EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

08 March 2011
EMA/158066/2011

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Minutes ENCePP Steering Group meeting

23 February 2011, 09.30-16.30 – Chaired by Peter Arlett

List of Participants	
Present:	Peter Arlett (PA), Stella Blackburn (SB), Hans-Georg Eichler (HGE), Henry Fitt (HF), David Haerry (DH), Joan-Ramon Laporte (JRL), Hubert Leufkens (HL), Jytte Lyngvig (JL), Ingemar Persson (IP), Yola Moride (YM), Nicholas Moore (NM), June Raine (JR), Miriam Sturkenboom (MS), Giuseppe Traversa (GT) *ENCePP SG Advisors*: Xavier Kurz (XK), Jim Slattery (JS) *ENCePP Secretariat*: Eeva Rossi (ER), Camilla Smeraldi (CS), Dagmar Vogl (DV) *EMA*: Rocio Fernandez Fresquet (RFF), Luis Prieto (LP), Stefanie Prilla (SP)
Apologies:	Corinne de Vries, Valerie Simmons

Item	Draft agenda
1.	**Adoption of draft agenda**
2.	**Tour de Table - General discussion/ Issues raised by ENCePP partners** 2.1 Interface ENCePP – Private Insurers/Re-insurers (D. Haerry) 2.2 Platform of Training Opportunities (JR Laporte)
3.	**ENCePP Plenary Meetings** • For discussion and advice: Proposals for future frequency and format
4.	**ENCePP Work Plan – Review of Progress** **4.1 Review of Code of Conduct** • For information and discussion of next steps: Log of issues **4.2 Review of MS checklist / Guide on MS in PE** • For information: Oral update **4.3 Accreditation system** • For discussion and advice: Merits of developing an accreditation system **4.4 Maintenance of ENCePP databases/possible further development** • For information: Agenda for EMA-EUnetHTA meeting on 7 March 2011 **4.5 Collaboration with EnprEMA** • For discussion and advice: Update on collaboration with EnprEMA

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 8416
E-mail encepp_secretariat@ema.europa.eu **Website** www.encepp.eu

Item	Draft agenda
	4.6 Increase of numbers in resource database • For discussion and decision: Systematic approach to increasing numbers in the resource database **4.7 Medical Journals** • For discussion and decision: Discussion paper – interaction with journal editors **4.8 Conduct of multi-national studies/data privacy laws** • For information: Oral update following submission of ENCePP statement to EC; endorsement of next steps • For information: ISO Data Protection new work item proposals **4.9 Interaction with regulatory decision-making** • For discussion and advice: Outline of possible funding options to support PhV studies **4.10 Interface medicines regulation/ENCePP** • For discussion: Discussion paper on interface between medicines regulation and ENCePP **4.11 Non-interventional studies consensus statement** • For information: Feedback from task force TC meeting 3 February 2011 • For information: EC Concept paper on revision of CT Directive 2001/20/EC for public consultation **4.12 Promotion of ENCePP** • For information and advice: List of events that could serve as a platform for the promotion of ENCePP **4.13 Impact Analysis** • For ADOPTION: Concept paper on the proposed strategy for impact evaluation
5.	**ENCePP Working Groups** • For decision: Updated mandates reflecting the work plan
6.	**Summary of discussions & next steps**
7.	**A.O.B** 7.1 BMJ Editorial: Post-marketing studies of drug safety 7.2 FDA Guidance "Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets"

NB: The SG were provided with a number of draft papers relating to the various agenda items in advance of the meeting. These are working documents which require further elaboration, and as such – although referenced - are not being published with these minutes.

1. Adoption of draft agenda

The draft agenda was adopted without changes.

2. Tour de Table – General discussion/Issues raised by ENCePP partners

2.1. Interface ENCePP – Private Insurers/Re-insurers

Following on from the discussions at the SG meeting in December 2010, DH reported briefly on his meeting with SwissRe which took place on 16 December 2011 to discuss a possible collaboration between the network and private insurers regarding analysis of real world aggregated data. DH

provided an overview of ENCePP to SwissRe who confirmed their interest in collaborating with the network. As a next step, DH is awaiting to be contacted by a representative from SwissRe's London offices.

