion

The presentations were followed by a discussion on how ENCePP can contribute to address methodological questions and provide access to data sources.

To stimulate and support the learning process, the importance of publishing and/or disseminating this type of study was highlighted (e.g. in the EU PAS Register).

Massoud Toussi stated that there is clearly confusion amongst stakeholders regarding ENCePP data sources and non-ENCEPP data sources. This misunderstanding should be addressed and clarified.

Susana Perez-Gutthann stated that Working Group 1 is considering including a 'lessons learned' in one of the next revisions of the ENCePP Methods Guide.

7. Estimation of renal function: implications for drug dosing in the elderly

Ulf Bergman provided an [update on a Swedish study on the effects of reduced renal function in the elderly and related implications for drug dosing](#). It was noted that a revised regulatory guidance will be published in December 2015.