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ENCePP Secretariat

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP activity report 2017

Executive Summary

Since its inception 10 years ago the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) has made a major contribution to the benefit-risk evaluation of medicinal products in Europe and beyond by providing methodological recommendations complementing regulatory guidance on post-authorisation safety studies. The adoption of the ENCePP e-Register of Studies as the European Union electronic Register of Post-Authorisation Studies (EU PAS Register®) has changed the landscape of pharmacoepidemiology in Europe by increasing transparency of observational research, giving access to study protocols and results and supporting the implementation of the pharmacovigilance legislation.

The overall goal of the new three year work plan 2017 to 2019 is the optimisation of the network's input to regulatory decision-making throughout the product life-cycle with particular focus on the development of methods in impact research and the identification of enablers and barriers to measuring the impact of pharmacovigilance.

The network has published the 6th revision of the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which includes revisions, amendments and new references in all the chapters. 2017 also saw the re-activation of the ENCePP working group on data sources and multi-source studies with an ambitious mandate, including the development of guidance on conceptual models for multi-national and multi-database studies.

During 2017 the registration of studies in the EU PAS Register continued to see a steady rise to a total of 1215 studies (a 25% increase over twelve months), with the 1000th study uploaded to the Register in February. Similarly, the use of the ENCePP website and information resources continues to increase.

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 – particularly those actively participating in working groups and special interest groups - for their contributions.

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Key achievements

- In February 2017 the Steering Group adopted the new **ENCePP work plan 2017-2019** which was consequently published on the ENCePP website. With this work plan the network has moved from the previous two to a three year planning cycle which also coincides with the mandate of the ENCePP Steering Group. The main goal during 2017 to 2019 will be to optimise the network's input to regulatory decision-making throughout the product life-cycle. Particular focus will be on the development of methods in impact research and to identify enablers and barriers to measuring the impact of pharmacovigilance.

- A major milestone was reached in February 2017 with the registration of the 1000th study in the **European Union electronic Register of Post-Authorisation Studies (EU PAS Register)**. The EU PAS Register® is now acknowledged internationally as a repository of observational post-authorisation studies. The use of the platform is widely recommended in scientific publications, guidelines and textbooks. Although initially the main aim of the EU PAS Register was to collect studies conducted in the European Union, researchers from outside the EU are also registering studies to increase transparency of their research.

  In July the European Union Intellectual Property Office (EUIPO) approved the registration of 'EU PAS Register' as a European Union trade mark (EUTM). The trade mark will reinforce the European Medicines Agency's (EMA) legal control over the name of the platform and its content. The same month saw the implementation of a new process that facilitates the transfer of ownership of a study record in the EU PAS Register.

- The sixth annual review of the **ENCePP Guide of Methodological Standards in Pharmacoepidemiology** was completed in July 2017 by the ENCePP Working Group on research standards and guidances. This latest version includes revisions, amendments and new references in all the chapters. Important changes were made to a number of chapters to take account of developments in some areas or the need for restructuring and clarification. Three new chapters have been added: Introduction, Patient registries, and Surveys. The Guide includes 31 authors and 424 references and continues to be the most popular document on the ENCePP website with around 850 downloads on average per month, plus around 5,000 views on average per month of individual chapters in the online version in 2017.

- 2017 marked the 10 year anniversary of ENCePP. On this occasion a manuscript titled '**Strengthening standards and collaboration to support medicines evaluation: Ten years of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)**' was accepted for publication in *Pharmacoepidemiology and Drug Safety*. The article reviews ENCePP's main achievements, discusses its impact on the benefit-risk evaluation of medicinal products in Europe and outlines future perspectives. In parallel, the ENCePP Secretariat published a new **infosheet** on ENCePP to coincide with the 10 year anniversary of the network.

Meetings and Networking

The ENCePP Secretariat organised the annual meeting of the plenary in November 2017; a report of the meeting and presentations given have been published on the ENCePP website.

The Steering Group met six times in 2017; minutes of all meetings are published on the ENCePP website. In addition, a meeting took place with representatives from the European CRO Federation (EUCROF) to explore areas of potential collaboration between the two networks.

