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ENCePP Secretariat

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP activity report 2018

Executive Summary

ENCePP is a network coordinated by the European Medicines Agency. The members of this network are public institutions and contract and research organisations (CRO) involved in research in pharmacoepidemiology and pharmacovigilance. This report summarises the main activities in 2018.

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.

A major revision of the ENCePP Code of Conduct was adopted by the Steering Group in March 2018. This 4th revision of the Code clarifies and supports the practical implementation of the Code's key principles of scientific independence and transparency.

The 7th revision of the ENCePP Guide on Methodological Standards in Pharmacoepidemiology was published in July 2018. This latest version includes some significant revisions, amendments and new references in all the chapters. This is complemented by the new Annex 2 which provides more detailed guidance on methods for pharmacovigilance impact research developed by the ENCePP Special Interest Group 'Impact of pharmacovigilance activities'.

By the end of 2018 the number of studies registered in the EU PAS Register reached a total of 1419 studies (a 17% increase over twelve months). The use of the ENCePP website and information resources increased further compared to the previous year.

The ENCePP Steering Group has started cooperating with the International Society of Pharmacovigilance (ISoP) in an effort to identify synergies and enhance closer cooperation in pharmacovigilance activities. The Steering Group also began to reach out to representatives from Eastern European countries in an effort to enhance cooperation with centres that are currently under-represented in the network.

ENCePP activities during 2018 were affected by the European Medicines Agency's (EMA) Brexit preparedness business continuity plan (BCP) which entered into its third phase on 1 October 2018 and

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which had an impact on ENCePP related activities requiring EMA organisational and meeting support, such as the ENCePP plenary meeting scheduled for November 2018, which did not take place. Meetings and teleconferences of the ENCePP Steering Group, Working Groups and Special Interest Groups from October 2018 onwards were also affected.

Key achievements

- Following its acceptance for publication in late 2017, the article titled **Strengthening standards, transparency, and collaboration to support medicine evaluation: Ten years of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)** was published in open access in January 2018 (Kurz X, Perez-Gutthann S, the ENCePP Steering Group. Pharmacoepidemiol Drug Saf. 2018;1–11. https://doi.org/10.1002/pds.4381).
- On 15 March 2018 the ENCePP Steering Group adopted the **4th revision of the ENCePP Code of Conduct** which provides a set of principles and recommendations to promote scientific independence and transparency of observational research, especially where they may be threatened by the influence of study funders. This major revision aims to clarify and support the practical implementation of the Code's key principles of scientific independence and transparency. It acknowledges personal interests of researchers but distinguishes commercial, financial and institutional interests in a revised definition of conflicts of interests. The Code also provides for research conducted with authorised medicines in the context of post-approval regulatory requirements for marketing authorisation holders. In addition, all processes for implementing the ENCePP Seal concept were removed and summarised on the ENCePP Study Seal pages on the ENCePP website.
- Following publication of the 4th revision of the ENCePP Code of Conduct a survey amongst five categories of stakeholders (patient and consumer organisations, healthcare professionals, pharmaceutical industry, public health body or regulators, and researchers) was conducted to evaluate how potential users understand and would apply the revised Code in practice. The results of the **Stakeholder Survey on the ENCePP Code of Conduct** were published on the EU PAS Register (ref.no. EUPAS26545).
- The seventh annual review of the **ENCePP Guide of Methodological Standards in Pharmacoepidemiology** was completed in July 2018 by the ENCePP Working Group on Research Standards and Guidances. This latest version includes some significant revisions, amendments and new references in all the chapters. This is complemented by the new Annex 2 which provides more detailed guidance on methods for pharmacovigilance impact research developed by the ENCePP Special Interest Group 'Impact of pharmacovigilance activities'. The Guide includes 34 authors and 593 references and continues to be the most popular document on the ENCePP website with around 1,000 downloads on average per month, plus around 4,500 views on average per month of individual chapters in the online version in 2018.
- In October 2018 the ENCePP Working Group on Research Standards and Guidances finalised **Revision 4 of the ENCePP Checklist for Study Protocols** which was published on ENCePP website with a reminder that the EMA Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies requires that a copy of the ENCePP Checklist for Study protocols, completed and signed by the main author of the study protocol, should be included in Annex 2 of the PASS study protocols.
- The ENCePP Steering Group agreed an **action plan for all ongoing and outstanding activities** of the current ENCePP work plan which will allow a smooth continuation once EMA resumes its

organisational support to ENCePP activities after European Medicines Agency's (EMA) Brexit preparedness business continuity plan (BCP).

