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ENCePP

European Network of Centres for
Pharmacoepidemiology and
Pharmacovigilance

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) survey of methodologies for European Union publicly funded multi-database safety studies

Current practice in European Union multi-database pharmacoepidemiology research

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1. Abstract

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) seeks to build capacity in the European Union to use multi-centre studies to monitor the benefit-risk profile of marketed drugs. In August 2012, an ENCePP working group launched a survey of researchers coordinating multi-database drug-safety projects that have been publicly funded by the European Commission with the aim of defining current practice in Europe in combining data from multiple sources.

The semi-quantitative questionnaire consisted of 14 categorised questions relating to the databases that were being used and the approaches in practice taken by researchers working across multiple databases. It was circulated to the research coordinators involved in consortia funded under the Seventh Framework Programme Cooperation Specific Programme Health 2007 – 2013 and/or European Medicines Agency funded drug safety studies and/or the PROTECT project.

Responses were received from 13 of the 14 researcher coordinators covering 16 of 18 projects. The number of databases used in individual projects ranged from 2 to 11 and 8 of the projects (44%) involved pooling data from different databases.

The survey documents an active research arena in multi-database research in Europe as a result of public funding. It also has shown the heterogeneity of the methods used to combine data from multiple databases. The interpretation of this heterogeneity is, however, complex and it has yet to be established if a single model is the best approach. To this end, ENCePP is well-positioned to conduct further research and develop guidance.

2. Introduction

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) is an initiative coordinated by the European Medicines Agency (EMA) and developed in collaboration with European experts in the relevant fields.[i] Its goal is to strengthen the post-authorisation monitoring of medicinal products in Europe by facilitating the conduct of multi-centre studies focussing on specific safety issues and assessment of the benefit-risk profile of marketed drugs. This is to be achieved by optimising the use of available expertise and research resources. In addition to building capacity, the network aims to increase trust in the findings of post-authorisation studies by improving study conduct and reporting. ENCePP has been acknowledged as having the potential to bring more transparency and rigour to pharmacoepidemiology.[ii]

As of 01 July 2014 the network consisted of 139 research centres, 22 research networks and 49 data sources across 18 European countries, all listed in the electronic ENCePP Resources Database.[iii] To achieve the objectives of the network, working groups have been established including one on data sources and multi-source studies.

Working collaboratively via networks such as ENCePP to build capacity and improve the use of available data sources and expertise is a current trend in pharmacovigilance and pharmacoepidemiology. More innovative means of funding research are also being explored involving partnership and both public and public/private monies such as the European Commission's (EC) Seventh Framework (FP7)[iv] and Horizon 2020[v] programmes and the Innovative Medicines Initiative (IMI)[vi]. Although collaborations for multinational studies are not new, they have been strongly encouraged over the recent past funding calls of the EC for drug safety research. It is a requirement of

EMA funded drug safety studies that research is conducted in at least two EU Member States to assess the generalisability of any findings. Furthermore, regulatory authority requested pharmaceutical industry-sponsored studies with multiple countries and data sources have also become the norm in Europe. This trend for increasing number of multi-country and multi-database collaborations not only occurs in Europe but other regions in the world.[vii]

Post-authorisation medicines research has encouraged the secondary use of administrative and other electronic medical records in recent years. However, most of available secondary data sources are limited to the geographical scope of one country and present among each other substantial differences concerning structure, type of collected data, drug and medical event terminologies. Consequently, using databases for research in multi-country studies often needs pooling and integration of heterogeneous data several approaches have been developed in recent projects.[viii]

Therefore an important component of ENCePP to enhance efficiency and capacity building is the potential for data pooling by participants in the network. This serves to improve the use of the information gathered in different databases, increase statistical power and assess generalizability as well as heterogeneity in drug use concerning rare adverse outcomes and infrequently prescribed drugs. An ENCePP working group on data sources and multi-source studies (WG3) seeks to describe approaches and processes for combining and sharing of European healthcare databases. This involves exploring ways of performing multi-database safety studies e.g. combining data, using common protocols. The ultimate goals include guideline development, seeking consensus and promoting further research to compare and identify the best approaches among those that have been used so far. To this end, the present paper describes the results of the survey of researchers working on multi-database drug-safety projects, which have been fully or partially publicly funded by the EC to map practice in the years 2008 - 2013 in Europe.

3. Methods

The approach was to target research coordinators of projects that had public funding from the EC and that had liaison with ENCePP (all except 1 of the coordinating research centres are ENCePP partners). The exception is the EpoCAN consortium which is coordinated by a non-EU centre and, therefore, cannot join ENCePP. Some projects were coordinated by the same principal investigator.

