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European Network of Centres for
Pharmacoepidemiology and
Pharmacovigilance

ENCePP activity report 2014

Introduction

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) aims to strengthen the European Medicines Agency (EMA) monitoring of medicinal products by facilitating the conduct of multi-center, independent studies focusing on safety and on benefit-risk throughout the product life-cycle. 2014 has seen significant growth and the network is now comprised of 147 centers, 22 networks and 51 data-sources. This growth is reflected in the registration of studies (an increase of 117%) and in an increased use of the website and information resources. The network also continues to contribute actively to the data, information and knowledge that feed into regulatory decision-making in the EMA's Scientific Committees. In 2014 key tools and guidance have been improved through working groups within ENCePP. Also in 2014, ENCePP has been surveyed on experience with research that might directly support health technology assessment (HTA), on public-private partnerships as governance models and on registration of post-authorisation safety studies. The findings of these surveys are the basis of the next work plan (to be published March 2015) that will see consolidation of the network's core activities for safety and benefit-risk.

The network's success is based on the expertise and commitment of those participating and the Steering Group takes the opportunity of the activity report to thank all the ENCePP partners for their contributions.

Key achievements

- The third annual review of the [ENCePP Guide of Methodological Standards in Pharmacoepidemiology](#) was completed in June 2014 by the ENCePP Working Group on research standards and guidances (Chair: Alejandro Arana). In addition to the general update of most chapters, it includes a new chapter on **Design and analysis of pharmacogenetic studies**, written in collaboration with the Special Interest Group in Molecular Epidemiology, Biomarkers and Pharmacogenetics of the International Society of Pharmacoepidemiology (ISPE). As in previous years, in 2014 the Guide remained the most popular document on the ENCePP website with around 13,000 downloads, plus around 21,000 views of individual chapters in the online version.



- In February 2014 the ENCePP Steering Group adopted **revision 3** of the [ENCePP Code of Conduct](#) by the ENCePP Working Group on transparency and independence (Chair: Laura Yates). This editorial revision of the Code was aimed at improving the overall readability of the Code and to provide further clarifications on the key concept of scientific independence in a new chapter and on the conditions for obtaining the [ENCePP Study Seal](#) for specific studies. The key concepts of the Code for transparency and independence remain unchanged.
- In October 2014 the Working Group on data sources and multi-source studies (Chair: Miriam Sturkenboom) published a report on the outcome of a [survey of researchers coordinating multi-database drug-safety projects that have been publicly funded by the European Commission](#). The survey synthesises and draws lessons from current practice in Europe in combining data from multiple sources.
- During May 2014 a **survey of ENCePP centres was conducted on registering studies in the ENCePP (EU PAS) Register and experience and perception of the ENCePP Study Seal**. Consequently, the Working Group on transparency and independence has been charged with elaborating proposals for the improvement and simplification of current processes relating to the ENCePP (EU PAS) Register and ENCePP Seal applications based on the survey responses (to be delivered in 2015). In addition, some key issues were identified from the survey responses which will feed into the new ENCePP communication plan due for adoption in early 2015.
- A further **survey of ENCePP partners** was conducted in Q2 2014 by the ENCePP Working Group on health technology assessment (**HTA**) (Co-Chairs: Marlene Sinclair & François Meyer). The survey aimed at mapping existing ENCePP experience in undertaking research with outcomes that might support decision making by **HTA** bodies in the European Union. The outcome of the survey confirmed that some ENCePP partners have considerable experience in conducting such studies and the network may, therefore, be a useful platform to develop European capacity to deliver such studies. The experience with the survey now provides a sound basis to further develop the contribution of ENCePP to the conduct of studies relevant to HTA.
- The ENCePP Working Group on Data Integration (Chair: Nawab Qizilbash) has progressed the development of a **guidance for conducting systematic reviews and meta-analysis of pharmacoepidemiology studies**. A public consultation on the new guide is expected to be launched during the first half of 2015.
- The joint ENCePP/[Enpr-EMA](#) Working Group on paediatric pharmacovigilance has contributed to the revision of the paediatric pharmacovigilance guideline.
- A priority for the Network is to generate data and information to **inform regulators on drug-safety issues and support regulatory decision-making** in a timely manner, e.g.
 - results of studies coordinated by ENCePP partners have resulted in further regulatory actions¹;
 - ENCePP has provided potentially relevant published and unpublished data in response to requests from EMA for information; and,
 - individual ENCePP partners have provided expertise in ad-hoc expert meetings on specific safety issues.