Meetings and Networking

- A meeting took place with the International Society of Pharmacovigilance (ISoP) to discuss suggestions from ISoP for the planning of future pharmacovigilance activities to be recommended by the ENCePP Steering Group (SG). A further TC took place with representatives from Eastern European countries to better understand the needs and possible solutions for the development of pharmacoepidemiology in those countries.
- The working group 'Research Standards and Guidances' (WG1) met twice to work primarily on the revisions of the ENCePP Methods Guide and the ENCePP Checklist for Study Protocols.
- During the first half of 2018 the special interest group 'Impact of pharmacovigilance activities' (SIG Impact) met regularly to finalise its contribution to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, i.e. a new chapter and Annex on methods for impact research.
- The working group on 'Independence and Transparency' (WG2) met a number of times to finalise Revision 4 of the ENCePP Code of Conduct and to agree on the contents of the stakeholder survey on the revised Code. This was followed by numerous meetings of a small subgroup which analysed the survey results, on the basis of which they drafted a summary report (as published in the EU PAS Register) that also informed a manuscript about the ENCePP Code of Conduct and its latest revision. The manuscript is scheduled for submission for publication in Q1/2019.
- Two sub-groups of working group 'Data Sources and Multi-source Studies' (WG3) met a number of times to progress work on the identification of dimensions to evaluate a data processing/data analysis strategy, and on an inventory of research scenarios useful for regulatory decision-making, respectively. A commentary on different strategies to conduct multi database studies in Europe is under development.
- The 2018 meeting of the ENCePP plenary did not take place due to impact of the European Medicines Agency's (EMA) Brexit preparedness business continuity plan (BCP) which entered into its third phase on 1 October 2018. The BCP allows safeguarding core activities related to the evaluation and supervision of medicines while the Agency prepares for the consequences of the United Kingdom's exit from the European Union, both in terms of the impact on the Agency's operations as well as its physical move to Amsterdam in March 2019. Measures of the third BCP phase include a temporary suspension of the activities of non-product related working parties and the development and revision of guidelines until 30 June 2019. This decision has a temporary impact on ENCePP related activities requiring EMA organisational and meeting support, and also affects meetings and teleconferences of the ENCePP Steering Group, Working Groups and Special Interest Groups. Following discussions within WG1 and the SG, a practical consequence of the BCP will be the postponement of the publication of eight ENCePP Guide on Methodological Standards in Pharmacoepidemiology to January or July 2020 depending on a decision to be made in September 2019.
- Prior to the coming into force of the BCP, the Steering Group met four times by virtual means; minutes of all meetings are published on the ENCePP website.
- In an effort to keep the network active and dynamic during the EMA BCP phase, informal meetings of the ENCePP Steering Group continued to take place; this was done on the initiative of the SG members, and without support from the ENCePP Secretariat.

Network growth & strengthening

- The ENCePP Steering Group is actively cooperating with the International Society of Pharmacovigilance (ISoP) in an effort to identify synergies and enhance closer cooperation in pharmacovigilance activities.
- The Steering Group has also begun to reach out to representatives from Eastern European countries in an effort to enhance cooperation with centres that are currently under-represented in the network.
- As of end December 2018, the number of centres in the ENCePP database had increased to 176 (up from 169 as of end 2017), whilst the number of networks remained unchanged at 24. ENCePP partners come from 19 different European countries. The characteristics of the 176 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 continued to rise from 116 at the beginning of the year to a total of 134 at the end of 2018. This increase is due to the fact that in the context of the EMA Patient Registry Initiative existing patient registries are encouraged to register their details in the ENCePP resources database.
- By the end of 2018 the number of studies registered in the EU PAS Register reached a total of 1419 studies (a 17% increase over twelve months).