The group agreed a semi-quantitative questionnaire (attached in Annex) which was first circulated in August 2012 to a target group of 14 individual research coordinators of the then current 10 FP7 consortia funded under the FP7 Cooperation Specific Programme Health 2007 - 2013, 7 EMA funded drug safety studies and the IMI - PROTECT project[ix] (see Table 1).

Table 1: Projects targeted in survey and drugs under study

Name of Project/Study Website	Drug/class of drug	Safety outcome	No. of databases in the project	Method of data pooling
Seventh Framework programme (FP7)				
SOS http://www.sos-nsaids-project.org/	NSAIDs	Cardiovascular and gastrointestinal risks	8	Pooling of elaborated individual patient level data.
ARITMO http://www.aritmo-project.org/	Antipsychotics; Anti-infectives (antibacterials, antimicotics, antivirals); H1-antihistamines	Arrhythmic potential risks	7	Pooling of elaborated individual patient level data.

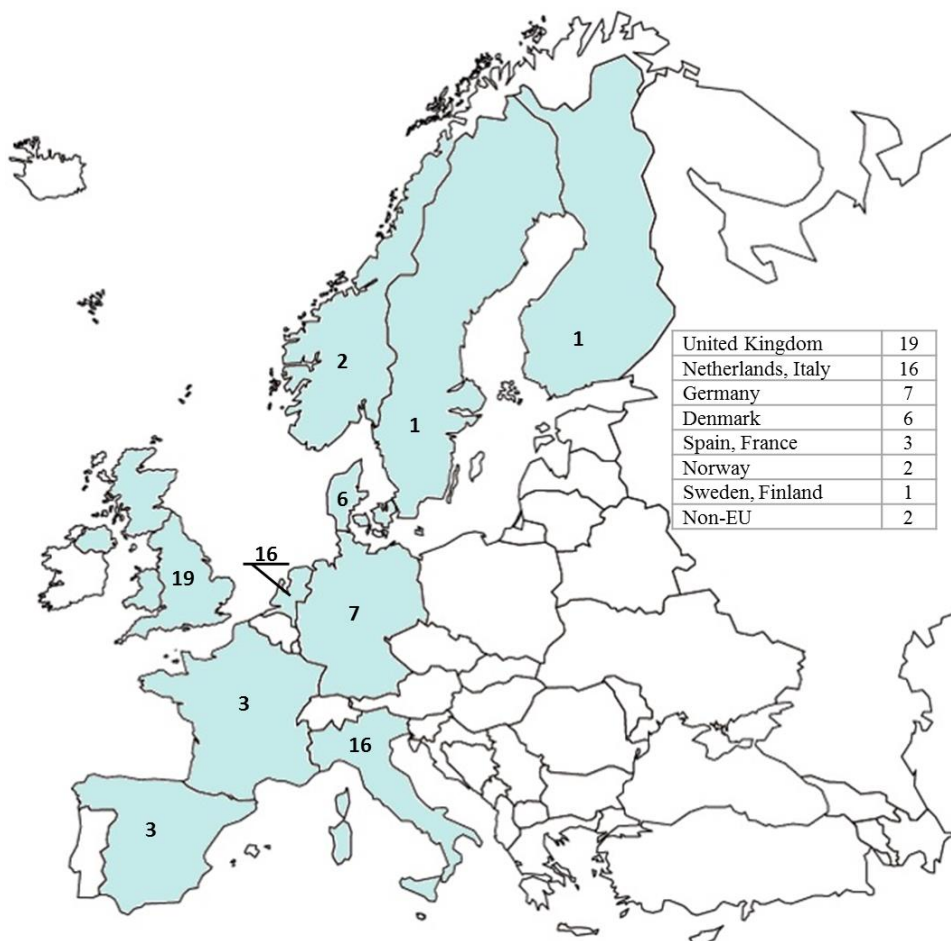|				
ADDUCE http://www.adhd-adduce.org/	Methylphenidate	Growth, neurological, psychiatric and cardiovascular side effects	3	n/a
EUROmediCAT http://euromedicat.eu/	New anti-epileptics; insulin analogues; anti-asthmatics; selective serotonin reuptake inhibitors, SSRIs	Pregnancy-related drug safety	6	Different approaches used. Comparison of countries for drug utilisation studies rather than pooling. Meta-analysis for safety studies.
PHARMACHILD https://www.printo.it/project_ongoing_detail.asp?ProjectID=15	Immune modulatory agents	adverse events		
STOP http://www.stop-study.com/	Risperidone; fluoxetine; montelukast	Conduct disorders; depression; asthma	3	Pooling of elaborated individual patient level data & central pooling of raw data
CARING http://www.caring-diabetes.eu/ http://www.encepp.eu/encepp/viewResource.htm?id=7046	Insulin; insulin analogues		3	Pooling of elaborated individual patient level data & meta-analysis of coefficients
SAFEGUARD http://www.safeguard-diabetes.org/	Non-insulin blood glucose lowering drugs	Cardio/cerebrovascular and pancreatic safety	9	Pooling of elaborated individual patient level data.
Astro-Lab http://www.astrolab-project.eu/	Long-acting β-agonist (LABAs) and Inhaled Corticosteroids (IC)		2	Pooling of elaborated individual patient level data.
Epo-Can http://www.epocan.com/	Epoetins	Long-term risks	3	n/a
Innovative Medicines Initiative (IMI)				
PROTECT http://www.imi-protect.eu/	Early detection of adverse events		8	n/a
EMA tender				
Isotretinoin and the Pregnancy Prevent Programme in Europe http://www.encepp.eu/encepp/viewResource.htm?id=4654	Isotretinoin		4	
Risk minimisation in patients treated with rosiglitazone http://www.encepp.eu/encepp/viewResource.htm?id=2236	Rosiglitazone and fixed combinations with metformin and glimepiride		2	n/a
A/H1N1 pandemic vaccines and pregnancy outcomes http://www.encepp.eu/encepp/viewResource.htm?id=5304	Influenza virus, TYPE A, H1N1	Drug exposure during pregnancy		
Use of Oral Contraceptives in the European Union http://www.encepp.eu/encepp/viewResource.htm?id=3520	Progestogens and estrogens, Progestogens.		4	Pooling of elaborated individual patient level data.
Risk minimisation in patients treated with pioglitazone http://www.encepp.eu/encepp/viewResource.htm?id=3221	Pioglitazone and fixed combinations with	metformin and alogliptin.	3	n/a
Cardiac valve disorders and biphosphonate use http://www.encepp.eu/encepp/viewResource.htm?id=2772	Bisphosphonates	Cardiac valve disease	4	Pooling of elaborated individual patient level data.
Anxiolytic or hypnotic drugs and total mortality http://www.encepp.eu/encepp/viewResource.htm?id=6269	Tetrazepam, clonazepam and Benzodiazepines.	Total mortality	2	n/a

