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EPIDEMIOLOGICAL REGISTRIES FOR RARE DISEASES IN BULGARIA

Methodology

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

- description of main features of rare diseases registries (goals and objectives, benefits and added value, key factors for planning, launching and managing epidemiological registries for rare diseases);
- presentation of European and international recommendations and guidelines in this field;
- summary of available data from the existing registries for rare diseases in the country.

The presented in this review registries have been identified by:

- keyword search in the Pubmed's scientific database;
- rare diseases portal Orphanet's information on rare diseases registries;
- analysis of the outcomes of the Bulgaria's Second National Conference on Rare Diseases and Orphan Drugs in 2011 (the event hosted a special panel session on epidemiological registries for rare diseases);
- call for information to leading clinical centres in Bulgaria, recommended by rare diseases patient organisations.

Definitions

- Rare disease – a disorder, affecting no more than 5 per 10 000 persons in the EU.
- Epidemiological registry – an organised system for collection, storage, retrieval, and dissemination of a clearly defined set of epidemiological data collected on identifiable individuals for a specific and specified purpose.

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CHARACTERISTICS AND FUNCTIONS OF EPIDEMIOLOGICAL REGISTRIES FOR RARE DISEASES

By their nature epidemiological registries are **an organised system for collection, storage, retrieval, and dissemination of a clearly defined set of epidemiological data collected on identifiable individuals for a specific and specified purpose**. Despite the numerous initiatives to create such databases for rare diseases, the number of rare diseases registries in Bulgaria remains low. A possible explanation is the lack of comprehension of the difference between traditional clinical records and epidemiological registries.

The so defined rare diseases epidemiological registries' **main characteristics** include:

- global, ongoing, observational databases;
- strict respect of both patient's and physician's confidentiality;
- governance by independent scientific boards;
- harmonisation with relevant European and national legislation.

The combination of these aspects clearly outlines and distinguishes the epidemiological registries from other types of records that exist in healthcare system. Pragmatism and universalism of epidemiological registries for rare diseases are the main reasons for their boom in many European countries and the USA.

Specific benefits of the implementation and maintenance of epidemiological registries can be synthesised in:

- producing epidemiological data about the incidence and prevalence of a disease on national and global level;
- enhancing knowledge of variability, progression, and natural history of rare diseases;
- monitoring and evaluating patient outcomes;
- providing data for governmental healthcare planning and allocation of funds when implementing prevention, diagnosis, treatment and follow-up policies.

The added value of these projects is huge, that's why the number of epidemiological registries in many European countries is impressive (e.g., France 122, Germany 86, UK 58). With further specification of additional objectives these databases can be actively used not only in healthcare sphere, but also wherever in modern society, where information is a resource of utmost importance.

To efficiently fulfill these tasks epidemiological registries for rare diseases need adequate planning and management. In this context, the **main challenges** to establish and successfully run such a register are: clear definition of the purpose of a registry, as well as precise case set; robust design of data collection format; data validation; data privacy protection.

Practical solution of these problems suggests **consensus and synergistic approach** involving various stakeholders, which can be both primary sources and final users of the registry. Therefore, when planning and implementing epidemiological registries for rare diseases, **specific groups** should be actively involved - patients and their families; medical specialists; industry; health authorities.

Participation of all these stakeholders helps increasing their motivation from one side, and it also makes the registry better functioning and practically useful on the other side. A key point here is planning and preparation. An analysis of the existing infrastructure has to be considered, assessing its ability to integrate and further co-operate with the epidemiological registry. Exploring and evaluating all these factors can justify the investment for establishment of epidemiological registries for rare diseases and ensure future efficient and sustainable development.