Figure 1: Classification of centres (2018)

y axis = number of centres (multiple answers possible)

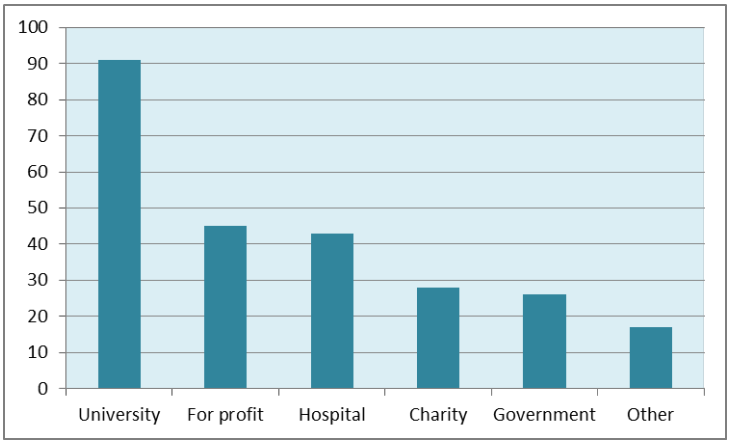


Figure 2: Expertise available in centres (2018)

x axis: number of centres (multiple answers possible)

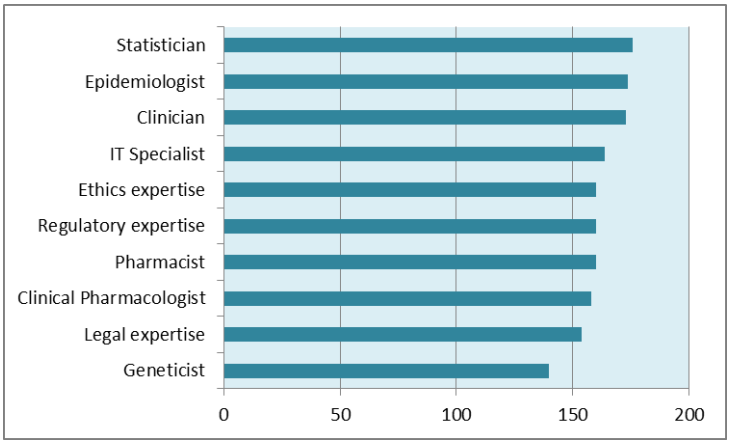


Figure 3: Experience with study designs (2018)
y axis: number of centres (multiple answers possible)

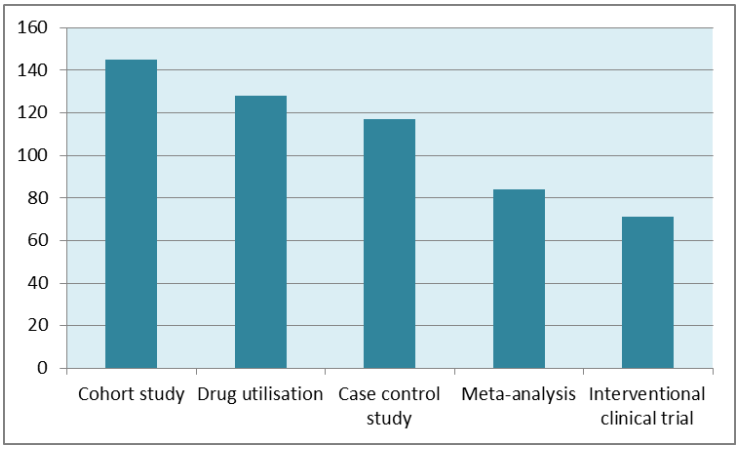


Figure 4: Experience in therapeutic areas (2018)

x axis: number of centres (multiple answers possible)