The special interest group 'Impact of pharmacovigilance activities' (SIG Impact) met regularly to work on its main deliverable which is the development of a new chapter on methods for impact research in the ENCePP Guide on Methodological Standards in Pharmacoepidemiology. This ongoing work is based

on a systematic review of methods for measuring impact of regulatory interventions published in the British Journal of Clinical Pharmacology (DOI:10.1111/bcp.13469).

The working group on Research Standards and Guidances met numerous times in an effort to progress Revision 4 of the ENCePP Code of Conduct. The aim of this revision is to (1) define and clarify the practical implementation of 'scientific independence', (2) to capture the provisions related to the ENCePP Seal in a separate document, and (3) to improve the operability of the Code.

The working group on Data Sources and Multi-source Studies (WG3) was reactivated following the adoption of its revised mandate by the Steering Group. To this end, a successful call for expressions of interest in contributing to the working group was launched among all ENCePP partners. A first meeting of the newly constituted group took place in the margins of the plenary meeting in November and work has started on drafting a concept paper on '*Models for multi-database pharmacoepidemiologic studies*'.

The joint ENCePP-EnprEMA working group reviewed and provided comments during the public consultation phase of the draft guideline on good pharmacovigilance practices (GVP) - Product- or population-specific considerations IV: paediatric population.

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.

Network growth & strengthening

ENCePP guidance has been cited in scientific articles, as well as industry and CRO publications. The article '*Strengthening standards and collaboration to support medicines evaluation: Ten years of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)*' (Kurz X, Perez-Gutthann S and the ENCePP Steering Group. Pharmacoepidemiology and Drug Safety) reviews ENCePP's main achievements and discusses its impact on the benefit-risk evaluation of medicinal products in Europe over the past ten years.

As of end December 2017, the number of centres and networks in the ENCePP database stood at 169 (*164*) and 24 (*25*), respectively from 19 different European countries (the figures in brackets and italics are the corresponding numbers as of end 2016). The decrease in the number of networks is due to the deletion of a research consortium which is no longer active. The characteristics of the 169 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.

The number of registered data sources has increased dramatically from 53 to 116. This is due to the fact that the ENCePP resources database is being utilised for the creation of the 'EMA inventory of registries' in the context of the EMA Patient Registry Initiative where patient registries have been invited to add their details in the ENCePP database.

Figure 1: Classification of centres (2017)

y axis = number of centres (multiple answers possible)

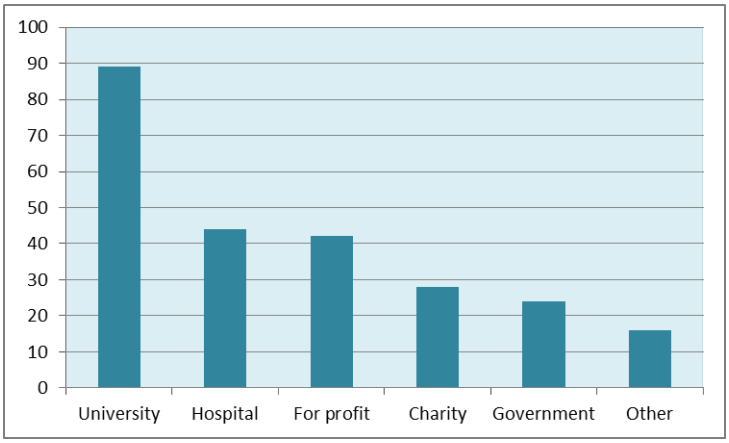


Figure 2: Expertise available in centres (2017)

x axis: number of centres (multiple answers possible)

