EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

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ENCePP Secretariat

Minutes - ENCePP Steering Group meeting

13 October 2017, 9.30-16.30

List of participants	
Present	Dinah Duarte, Rosa Gini, Teresa Herdeiro, Johann Hillege, Hervé Le Louet, Olaf Klungel, Xavier Kurz (Chair), Yola Moride, Gianluca Trifirò, Patrice Verpillat Principal Scientific Adviser to the SG: Giampiero Mazzaglia Statistical Adviser to the SG: Jim Slattery ENCePP Secretariat: Thomas Goedecke, Eeva Rossi, Dagmar Vogl EMA: Patricia McGettigan, Carla Alonso Olmo
Apologies	Kathi Apostolidis, Corinne de Vries, Vera Ehrenstein, Hans-Georg Eichler, Tom MacDonald

1. Welcome & Adoption of draft agenda

The Chair welcomed the attendees to the meeting and the draft agenda was adopted without changes. During a review of the action points from the previous meeting (TC on 04/09/2017) it was confirmed that all points had been addressed.

Hans Hillege re-confirmed that he will be presenting the benefit/risk effect table for discussion at this year's ENCePP plenary in November.

2. Role of ENCePP in supporting collaborative studies

2.1. Models for multi-database pharmacoepidemiological studies

Gianluca Trifirò first provided a brief update on the symposium "Real-world battles with real-world data" which took place in the margins of this year's ICPE meeting in Montreal. The aim was to identify experiences and challenges with the standardisation of different data types. He said that one of the key messages from the discussions was that a consensus meeting would be helpful to propose clear solutions for issues encountered. He suggested that EMA could play an important facilitator role in this context and that the workshop on common data models scheduled to take place in early December 2017 would be a good starting point.

Next Gianluca and Rosa gave an update on the work plan and timelines for the ongoing initiative on models for multi-database pharmacoepidemiological studies. They thanked the Steering Group members for their contributions received so far, including key publications for which they are suggesting a systematic review. They presented a list of identified models for multi-database studies, a draft list of dimensions which will require further revision based on comments received from the Steering Group, as well as a number of research scenarios.

In order to get a good picture of the various scenarios through which regulators require studies to be made, it was suggested to perform a survey of regulatory authorities. More specifically, Gianluca and Rosa proposed to conduct a survey on research questions addressed in multi-database studies requested by regulatory authorities. The Steering Group agreed this information would be of great interest and in this context Xavier Kurz suggested the EU PAS Register as an excellent repository of relevant information.

In conclusion, Gianluca and Rosa confirmed that further discussions will be taking place and that a draft questionnaire will be presented at the November plenary meeting. They also confirmed that a meeting of the refreshed Working Group 3 would be taking place on the day preceding the plenary.

2.2. EMA inventory of EU/EEA data sources for longitudinal patient-based studies

Xavier Kurz stated that following consultation of the Steering Group on the EMA inventory of data sources further data sources had been added and some information corrected. He asked the SG's views about the opportunity and the possible channels for the publication of the inventory.

The Steering Group agreed that it could be useful to publish a manuscript on the scoring methodology used for this exercise.

Xavier confirmed that as a next step the revised inventory and summary document will be circulated to the Steering Group for written consultation. Following endorsement of the revised documents by the Steering Group a manuscript for publication in a scientific journal will be drafted and circulated.

3. Review of ENCePP Code of Conduct

Rosa Gini presented an update on the discussions that had taken place at the level of Working Group 2 which focused on the following objectives a revision of the Code:

- Definition and clarification on the practical implementation of the principle of 'scientific independence';
- Reassessment of the ENCePP Seal concept;
- Improving operability of the Code taking into account the structure of the ADVANCE Code of Conduct as appropriate.