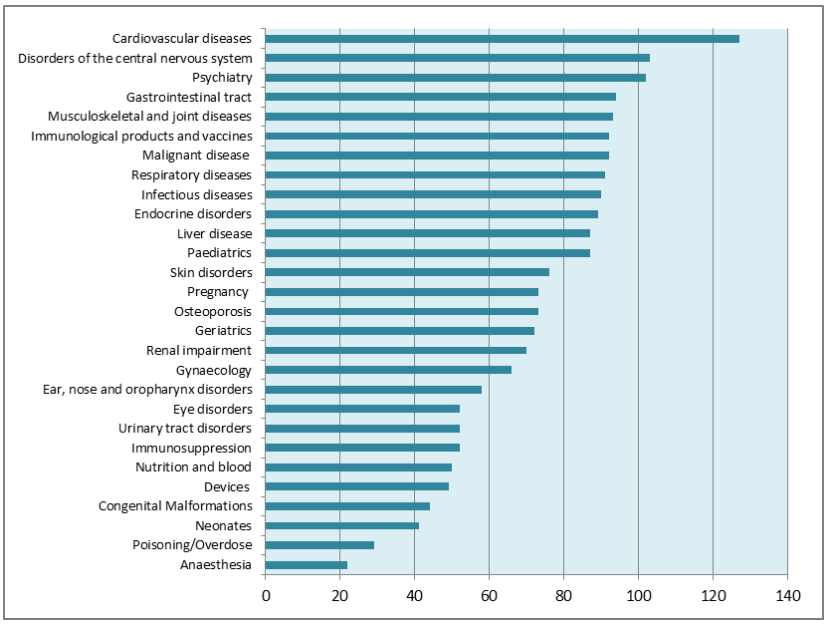


Figure 5: Research experience (2018)

y axis: number of centres (multiple answers possible)

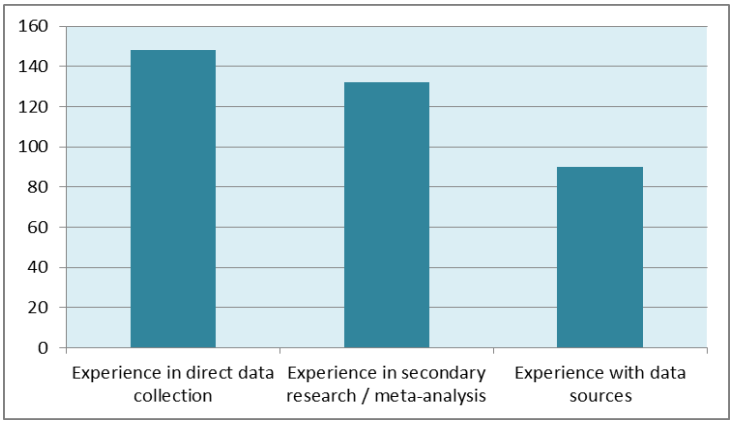
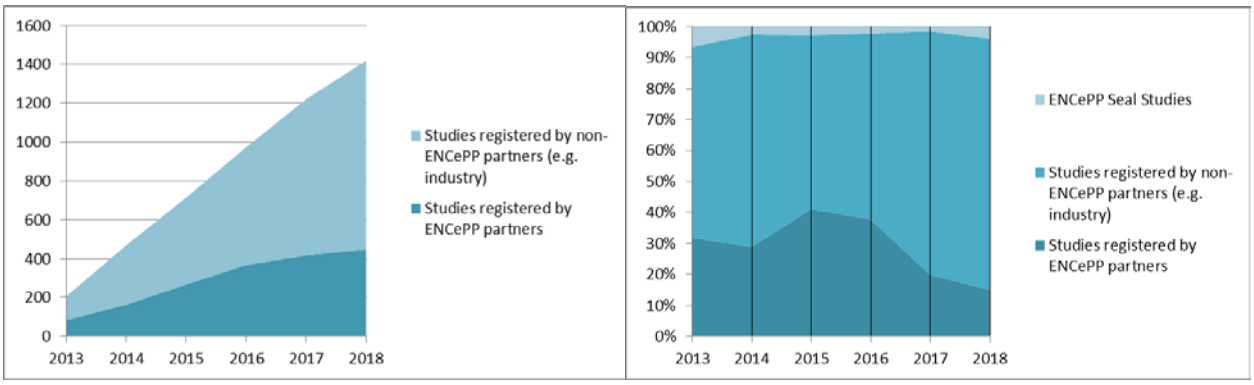