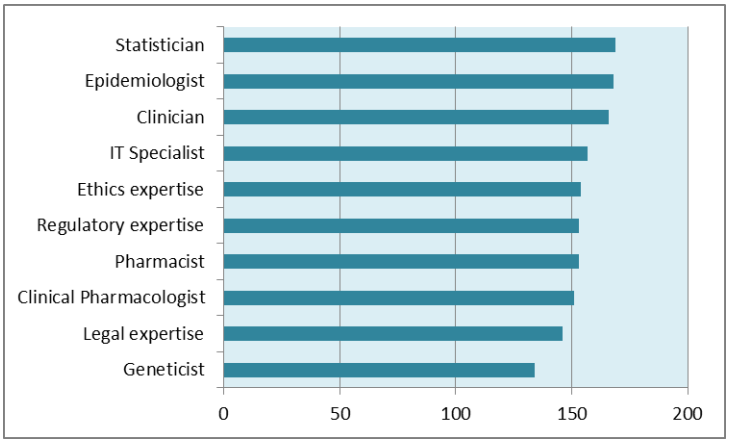


Figure 3: Experience with study designs (2017)

y axis: number of centres (multiple answers possible)

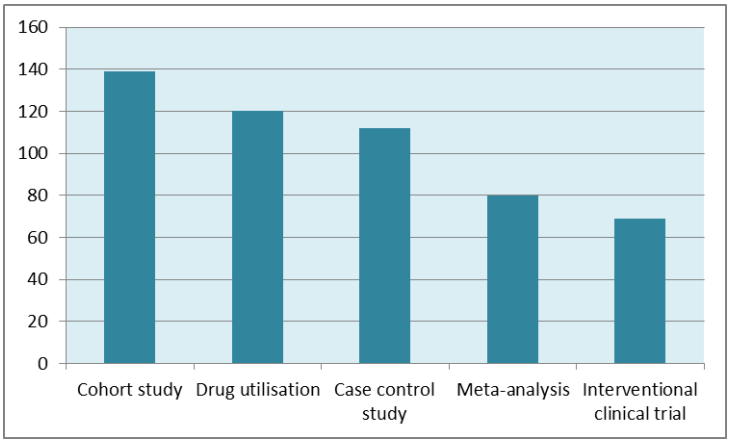


Figure 4: Experience in therapeutic areas (2017)

x axis: number of centres (multiple answers possible)

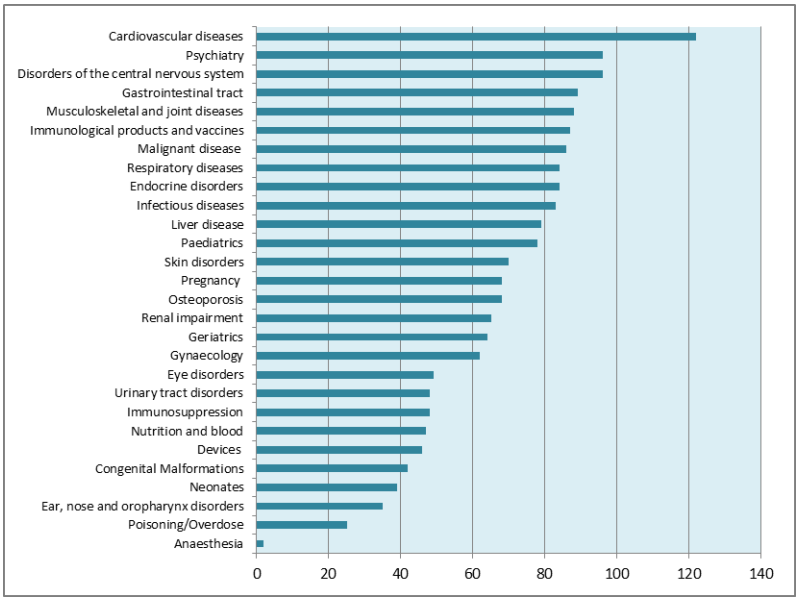


Figure 5: Research experience (2017)

y axis: number of centres (multiple answers possible)

