# THE ROMANIAN PERSPECTIVE ON RARE DISEASE REGISTRY

**LĂCRĂMIOARA AURELIA BRÎNDUȘE[1], DANA GALIETA MINCĂ[2]**

[1,2] *"Carol Davila" University of Medicine and Pharmacy Bucharest*

***Keywords:*** *rare diseases, registry, patient registration, common data elements*

***Abstract:*** *The rare disease registries were recognized by the European Commission as one of the priorities of the health system in the European Union, as they constitute the necessary foundation for the development of scientific research in this domain. The development of a rare disease registry in Romania has the purpose to carry out a systematic procedure of gathering rare disease cases in order to supervise the epidemiological indicators (incidence, prevalence, mortality, burden of diseases, costs, quality of life etc.). The Romanian rare disease registry will be able to create a connection between the patients with rare diseases, their families and the stakeholders, and to contribute to the understanding of the natural history, the evolution, the risks and the outcomes of a specific disease. A genetic, molecular, orphan drugs, and medical devices research can be developed with the help of the patients included in the registry, and the epidemiological evaluation of morbidity will contribute to health-planning and the development of various policies.*

## INTRODUCTION

In the countries of the European Union, any disease affecting less than five people in 10 000 is considered rare. Most patients suffer from even rarer diseases affecting one person in 100 000 or more.(1,2) Nearly 80% of the rare diseases are genetic, and half of the patients with rare diseases are children. Almost 50% of rare diseases do not have a specific foundation supporting or researching their disease.(3) The medical and social impact of rare diseases is recognized, and in the last years there has been an increase in the attention dedicated to the research of these diseases. One of the methods necessary to expedite the research in this domain is the establishment of a rare disease registry.(4) The Registry should not be viewed as a simple database, but as a systematic data collection programme.(5) The rare disease registries were recognized by the European Commission as one of the priorities of the health system in the European Union. This particular importance given to the rare disease registry derives from the fact that these constitute the foundation for the development of scientific research regarding new specific treatments (orphan drugs), the improvement of the quality of life for the patients with rare diseases by providing adequate healthcare, as well as the planning of health services.(5,6) The main types of registries are: population – based registries (contain data about patients with a certain disease or a group of diseases from a well-defined population, and have a significant interest for epidemiology and public health) and hospital-based registries (contain data about all the patients diagnosed and treated for a certain condition inside a sanitary institution, have an important relevancy for the clinical activity and for the administration of the hospital and at the same time can constitute the nucleus for the development of a population registry). (8)

In Romania, the development of a national rare disease registry was included in the 2010-2014 national health plan for the previously mentioned diseases, even since 2009, but it has not been initiated yet.(7) There are two national registries for two types of illnesses (The Romanian biliary atresia registry, a national and public registry and The Romanian cystic fibrosis patient registry, a non-profit private registry which contributes to the EUROCARE CF), but the potential of these registries is limited.(8)

## PURPOSE

The main goal of the study is to develop a model of the Romanian rare disease registry. The objectives of the study are: (1) to establish the registry life cycle, (2) to define the aim of the rare disease registry, (3) to develop a common data set for the registry.

## MATERIALS AND METHODS

Based on the review of the relevant literature, this article started by defining the concept of rare disease registries and the description of different types of registry. An automated literature search was done using the Medline databases. We used the following text words and MeSH headings in this search: "patient registry," "registries," "common data collection", "rare disease" and combinations of these terms. The automated search spanned the years from 2000 to 2014. In order to complete this search we carried out a manual search by using the bibliographical sources of the scientific articles that we found, based on the reputation of the authors and the time when the article was published. We supplemented the research of relevant literature by searching on the internet the same notions, without limiting ourselves to the medical websites and to certain periods of time.