Figure 6 - 8: EU PAS Register®

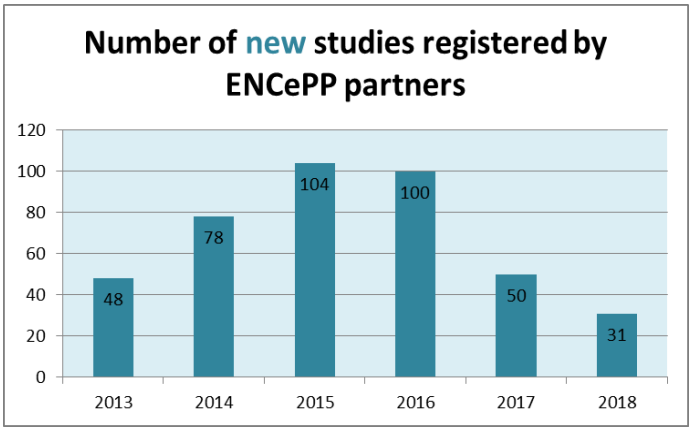
Between January and December 2018 the number of studies registered in the EU PAS Register (currently hosted on the ENCePP website) has risen from 1215 to 1419 (17%). Although this is a lower rate of increase compared to the previous year, the overall number of study registrations continues to rise steadily, including the registration of non-EU studies.

The trend of falling numbers in new studies registered by ENCePP centres continues. Although no information is available to identify the exact reasons for the decline, this may be explained by several possible reasons: 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.

A total of 54 of studies registered have the ENCePP Study Seal. Although overall number remains very low, 2018 saw a 100% increase in study seal applications over the previous year. The reason for this increase is unclear, but may be due to the major revision of the ENCePP Code of Conduct clarifying and supporting the practical implementation of the Code's key principles of scientific independence and transparency.



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

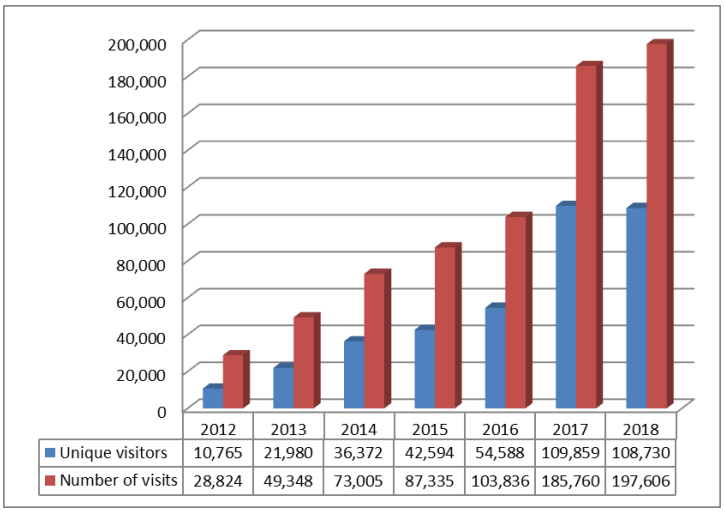
ENCePP Database of Research Resources and the *EU PAS Register*. Both databases are publicly accessible and searchable by any stakeholder.

In 2018 the ENCePP Secretariat continued to deal with a large number of queries (~280) which were mostly related to the EU PAS Register, but also to ENCePP in general. The number of EU PAS Register queries remained stable 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 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 (2012-2018)



	2012	2013	2014	2015	2016	2017	2018
Unique visitors	10,765	21,980	36,372	42,594	54,588	109,859	108,730
Number of visits	28,824	49,348	73,005	87,335	103,836	185,760	197,606

Figure 9 shows a steady increase in visits since 2012, whilst the number of unique visitors has decreased slightly over the past twelve months.

Figure 10: Pages viewed by country (2018)

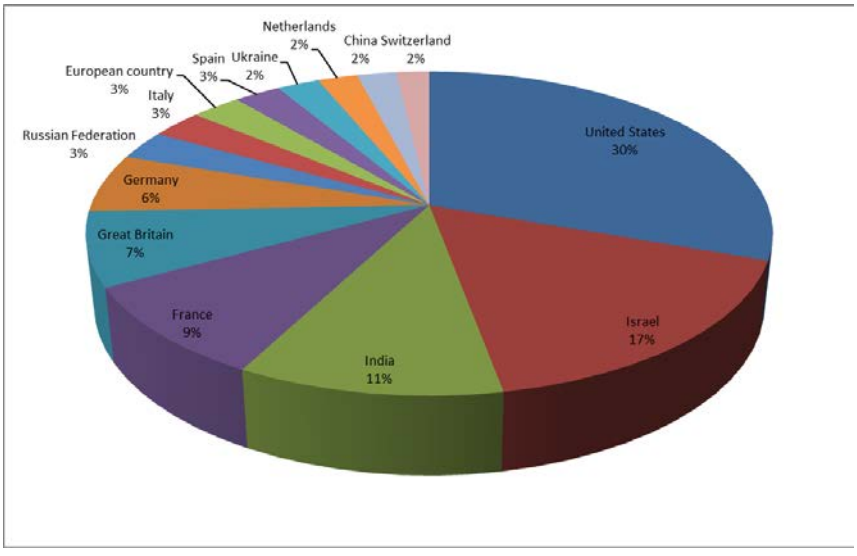


Figure 10 shows increased global interest in ENCePP and the EU PAS Register. 'European country' refers to country domain names ending in '.eu'.

