INDEPENDENT DATA SOURCES OF USE IN PHARMACOVIGILANCE.- THE SPANISH EXPERIENCE

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The Spanish Agency on Medicines and Medical Devices legislation states explicitly the need to support and generate data related to the safety of medicines. The AEMS therefore, financially supports specific programs run by independent researches and owns a data source, BIFAP for performing specific studies.

BIFAP

1. Description of the data source

BIFAP (Spanish database for pharmacoepidemiological research in primary care) database (www.bifap.org) is a longitudinal population-based database of anonymized computer based medical records of general practitioners (GPs) and pediatritians throughout Spain (Salvador-Rosa A, 2002). BIFAP is a non-profit research project, kept by the Spanish Medicines Agency (AEMPS) -a public agency belonging to the Spanish Department of Health- in collaboration with 9 autonomous regions of Spain. BIFAP was launched in 2003, including anonymized information registered in the primary care electronic medical records (EMR) after the year 2001, when the EMR were fully implemented throughout Spain. Retrospective clinical information previous to EMRs disposal is also available as registered by the GP.

In the Spanish National Health Service (NHS) primary care physicians, either GPs or pediatritians, act as gatekeepers for and receiver of information from primary and secondary care. In addition, most drug prescriptions are driven at primary care level. The whole population is entitled to be registered with a local general practitioner and almost all population are registered with a GP/Pediatritian under the Spanish NHS. Given this, BIFAP database includes all the data elements required to perform most of pharmacoepidemiological studies.

BIFAP database includes anonymized information provided by 2653 GPs and pediatritians collaborating with the project. The total number of patients usable for research in BIFAP database is 4.8 million representing 25.9 million person-years of follow-up. This is the cumulative amount of patients who have ever been part of the dynamic cohort of patients who have ever been registered. The records of patients leaving the cohort –either for being transfer to new practices or GPs stopping collaboration- remain in the database and are available for retrospective studies. BIFAP dataset is comparable with the Spanish population with respect to its age and sex distribution covering 20.1% of total Spanish population.

Information in BIFAP database is updated yearly and contains coded and anonymous data on patient demographics, prescription details, clinical events, specialist referrals, laboratory test results. Prescription data information in BIFAP includes product name, quantity dispensed, dosage regimens, strength and indication. Prescriptions are coded according to the Anatomical Therapeutic Chemical (ATC) classification scheme recommended by the WHO. The system complies with European Union guidelines on the use of medical research and has been proven valid for pharmaco-epidemiological research.

2. The data source utility in the pharmacovigilance context
BIFAP database is fully integrated in the AEMPS roles and activities as an useful tool for postmarketing regulatory decision-making and for generating scientific evidence on drug related issues. This is performed by supporting routine pharmacovigilance; performing pharmacoepidemiological studies; assessing drug use patterns of medicines and by evaluating the effectiveness of risk minimisation activities.

Examples of studies performed in BIFAP to support pharmacovigilance activities in the above mentioned areas are the following:

- **Signal strengthening:** Information from the spontaneous reporting system raised the hypothesis of an increased risk of meningioma in patients treated with high doses of cyproterone acetate (CPA). The summary of product characteristics was modified accordingly including a formal contraindication of these formulations in patients with meningioma or a history of meningioma. A retrospective cohort study performed in BIFAP showed that patients exposed to high dose CPA had an increased risk of meningioma of 11.4 (95% CI 4.3, 30.8) as compared with non-users after adjusting for age and sex (Gil M, 2011).

- **Risk assessment:** A significant number of studies to evaluate drug adverse events have been performed in BIFAP producing relevant information for regulatory decision making including the following: A program of studies to evaluate the cardiovascular risk of patients exposed to several drugs including: NSAIDs and non-narcotic analgesics (de Abajo FJ, 2014; Garcia-Poza P, 2015, allopurinol (de Abajo FJ 2015), antidepressant drugs (results not published); risk of typical and atypical fractures in patients exposed to oral bisphosphonates (Erviti J, 2012) or pneumonia risk in patients exposed to IBP (doctoral thesis), etc.

- **Drug utilization studies:** these studies are performed systematically within referrals triggered by pharmacovigilance data in order to gather knowledge on how the medicines involved in the referral are used and managed in Spain. This information is considered very useful for measuring the impact of risk minimisation measures and tailor communications. Besides this regular activity, specific studies are performed ad-hoc: characterization of patients using standard or intensive lipid lowering therapy with statins for primary and secondary prevention (Macias D, 2013; Macias D, 2015); Trend patterns of drug use in patients with Alzheimer disease (Bonis J, 2013); Trend patterns in benzodiazepine drug use in seven European electronic healthcare databases (Huerta C, 2015) etc.