The SG was supportive of a continued dialogue with the re-insurance companies (e.g. SwissRe and MunichRe), and it was agreed to invite representatives from these companies to a future ENCePP Plenary which would help in working out the best forum to progress these discussions. It was however considered that there was a need to better clarify the role of reinsurance company in their interaction with ENCePP and to this end DH agreed, with the support of the ENCePP Secretariat, to draft a reflection paper on this subject and circulate to the SG to gather comments.

2.2. Platform of Training Opportunities

Due to time constraints, this item was postponed to a future SG meeting.

2.3. ENCePP Study Applications

IP raised the question of how many ENCePP study applications had been received so far and whether the ENCePP Secretariat was planning any initiatives to increase the numbers.

CS confirmed that the E-Register currently contained a total of 10 studies, 4 of which are ENCePP studies.

In response to a concern raised by NM, it was confirmed that it is not necessary to provide a full protocol in English, but a synopsis only. This concern will be taken on board for the upcoming review of the Code of Conduct to ensure that the wording is absolutely clear in this regard.

MS mentioned that the issue of the study start/feasibility study could be a stumbling block for entering a study in the E-Register. This concern has already been logged and will be addressed during the review of the Code of Conduct.

In an effort to raise the profile of ENCePP and the E-Register, HL suggested that it could be promoted further through the EMA and its committees. IP suggested the organisation of another Info Day.

PA summarized the discussions by saying that, although the number of applications remains relatively low for the moment, this is to be expected since this is a new tool which will take time to establish itself and gain recognition. However, the concept is strong and needs to be communicated to both regulators and industry to encourage registration of studies and develop the E-Register into a useful and recognised European resource. Raising awareness of the E-register with the CHMP was considered an essential first step, also in view of its potential application in the framework of the new PhV legislation. The ENCePP Info Day will likely be repeated later this year, and a Q&A document will be developed by the ENCePP Secretariat (e.g. similar to that developed for the PROSPERO NIHR database).

3. ENCePP Plenary Meetings

XK informed the SG that feedback received from previous ENCePP Plenary meetings suggested that it might be time to re-think the format and content of the meetings. It was felt that the agenda was too procedural and EMA-driven with not enough room for scientific discussion. This issue had been discussed internally and a document had been drafted outlining some options for future Plenary meetings. Therefore, the ENCePP Secretariat considered that there was a need to discuss this issue at the level of the SG, looking for opinions and advice.

MS and IP suggested that the ENCePP partners should be surveyed on what they would like to see covered during a Plenary meeting and what subjects would be relevant to them.

JL remarked that administrative items could be covered by email, rather than being a major focus of face-to-face meetings. In her opinion, a survey of ENCePP partners should focus on what is expected of ENCePP, any problems that need solving, and what contributions partners could make to the Plenary.

JR suggested consulting the plenary on research topics to be included in public funding programmes.

It was acknowledged that plenary meetings represent a good opportunity for networking activities. NM and SB suggested this aspect of the plenary could be further enhanced by allowing people to sit randomly and no longer according to fixed seating arrangements and allowing longer coffee breaks to facilitate exchange of information.

PA concluded by saying that there is a need to ensure that the content of the meetings is relevant to academic centres and useful to the project. The ENCePP Secretariat will consider a survey of ENCePP partners. Regarding the format of the meeting, the SG was open to the organisation of parallel working group sessions during the Plenary and the organisation of dedicated ENCePP sessions at scientific meetings where appropriate. The agenda should focus on education and new methods, and in the future SG members will be involved more closely in drafting the agenda. Options for the seating plan will be explored.

4. ENCePP Work Plan – Review of Progress

4.1. Review of Code of Conduct

SP announced that the review of the Code of Conduct was going to take place soon. All known issues have been compiled in a log and put into categories. As a first step, the Task Force on access to data will meet at the beginning of April for a review of the access to data issues and to draft a concrete proposal. As a second step, the whole working group 2 will meet for the general review of the Code, followed by review and adoption of the revised Code by the Steering Group.

SP urged all SG members to notify any issues that require review in their opinion; she also confirmed that the definition of the language requirements for the protocol and synopsis (as raised by NM during an earlier discussion) will be added to the existing log of issues.

The group agreed that access to data was an extremely important issue which needed careful consideration. In this respect, JR suggested that the working group take into consideration also the reporting guidelines issued by the EQUATOR Network[1]

4.2. Review of MS checklist / Guide on MS in PE

XK provided an oral update on this agenda item.