Figure 11: Most downloaded documents (2018)

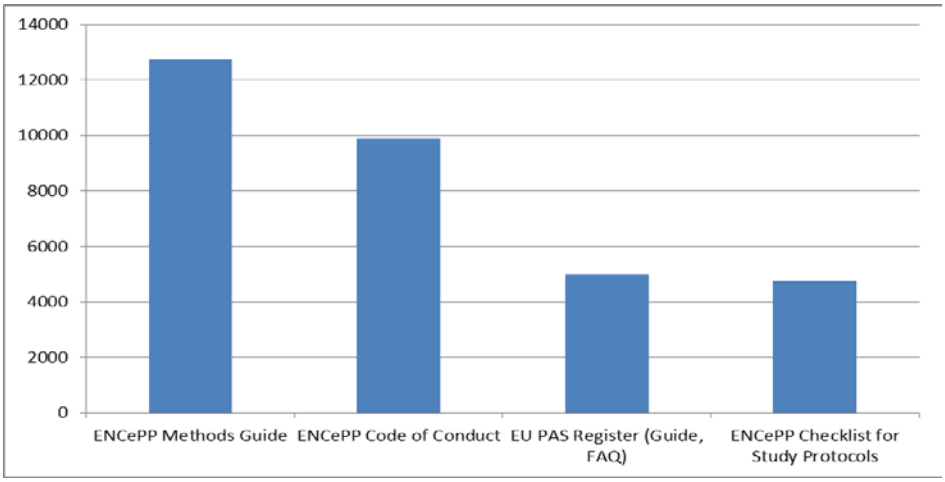


Figure 11 demonstrates the continued interest in the Guide on Methodological Standards in Pharmacoepidemiology, although stakeholders make more and more use of the online version of the Guide. It also reflects a surge in interest in the Code of Conduct during a year when a new revision was published and a stakeholder survey conducted. The figures for the Guide and Code include all published versions plus related documents.

Figure 12: Top ten ENCePP URLs (2018)

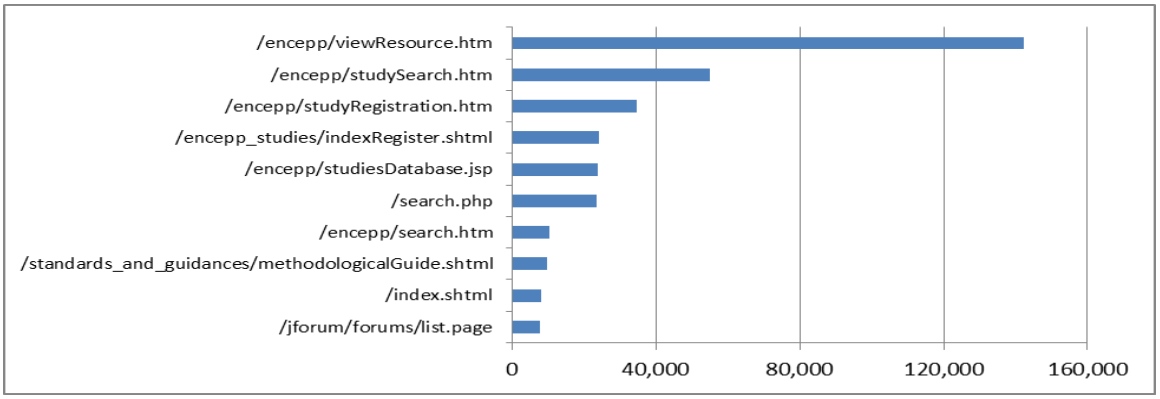


Figure 12 demonstrates interest in the EU PAS Register, but also reflects the popularity of ENCePP standards and guidances; the Methods Guide and its individual chapters received approx. 52,000 views in total.