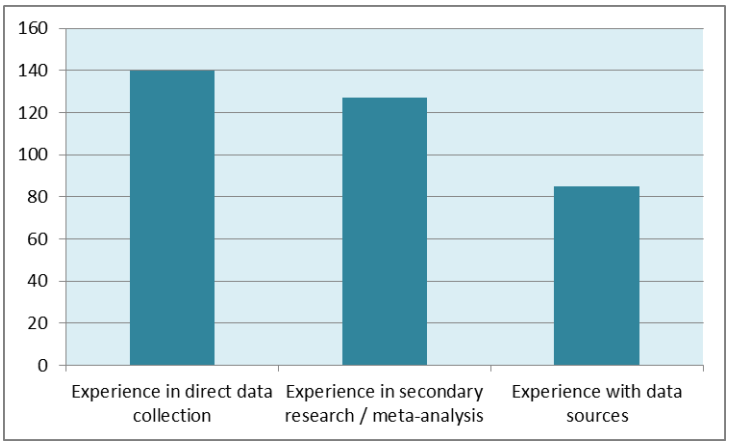
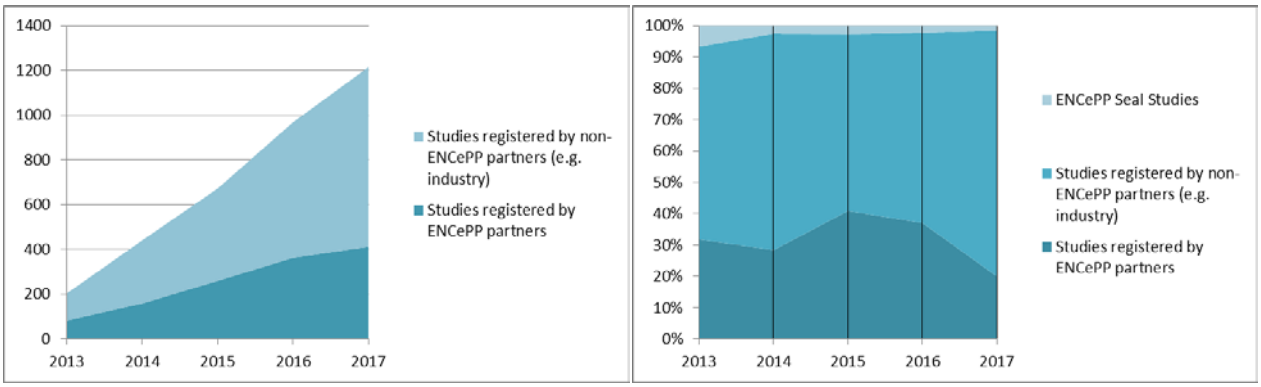


Figure 6 - 8: EU PAS Register®

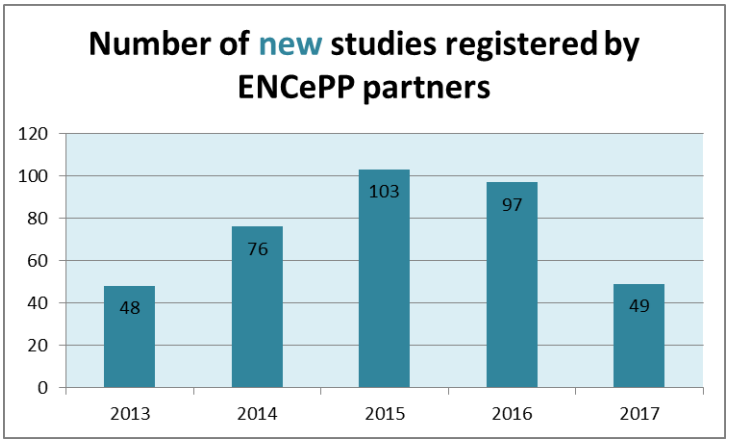
Between January and December 2017 the number of studies registered in the EU PAS Register (currently hosted on the ENCePP website) has risen from 968 to 1215 (25%). Whilst the rate of increase in 2017 was lower than during the previous year, the overall number of study registrations continued to rise steadily. This is not only due to the EU PAS Register being referred to in the guideline on Good Pharmacovigilance Practices (GVP) module VIII, chapter VIII.B., but also thanks to the voluntary registration of studies by pharmaceutical industry and academic researchers outside any regulatory framework. An increase in the registration of non-EU studies has also been noted.

On the other hand, the number of new studies registered by ENCePP centres has seen a decline over the past two years. Several reasons may be hypothesised to explain this decline: a lower number of studies performed by ENCePP centres, the fact that studies registered in the previous years represented a pool of past or ongoing studies which has been exhausted, explaining that only new studies are currently registered, or the fact that company-funded studies conducted by ENCePP partners were initially registered by ENCePP centres but study records are maintained by the marketing authorisation holder. No information is available to identify the possible reasons for the decline.

