Review Article

# Overview of epidemiological rare diseases registries in Bulgaria

**Tsonka Miteva-Katrandzhieva[1,2], Georgy Iskrov[1,2], Rumen Stefanov[1,2], Elisaveta Naumova[3,5], Velina Guergueltcheva[3], Alexey Savov[4]**

[1]Department of Social Medicine and Public Health, Medical University Plovdiv, Plovdiv, Bulgaria
[2]Bulgarian Association for Promotion of Education and Science (BAPES), Plovdiv, Bulgaria
[3]Clinic of Neurology, University Hospital Sofiamed, Sofia, Bulgaria
[4]National Genetic Laboratory, Sofia, Bulgaria
[5]Clinic of Neurology, University Hospital Akexandrovska, Sofia, Bulgaria

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**Correspondence to**
Dr Tsonka Miteva-Katrandzhieva, DD, PhD
Chief Assistant Professor
at Medical University Plovdiv
Department of Social Medicine and Public Health
Medical University Plovdiv
Blrd Vasil Aprilov 15A
Plovdiv 4002, Bulgaria
Tel +359 898 942 607
Email: miteva@raredis.org

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## Abstract

**Background.** Understanding the importance of collecting epidemiological data, Bulgarian association for promotion of education and science (BAPES) was motivated to start an important initiative in 2008, namely tracing the way for establishing a rare disease epidemiological registry in Bulgaria. This initiative was in conformity with one of the basic aims of the Bulgarian National program for development in the field of rare diseases. Till now several private initiatives on rare diseases registries have been realized in the country resulting in excellent-working databases. This is a costless experience that could be shared in order to support design, implementation, analysis, interpretation and quality evaluation.

**Aim.** The aim of this study was to provide up-to-date and reliable information on the epidemiological registries for rare diseases officially processing in Bulgaria.

**Study design.** The authors did a literature review of the available data from the existing registries for rare diseases in the country.

**Material and methods.** For originating the rare diseases epidemiological registries report several sequential strategies were used. The inquiry contained the following summary indicators: 1. year of launch; 2. year of latest update; 3. number of patients from latest update; 4. distribution by sex; 5. distribution by age. Also the main features of rare diseases registries were described.

**Results.** Consent forms and date information were provided by 13 registries on rare diseases.

**Conclusion.** The benefits of rare diseases registries are many and they stimulate all Bulgarian stakeholders to continue to give their best to support the management of the epidemiological rare diseases registries in the country.

## Key words

Epidemiological data, epidemiological registries, rare diseases.

## Introduction

Until recently, epidemiological registries were considered as a research tool that was exclusively used by epidemiologists. Technology progress has dramatically changed this view. Today epidemiological registries solve major problems in the field of rare diseases, most importantly the collection of information from various geographically and structurally scattered sources, and the use of these data for public health and research purposes. The combined benefits of epidemiological registries for rare diseases are widely known: producing epidemiological data about the incidence and prevalence of a disease at national and global levels; enhancing knowledge on variability, progression, and natural history of rare diseases; monitoring and evaluating patient outcomes; providing data to health authorities for planning prevention, diagnosis, treatment and follow-up in healthcare services for rare diseases and for allocation of resources[1-4].

There has been intensive work going on at EU level for joining efforts on registries for rare diseases. Different stakeholders combine their activities to achieve progress not only in pure science, but also on a number of very practical issues. The existence of well-functioning registries is itself an important prerequisite for the development and application of effective treatments for rare diseases. Patients and their families are the most interested in the consistent and proper collection of epidemiologi-

cal data, because elaboration of standards for care and treatment is greatly facilitated in this way[5]. Subsequently, this significantly improves the quality and expectancy of life, even in the absence of new therapies. These arguments logically define epidemiological registries as a key element of any reasonable policy on rare diseases and orphan drugs at national, European and international levels.

Registries as an epidemiological tool are still a relatively new concept to rare diseases, which explains the presence of some practical inconsistencies, especially the lack of a unified approach to data registration and administration[6]. This is due to many reasons:

- different number of stakeholders involved in the administration and management of the registry, as well as large variety of stakeholder needs and goals;
- failure to apply common standards, leading to fluctuations in the frequency of data collection and in quality control;
- financial instability of registries;
- lack of human, financial and structural resources to make possible maintaining separate registries for each rare disease or for each of the different stakeholder objectives.

The specificities of rare diseases represent additional challenges for the registration of patients.

- The genetic nature of most rare diseases suggests the need to investigate and track family related cases, which is not always possible.
- The combination of a small number of cases and a large geographic scope of data collection requires multiple collaborations and exchange of information, usually at international level, often constrained by legal frameworks.
- The need for resources to create and maintain registries for rare diseases. This need is almost equal to that required from the registries for common diseases, but at the same time it is much more difficult to achieve financial sustainability in the long-term for rare diseases.