The survey consisted of 14 categorised questions relating to the number, purpose and the important features of the electronic healthcare record (EHR) databases that were being used; the way databases were selected for the projects; the design of studies being conducted; characterisation of how researchers worked in practice across multiple databases, including protocol writing, dealing with heterogeneity, pooling of data and subsequent analysis of the pooled data; and the time taken from start of protocol writing to start of data analysis. A question was also posed on governance/ethical issues encountered. The questionnaire was sent and the results collected via email. Frequency statistics were calculated to describe the responses. The researchers involved reviewed the results of the questionnaire and were invited to contribute or comment on the draft manuscript.

4. Results

Responses were received from 13 of the 14 researcher coordinators covering 16 of the 18 projects. In fourteen of the 16 projects, data from routine EHR databases and registries established for routine administrative purposes were used, the other two related to registry data. The number of EHR databases used in individual projects ranged from 2 to 11 (see Table 1) and their distribution is described in Figure 1.

Figure 1: Geographical spread and number of databases used by country*

* a given database may be counted in more than one project

United Kingdom	19
Netherlands, Italy	16
Germany	7
Denmark	6
Spain, France	3
Norway	2
Sweden, Finland	1
Non-EU	2

The purpose for the use of these EHR databases within the respective projects is described in Figure 2. Of note, multiple projects had multiple purposes for using their available EHRs.