A total of 46 of studies registered have the ENCePP Study Seal.



Figures 6 and 7 represent numbers and percentages of all studies registered.



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 and its principles. It is used for ENCePP-related announcements and for making ENCePP outputs (e.g. standards and guidance documents, code of conduct, meeting minutes, mandates etc.) publically available. Key features of the website are

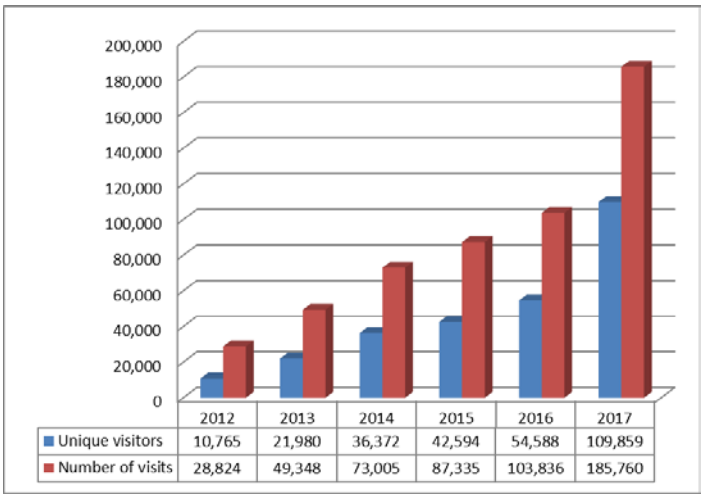
the *ENCePP Database of Research Resources* and the *EU PAS Register*. Both databases are publicly accessible and searchable by any stakeholder.

In 2017 the ENCePP Secretariat dealt with a large number of queries (~250) which were mostly related to the EU PAS Register, but also to ENCePP in general. The number of EU PAS Register queries has slightly decreased compared to the previous year, the majority of which were requests for information (e.g. forgotten login details, reference numbers etc.), queries on principles and process of registration, requests for amendments and transfer of ownership requests.

The Secretariat provides technical and administrative support for the EU PAS Register, and notifies Member States when a PAS (post-authorisation study) that has been requested by a regulator and funded by industry is registered. It also performs compliance and disclosure checks related to ENCePP Seal Studies and imposed non-interventional post-authorisation safety studies (PASS) in the context of GVP VIII regulatory requirements.

The number of visits to the ENCePP website has continued to rise. The following figures provide some statistics on the use of the website. All figures represent external (i.e. non-EMA) access only.

Figure 9: Visitor statistics (2009-2017)



	2012	2013	2014	2015	2016	2017
Unique visitors	10,765	21,980	36,372	42,594	54,588	109,859
Number of visits	28,824	49,348	73,005	87,335	103,836	185,760

Figure 9 shows a steady upward trend in visitors since 2012 with a steep increase over the past twelve months. The number of visits have nearly doubled in 2017 which is likely to be due to the increased use of the EU PAS Register.

Figure 10: Pages viewed by country (2017)

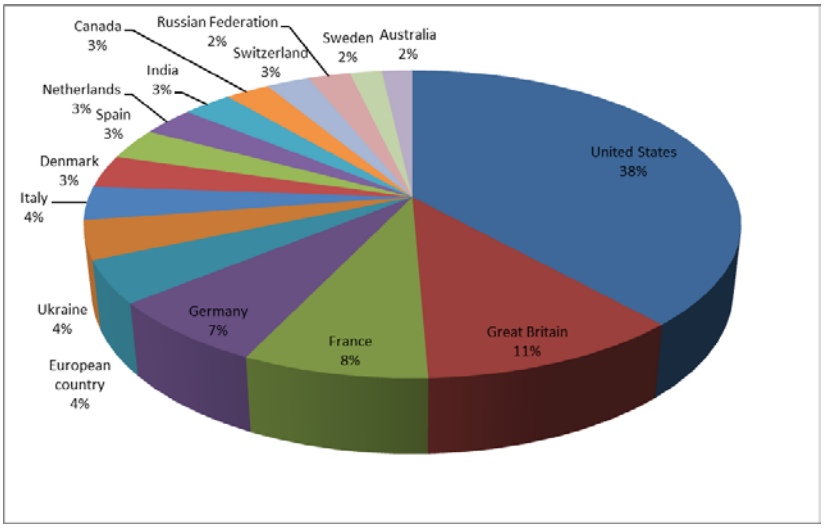


Figure 10 shows global interest in ENCePP in particular from EU countries and the United States. 'European country' refers to country domain names ending in '.eu'.