Recognizing the currently existing rare disease registries, the results achieved, but also the problems encountered, the EU Committee of Experts on Rare Diseases (EUCERD) adopted at the end of its term some recommendations for the development of registries for rare diseases, focusing on compatibility of the information and the use of common codification protocols[7]. The strategic objective of the European Commission is the creation of a European Platform on Rare Diseases Registration providing common services and tools for the existing (and future) rare diseases registries in the European Union[8].

Given the importance of registries, a number of steps for international coordination of these issues have been taken in recent years. The most significant one was undoubtedly the establishment of the International Rare Diseases Research Consortium (IRDiRC). This was a joint initiative of the European Commission and the US National Institutes of Health, launched in April 2011.

Though there is overall progress at international level, the support for the launch and development of rare disease registries at national level remains a crucial point. Despite the strong support of the European Commission and the adoption of a targeted national policy for creation of national registries for rare diseases, a national registry for rare diseases does not exist yet in Bulgaria. One of the priorities of the Bulgarian National Program for Rare Diseases (2009-2013) was the collection of epidemiological data for rare diseases in Bulgaria by creation of a National registry[9]. Despite initial enthusiasm, the Program had been left without appropriate legislation, funding, organization, and management, so at present day this objective had not been implemented. Yet various private initiatives on rare diseases registries have been realized to date, resulting in several excellent-working databases.

The aim of this study is to provide up-to-date and reliable information on the epidemiological registries for rare diseases in Bulgaria. Only the epidemiological registries for rare diseases are the subject of this review while the clinical records maintained in hospitals and other medical treatment facilities are out of the review's scope.

## Material and methods

The review was accomplished through:

1. description of main features of rare diseases registries and presentation of European and international recommendations and guidelines in this field;
2. summary of available data from the existing registries for rare diseases in the country.

For originating the rare diseases epidemiological registries report several sequential strategies were used:

- a literature search-keyword search in the PubMed's scientific database;
- rare diseases portal Orphanet's information on rare diseases registries;
- analysis of the scientific attainments presented during the Bulgarian National Conferences on Rare Diseases and Orphan Drugs (2010, 2011, 2012 and 2013)[10-12];
- personnel call for information on leading clinical centers in Bulgaria, recommended by rare diseases patient organizations;
- roundtables, held with a purposive sampling of rare diseases stakeholders from across Bulgaria to gain information not readily accessible from the public domain (2010, 2012).

To present the registries, the following summary indicators have been selected:

1. year of launch;
2. year of latest update;
3. number of patients from latest update;
4. distribution by sex;
5. distribution by age.

Administrators of the epidemiological registries were asked to identify the bibliography of publications, confirming the operation of the epidemiological registry. Finally an analysis of strengths and weakness of registries was performed.

## Results and discussion

The Bulgarian rare disease stakeholders realized the importance and benefits of the registries as an epidemiological tool. A number of such databases were created as a result of joint activities between scientific societies, clinical centers, patient organizations and Non-Governmental Organizations (NGOs).

The Information Centre for Rare Diseases and Orphan Drugs called for taking part in this survey the known functioning in Bulgaria epidemiological registries for rare diseases. Consent forms and date information were provided by 13 registries (listed in alphabetical order):

- National registry of adult patients with chronic myeloid leukemia;
- National registry of patients with Becker muscular dystrophy;
- National registry of patients with Duchenne muscular dystrophy;
- National registry of patients with Gaucher disease;
- National registry of patients with mucopolysaccharidosis type II;
- National registry of patients with myotonic dystrophy type I;
- National registry of patients with myotonic dystrophy type II;
- National registry of patients with neuroendocrine tumors;
- National registry of patients with phenylketonuria;
- National registry of patients with primary immunodeficiencies;
- National registry of patients with spinal muscular atrophy;
- National registry of patients with thalassemia major;
- National registry of patients with Wilson disease.

Table 1 presents a summary of the main features of the above mentioned registries.

Although it was difficult to generalize registries' information, as they greatly differed, some common features were observed.

### *Strengths*

- Involvement of multiple stakeholders.
- The registries are population-based.
- Provision of important public health information.
- Capacity to collect longitudinal data.

### *Weaknesses*

- No interaction with the Bulgarian health information system.
- No long-term financial sustainability for most registries.
- Lack of a strong motivation of physicians in providing information, since this is a voluntary activity.
- No use of e-tools (e.g., they were not web-based registries).