The public consultation phase of the *Guide on Methodological Standards in Pharmacoepidemiology* finished in early January 2011 and had raised a lot of interest. A large number of comments have been received, the majority of which were very positive, particularly relating to the guide's usefulness. A number of comments requested a clear and transparent procedure for the future update of the Guide which is currently foreseen to take place once a year. The target is to finalise the new draft by end

1 Simera I, Moher D, Hirst A, Hoey J, Schulz KF, Altman DG: **Transparent and accurate reporting increases reliability, utility, and impact of your research: reporting guidelines and the EQUATOR Network**.BMC Medicine 2010, **8**:24 http://www.biomedcentral.com/1741-7015/8/24

March, consult the SG in April, followed by the Guide's adoption either by written procedure or at the next SG meeting.

The MS checklist is due for review in June and will take into consideration comments received and issues raised in the context of the practical application of the checklist.

4.3. Accreditation system

XK reminded the SG that the longstanding mandate of working group 1 includes the exploration of the merits of developing an accreditation system for ENCePP. However, in the past months, priority was given to developing the Guide on MS and checklist while discussions on this topic were put on hold. To provide the SG with further information and help the discussion on whether WG1 should progress this topic, a list of possible objectives was presented to the SG.

Overall the SG was of the opinion that the focus of ENCePP should be on improving the quality of studies and on capacity building. Rather than developing an accreditation system for the centres, ENCePP could think of conducting a benchmarking exercise for its partners where an evaluation of the processes is performed by peers.

However, it was agreed that a significant debate on this subject was needed and ENCePP partners should be consulted. As a first step, the subject of accreditation will be included in the agenda of the next Plenary meeting (30 June 2011). Following these initial discussions, the topic will be handed back to WG1 for further elaboration. Considering the complexity of the subject, the working group will be given a long timeframe (e.g. 12 months) to report on its recommendations.

4.4. Maintenance of ENCePP databases/possible further development

PA informed the group that a meeting between the EMA and EUnetHTA will be taking place on 7 March 2011. HGE briefly introduced the draft meeting agenda to highlight the main topics for discussion and to give more background on this ongoing dialogue between the regulatory community and HTA community in Europe, one important topic being the update of the EPAR template.

PA invited the SG members to provide their opinions as to whether there would be a synergy between ENCePP and HTA and whether broadening the perspective to post-authorisation research may be advantageous for ENCePP.

The SG agreed that an exchange with HTA would be useful. During the ensuing discussions it was suggested to invite EUnetHTA to one of the next Plenary meetings in order to familiarise the group with ENCePP and explore possible avenues of cooperation. HTA is an area of rapid dynamics, and the SG acknowledged the fact that in the near future some areas of convergence with the scope of ENCePP are likely to be found. A decision needs to be made as to what tools ENCePP could offer to HTA, the E-Register of studies being the most obvious one. It should, however, be kept in mind that a modification of the database, although not envisaged at the moment, may be requested to accommodate future collaboration, and ENCePP should be prepared to accept this.

In conclusion, it was agreed to establish a mechanism for an ongoing dialogue with EUnetHTA and to inform the group about ENCePP. No objections were raised to open the dialogue regarding a possible adaptation of the functionality of the E-register to meet EUnetHTA's needs. EMA agreed to feed back to SG on the outcome of the discussions on 7 March.

4.5. Collaboration with EnprEMA

CS briefly summarised the document which had been circulated prior to the meeting outlining possible areas of collaboration with EnprEMA (European Network of Paediatric Research at EMA), one of the key items being a reciprocal observership on each other's governing bodies (i.e. Steering Groups).

She informed the SG about the upcoming meeting of the network where one of the agenda items will be a presentation on ENCePP.

It was noted how at the moment the focus of EnprEMA is mainly on clinical trials and it was highlighted how a better use of observational data can be of particular utility in the field of paediatrics. MS drew the attention of the group to a new initiative called the Global Research in Paediatrics (GRIP) funded by the 7th Framework Programme.

In conclusion, the SG agreed that there would be obvious benefits in reciprocity and cooperation.

Following an intervention by JL it was agreed that a strategic decision needs to be made as to whether ENCePP will adopt an inclusive or selective policy in collaboration with other networks.