## RESULTS

A registry constitutes an organized system which gathers, stocks, recovers, analyses, and spreads the information regarding the people who suffer from a certain disease or condition (e.g. risk factor) in order to avoid the emergence of an event or of certain known factors that could have a negative impact on the patient's health. The Registry should not be viewed as a simple database, but as a systematic data collection program.(9) The main types of registries are: population – based registries (contain data about patients with a certain disease or a

[1]Corresponding author: Lăcrămioara Aurelia Brînduș, Str. Dr. Leonte Anastasievici, Nr. 3-5, București, România, E-mail: l.brinduse@yahoo.com, Phone: +4021 3180713

Article received on 18.03.2015 and accepted for publication on 26.05.2015
ACTA MEDICA TRANSILVANICA June 2015;20(2):4-7

group of diseases from a well-defined population, and have a significant interest for epidemiology and public health) and hospital-based registries (contain data about all the patients diagnosed and treated for a certain condition inside a sanitary institution, have an important relevancy for the clinical activity and for the administration of the hospital and at the same time, it can constitute the nucleus for the development of a population registry).(10)

The main stages in the registry life cycle are: planning, implementation, analysis and evaluation (figure no. 1).

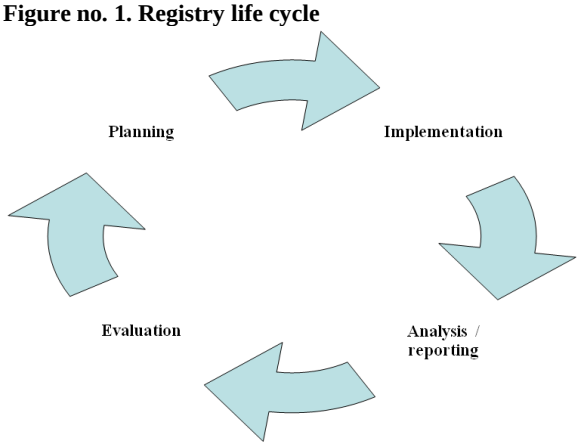
The first stage – planning - includes establishing the purpose and the goals of the registry, and the stakeholders, determining the feasibility of the registry regarding financing, establishing the registry team (knowledge, expertise, and skills are needed to plan and implement a registry), establishing a governance and oversight plan (governance refers to guidance and high-level decision-making, including purpose, funding, execution, and dissemination of information), considering the scope and rigor needed, defining the core data set, patient outcomes, and target population, and developing a study and project protocol.

The implementation stage of the rare disease registry will include creating a team for the registry, collecting data according to the planning and the assurance of quality.

The analysis stage of the results obtained with the help of the registry will take place according to the communication plan and will include the dissemination in publications and scientific events, but also in the mass media in order to promote the results.

The evaluation of the results of the registry will underline the implications for further research.

**Figure no. 1. Registry life cycle**



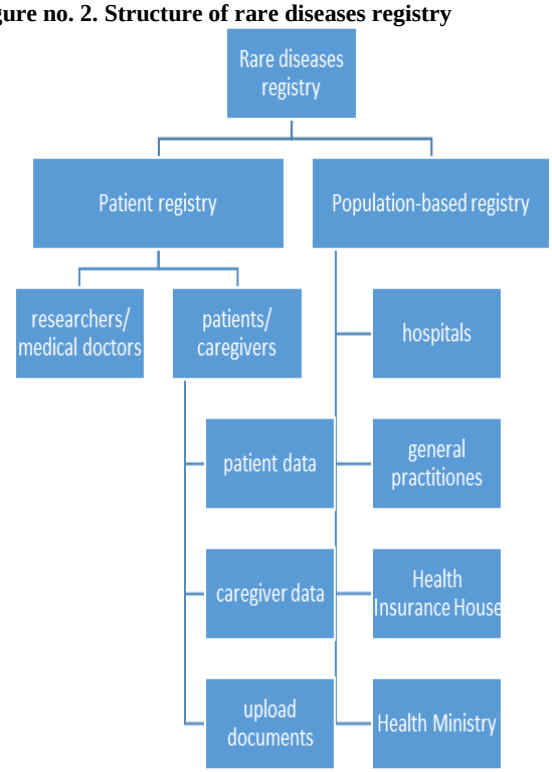

The Romanian Rare Disease Registry's aim is: to carry out a systematic procedure of gathering rare disease cases in order to monitor epidemiological indicators (incidence, prevalence, mortality, burden of diseases, costs, quality of life etc.)