- **Evaluation of the impact of risk minimization activities:** ad-hoc studies are being performed. As examples, a study to evaluate the impact of risk minimization activities for calcineurin inhibitors and the impact of tetrazepam withdrawal (results from both were presented at PRAC meetings).

In addition, BIFAP has actively participated in multiple international collaborative projects with other datasources worldwide in the context of European commission work programs. This projects are mainly aimed to: address safety issues (i.e SAFEGUARD; www.safeguard-diabetes.org); improve the information available on benefit-risk of marketed vaccines (ADVANCE; www.advance-vaccines.eu) or to develop, test and disseminate methodological standards for the design, conduct and analysis of pharmacoepidemiological studies applicable to different safety issues and using different data sources (PROTECT; http://www.imi-protect.eu/).

3. **How it is used in Spain and the added value that could be obtained (useful examples, projects etc).**
Beside the use of BIFAP database by AEMPS, this tool is accessible to independent researchers belonging to the Spanish National Health System and researchers from the public sector for performing studies.

In addition, several informatics tools (BIFAP EXPRESS) have been developed for BIFAP collaborators and health authorities of the participant autonomous regions to perform drug utilization studies. BIFAP EXPRESS is an informatic data analysis tool based on pre-aggregated data to perform customize analysis on BIFAP database. BIFAP EXPRESS allows getting almost immediate drug utilization indicators population based at any aggregation level according ATC classification and demographic characteristics (age groups/gender). Several modules have been developed to date including: prevalence drug use module and trends; indication of use and prescribed daily dose.

4. Challenges and limits

The use of secondary databases for pharmacoepidemiological research has a number of advantages mainly related to their larger sample size and their representativeness of routine clinical care that makes possible to study real-world effectiveness and utilization patterns and their availability at relatively low cost and without long delays. Main limitations of this datasources are derived of the data mainly recorded for clinical management purposes and not for research. Consequently, careful consideration of the limitations of the data is needed when conducting the studies and interpreting the results.

Specific considerations when using BIFAP data are the following:

- Uncertain completeness of the data from other level of care (specialist, hospital)
- Uncertain validity of diagnosis data, especially related with the low granularity of the ICPC-2 medical terms dictionary. This is balanced by the richness in clinical notes as free text and access to medical records is available for validation purposes of BIFAP database.
- Radiology and laboratory results may not be entered in all cases (and maybe more likely to be entered if abnormal).
- Limited information on patient-based socioeconomic status.
- Data on drugs given during hospitalization or drugs dispensed over the counter are not available.
- Medical compliance is often not recorded so notation of a prescription does not necessarily mean that the drug was taken.

Future areas of development and main BIFAP challenges include the following:

- Increase the size and representativeness of the database in the different autonomous regions. In this regard currently, the information of the whole population is available for 2 autonomous regions participating in BIFAP.

- Linkage with other health care datasources. Currently BIFAP is a primary care database. Main interest for BIFAP is to link primary care information with other health databases specially hospital and mortality records.

- Harmonization processes of information from different electronic medical records. There are different EMR in the regions participating in BIFAP with different data models. This includes, among others, different medical terms coding systems (ICPC-2, CIE-9), prescription registration characteristics including the progressive implementation of electronic dispensing in Spain allowing to analyze the drug effectively dispensed in the pharmacies, in addition to the prescriptions.
OTHER DATA SOURCES

AEMPS supports the financing of data sources owned by independent researchers mainly from academia or learned societies that could be of value for drug safety. Specific agreements are signed whereby researchers are compromised to send periodic results to AEMPS as well as to give immediate response to any query (ie. based in a new signal). Currently, the following data sources are supported:

- Biobadaser: registry of biologicals in rheumatology. Run by the Spanish Society of Rheumatology (www.ser.es)
- Biobadaderm: registry of biological in dermatology. Run by the Spanish Academia on Dermatology (www.aedv.es)
- Registry on hepatotoxicity (Spanish dili): network of hospitals for the study of idiosyncratic hepatitis. Coordinated by the University of Malaga (www.spanishdili.uma.es)
- Piel en Red (Platform for the Study of Serious Cutaneous Reactions). Coordinated by the University of Alcalá de Henares, Madrid.
References