Figure 2: Purpose for the use of the healthcare databases within the projects (n = 16)
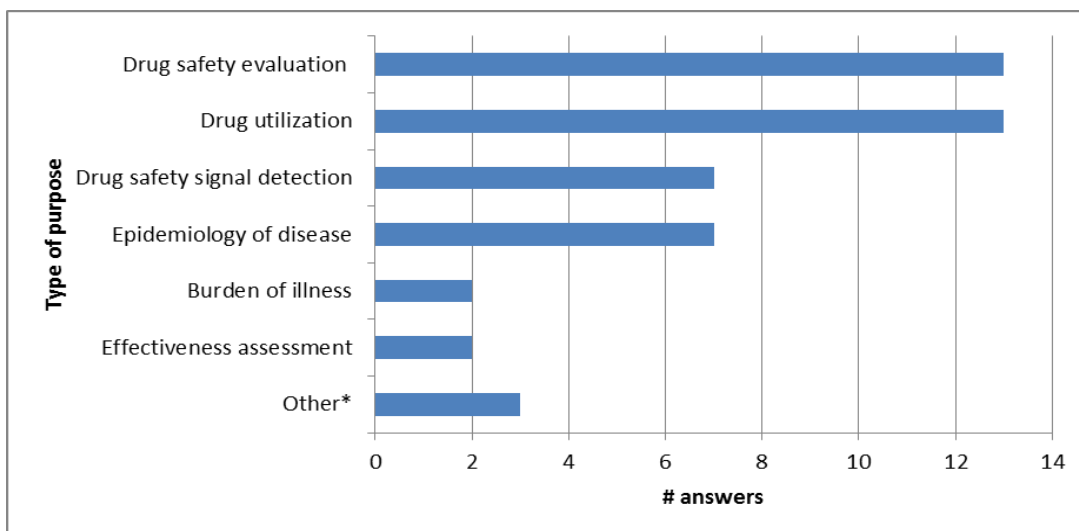
The 'other' category consisted of one study (STOP) which used 3 databases with collection of data on clinical scales as well as adverse events. When asked to rank in order of importance, the twelve features of a database that might be sought in terms of possible inclusion of a given database in a project, the frequency of the individual features picked are displayed is Figure 3.

Figure 3: Importance of specific features in database selection (n = 15)*

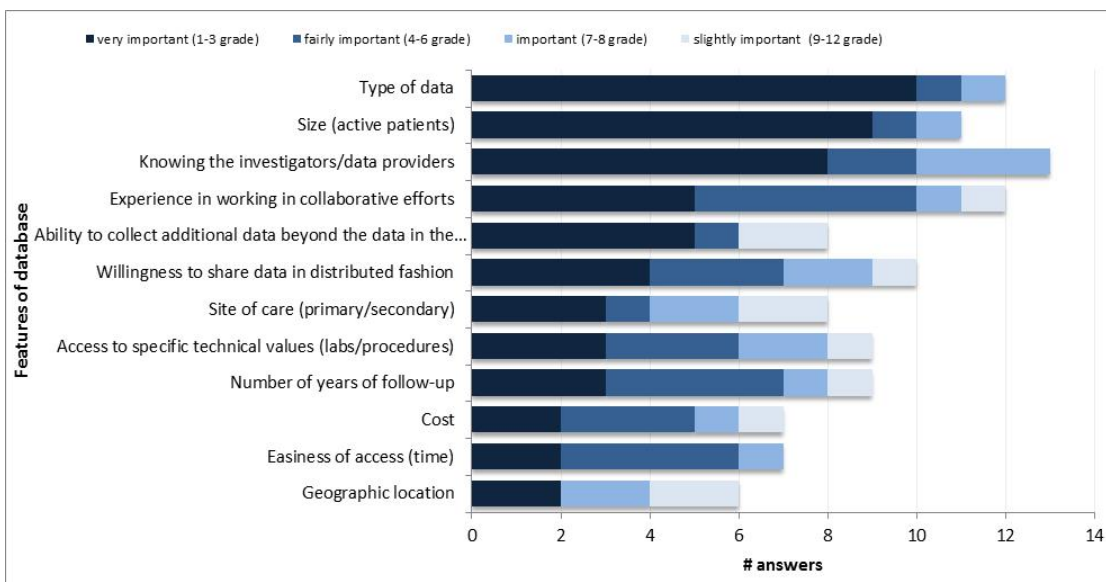*each feature has been ranked in order of importance*

Figure 4 describes how investigators work together in integrating data across multiple databases. Irrespective of using multiple approaches in the same project, using common protocol and using common data model with centrally prepared script were the most frequently used approaches.