The Romanian Rare Disease Registry objectives are:

1. To connect the rare diseases patients and their families with stakeholders
2. To understand the natural history, the evolution, the risks and the outcomes of a specific disease
3. To develop a patient base for genetic, molecular, orphan drugs, medical devices research
4. To contribute to health-planning and policies development

The Structure of the rare disease registry will be established based on one of the key principles developed by the European Organisation for Rare Diseases – EURORDIS, the National Organisation for Rare Disorders – NORD and the Canadian Organization for Rare Disorders – CORD, thus the registry will have to include at the same time data that were directly communicated by patients with the data released by health care professionals.(11) The registry will have two components: patient registry (voluntary registration for patients by the patient himself and by the caregivers, patients included by researchers / medical doctors - researchers can include rare disease patients, rare cancer patient – directly included from Romanian Cancer Registry) and population-based registry (data from hospitals, general practitioners, Health Insurance House, Health Ministry) (figure no. 2).

**Figure no. 2. Structure of rare diseases registry**




The patient registry is composed of three parts: the first is the part that includes the voluntary registration of the patients, the second includes the registration by researchers and the third includes the rare cancer patients, provided by The Romanian Cancer Registry directly. The patient part is developed on voluntary registration. The patient registry can be filled out by patients themselves or by caregivers. It has three sections: first, for patient data, second, for caregiver data, and third, for uploaded data (medical letter or other medical documents attesting a rare disease diagnosis, informed consent).

The researcher part is an important component of the patient registry. Data about rare disease patients can be provided by the researchers in the field of rare diseases (researchers, medical doctors, professional societies etc.). They can include a large base of patients in the registry.

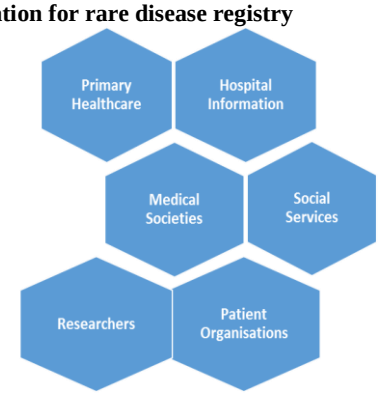
The patient data that are recorded by the researchers or by medical doctors can include medical investigations, patient evolution, medication etc.

Based on the signature of the Informal Consent, the data of the patient can be included in the anonymous statistics and the patient can be asked whether he/she wants to participate in clinical trials, to complete questionnaires, to donate samples for the bio bank.

Regarding the fulfilment of the purpose of the registry to compile all the data from patients with rare disease, it is necessary to establish a sustained collaboration between the main data providers: patients (patients themselves, caregivers

and patient organizations), the medical services providers (the data provided by the general practitioners data provided by the hospitals, especially the university medical centres where there are gathered the majority of the cases of diagnosed rare diseases), the social services (data regarding the people with rare diseases who have different degrees of disability), the researchers (data used in or obtained from different studies), and the medical societies (data regarding a certain rare disease) (figure no. 3).

**Figure no. 3. The collaboration among different sources of information for rare disease registry**




The mandatory registered data common set for a patient with a rare disease must be structured on three domains: socio-demographic data, data regarding the diagnosis and the treatment and data regarding the quality of life and the access to healthcare services (table no. 1). The patients' data are checked by the registry's team to avoid the duplicates. The criteria for crossing the data from the patient registry with the population-based registry are (in order): (1) the personal code, (2) the last name, (3) the first name, (4) the date of birth.

