

## Establishing an Adverse Drug Reactions Database in Romania: Practical Value

Andreea Maria FĂRCAȘ<sup>1</sup>, Tarfin CHIOREAN<sup>2</sup>, Daniel Corneliu LEUCUȚA<sup>3</sup>, Răzvan CHERECHES<sup>2</sup>, Marius BOJIȚĂ<sup>1</sup>

<sup>1</sup> "Iuliu Hațieganu" University of Medicine and Pharmacy Cluj-Napoca, Drug Information Research Center, 6 Louis Pasteur, 400349 Cluj-Napoca, Romania.

<sup>2</sup> Babeș-Bolyai University, Center for Health Policy and Public Health, 71st G-ral Traian Moșoiu Street, 400132 Cluj-Napoca, Romania.

<sup>3</sup> "Iuliu Hațieganu" University of Medicine and Pharmacy Cluj-Napoca, Department of Medical Informatics and Biostatistics, 6 Louis Pasteur, 400349 Cluj-Napoca, Romania.

E-mails: afarcas@umfcluj.ro; t\_rexdino@yahoo.com; dleucuta@umfcluj.ro; razvan\_chereches@healthpolicy.ro; mbojita@umfcluj.ro

\* Author to whom correspondence should be addressed; Tel.& Fax: +4-0264-430368.

Received: 24 March 2011 / Accepted: 9 June 2011/ Published online: 15 June 2011

### Abstract

*Objectives:* The need to monitor, track, evaluate and properly manage adverse drug reactions (ADRs) in the hospital setting has become a fundamental component of the routine clinical practice and of the healthcare system. Computerized systems are used for such data entry, storage and further analysis with the final goal of avoiding ADRs. This paper describes a database designed for this purpose as part of a pharmacovigilance program in Romania. *Methods and Setting:* Stimulated spontaneous reporting is the method used for the detection of ADRs in two internal medicine departments. The ADRs collection is paper based. The information is further evaluated for various parameters and then the data is entered into the database. In the design of the database we took into consideration some basic requirements for such a database: comfortable user interface with easy access and handling, high level of security, data protection and desired statistics. *Results:* The database was designed in order to include a complete description of ADRs (e.g. causality, preventability, severity, outcome, type of ADR, risk factors, drug interactions). Auxiliary databases such as ICD-10, ATC codes and the MedDRA terminology are being used. The database has been in operation for a year, during which approximately 250 ADR case reports have been evaluated and entered. *Conclusions:* To improve and strengthen the ADRs reporting at a hospital level we developed and populated a computer-based system for standardized collection, evaluation and storage of ADRs that could be further adopted by other academic hospitals that want to keep track of preventable ADRs.

**Keywords:** Adverse drug reactions; Pharmacovigilance program; Database; Hospital setting.

### Introduction

It was emphasized that pharmacovigilance is a clinical specialism essentially concerned with the diagnosis and treatment of patients with adverse drug reactions and the proper study, documentation and reporting of such cases would be a natural part of the hospital setting [1].

Adverse drug reactions (ADRs) are widely recognized as a common problem in hospitalized patients. According to the literature, the incidence of the ADRs leading to hospitalization varies from 1.8% to 12.8% [2-5]. A meta-analysis of observational studies concluded that ADRs related hospital admissions in general population account for 4.1% and subgroup analysis showed that for elderly people the odds of being hospitalized for an ADR is 4 times higher [6]. ADRs can also occur during the hospitalization, affecting up to 19.2% of the patients [7, 8]. In Romania data are limited. A prospective observational study conducted at the University of Medicine and Pharmacy in Cluj-Napoca reported that the overall incidence of serious ADRs in the hospitalized patients was 4.7% [9].

In Western countries computers and information technology have increasingly been adopted to assist the healthcare system, modern and reliable information technology now being used for various purposes: from administrative ones to public health surveillance and research purposes based on the collection of health data, on a routine basis, mainly from hospitals and general practitioners [10, 11].

With respect to postmarketing drug safety surveillance, either large routine data sources are being used for different hypothesis testing studies, either especially designed pharmacovigilance databases. Adverse drug reactions databases such as the ones maintained by the regional or national pharmacovigilance centers or the WHO database (Vigibase) are used for data storage, data screening, data retrieval and analysis. They have permitted the generation of signals in pharmacovigilance and a timely communication of safety issues [12-14].