Figure 4: Characterisation of work across multiple databases (n = 11)*

*categories are not mutually exclusive*
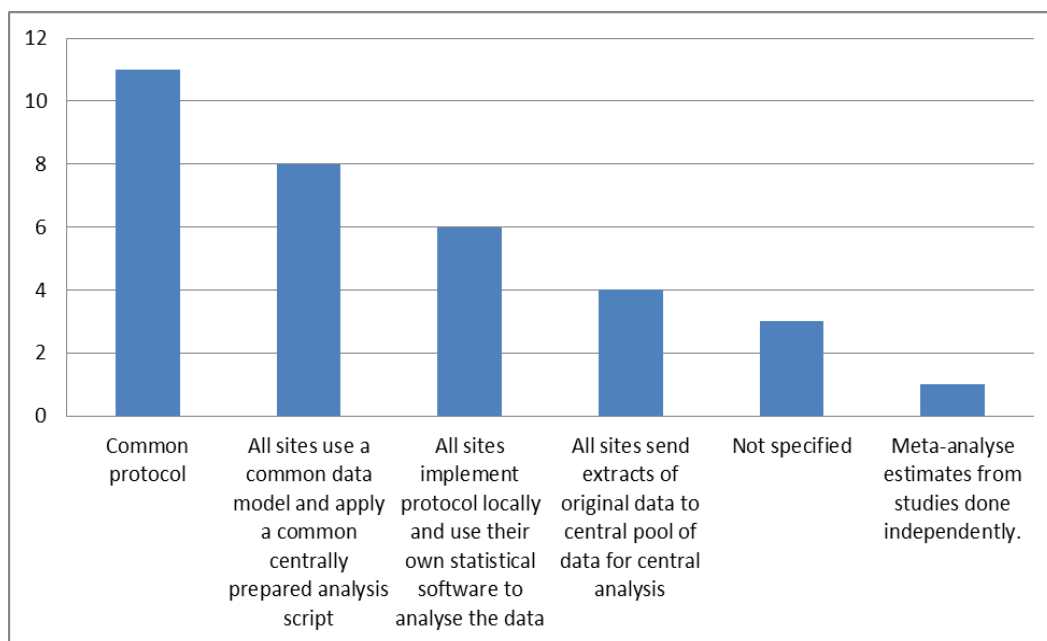
Nine out of 13 (69%) of respondents described the organisation of protocol writing as one in which a writer or group led, drafts were circulated and consensus achieved. Five respondents describe a work-package or task-force approach to writing protocol(s).

Figure 5 describes the pooling of data at the end of data extraction and subsequent sharing among the 8 of the 18 (44%) projects that confirmed they pooled data from different databases. Two of these 8 (25%) used more than one approach. A further 6 of the 18 projects (33%) confirmed they did not pool data.

Figure 5: Pooling of data for analysis (n = 8))*

categories are not mutually exclusive
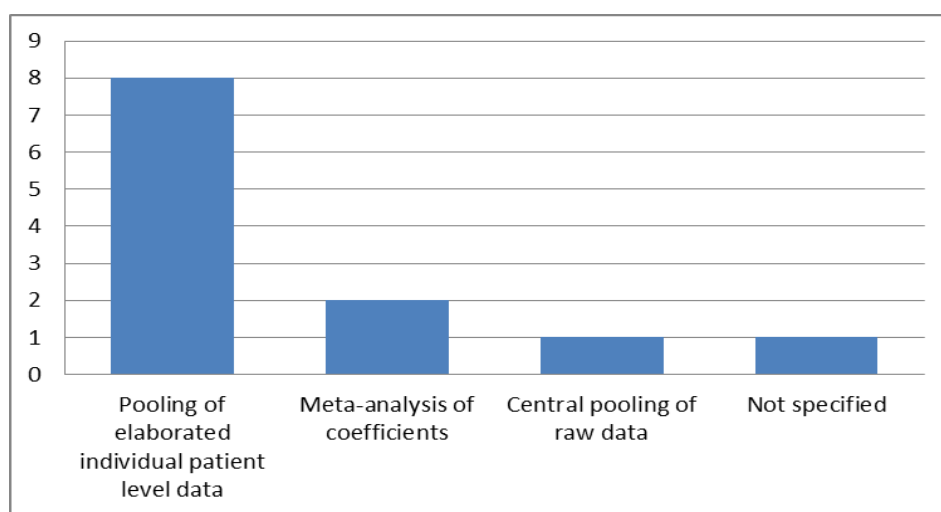
Of the nine projects for which the organisation of the analysis of pooled data was described, 2 (22%) (EUROmediCAT and STOP) used more than one approach. Five out of the 9 (56%) (the SOS,

SAFEGUARD and AstroLab consortia and the EMA studies on oral contraceptives and bisphosphonates) did so by multiple partners involved in analysis/pooling through access to data on a central server, for 4 (44%) (AstroLab, EUROmediCAT, STOP and CARING) multiple partners used local copies of the pooled data and for 3 (33%) (EUROmediCAT, PHARMACHILD and STOP) a data management centre analysed/pooled data.