¹ Arlett, P., Sarac, S. B., Thomson, A., Davies, C., Teixeira, T., Blake, K. V. and Stenver, D. (2014), [The European Medicines Agency's use of prioritised independent research for best evidence in regulatory action on diclofenac](#). *Pharmacoepidemiol Drug Saf*, 23: 431–434. doi:10.1002/pds.3594

Meetings and Networking

Early in 2014 a decision was made that in the foreseeable future the available meeting budget would be used towards funding a single annual plenary meeting thereby making available more of the budget for working group meetings. The ENCePP Secretariat organised the annual meeting of the plenary in November 2014; a [report of the meeting and presentations given](#) have been published on the ENCePP website.

A meeting of the special interest group (SIG) 'Pregnancy' took place in the margins of the plenary. The [ENCePP working groups](#) met regularly – either face to face or via TC – making good progress on their work plan deliverables. Working group chairs provide regular reports on their groups' activities to the ENCePP Steering Group and these are published on the ENCePP website.

The Steering Group met three times in 2014; [minutes](#) of those meetings - together with progress reports from Working Group Chairs to the Steering Group - are published on the ENCePP website.

The exchange of information with other international initiatives with similar goals continues to be an important part of ENCePP networking activity, and representatives from Health Canada, US FDA and PMDA Japan are invited regularly to attend the ENCePP plenary meetings as observers.

A meeting took place with EMIF (European Medical Information Framework – an IMI project) to look at commonalities in areas of mutual interest. In addition a meeting took place with the European CRO Federation (EUCROF) to explore possible areas of collaboration. A presentation on ENCePP and research that supports HTA was given to the joint EMA-EUnetHTA meeting in December 2014, where discussions took place to explore avenues of closer cooperation between ENCePP and EUnetHTA.

Presentations and posters on ENCePP were given in various fora including to a delegation from the Italian Consiglio Superiore di Sanità, to Euro DIA in Vienna (March 2014), and to the South-Asia Chapter of American College of Clinical Pharmacology in Mumbai (April 2014). A poster on the outcome of the ENCePP survey on partners' experience in conducting research supporting HTA was presented at the 2014 ICPE and ISPOR conferences. The [poster](#) has been published on the ENCePP website.

Network growth & strengthening

A number of articles in peer reviewed journals that were published in 2014 referenced ENCePP. The references ranged from ENCePP being cited as an example of applying the strategy to develop infrastructure and methodologies for pharmacoepidemiological research and the network's role in generating best evidence in Europe¹ through to an example of research working groups on drug utilisation across Europe² and as a source of extensive and valuable information that can benefit those undertaking pharmacovigilance³

A letter to BMJ in response to an article highlighting the urgent need for reporting guidelines for pharmacoepidemiological studies cited better uptake of the existing ENCePP Checklist for Study Protocols complemented by the ENCePP Guide on Methodological Standards in Pharmacoepidemiology⁴ as the solution rather than the need for new guidance.

ENCePP guidance continues to be cited in a number of international regulatory, clinical and pharmacoepidemiological guidances. ENCePP in current practice is also cited in a number of industry and CRO publications.

² [A compilation of research working groups on drug utilisation across Europe](#). Sabaté et al; BMC Res Notes. 2014 Mar 13; 7: 143. Doi: 10.1186/1756-0500-7-143

³ [Taking a Proactive Approach to Patient Safety Monitoring](#), Contract Pharma, September 2014

⁴ [Rapid response](#) to article 'Reporting guidelines for pharmacoepidemiological studies are urgently needed'; Oct 2014

As of end December 2014, the number of centres and networks in the ENCePP Database stood at 147 (129) and 22 (22), respectively from 19 different European countries. The number of data sources stood at 51 (49). The figures in brackets and italics are the corresponding numbers as of end 2013. The characteristics of the 147 ENCePP centres registered in the database are described in figures 1 - 5. These figures demonstrate the engagement in ENCePP and its important role in research capacity building across Europe.

Figure 1: Classification of centres (2014)

y axis = number of centres (multiple answers possible)

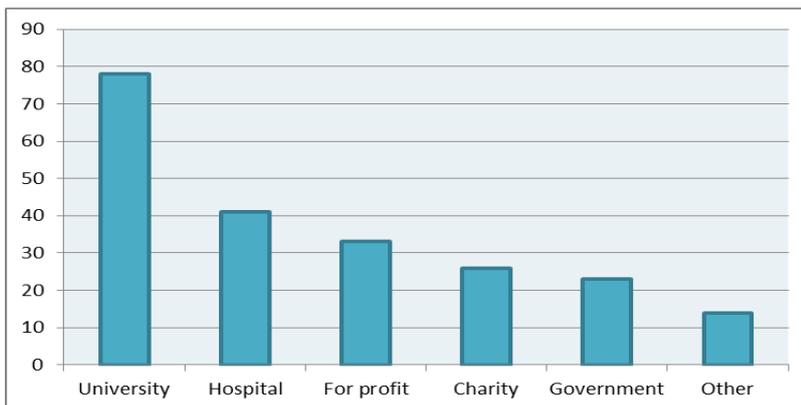


Figure 2: Expertise available in centres (2014)

x axis: number of centres (multiple answers possible)