At a hospital level, the existence of computerized prescription and laboratory results databases has enhanced the possibility for screening and signaling ADRs and drug-drug interactions in hospitalized patients. Hospital-based systems can increase the reporting of known ADRs, but their value for detecting new, unlabelled ADRs is yet unclear. All these programs are mostly meant to prevent medication errors arising from inappropriate prescription [15-17].

In Romania computerization in primary and in secondary care was introduced late, only in the 1990s. Nonetheless, routine hospital patient administration systems are not fully available in many hospitals. Moreover, pharmacovigilance activities are at their very beginning compared to other developed countries. Information on ADRs can only be collected if physicians report through the Spontaneous Reporting System. Unfortunately, even this system is poor, since only 363 ADRs were reported in 2009 at the National Pharmacovigilance Centre [18].

### *Objectives*

In this context and in order to come with new data on ADRs, we aimed at developing a database to record the ADRs collected at a university based Drug Information Research Center (DIRC). The center coordinates a stimulated spontaneous reporting program in two internal medicine departments from two secondary care academic teaching hospitals in (Cluj-Napoca) Romania. Besides strengthening the ADRs reporting at the hospital level, this program and this continuously updated database could serve for systematic analysis of ADRs and they could help identifying common and repetitive patterns of preventable ADRs in hospitalized patients.

### **Methods and Setting**

The stimulated spontaneous reporting program was initiated by DIRC in 2009. All the physicians in the two departments were informed about the program, outlining the ADRs' negative impact, and were asked to report all observed adverse events. In order to ensure that the rate of notifications remains constant, the physicians are regularly reminded about the program in place.

The ADRs' collection is paper based. A specially designed ADR form is filled out by the treating physicians when an adverse event is identified. This form requires for information on age and sex, main reason for hospitalization, active diagnoses, renal and hepatic function, history of alcohol intake, previous ADRs or known allergies, all drugs administered (including self-medication) before and during hospitalization with respective doses and duration of therapy, all available clinical and

biological data, dechallenge and rechallenge, ADR treatment and outcome, and length of hospital stay.

As the proper documentation and study of these reports is part of the pharmacovigilance activities, the ADRs collected, reflecting daily practice, are impartially evaluated by an independent group of trained pharmacists and pharmacologists. The information in the paper form is evaluated for various parameters such as causality, preventability, severity, outcome, type of ADR (as in type A or B), risk factors, drug interactions and other possible causes for the adverse reaction. We define adverse drug reactions according to the World Health Organization definition [19].

In the design of the database we took into consideration the following requirements:

- Complete and accurate description of ADRs
- Easy data access, selection, retrieval and manipulation
- Friendly interface
- High level of security
- Protection from data loss
- Descriptive statistics.

## **Results**

### *Database Structure, Coding and Auxiliary Databases*

The structure of the database, the data entered, coding and the auxiliary databases used are presented in Table 1. In the database design we included all the aspects that characterize an ADR in a certain patient. Preventability of the ADRs is determined using the French scale proposed by Imbs et al. and tested for feasibility [22, 23]. This standardized scale is more detailed than other methods for assessing preventability and includes criteria such as knowledge and communication of the ADR, existence of detectable risk factors for the patient experiencing the ADR, conformation with the recommendations for the administration of the drug, quality of prescription and ADR management. The causes of the ADRs are also rigorously evaluated and classified in order to serve for future analysis as well as for implementing preventive measures.

### *Database Design and Security*

The database was developed under Microsoft SQL Server 2003. Microsoft SQL Server is a Structured Query Language (SQL) based, relational database server. The relational database is the most commonly used database model today. The relational database is made up of logically connected tables (data that has a relation to other data). Using a relational database management system is a good way to improve data integrity, efficiency, retrieval, sorting and filtering, to provide stronger security, and to better share information.

One of the prerequisites of such a database, that involves handling of confidential individual medical data, is a high-level of security and data protection. Moreover, all procedure shall comply with the ethical requirements of medical research. To allow data protection and security, authentication and authorization takes place in several individual points at every application level. Authentication and authorization services are mainly provided by Internet Information Services (IIS), ASP.NET and SQL Server.

In order to secure data against partial or complete data loss, database back-ups are performed. The frequency with which back-ups are performed is determined by the amount of work on the database and by the amount of data entered every month.

Only the DIRC's staff has permission to entry data into the database. The physicians in the program are only allowed to visualize, search and print case reports or statistics on ADRs from the database, but not to modify any data that have been entered.

