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MEETING REPORT

Healthcare Database Networks for Drug Regulatory Policies: International Workshop on the Canadian, US and Spanish Experience and Future Steps for Italy

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1 Introduction

Healthcare databases are very useful sources of post-marketing real-world information, generating evidence on drug use, safety and effectiveness, particularly in populations where such information may be lacking in pre-clinical studies, such as paediatric and geriatric populations. However, healthcare databases can also provide pre-marketing information by measuring the burden of disease, identifying unmet clinical needs and estimating the number of patients potentially eligible for innovative and costly treatment. Whether in a pre- or post-marketing setting, these data sources can provide regulatory agencies with evidence that can inform the development/implementation of regulatory interventions and answer questions of high, and often urgent, public health interest. In April 2019, the Italian Drug Agency (Agenzia Italiana del Farmaco) organised a workshop on the role of healthcare databases in supporting drug regulatory agencies in their pre- and post-marketing regulatory activities. The experiences of the USA, Canada, Spain and Italy in this context were presented.

The workshop brought together key experts in healthcare data networks, who presented the different legislative backgrounds in their countries as well as the different data utilisation strategies and governance approaches that were used to create such networks in close collaboration with respective regulatory agencies. The experiences of international experts can also provide insight into potential future steps for the creation of a stable database network in Italy that can provide accurate and rapid answers to public health questions. The Director General of the Italian Health Agency, Luca Li Bassi, opened the workshop, which was moderated by Francesco Trotta (Italian Medicines Agency) and Francesca Menniti-Ippolito (Italian National Health Institute). The workshop consisted of four talks, which were all given by speakers involved in the creation and use of database networks from their inception onward. Jeffrey Brown (Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, USA) provided a detailed overview of the origins of the Sentinel network in the USA; Samy Suissa (McGill University, Canada) introduced the Canadian Network for Observational Drug Effect Studies (CNODES), a Canadian nationwide network of

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claims databases; and Miguel Gil (Spanish Agency of Medicines and Medical Devices, Spain) described the BIFAP (Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria) general practice database. A description of these networks is found in Electronic Supplementary Material 1. Gianluca Trifirò (University of Messina, Italy) provided a detailed description of the scientific contribution of the Italian European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) node, a network of Italian data providers and experts in pharmacoepidemiology, pharmacovigilance and public health.

2 Sentinel

Dr Brown explained that the US Food and Drug Administration (FDA) Sentinel System is a distributed data system containing data on over 100 million persons, where each data partner retains their own data but converts it into a common data model, such that that each data partner can run a data analysis code that was sent to them after being developed and tested by the coordinating centre [1]. Each data partner maintains physical and operational control over their data, providing a high level of privacy for patients. Sentinel was mandated by the FDA, which was legally required to develop such a system. He noted that the Sentinel Initiative is a stable database network, i.e. it is developed as a long-term database network able to respond to a large number of FDA questions per year rather than as a specific project-based network. The Sentinel Initiative is funded via a renewable contract that is open for competition at least every 5 years. The Sentinel Operations Centre team coordinates 18 data partners who are contracted to provide a specific set of services, as well as other partners who are not contracted but can offer expertise. Partner selection was carried out through professional networks rather than a formal search for collaborators. The minimum ongoing costs of maintaining the Sentinel System are approximately $US12 million per year; however, with additional activities requested by the FDA (e.g. expansion of the common data model, methods development and query tool development), they can amount to more than $US20 million per year, depending on the number and type of queries run. The Sentinel Data Partners are willing and able to use their curated Sentinel data for other purposes through separate collaborations either directly with the Data Partners or through the Sentinel Operations Centre at Harvard Pilgrim. Several US-based networks and individual studies use the Sentinel data through agreement with the Sentinel Data Partners.

3 Canadian Network for Observational Drug Effect Studies (CNODES)

Professor Suissa described CNODES, which was founded in 2011 with the support of Health Canada, through the Drug Safety and Effectiveness Network (DSEN) and the Canadian Institutes of Health Research (CIHR), although not by act of government like Sentinel [2]. Unlike Sentinel, CNODES uses a distributed database network that currently does not employ a common data model, but where a common protocol is applied to all the claims databases in the Canadian provinces. A meta-analysis of the study results is then conducted, pooling results, not data, from each study. This approach was used because of data protection and ownership issues. Canadian provinces have their own healthcare policies, so drug availability may vary from province to province. In addition to Canadian data from each province, CNODES also uses non-Canadian data such as Clinical Practice Research Datalink (CPRD), a UK nationwide electronic health records (EHRs) database and the US MarketScan® claims database (IBM Corp., Ann Arbor, MI, USA), to conduct research. The total estimated population covered by all CNODES databases is over 100 million persons. CNODES is currently piloting a common data model project across several Canadian databases to develop the possibility of more rapidly investigating drug utilisation and safety.