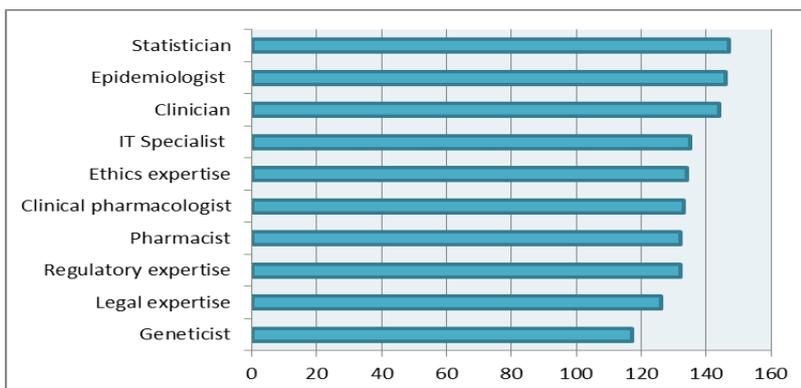


Figure 3: Experience with study designs (2014)

y axis: number of centres (multiple answers possible)

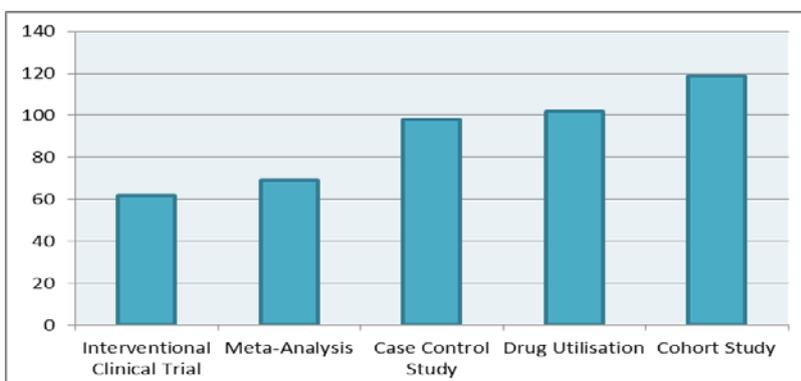


Figure 4: Experience in therapeutic areas (2014)

x axis: number of centres (multiple answers possible)

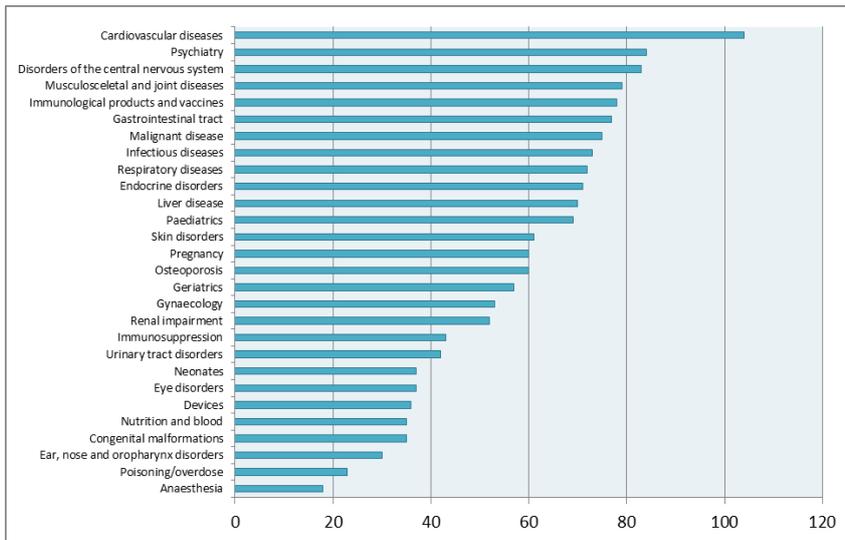


Figure 5: Research experience (2014)

y axis: number of centres (multiple answers possible)