**Table 1.** The structure of the database, coding and auxiliary databases

Items	Form element	Description (coding, auxiliary databases)
<b><u>Data about the patient</u></b>		
First and last name	Text field	
Age	Text field	
Sex	Combo box	
<b><u>General data at admission</u></b>		
Main reason for hospitalization and all the other active diagnoses	Combo box	3 levels coding according to the International Classification of Diseases (ICD-10) [20]
Description of the admission symptomatology of the patient	Text field	
Predisposing factors	Radio button and text field	Renal and hepatic insufficiency, history of alcohol intake, tobacco use and previous drug allergy
Drugs administered before the appearance of the ADR	Combo box Text field	Auxiliary connected database with the drugs authorized in Romania (International Nonproprietary Names - INN and brand name); Anatomical Therapeutic and Chemical (ATC) code [21]; Doses/ route of administration/ indication/ start and end date of the treatment/ self-medication
All available clinical and biological data	Text field	Data followed up from admission, during the hospital stay and at discharge are also entered into the database
<b><u>Adverse drug reaction (ADR)</u></b>		
Adverse drug reaction	Combo box	MedDRA terminology (3 levels coding: SOC/ HLT/ PT)
Description of ADR	Text field	
Time of onset and end date	Text field	
Suspected drug	Combo box	INN/ brand name/ATC code
<b><u>Characterization of the adverse drug reaction</u></b>		
Seriousness	Combo box	According to the international definition [19]
Severity	Combo box	Mild/ moderate/ severe
Type	Combo box	Type A/ type B
Duration of the ADR	Combo box	Less than a day/ more than a day/ more than a week
Outcome	Combo box	Recovery without sequelae/ recovery with sequelae/ death due to the adverse drug reaction
Causality assessment	Combo box	Naranjo or/and a modification of the Karch-Lasagna algorithm; Scores for each criteria evaluated and the causality term are entered
Preventability	Combo box	Definitely not preventable/ potentially preventable/ definitely preventable according to the French scale proposed by Imbs et al.
<b><u>The causes of the ADR</u></b>		
Contraindication for administration	Check-box and text field	Text field for supplemental observations
Inappropriate medication	Check-box and text field	Inappropriate medication use in elderly population accordingly to Beers criteria [24]; supplemental observations
Wrong dose	Check-box and text field	Text field for supplemental observations
Wrong route of administration	Check-box and text field	Text field for supplemental observations
Drug interactions	Check-box and text field	Severity of the interaction described; supplemental observations
Inadequate therapy monitoring	Check-box and text field	Text field for supplemental observations
Treatment non-adherence	Check-box and text field	Text field for supplemental observations

*Database Queries. Analysis of ADRs and Statistics*

The database has been in operation for a year, during which approximately 250 ADR case reports have been evaluated and entered. A user needs around 30 minutes to enter a case, depending on the complexity of the data. Once the data have been entered different queries can be performed. Queries are made according to our developed routines for ADRs analysis.

The information entered can be searched and retrieved for additional analysis filtered by ADR (System Organ Class and Preferred term), by suspected drug, by severity, outcome, preventability, seriousness or a combination of these parameters. Also, the different causes of the ADRs can be filtered by type (e.g. contraindication, wrong dose, wrong route, drug interaction) for future in-depth evaluation.

The database offers descriptive statistics (such as frequencies, means and percentiles) on the following key parameters: sex, age, number of days of hospitalization, risk factors, main reason for the hospitalization, active diagnoses, previous therapy, ADR and drug suspected, seriousness, type, severity, duration, outcome and preventability of the ADR. The causes for ADRs can also be quantified. The statistics can be performed differentially, taking into account the provenience of the data (which internal ward), date of the hospitalization interval, sex, and age interval, ADR leading to hospitalization or ADR occurring during the hospitalization. The application generates reports containing the desired statistics and also charts for the data. These reports can be saved in popular file formats (PDF or EXCEL).

## **Discussion**

Taking into account the benefits of a database designed for adverse drug reactions analysis and prevention, we developed and populated a computer-based system for standardized collection, evaluation and storage of ADRs [14-16, 25]. The database covers general adult (> 18 years) and elderly population and provides a comprehensive and detailed documentation of serious, but also minor ADRs. All available adverse drug reaction related medical data are recorded in order to provide secure, real-time, patient-centric information needed to clinical decision-making and ADRs avoiding by providing the easy access to a patient's medical record and to information on previous adverse events reports.