4.6. Increase of numbers in the resource database

CS reported that the ENCePP database of research resources currently contained just over 100 entries, whereby the number of data sources is limited (11). The ENCePP Secretariat has given this some thought and drafted a document listing possible strategies for increasing these numbers. The SG members were invited to provide their feedback on these strategies and to possibly present any other suggestions.

MS informed the group that one of the deliverables of GRIP (global paediatric research initiative) is an inventory of databases. Since this was an excellent opportunity for collaboration she agreed to request that the information gathered through this exercise be fed into the ENCePP resource database.

The interventions by the SG members supported the suggestions made in the strategy paper, while highlighting the need for prioritisation. There was additional agreement on conducting a survey of industry data sources.

NM noted that under the current rules only data owners are able to enter a data source which is a potential problem.

In conclusion, PA suggested to survey the Plenary for any existing barriers to entering data sources into the database. The removal of the restriction that a data source has to be entered by the data owner should be considered.

4.7. Medical Journals

One of the milestones in the ENCePP work plan 2011-2012 is the development of a strategic plan for interaction with journal editors. As a first step and to initiate discussion, HF has drafted a paper listing key issues and proposed next steps.

The ENCePP Secretariat, in cooperation with the EMA press office, is proposing to organise a workshop for journal editors during the afternoon before the ENCePP Plenary, i.e. on 29 June 2011. This proposal was supported by the SG. The workshop is intended as a trust-building exercise and will be used to explain ENCePP and convey the concept of the ENCePP seal and ENCePP studies. It was agreed that the SG will be closely involved in the preparations for the workshop.

The SG proposed a number of additional issues which should be elaborated with journal editors in the long term and which will be added to the existing list of issues for discussion (e.g. free access to

publications relating to publicly-funded studies, endorsement of registration of studies in ENCePP E-Register, acceptance of manuscripts that have been registered etc.).

4.8. Conduct of multi-national studies/data privacy laws

CS gave a brief update following the submission of the ENCePP statement in response to the public consultation on the Commission's comprehensive approach on personal data protection in the European Union. In a follow-up letter a meeting has been requested between an ENCePP delegation (which will also include a representative from ECDC) and the responsible Head of Unit in DG Justice.

In an effort to maximise the ENCePP response, the SG endorsed the organisation of such a meeting, and that ECDC should join the delegation. The ENCePP statement was circulated to all ENCePP partners and is also available on the ENCePP website.

Under this agenda item the SG was informed about a new work item proposal from ISO entitled "Health informatics – data protection in trans-border flows of personal health information". The SG will be kept informed of any significant developments on this topic.

4.9. Interaction with regulatory decision-making

CS presented a paper listing options for funding mechanisms of post-authorisation studies linked to medicines regulation. The document was drafted with a view to serve as a tool in addressing the funding of safety issues in the future. The SG members were asked whether the full scope of funding options had been captured, and whether they felt that an options paper should be developed to support decision-making on funding and oversight.

MS suggested the addition of two options to the list: funding for the provision of infrastructure, and secondly study funding via a dedicated industry fund (e.g similar to the model developed by the Italian Medicines Agency). It was agreed that these two points would be added to the paper.

On the same subject it was agreed that a reflection on coordinated action to make the case for public funding is needed, particularly on the back of the new pharmacovigilance legislation and taking into consideration the recent experience with the pandemic influenza.

In conclusion, the SG agreed that further development of the draft paper is useful, and that it would be broken down into sub-sections (speed of study, product type, funding, governance…). SG members were invited to provide written comments on the paper. A dedicated discussion on this subject will be scheduled during the next SG meeting.

4.10. Interface medicines regulation/ENCePP

PA presented a paper which aims to initiate discussions on the interface between medicines regulation and ENCePP, particularly in light of the new PhV legislation. He reminded everyone that the ENCePP work plan includes as a milestone the development of a discussions paper on this subject by Q2 2011.

The SG agreed that the present document was a good starting point, but that more substantial discussions were needed. It was agreed that SG members would provide written comments on the current draft document within one month. A decision on the next steps will be taken at the next SG meeting.

4.11. Non-interventional studies consensus statement

PA informed the group that a TC meeting between the ENCePP Task Force had taken place on 3 February 2011. He gave a brief oral report on the outcome of the meeting and the next steps.

It was agreed that the rapporteurs would start drafting an orientation which is to be used in the current legal framework on the definition of non-interventional trials. In addition, the Task Force is collecting examples where difficulties with the definition had been encountered. There will be another TC taking place on 28 February 2011.