The Steering Group felt that the proposed new definition and related revisions of the Code regarding the principle of 'scientific independence' need to be further revised. The revised proposal should take into account the following limitations:

  - Industry-funded studies generate data for regulatory purposes, and therefore such research cannot be considered independent per se; however, such studies represent a large proportion of post-authorisation studies in Europe and excluding them from the field of application of the Code of Conduct would exclude a large number of studies.
  - By acknowledging that any organisation (industry, academia, government, CROs etc.) conducting research might have interests in a particular outcome of a study the Code should include provisions to reduce the chance that these interests affect the results of the study;

- A clear distinction between the scientific, regulatory and legal responsibilities of the primary lead investigator (PLI) and the study funder might clarify how scientific independence can be ensured in practice; e.g. studies might be subject to regulatory requirements for which the marketing authorisation holder is legally responsible and these responsibilities cannot be transferred to the PLI;
- Legal expert advice on the practical implementation of scientifically independent research might provide further clarifications;

The Steering Group supported the proposal of separating the Seal-related processes from the Code's general principles of scientific independence and transparency into an annex. The current draft should be further elaborated and feasibility tested.

The Steering Group also endorsed relevant structural changes and the removal of duplication where appropriate. However, the alignment of the Code's structure with the ADVANCE Code of Conduct was not considered a priority at this stage.

Working Group 2 has been tasked to produce a draft revision of the Code for discussion at the ENCePP plenary meeting in November.

4. Patient Registries Initiative

Patricia McGettigan – the scientific lead of the EMA Patient Registries Initiative – presented a summary of the outcome and lessons learned from the two multi-stakeholder disease registry workshops on Cystic Fibrosis registries and Multiple Sclerosis registries held in June and July this year. She outlined the next steps for the Cross-Committee Task Force which include discussions on establishing an independent quality certification for registries.

Carla Alonso Olmo complemented the presentation with an update on the ongoing initiative of identifying and adding registries in the data source inventory of the ENCePP resources database. Her presentation also included suggestions for improving the inventory based on the experience. In terms of next steps it is planned to publish a guideline providing information about how to search and upload information on the ENCePP database. It was also noted that a poster on patient registries will be presented at this year's ISoP meeting. The Steering Group was reassured that discussions were ongoing and cross links are being made to avoid duplication of existing registries. However, the ENCePP database was chosen for reasons of complete transparency and with the purpose of supporting European regulatory decision-making in mind.

The Steering Group discussed how the registries initiative could be relevant for ENCePP and how ENCePP may contribute. The group suggested that there is a need to educate registries about the regulatory environment and requirements, particularly in terms of reporting safety data and adverse drug reactions. To this end, it might be helpful to expand the scope of the guideline on registries in ENCePP in terms of conducting registries. It was agreed that an outline of the guideline document would be circulated to the Steering Group for consultation and further input.

5. Pharmacovigilance in ENCePP

Hervé Le Louet in his role as ISoP representative on the Steering Group led the discussions on whether there is a need to strengthen pharmacovigilance in ENCePP, and if so, how this could be achieved. He stated that the consultation with ISoP should result in a clear roadmap on this topic which he hopes to present at the next SG meeting.

In terms of concrete next steps, the Steering Group agreed that the next revision of the ENCePP Methods Guide should take into account pharmacovigilance aspects. A potential re-naming of the document was also suggested to include reference to pharmacovigilance. Although the current guide includes sections on spontaneous reporting and signal detection, these are rather small and could be

developed further. It was also suggested that ISoP has an important role in contributing to the common data model initiative.

Considering a potentially substantive review of the Guide, including strategy development and gap analysis of where the Guide could be augmented, the establishment of a new working group or the addition of pharmacovigilance expertise to the existing Working Group 1 should be considered.

6. ENCePP Communication

6.1. Promoting ENCePP at national level (Italian model)

Gianluca Trifirò introduced the Italian network of ENCePP centres which has proven to be very useful in promoting regulatory science and in providing education at national level. He suggested that similar national or regional sections of ENCePP could help in disseminating information and ENCePP principles with the ultimate goal of supporting the national regulator and reinforcing interaction between regulation and expert network level.

The Steering Group considered whether the establishment of similar models should be explored systematically, but agreed that whilst such a group has proven very useful in Italy, it may not be applicable to other countries where strong networks are already in existence.

To obtain additional feedback from ENCePP partners on this issue it was agreed that the Italian network would provide a presentation to the Plenary in November.

6.2. ISPE mid-year meeting April 2019

The 2019 Midyear Meeting of the International Society for Pharmacoepidemiology will be held in Rome/Italy, and the co-chairs submitted an official request for scientific endorsement by the ENCePP Steering Group.