**Table no. 1. The mandatory set of common data elements for the Romanian Rare Disease Registry**

| Domain | Data | Definition |
|---|---|---|
| Socio-demographic domain | Last name | Family name of patient as recorded in birth certificate, passport or identity card |
| | First name | First name of patient as recorded in birth certificate, passport or identity card |
| | Code | National Unique Identification Code |
| | Gender | Patient's physical gender at birth |
| | Date of birth | Date of patient's birth recorded in birth certificate, passport or identity card |
| | Place of birth | Name of city/town/village and country where the patient was born as it appears on the birth certificate, passport or identity card |
| | Complete address | Name of street, city/town and country where the patient usually lives |
| | Patient vital status | Live / dead (if dead: complete date of death: year, month, day) |
| | Education level | Values from 0 to 8, based on the International Standard Classification of Education (ISCED 2011) |
| | Occupational status | Self – defined current economic status |
| | Patient consent | Based on graduated consent forms |
| | Patient contact | Contact details. Preferred means of contact (including via intermediary physician) |
| Diagnosis and treatment domain | Diagnosis | Multiple coding according to current relevant classification systems is recommended (International Statistical Classification of Diseases and Related Health Problems - ICD – 10, Online Mendelian Inheritance in Man (OMIM) code, Orphanet classification) |
| | Date of current diagnosis | Date when the current rare disease diagnosis was made |
| | Comorbidity | Other diseases observed in the patient |
| | Willingness for future clinical trial | Yes / No<br>Patient willingness to be contacted to participate in a future clinical trial |
| Quality of life and health care services | Patient HRQoLindex score | Patient Health-Related Quality-of-Life (HRQoL) generic questionnaires with calculation of quality-adjusted life years - QALY or the utility score |
| | Centre/physician referring the patient to the Rare Disease (RD) centre | Centre/Physician Full name/code |

## DISCUSSIONS

The Structure of the rare disease registry will be established based on one of the key principles developed by the European Organisation for Rare Diseases – EURORDIS, the National Organisation for Rare Disorders – NORD and the Canadian Organization for Rare Disorders – CORD, thus the registry will have to include at the same time data that were directly communicated by patients with the data released by health care professionals.(11) The registry's team completes the different classification of rare diseases, using the own extended classification for ICD – 10. Most rare diseases are absent in ICD – 10, because they are subtypes of common diseases. So, it is necessary to complete this classification with an own extension formed by 2 numbers in order to correctly classify any rare disease included in this registry. The complete name of the disease is completed based on the medical documents.(12) In addition, for genetic diseases the patient registry can use the OMIM code if this exists, because many hereditary diseases do not have OMIM code.(13) Another classification that can be used is the Orphanet classification. Orphanet has established a partnership with WHO to ensure a fair representation of rare diseases in general. Orphanet has collected all published expert classifications and established a database of phenotypes indexed with ICD 10 codes, OMIM codes, genes, mode of inheritance, age of onset and class of prevalence.(14) The European Union policy stipulates the usage of a set of common data for the establishment of a unique reference system in the domain of rare diseases, thus being able to achieve a complete analysis of the situation and a comparison between the situations in the countries of the European Union.(15) The rare disease registries can be created and successfully implemented by involving all the important actors. Thus, there will be gathered data about as many patients as needed, in order to have a complete analysis of the morbidity of rare diseases. The data gathered in the registry of rare diseases must include a uniform data set for each patient. Each variable must be clearly defined in order to ensure consistency in interpretation across participating sites, and data collection and management procedures should be designed to support the collection of high quality data.(16,17) The registry's team will develop, coordinate and control the registry, the

members of the team will be selected based on their expertise and experience.

The elements described in the planning phase of the registry constitute the basic elements for a successful registry, whether we refer to the set of collected data, or the structure of the registry's team, or the funds necessary for a good functioning, or the ethical aspects. The main purpose of creating a rare disease registry is to expedite the research of rare diseases. The rare disease registries must be components of the international registry of rare diseases, by using common data. This approach will contribute to the establishment of a common database containing clinical and contact information. Thus, it will be possible to study the natural evolution of a disease, as well as the patients' responses to various treatments, and it will also constitute a mechanism to bring together an important part of the patients with rare diseases and help the researchers identify and contact the patients interested in taking part in various studies.

## CONCLUSIONS

The main particularity of the rare disease registry is the importance given to the component of patient registry. Creating a link between the existing rare-disease registries can help taking into consideration a large number of patients diagnosed with rare conditions.(18) The set of data gathered can be used to calculate various indicators for disease surveillance, study of socio-economic burden, health system monitoring, research and product development, policy equity and effectiveness. The necessity of attaching a bio bank which would include samples from patients with rare-diseases, as well as from family members derives from the necessity to develop the research of rare diseases. Implementing a registry which would include biological samples can lead to a better understanding of the natural history of the disease and the disease pathways, which then may be used as a new target for treatment. The success of the implementation of a rare disease registry in Romania can be achieved by combining the institutional registries from the university medical centres which have information regarding the majority of the patients with rare diseases, with the population-based control mechanisms by adopting pieces of legislation which would allow access to the data regarding the morbidity and the mortality of rare diseases. The registry, built on high-quality information, can contribute to the development of interdisciplinary research and to the establishment of an interactive platform between the patients, thus facilitating the cooperation among the patients' organizations, the clinicians and the researchers.