POLICIES, GUIDELINES AND PUBLIC HEALTH INITIATIVES IN THE FIELD OF EPIDEMIOLOGICAL REGISTRIES FOR RARE DISEASES

While in Bulgaria the epidemiological registries for rare diseases are relatively new topics, it is not the same situation in Europe and globally. The public health's hard work in the field of rare diseases for more than three decades has formulated a new understanding of the importance and benefits of these epidemiological tools. The real boom came during the last ten years, as the culmination was the adoption of the **EU Council Recommendation of 8 June 2009 on an action in the field of rare diseases**. This document has predetermined a road map of the rare diseases policies and initiatives at least for a decade ahead. Along with the call for the elaboration and adoption of national plans for rare diseases in Member States, the necessity to launch rare diseases epidemiological registries was once again reaffirmed, namely *"…consider supporting at all appropriate levels, including the Community level, on the one hand, specific disease information networks and, on the other hand, for epidemiological purposes, registries and databases, whilst being aware of an independent governance*". This importance of epidemiological registries stems from the coordinating role that they play for the successful implementation of any action or strategy in the field of rare diseases.

EU's support for the development of epidemiological registries for rare diseases is not only within regulations. Before the Council Recommendation the Commission had already financed the creation of **a significant number of European registries and reference networks for rare diseases**, which had gathered segmented and scarce experience at the national level, as well as had provided a powerful incentive to produce new knowledge and experience of rare diseases. The role of these projects for the global development of the medical science is enormous.

Shortly after the Council Recommendation, initiatives have been taken in many Member States to develop such infrastructure. The Commission has responded strategically by deciding to support the launch of the **EPIRARE** project, which is aimed at creating a common European platform for epidemiological registries for rare diseases. It would ensure that the various efforts at national level are combined in a comprehensive European approach to this problem, whose results to be felt by all stakeholders. EPIRARE will analyse and summarise both common (protection and sharing of personal data, effective management and sustainable development) and rare diseases specific (set of epidemiological indicators, data collection and processing, collaboration and dissemination) challenges for registries. EPIRARE gathers together partners from the EU, USA, China and Russia and the expectations of all are great. Bulgaria is also represented in the project through the participation of BAPES as an associated partner.

Before EPIRARE epidemiological registries were subject to other major European project on rare diseases – **EUROPLAN**. This project has largely explained and implemented the Recommendation, performing systematic review and analysis of measures and initiatives in the field of rare diseases taken so far at the national level. Based on this extensive information, detailed guidelines for planning, development and management of national plans and strategies for rare diseases were elaborated. So, having the Recommendation as a primary landmark, the Member States have also available specific examples and guidelines for the formation of national policies in this area. Exploring the existing successful registries, EUROPLAN has made the following recommendations:

- *Initiatives are promoted at national level for the integrated use of administrative, demographic and health care data sources to improve the management of rare diseases.*
- *International, national and regional registries for specific rare diseases or groups of rare diseases are promoted and supported for research and public health purposes, including those held by academic researchers.*
- *Collection and sharing of data from any valid sources, including Centres of Expertise, and their availability for public health purposes is promoted by public health authorities, in compliance with national laws.*
- *Participation of existing national registries in European/International registries is fostered.*
- *Instruments are identified for combining EU and national funding for registries.*

Finally, EUROPLAN has also set indicators to monitor the progress of implementation of rare diseases activities. For the registries field these indicators include number, territory scope, observed rare diseases, governing body and funding. These observations were confirmed by the recently created **European Union Committee of Experts on Rare Diseases (EUCERD),** which is the highest advisory body in Europe for rare diseases.

Looking back at national level, Bulgaria was among the first countries in the EU to begin actively discussing the creation of policies for rare diseases. This was largely the result of the efforts of patients, doctors and NGOs. It is correct to admit that today, even without an explicitly formulated and adopted national plan for rare diseases, some countries like Denmark ensure that patients have access to appropriate and adequate treatment, monitoring, rehabilitation and social cares. However, it is largely the opposite situation in the countries of Eastern Europe, where after the democratic transition many changes have taken place, including in healthcare provision. This has led to serious transformations in decade-long organisational and managerial structures and processes, which are still subject to mixed reviews. In the current situation of these countries the adoption of such an official document as the national plan for rare diseases is more than necessary in order to create efficient and sustainable framework for addressing the problems for patients with rare diseases, their families, their physicians, health and social institutions, involved in this filed. Therefore, the adoption of **the Bulgarian National Programme for Rare Diseases (2009-2013)** itself is an indisputable success, because it has institutionalised rare disease problems and provided a basis for further actions in this area.