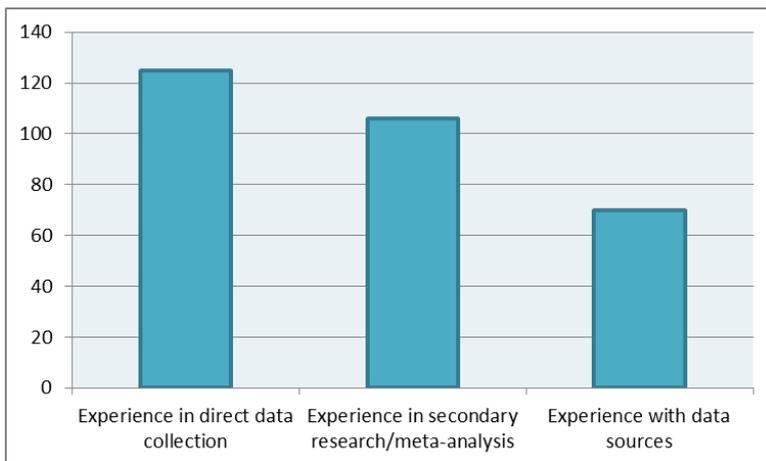
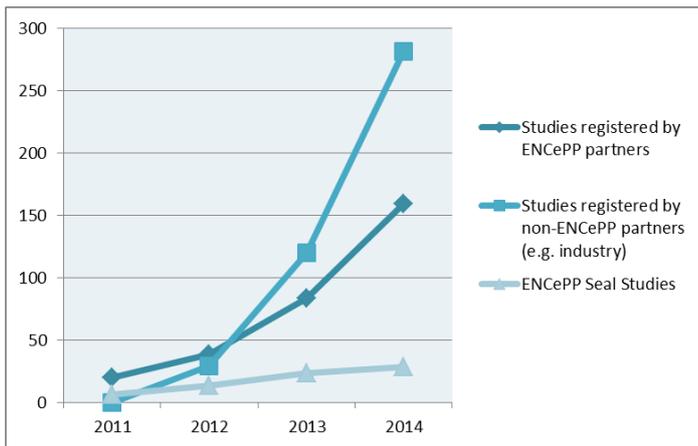
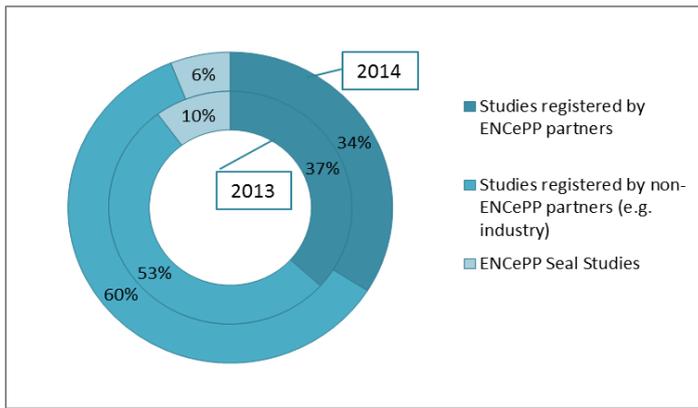


Figure 6 & 7: ENCePP (EU PAS) Register

The number of studies registered in the ENCePP (EU PAS) Register has continued to rise significantly from 203 to 440 between January and December 2014. A total of 28 of studies registered have the [ENCePP Study Seal](#).

The sharp increase in study registrations (~117%) can be explained in part by the E-Register of Studies currently serving as the 'EU PAS Register' as referred to in the guideline on [Good Pharmacovigilance Practices \(GVP\) module VIII](#), chapter VIII.B.4. However, there has also been a substantial increase in the number of studies registered voluntarily by ENCePP partners and pharmaceutical industry.



ENCePP Website statistics

The [ENCePP website](#) – hosted by the European Medicines Agency (EMA) – is the Network’s interactive platform to maintain access and promote ENCePP. It is used for ENCePP-related announcements and for making ENCePP outputs (e.g. meeting minutes, mandates, code of conduct, standards and guidance documents, etc.) publicly available. Key features of the website are the [ENCePP Database of Research Resources](#) and the [ENCePP E-Register of Studies \(de facto the ‘EU PAS Register’\)](#). Both databases are publicly accessible and searchable by any stakeholder.

The number of visits to the ENCePP website continues to rise steadily. The following figures provide some statistics on the use of the website. Figure 7 includes EMA internal access. All other figures represent external (i.e. non-EMA) access only.

During 2014 the ENCePP Secretariat dealt with a substantive number of queries (~200) relating to the ENCePP (EU PAS) Register or to ENCePP in general. The Secretariat also continues to provide technical and administrative support for the EU PAS Register, as well as notifying Member States when a PAS (post-authorisation study) that has been requested by a regulator and funded by industry is registered.