CNODES places much emphasis on pharmacoepidemiology training for researchers and programmers. This is of importance as the level of specific expertise in pharmacoepidemiology methods and database analysis may not be the same among all the provinces. CNODES has so far provided real-world evidence that has led to regulatory actions in knowledge translation on product characteristics and usage. The initial financial investment to launch CNODES was 3.5 Canadian dollars per year. Similar to Sentinel, the creation of CNODES was strongly based on personal and professional contacts. The mandate of CNODES must be renewed every 5 years.

4 Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria (BIFAP)

In contrast to Sentinel and CNODES, BIFAP consists of EHRs from primary care rather than claims. Dr Gil described how BIFAP was launched in 2003 and currently contains data on nine of the 17 autonomous Spanish regions for a total population of approximately 12 million persons [3]. Although it has the full financial support of the Spanish Drug and Medical Devices Agency as well as of the major primary care scientific societies in Spain, it was not mandated by law as in the USA. Healthcare data are sent by the data managers of the participating autonomous regions to the BIFAP coordinating centre, which pools the data into a single database. There is significant heterogeneity among the data from the individual regions data, which are harmonized by the coordinating centre into a common data model. Like CNODES and Sentinel, the data in BIFAP are mainly used for public health purposes by the national drug agency but can also be used for independent research by other non-commercial entities. Unlike Sentinel, BIFAP data are made available to researchers, conditional to protocol approval, at no cost to researchers. BIFAP has been used extensively to support regulatory activities by conducting routine pharmacovigilance, post-authorisation safety studies and evaluating the impact of regulatory actions. Additional informatics platforms are also available for BIFAP users, such as a drug utilisation query tool known as BIFAP Express, which allows the quick generation of descriptive data on drug use. BIFAP Express results cannot be published without prior notification to the coordinating centre. Activity tracking tools have been built into this system to track users' activity, overcoming this issue and regulating the use of public resources.

5 Italian European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Nodes

Professor Trifirò described the large volume of healthcare data available in Italy, including the national adverse drug reaction spontaneous reporting database, nationwide general practitioner and family paediatrician EHRs, regional claims databases and several drug or disease registries [4]. The first Italian database study leading to major regulatory actions concerned ganglioside use, dating back to the early 1990s [5]. Several Italian multiple-database networks have been created in recent years [6]; however, these database networks tend to be project-based and focused on a specific research area, rather than long-term stable networks that can be used to investigate any type of public health question. Like the Sentinel Initiative and CNODES, these Italian database networks were often born out of professional networks rather than a formal search for scientific partners. Over time, the Italian node of ENCePP became consolidated, with a large number of research centres joining the network from all over Italy. It was emphasised that the creation of database networks in Italy should evolve from project-based networks to stable long-term database networks that can be used systematically to answer the Italian Drug Agency's public health questions.

6 Discussion

Dr Antonio Addis (Lazio Regional Health Service, Italy) closed the workshop with some reflections. He noted that the usefulness of the workshop was to allow the Italian Drug Agency to learn from the experience of strategies that were successful in creating data networks, which, although very different, all managed to support the needs of the national regulatory agencies. He highlighted the importance of a practical and judicious strategy to create a data network, of consistently applying robust methods and of developing good governance. He also emphasised the importance that regulators see pharmacoepidemiology as a foundation for evidence-based public health policies. Another reason why drug agencies and other public Health entities should give more importance to the creation and use of a long-term database network, i.e. not a project-based network, because these networks have the capacity to provide rapid answers to urgent public health questions. Such research questions often concern the post-marketing setting, including addressing information gaps concerning drugs marketed through accelerated approval pathways, where pre-marketing safety data are often lacking or very limited. Another type of support that a database network in Italy could also offer in the post-marketing setting is measuring the impact of risk-minimisation measures. Evaluating the impact of public health interventions is of increasing interest, as shown by the fact that the European Medicines Agency's pharmacovigilance regulation/directive adopted in 2012 contains a provision giving the agency the mandate to request and obtain information on the impact of risk-minimisation measures implemented by the marketing authorisation holder. The role of electronic healthcare data is also clear in the pre-marketing setting, where a regulator may request impartial real-world evidence on several aspects of innovative and costly drugs, such as the size of the population eligible for treatment, clinical outcomes of patients treated with current standards of care and other information that can influence cost negotiations and even the decision to grant the marketing authorisation.