Most of the registries started their activities during the period 2008-2011. Only one registry had been accomplished in the last 70's of the last century. This could be referred to two basic reasons. On one hand the technology achievements changed dramatically the gathering, processing and storage of information. On the other hand all stakeholders clearly realized the benefits of such registries and make every effort to create a greater number of registries for rare diseases.

The data updating is determinant for the accuracy of the submitted information. It was found that most of the investigated registries were not annually updated. The lack of an annual renewal has questioned the relevance of the information and has suggested the doubt that the registries can be used as a reliable source of information. These results raised important issues related to some factors influencing the frequency of information updating.

### *Legislation*

At this point there are three legal acts that treat the question of the establishment and functioning of epidemiological registries for rare diseases. Health Act only defines who has the right to collect health information of individuals, and in which cases these data may be provided to third parties. The Personal Data Privacy Act limits the gathering of sensitive personal data to be done only by administrators who were registered by the Commission for protecting personal data. Last year Bulgarian Ministry of Health issued a regulation on the procedure for registration of rare diseases and centers of expertise and reference networks for rare diseases that settled the topic for National registry of rare diseases patients. The studied epidemiological registries meet the legislation requirements. Hopefully strict compliance with the new legal framework regulating the operation of registries will support data updating in shorter period of time. This will raise the data timeliness and will allow real description of a number of important indicators such as incidence, prevalence, survival, etc upon which more adequate and timely solutions could be taken for problems in the field of rare diseases.

**Table 1.** Bulgarian rare diseases epidemiological registries basic features summary

| | Year of launch | Year of latest update | Number of patients from latest update | Distribution by sex | | Distribution by age | |
|---|---|---|---|---|---|---|---|
| | | | | men | women | under 18 years of age | above 18 years of age |
| Registry of adult patients with CML | 2010 | 2012 | 328 | 163 | 165 | 0 | 328 |
| Registry of patients with Becker muscular dystrophy | 2008-2010 | 2013 | 33 | 31 | 2 | 30 | 3 |
| Registry of patients with Duchenne muscular dystrophy | 2008-2010 | 2013 | 87 | 87 | 0 | 67 | 20 |
| Registry of patients with Gaucher disease | 2011 | 2014 | 17 | 9 | 8 | 1 | 16 |
| Registry of patients with mucopolysaccharidosis type II | 2011 | 2011 | 7 | 7 | 0 | 7 | 0 |
| Registry of patients with myotonic dystrophy type I | 2008-2010 | 2013 | 47 | 23 | 24 | 3 | 44 |
| Registry of patients with myotonic dystrophy type II | 2008-2010 | 2013 | 3 | 0 | 3 | 0 | 3 |
| Registry of patients with neuroendocrine tumors | 2013 | 2013 | 127 | 57 | 70 | 4 | 123 |
| Registry of patients with phenylketonuria | 1977 | 2014 | 171 | 87 | 84 | 95 | 76 |
| Registry of patients with primary immunodeficiencies | 2010 | 2014 | 131 | 66 | 65 | N/A | N/A |
| Registry of patients with spinal muscular atrophy | 2008–2010 | 2013 | 52 | 29 | 23 | 31 | 21 |
| Registry of patients with thalassemia major | 2009 | 2012 | 270 | 141 | 129 | 104 | 166 |
| Registry of patients with Wilson disease | 2011 | 2011 | 162 | 90 | 72 | 14 | 148 |

***Funding***

Indirect public funding is available for some registries, established within healthcare structures of national significance. The majority of rare disease registries in Bulgaria are funded by grants, public-private partnerships or in a voluntary manner. According to regulation on the procedure for registration of rare diseases and centers of expertise and reference networks for rare diseases the future National registry of rare diseases patients will be funded by the State. Stable funding will ensure regular data updating.

***Data set***

It was revealed that a centralized approach to rare disease registries and rare diseases field in general was missing in Bulgaria and registries' design substantially varied. Bulgarian association for promotion of education and science, managing 7 of the identified rare diseases registries, had set a uniform data set of 18 indicators (regarding the demography, the disease, the general practitioner and the medical specialist information) for some of its registries. It was observed in the other rare disease registries that the more detailed the registry was, the wider data set was used.

## Conclusions

Rare disease epidemiological registries are still a new topic for the Bulgarian public health. Yet the growing number of such initiatives shows that the rare diseases community in Bulgaria is interested and willing to participate in a registry activity. To facilitate this process and ensure better outcomes, it is recommended that:

1. the legal bases for starting and running epidemiological registries must be even more clarified and equalized;
2. the State should take the financial responsibility for the establishment and continuous work of rare diseases registries;
3. a mechanism (regulation) for mandatory registration of the rare diseases patients under surveillance should be put in place.

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