Since CTFG is an informal subgroup of HMA, JL suggested that HMA be kept informed about these activities. It was agreed to keep the HMA as well as the ad-hoc group at the European Commission updated on progress.

PA informed the group that the European Commission has released a public consultation on a revision of the Clinical Trials Directive. The EMA will respond to this consultation, but ENCePP may wish to consider submitting a separate reply. As it may be difficult to get consensus on this issue at ENCePP level, the response should focus on a list of important considerations in the event that the Clinical Trials Directive is expanded to include "borderline" studies. Deadline for replies is 13 May 2011.

NM agreed to take leadership on drafting an ENCePP statement to the EC consultation, with support from the Agency (input from XK, CS to coordinate).

4.12. Promotion of ENCePP

A list of PhEpi and PhV events that could serve as possible platforms for the promotion of ENCePP has been compiled by the ENCePP Secretariat. It was agreed to circulate this list to the SG, asking for review and suggestions for additions.

4.13. Impact Analysis

The "Concept paper on the proposed strategy for the impact evaluation of ENCePP" will be presented and adopted at the next SG meeting (19 May 2011).

5. ENCePP Working Groups

CS presented the working group mandates which were revised following achievement of certain deliverables, but also to reflect the adopted work plan 2011-2012.

The following additional changes were agreed:

- WG1: the item on accreditation will be maintained.
- WG2: it was agreed to take out the item on funding which will be dealt with at SG level until the concept paper has been elaborated further. Subgroup 2 (study register) will remain active to deal with further development of databases (HTA, EnprEMA etc.).

The ENCePP Secretariat will re-circulate the revised mandates for final agreement by the SG. The agreed mandates will then be circulated to all ENCePP partners, including those representatives that had responded to the call for volunteers in the past, to re-define the individual working groups.

Finally, working group meetings will be organised in coordination with the respective Chair. These meetings will either be organised separately or as parallel sessions during future Plenary meetings.

6. Summary of discussions & next steps

Action Points arising from the discussions:

- DH to draft reflection paper on "Interface ENCePP - private insurers/re-insurers".
- ENCePP Secretariat to develop a Q&A document on E-Register of Studies.

- ENCePP Secretariat to consider survey of ENCePP partners regarding input to Plenary meetings.
- ENCePP Secretariat to initiate discussion at Plenary level re: accreditation system.
- ENCePP Secretariat to report to SG on outcome of discussion with EUnetHTA.
- ENCePP Secretariat to include item on 'funding options' on next SG meeting agenda.
- ENCePP Secretariat to survey the Plenary for any existing barriers to entering data sources into the database.
- ENCePP Secretariat to organise a workshop for journal editors in conjunction with the June 2011 Plenary meeting; SG to be involved closely. List of issues to be updated.
- ENCePP Secretariat to organise meeting with DG Justice to follow up the ENCePP response to the public consultation on personal data protection.
- ENCePP Secretariat to update and circulate to SG the discussion paper on "Interface between medicines regulation and ENCePP" for comment by end March 2011.
- NM to take leadership on drafting an ENCePP statement to the EC consultation on the revision of the Clinical Trials Directive, with support from Agency.
- ENCePP Secretariat to circulate to SG list of events that could serve as platforms for the promotion of ENCePP for review and additions.
- "Concept paper on the proposed strategy for the impact evaluation of ENCePP" to be presented and adopted at the next SG meeting (19 May 2011).
- ENCePP Secretariat to revise WG mandates and re-circulate for agreement by the SG.
- WG1 to submit ENCePP SG draft response to FDA consultation on Guidance "Best Practices for Conducting and Reporting PhEpi Safety Studies Using Electronic Healthcare Data Sets".

7. AOB

7.1. BMJ Editorial: Post-marketing studies of drug safety

The SG was informed about a recent BMJ editorial quoting the ENCePP study concept.

7.2. FDA Guidance

The FDA has released for consultation a draft guidance on "Best Practices for Conducting and Reporting PhEpi Safety Studies Using Electronic Healthcare Data Sets".

PA informed the group that EMA will submit comments to this guidance. It was agreed that Working Group 1 (Acting Chair: XK) would prepare a draft response and submit it for comments and approval by SG. The deadline for the consultation is 18 April 2011.

Next meetings:

- Vitero/TC meeting: 19 May 2011