Figure 7: Visitor statistics (2009-2014)

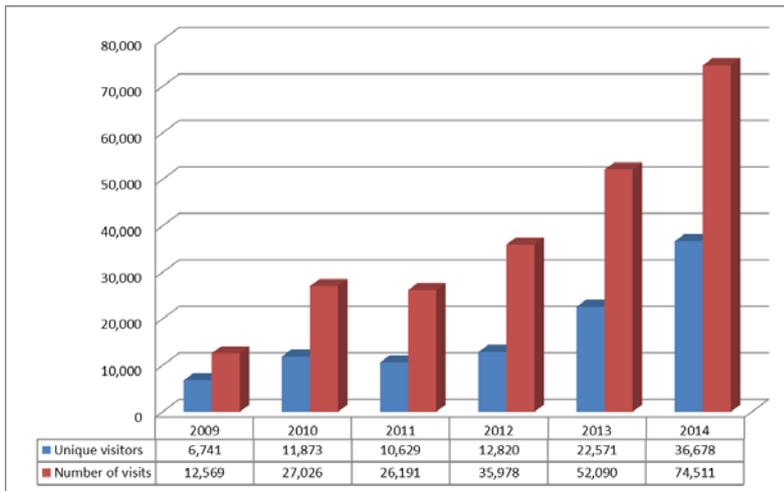


Figure 7 shows a continued upward trend in visitors since 2012.

Figure 8: Pages viewed by country (2014)

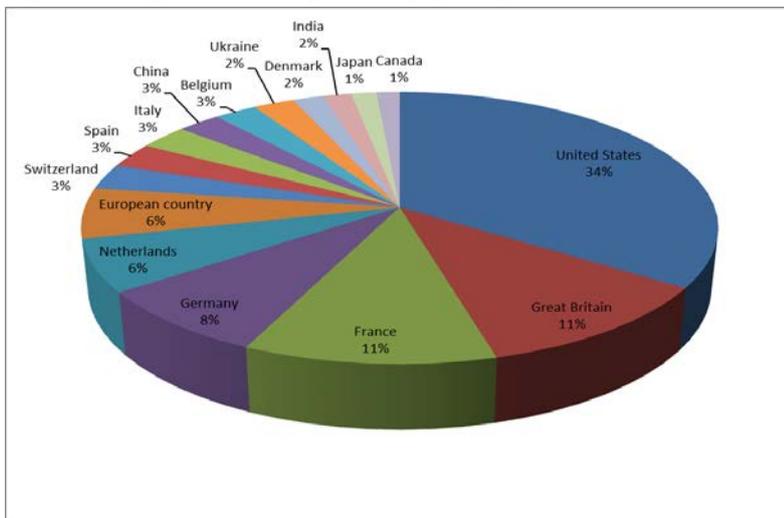


Figure 8 shows global interest in ENCePP in particular from the United States.

Figure 9: Most downloaded documents (2014)

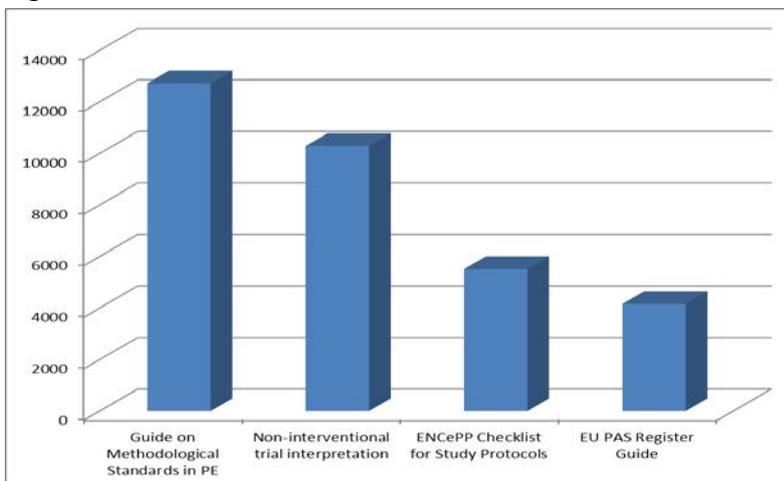


Figure 9 demonstrates the continued interest in the Guide on Methodological Standards in Pharmacoepidemiology, although the number of downloads has decreased since the previous year, as stakeholders appear to make more use of the online version of the Guide with approx. 21,000 views of individual chapters.

Figure 10: Hits on databases & partners' forum (2013-2014)