Few such databases, created especially for ADRs evaluation and storage, allowing for a proactive approach, are described in the literature [15, 25, 26]. Most of the databases described are either databases with clinical records from primary care or administrative claims databases, (e.g. GPRD, Saskatchewan, Medicaid, Group Health Cooperative of Puget Sound) or prescription databases [17, 27-29]. These databases meet the need for conducting post-marketing surveillance studies, but are lacking information on drugs taken intermittently for symptom relief, over-the-counter drugs, and sometimes, outcomes. Comparing to these databases, one advantage of our database is that, by using a prospective method for the collection of ADRs (the stimulated spontaneous reporting system), the data collected reflects daily practice, including off-label use of drugs and self-medication, allowing also for drug utilization and preventability studies. Another added value of our system is that the prospective approach allows for a timely feed-back with the treating physicians, either for collection of all necessary information for the quality and the completeness of data, or for assisting the clinicians in the management of the suspected ADRs. A limitation of our database, compared to the above mentioned ones, would be the low number of ADRs collected and entered in the database, which will not allow for the observation of rare events.

Another approach for identifying and characterizing ADRs in the hospital setting would be the use of special alerts provided by the hospital information system on medication stop orders, use of antidotes, and certain abnormal laboratory values. This kind of systems, if used correctly, can alert physicians to the existence of ADRs. However, the use of abnormal laboratory results may potentially predict only 29% of ADRs and the alerts need further evaluation and reporting [30, 31]. Of course, a drawback of the stimulated spontaneous reporting system used for ADRs collection

for our database would be a certain level of under-reporting which might lead also to a low number of ADRs detected.

The database we developed could be further adopted by other academic hospitals that want to keep track of preventable ADRs that may lead to prolonged hospitalization and increased hospital costs. By proper and impartial evaluation of ADR case reports, the database can be used for drug safety research, allowing the retrieval of information of interest.

## Conclusions

We developed an adverse drug reaction data storing and management system that allows for the retrieval of data for regular evaluation of patterns of ADRs and further dissemination with the final goal of achieving, on the one hand, better individual care in the hospital setting and, on the other hand, for conducting advanced research. Altogether, the ADRs database developed represents a further step into pharmacovigilance in a country where little has been done in this field.

## Acknowledgements

This project was supported by a research grant financed by the Romanian Ministry of Education, Research and Innovation - PNII 12-102/2008. All the work described was independent of the funder.

## Conflicts of interest

There are no conflicts of interest to declare.

## References

1. Meyboom RHB, Egberts ACG, Gribnau FWJ, Hekster YA. Pharmacovigilance in Perspectives. *Drug Saf* 1999;21(6):429-447.
2. van der Hooft CS, Sturkenboom CJM, van Groothest K, Kingma HJ, Stricker HC. Adverse Drug Reactions-Related Hospitalizations. A Nationwide Study in the Netherlands. *Drug Saf* 2006;29(2):161-168.
3. Pouyanne P, Haramburu F, Imbs JL, Bégaud B. Admissions to hospital caused by adverse drug reactions: cross sectional incidence study. *BMJ* 2000;320:1036.
4. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ et al. Adverse drug reaction as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004;329:15-19.
5. Alexpoulou A, Dourakis SY, Mantzoukis D, Pitsariotis T, Kandyli A, Deutsch M, et al. Adverse drug reactions as a cause of hospital admissions: A 6-month experience in a single center in Greece. *Eur J Int Med* 2008;19:505-510.
6. Beijer HJM, Blaeij CJ. Hospitalizations caused by adverse drug reactions: a meta-analysis of observational studies. *Pharm World Sci* 2002;24(2):46-54.
7. Lagnaoui R, Moore N, Fach J, Longy-Boursier M, Bégaud B. Adverse drug reactions in a department of systemic disease-oriented internal medicine: prevalence, incidence, direct costs and avoidability. *Eur J of Clin Pharmacol* 2000;55:181-186.
8. Davies EC, Green CF, Mottram DR, Pirmohamed M. Adverse drug reactions in hospital in-patients: a pilot study. *J Clin Pharm Ther* 2006;31:335-341.