Whilst the Steering Group endorsed the principle of such an endorsement, Xavier Kurz noted that clarification is needed on the meaning and implications of such "endorsement". Further reflection at EMA level will be necessary and feedback will be provided to the co-chairs before the end of 2017. Rosa Gini agreed to provide further explanation and information regarding what such an endorsement would entail.

7. Governance of PE studies

Xavier Kurz presented the two draft governance models for joint studies as proposed by ENCePP Working Group 2 ('Pharmavig-Pregnancy') and Tom MacDonald ('European Council for Regulatory Science'). He also included the proposal for a modified ADVANCE governance structure and invited the Steering Group to discuss the merits and feasibility of the proposals. He asked a number of questions to the SG as regards a possible implementation of the proposals.

It was emphasised that the current legislation does not allow the EMA and other regulators to impose companies to contribute to a funding pot for studies and this system should be a voluntary scheme. In addition, the Steering Group did not fully share the concern that many/most academics prefer to avoid working with industry due to perceived conflicts of interest and the problem that such collaboration would prevent participating in regulatory expert groups. The SG also raised concerns in relation to the proposed models and was invited to submit additional comments in writing. It was highlighted that it may be necessary to better separate problems related to the funding of PASS and problems related to their governance, which may be at least partially addressed through the ENCePP Code of Conduct. Furthermore it was agreed that further discussion on this topic at this year's ENCePP Plenary meeting would be premature.

The question was also raised whether ENCePP would be the right forum to discuss voluntary participation of companies into an independent funding scheme, as ENCePP does not generally consult companies on its recommendations.

8. EU Initiatives related to RWE and RWD

A copy of the poster titled 'Inventory of EU funded Real World Evidence (RWE) Initiatives to support Regulatory Decision making' was shared with the Steering Group. The poster reflects the outcome of a mapping performed by EMA of EU-funded initiatives linked to RWE and is to be presented at the 2017 ISoP meeting. The Steering Group was informed that a scientific publication based on this mapping exercise is under preparation.

9. Issues raised / A.O.B.

9.1. Meetings 2018

The Steering Group was informed that the impending relocation of the Agency will have implications in terms of missions and meetings in 2018. Whilst the ENCePP plenary will go ahead, no other face-to-face meetings will be taking place during next year and this restriction may also apply in 2019; this includes Steering Group and Working Group meetings.

9.2. ENCePP plenary 2017

The Steering Group agreed on adding to the agenda a presentation on the Italian ENCePP network ('Italian model'). The presenter is yet to be confirmed.

Furthermore, it was agreed that a general invitation for ENCePP partners to join existing working groups should be issued at the plenary meeting.

10. Action points

- Hans Hillege to prepare presentation on the benefit/risk effect table for discussion at this year's ENCePP plenary meeting.
- Gianluca Trifirò and Rosa Gini to present draft questionnaire on common data models at this year's plenary meeting and to review studies registered in the EU PAS Register to identify scenarios of regulatory PAS.
- ENCePP Secretariat to support Gianluca and Rosa in the review of the EU PAS Register.
- ENCePP Secretariat to organise a meeting of the refreshed Working Group 3 on the day preceding the plenary.
- ENCePP Secretariat to circulate the revised version of the EMA inventory of EU/EEA data sources and summary document to the Steering Group for written consultation.
- A draft manuscript will be drafted and circulated by EMA to the Steering Group following endorsement of the revised inventory.
- Working Group 2 to produce a revised Code with separated Seal processes for discussion at the plenary meeting in November, and a proposal how scientific independence could be better achieved in practice, providing clarifications on the scientific and regulatory aspects etc.
- ENCePP Secretariat to circulate to the Steering Group the outline of the registries guideline document for consultation and further input.
- Hervé Le Louet to present ISoP roadmap on strengthening pharmacovigilance in ENCePP at an upcoming SG meeting.

- Working Group 1 to consider enhancing pharmacovigilance expertise within the group and to reflect on taking into account pharmacovigilance aspects with the next revision of the Guide, including re-naming the document to include reference to pharmacovigilance.
- Rosa Gini to provide further information regarding scientific endorsement of ISPE mid-year meeting April 2019.
- Steering Group members to submit additional comments on the proposed governance models for joint studies in writing.
- ENCePP Secretariat to revise Plenary agenda in line with discussions.
- Gianluca Trifirò to propose a presenter for the 'Italian model' to the plenary meeting.