Figure 11: Most downloaded documents (2017)

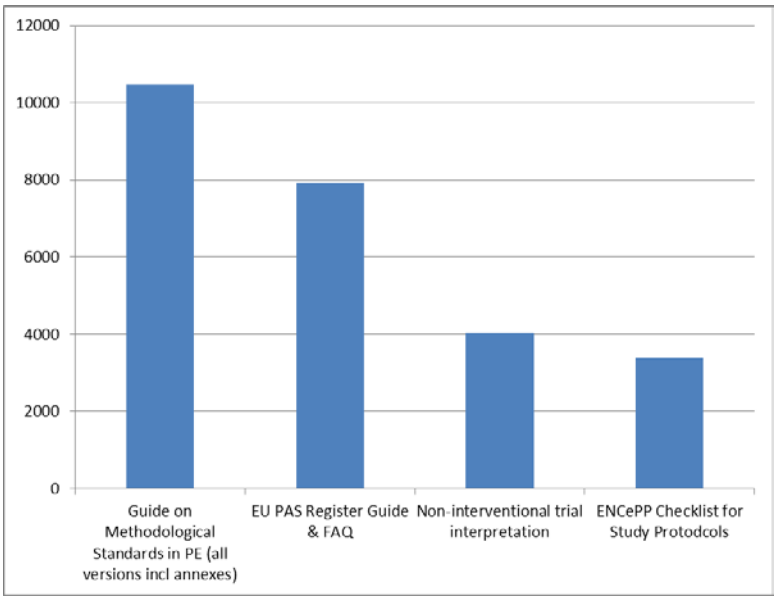


Figure 11 demonstrates the continued interest in the Guide on Methodological Standards in Pharmacoepidemiology, although the number of downloads continues to decrease, as stakeholders make more use of the online version of the Guide.

Figure 12: Top ten ENCePP URLs (2017)

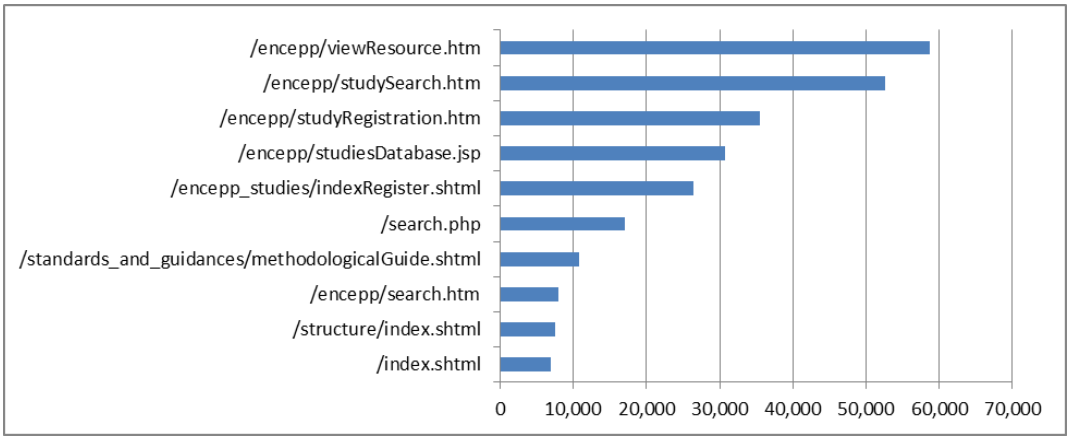


Figure 12 demonstrates interest in the EU PAS Register, but also reflects the popularity of ENCePP standards and guidances; the Methods Guide and its individual chapters received approx. 60,000 views in total.