Nine (75%) of the survey respondents confirmed they had processes in place for verification of differences between data sources, 5 (42%) said they did not and the response from one was unclear.

The majority of the projects used cohort study designs i.e. 14 (88%). Seven (44%) used case-control, 4 (25%) self-controlled case series and 4 (25%) cross-sectional designs. Additionally, there was 1 (6%) nested case-control and 1 (6%) case-crossover design used and a retrospective review of databases for specific adverse events was conducted.

In terms of time required from the start of protocol writing to the start of data analysis, 5 of the 11 projects that described a timeframe took between 4 - 6 months (42%). Two studies required 7-12 months (18%) and one study each took between 1 – 3 months (9%), 2 years (9%) and 3 years (9%). For a further project, the timeframe was not yet known.

The respondents reported for 7 of the projects (50%) using routine EHR that they had encountered governance/ethical issues. One described how some ethics committees did not permit the collection of patients personal data (e.g. for French patients, the country of birth could not be collected) and how some other centers (e.g. in Norway) required many different International Classification of Functioning, Disability and Health (ICF) versions for different age groups. For two (29%) projects the issues encountered related to access to individual databases.

5. Discussion

The various initiatives described in the present paper i.e. ENCePP, EMA funding of drug safety studies, FP7 funding and IMI-PROTECT should all be seen in the context of a global shift in the role of medicines regulators as assessors of results and studies generated by others to that of proactively driving the research agenda of public health studies and catalysts of collaboration in the context of a much more proactive post-marketing drug surveillance.[x] Further examples include the FDA's Critical Path Initiative[xi] and Sentinel program, the Mini-Sentinel pilot for which has developed technical specifications for developing and operating a secure distributed data system comprised of separate data sets that conform to a common data model.[xii] Assessments are performed by distributing computer programs that are executed locally by each data partner.

In comparison, the results of the present survey overall highlight the heterogeneity of the methods used by the various publicly funded projects in the EU in using EHR data by combining data from multiple databases. These range from less to more harmonised approaches. Further research is, however, needed to establish if it is the case that there exists a single best performing and most efficient method to be adopted when utilising multiple databases for pharmacoepidemiological research or if a single model is not the best approach.

The selection of databases in which to conduct such research tends to be driven by the characteristics (medication use, population) and size of the individual databases. However, for recruiting into a consortium, personal networks are important. Interestingly, cost was considered less important.

Timeframes were described from the start of protocol writing to the start of data analysis. While the majority took between 4 - 12 months, it may be that considerable time was taken to reach the protocol writing stage, and these timelines may not reflect the total time a study takes to get results.

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The number of researchers reporting governance/ethical issues may reflect researchers knowing the ethical/governance issues per country in advance and hence not experiencing issues during the project. For instance, in CARING it was known beforehand that Danish data cannot leave the country and hence pooling of data needs to take place in Denmark. Several steps were therefore needed to be able to pool the data.

The FP7 funded projects included in the present analysis have demonstrated the great potential of the combination of multiple healthcare databases for drug safety studies on an international level. The results have been shown as key to the EMA's strategy of using of independent research to support regulatory decision-making.[xiii]

As the period of the relevant FP7 specific programme closed at the end of 2013, it is observed that the approach of funding around individual projects has taken place in the absence of a longer term strategy around how the expertise and resources involved in individual projects might be captured and utilised as platforms to conduct research involving multiple databases as new safety concerns arise in the future. Similarly, while informal networking and experience have been facilitated by the development of ENCePP, there is an unparalleled opportunity to address the sustainability of the existing projects. This may result in some of the learning being lost, so representing a missed opportunity to significantly improve timeliness and efficiencies in conducting multi-source database studies throughout the EU.

Finally, the results of the survey support the importance of the development and dissemination of standard methods and tools for the conduct of multi-source studies.

In conclusion, the survey documents an active research arena in multi-database research in Europe as a result of active public funding and an increasing number of research collaborations across countries and research groups. As more studies are completed, the impact of different designs, coordination and data integration approaches will continue to advance the field. ENCePP is well placed to feed new and emerging observations and learnings into guidance e.g. the ENCePP Guide on Methodological Standards in Pharmacoepidemiology and the ENCePP Code of Conduct for governance issues.

6. Authors and acknowledgements

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