***Acknowledgement:***

*This paper was co-financed from the European Social Fund, through the Sectoral Operational Programme Human Resources Development 2007-2013, project number POSDRU/159/1.5/S/138907 "Excellence in scientific interdisciplinary research, doctoral and postdoctoral, in the economic, social and medical fields – EXCELIS", coordinator, The Bucharest University of Economic Studies.*

## REFERENCES

1. http://ec.europa.eu/health/rare_diseases/policy/index_en.htm, accessed on February 26th 2015.
2. Moliner AM. Creating a European Union framework for actions in the field of rare diseases. Adv Exp Med Biol. 2010;686:457-73.
3. https://globalgenes.org/rarefacts/, accessed on February 27th 2015.
4. Schieppati A, Henter JI, Daina E, Aperia A. Why rare diseases are an important medical and social issue. Lancet. 2008;371(9629):2039-2041.
5. Orphanet Report Series, Rare Disease Collection. Rare Disease Registries in Europe, January 2015, available at http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf, accessed on March 2nd 2015.
6. European Commission: Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Rare Diseases: Europe's challenges. Brussels; 11.11.2008 COM(2008) 679 final. 2008, available at [http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf, accessed on February 12th 2015.
7. European Council: Council recommendation of 8 June 2009 on an action in the field of rare diseases. Official Journal of the European Union (2009/C 151/02), available at http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF, accessed on February 2nd 2015.
8. Posada De La Paz M, Groft S. Rare disease epidemiology, Springer Library, New York; 2010.
9. http://www.europlanproject.eu/DocumentationAttachment/NATIONALPLANS_ROMANIA2_ROPlan_en.pdf, accessed on March 1st 2015.
10. United States Department of Health and Human Services, National Committee on Vital and Health Statistics, available at http://ncvhs.hhs.gov/9701138b.htm, accessed on February 12th 2015.
11. EURORDIS-NORD-CORD Joint declaration of 10 key principles for rare disease patient registries, available at http://rarediseases.org/docs/registries-2012, accessed on February 10th 2015.
12. WHO. International Statistical Classification of Diseases and Related Health Problems 10th Revision. Available at http://apps.who.int/classifications/icd10/browse/2015/en, accessed on March 2nd 2015.
13. Online Mendelian Inheritance in Man® Online Catalog of Human Genes and Genetic Disorders. Updated 27 May 2015, available at http://www.omim.org/, accessed on March 2nd 2015.
14. Orphanet Report Series, Rare Disease Collection. List of rare diseases and synonyms. July 2014. Available at http://www.orpha.net/orphacom/cahiers/docs/GB/List_of_rare_diseases_in_alphabetical_order.pdfaccessed on March 2nd 2015.
15. Taruscio D, Vittozzi L, Choquet R, Heimdal K, and al. National registries of rare diseases in Europe: an overview of the current situation and experiences. Public Health Genomics. 2015;18(1):20-5
16. Gliklich RE, Dreyer NA, editors. Registries for Evaluating Patient Outcomes: A User's Guide. 2. Rockville, MD: Agency for Healthcare Research and Quality; 2010.
17. Taruscio D, Mollo E, Gainotti S, Posada de la Paz M and all. The EPIRARE proposal of a set of indicators and common data elements for the European platform for rare disease registration. Arch Public Health. 2014;72(1):35.
18. Nagel G, Unal H, Rosenbohm A, Ludolph AC, Rothenbacher D. ALS Registry Study Group. Implementation of a population-based epidemiological rare disease registry: study protocol of the amyotrophic lateral sclerosis (ALS)-registry Swabia. BMC Neurol. 2013;17:13:22.