9. Farcas A, Sinpetrean A, Mogosan C, Palage M, Vostinaru O, Bojita M, Dumitrascu D. Adverse drug reactions detected by stimulated spontaneous reporting in an internal medicine department in Romania. *Eur J Intern Med* 2010;21(5):453-457.
10. Curie CJ, MacDonald TM. Use of Routine Healthcare Data in Safe and Cost-Effective Drug Use. *Drg Saf* 2000;22(2):97-102.
11. Wood L, Martinez C. The General Practice Research Database. Role in Pharmacovigilance. *Drug Saf* 2004;27(12):871-881.
12. Harmark L, van Groothest AC. Pharmacovigilance: methods, recent developments and future perspectives. *Eur J Clin Pharmacol* 2008;64:743-752.
13. Olsson S. The Role of the WHO Programme on International Drug Monitoring in Coordinating Worldwide safety Efforts. *Drg Saf* 1998;19(1):1-10
14. Lindquist M. Data Quality Management in Pharmacovigilance. *Drug Saf* 2004;27(12):857-870.
15. Winterstein AG, Hatton RC, Gonzales-Rothi R, Johns TE, Segal R. Identifying clinically significant preventable adverse drug events through a hospital's database of adverse drug reactions reports. *Am J Health-Syst Pharm* 2002;59:1742-1749.
16. Egger T, Dormann H, Ahne G, Runge U, Neubert A, Criegee-Rieck M, et al. Identification of Adverse Drug Reactions in Geriatric Inpatients Using a Computerized Drug Database. *Drugs Aging* 2003;20(10):769-776.
17. Gaus W, Westendorf J, Diebow R, Kieser M. Identification of Adverse Drug Reactions by Evaluation of a Prescription Database, Demonstrated for "Risk of Bleeding". *Methods Inf Med* 2005;5:697-703.
18. National Medicine Agency. Informative Bulletin No.2/2010 [Internet]. [cited 2011 February 16]. Available from: URL: [http://www.anm.ro/html/buletin\\_informativ.html](http://www.anm.ro/html/buletin_informativ.html)
19. International Conference on Harmonisation (ICH). ICH topic E2a: clinical safety data management: definitions and standards for expedited reporting; 1994 [Internet]. [cited 2011 February 16]. Available from: URL: <http://www.ich.org/LOB/media/MEDIA436.pdf>
20. World Health Organization. Programme and projects: classifications [Internet]. [cited 2011 February 16]. Available from: URL: <http://www.who.int/classifications/icd/en/index.html>
21. Anatomical therapeutic chemical (ATC) classification index. Geneva: WHO Collaborating Center for Drug Statistics Methodology; 1992.
22. Imbs JL, Pletan Y, Spriet A. Evaluation de la iatrogénèse médicamenteuse évitable: méthodologie. *Thérapie* 1998;53:365-370.
23. Olivier P, Boulbes O, Tubery M, Lauque D, Montastruc JL, Lapeyre-Mestre M. Assessing the feasibility of using an adverse drug reaction preventability scale in clinical practice. *Drug Saf* 2002;25(14):1035-1044.
24. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *Arch Intern Med* 2003;163:2716-2724.
25. Jose J, Jimmy B, Rao PGM. A Computerized Database for Adverse Drug Reactions. Strengthening a Hospital-Based Pharmacovigilance Programme in India. *Drug Saf* 2008;31(12):1063-1067.
26. Chicano PV, Planells C, Escriva J. Programa BDRAM: gestion informatica de las reacciones adversas a medicamentos. *Farm Hosp* 1996;20(3):173-179.
27. Downey W, Beck P, McNutt M, Stang MR, Osei W, Nichol J (2000) Health databases in Saskatchewan. In: Strom BL, ed., *Pharmacoepidemiology*, 3rd edn. New York: Wiley, pp. 325-46.
28. Carson JL, Ray WA, Strom BL (2000) Medicaid databases. In: Strom BL, ed., *Pharmacoepidemiology*. 3rd edn. New York: Wiley, pp. 307-24.

29. Saunders KW, Davis RL, Stergachis A (2000) Group Health Cooperative of Puget Sound. In: Strom BL, ed., *Pharmacoepidemiology*, 3rd edn. New York: Wiley, pp. 247-62.
30. Azaz-Livishits T, Levy M, Sadan B, Shalit M, Geisslinger G, Brune K. Computerized surveillance of adverse drug reactions in hospital: pilot study. *Br J Clin Pharmacol* 1998;45:309-314.
31. Tegeder I, Levy M, Muth-Selbach U, Oelkers R, Neumann F, Dormann H, et al. Retrospective analysis of the frequency and recognition of adverse drug reactions by means of automatically recorded laboratory signals. *Br J Clin Pharmacol* 1999;47:557-564.