Dr Addis also mentioned that the Italian Drug Agency can provide funds to promote research on drug use, safety, effectiveness and cost effectiveness, so the financial means to support the creation of a long-term database network may already be available. Dr Addis concluded by mentioning that all the different database networks discussed in the workshop, i.e. Sentinel, CNODES and BIFAP, have similar challenges, including the need to develop data access and sharing policies acceptable to all stakeholders. However, the success of these networks is very encouraging regarding the potential to establish a stable Italian database network in the near future. This is particularly important since Italian observational data could be leveraged much more effectively for public health purposes than it currently is. All speakers agreed that the use of EHRs/claims collected through these data networks is very useful for a better understanding of treatment safety and effectiveness in Italy, as in other countries [7, 8].

The development of a consolidated healthcare data network in Italy might initially be best modelled on the experience of CNODES in the short-term, i.e. implementing a common protocol in a distributed database network, with local data analysis and central pooling of results. This approach has the advantage of being rapidly implementable as it overcomes data ownership issues and does not require a specialised coordinating centre to prepare code for local implementation and run the analyses centrally. The approach used by the Sentinel Initiative, i.e. a distributed data network with a common data model, may be more suitable as a long-term strategy, using a generalised common data model with data analyses carried out by a specialised coordinating centre. Italian multi-database networks have mostly been carried out based on sharing and central pooling of patient-level data, which does not appear to be a feasible approach anymore in light of updated European data privacy regulations. The Italian ENCePP network can obtain the resources needed to develop the infrastructure and organisational systems bridging data partners and the central coordinating hub, as well as the expertise to found a coordinator centre itself. The BIFAP system also uses approaches that can be very useful in Italy, notably the BIFAP Express platform to allow the rapid generation of summary data on drug use, which may be of interest for researchers and healthcare professionals.

Several important recommendations for the future of data networks in Italy emerged from the workshop:

- Initial strategies to create a data network might involve a small number of regions, coordinated by trusted partners. An Italian version of Mini-Sentinel, using Lazio region data for near real-time monitoring of drug use and safety, has already been implemented [9].
- It is important to have key experts and opinion leaders supporting the project in its initial phases.
- Early efforts to create a database network should focus on answering simple rather than complex questions, such as descriptive analyses (e.g. describing demographic and clinical characteristics of patients exposed to specific medications) rather than carrying out comparative analyses using complex designs and statistical methods for adjustment and confounder control.
- The support and understanding of the competent authority is essential in giving the database network the time to reach their expectations and the freedom to independently develop the required governance (i.e. data policies, working procedures, partner selection, etc.).
- Judicious and far-sighted governance is essential to the success of a stable database network.
- The possibility of fixed-term contracts for database network coordination means that the competent authority can renew its mandate based on the performance of the network.
- A strong and productive database network can be leveraged best if all persons who conduct research are trained regularly.
- The impact of the database network in terms of using its results to make public health decisions should be documented. It would be very useful if such networks would make the informatics tools developed publically available, as done by the Sentinel Initiative. It would also be important to make the research products of the networks publically available.

7 Conclusion

There are several approaches to creating and using a network of databases. Such approaches include converting all the loco-regional data into a common data model or using a common protocol approach with a distributed database network. The common element between existing data networks in the USA, Canada and Spain are that they all serve to answer the public health questions of the national competent authority. Italy has much potential to create a stable network of databases, because of the large amount of electronic healthcare data available and the national expertise developed thus far. A stronger alliance between the Italian regulatory entity and research institutions is essential to leverage Italian data more effectively for public health purposes.

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Compliance with Ethical Standards

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Conflict of interest Antonio Addis, Janet Sultana, Federica Milozzi, Francesca Menniti-Ippolito, Francesco Trotta, Miguel Gil and Jeffrey S. Brown have no conflicts of interest to declare. Samy Suissa has received research funding from, participated in advisory board meetings for or acted as a speaker for Bayer, Boehringer-Ingelheim, Bristol-Myers-Squibb and Novartis. Gianluca Trifirò' has attended advisory boards in recent years on topics not related to this paper and organised by Sandoz, Hospira, Sanofi, Biogen, Ibsen and Shire and is a consultant for Otsuka. He is the principal investigator of observational studies funded by several pharmaceutical companies (e.g. Amgen, AstraZeneca, Daiichi Sankyo, IBSA) to the University of Messina as well as being the scientific coordinator of the Master's programme "Pharmacovigilance, pharmacoepidemiology and pharmacoeconomics: real-world data evaluations" at the University of Messina, which is partly funded by several pharmaceutical companies.

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