Logically to the outlined here, the first priority in the Programme was to set out epidemiological registries – *provision of epidemiological data on rare diseases in Bulgaria by the establishment of a National Register.*

The arrangements for the establishment and operation of the registry are within the competence of the Programme's **National Consulting Council for Rare Diseases (NCCRD)** within the Ministry of Health. The registry's tasks include:

- *collect, summarize, and provide epidemiologic information on the incidence and prevalence of rare diseases in Bulgaria;*
- *assist the preparation of diagnostic and therapeutic protocols and standards for treatment of rare diseases;*
- *assist the Ministry of Health, the Ministry of Labour and Social Policy, and the National Health Insurance Fund in the planning and delivery of expensive treatment and medical care to patients with rare diseases;*
- *improve the interaction between health services and patient organizations;*

- *provide and publish data needed for planning and comparison on a regional and national level.*

Unfortunately for everyone in Bulgaria, more than three years after the adoption of the programme a national registry for rare diseases is not yet built. This lack has negative effect on all parties concerned, because without updated and reliable data rare diseases policies, activities and initiatives can not be planned and carried out in a manner satisfying the needs of both patients and doctors. The non-existence of a national registry makes seem all health and social services for rare diseases in the country partial and provisional. They solve some problems, but the effect is not optimal and this is precisely the fragmentation of efforts and resources, which all European recommendations warn about.

The absence of a single national registry in Bulgaria does not mean that the Bulgarian rare diseases stakeholders have not realised the importance and benefits of this tools. Rather, several epidemiological registries for rare diseases are a fact as a result of joint projects between patient organisations, medical research societies, university hospitals, NGOs and industry. The Bulgarian Second National Conference for Rare Diseases and Orphan Drugs in 2011 was an opportunity to present and discuss these issues. The forum demonstrated a growing interest and motivation for the establishment and implementation of these registries. Consensus was evident among patients and physicians on the need to continue providing support to all the existing epidemiological registries for rare diseases in the country, as an initial step to create the long-expected and so necessary national registry for rare diseases.

SUMMARY PRESENTATION OF EPIDEMIOLOGICAL REGISTRIES FOR RARE DISEASES, CURRENTLY ON PLACE IN BULGARIA

The Information Centre for Rare Diseases and Orphan Drugs has called for taking part in this survey all known functioning in Bulgaria epidemiological registries for rare diseases. Consent forms and date information have been provided by 9 registries (listed in alphabetical order):

- National registry of patients with phenylketonuria;
- National registry of patients with thalassemia major;
- National registry of adult patients with chronic myeloid leukemia (CML);
- National registry of patients with primary immunodefficiencies (PID);
- National registry of patients with Crohn disease;
- National registry of patients with Gaucher disease;
- National registry of patients with mucopolysaccharidosis type II (MPS2);
- National registry of patients with Wilson disease.

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

- year of launch;
- year of latest update;
- number of patients from latest update
- distribution by age;
- distribution by sex;
- territorial scope.

Administrators of the epidemiological registries were asked to identify bibliography of publications, confirming the operation of the epidemiological registry.

NATIONAL REGISTRY OF PATIENTS WITH PHENYLKETONURIA

Rare disease's name (ICD-10 code)	Phenylketonuria (E70.0)
Year of launch	1977
Year of latest update	2012
Number of patients from latest update	178
Distribution by age	Children (under 18) – 92; Adults – 86
Distribution by sex	Male – 97; Female – 81
Territorial scope	Nationwide
Coordinator	Assoc. Prof. Alexey Savov, MD, PhD National Genetic Laboratory, Sofia
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NATIONAL REGISTRY OF PATIENTS WITH THALASSEMIA MAJOR

Rare disease's name (ICD-10 code)	Thalassemia major (D56.1)
Year of launch	2009
Year of latest update	2011
Number of patients from latest update	255
Distribution by age	Children (under 18) – 104; Adults – 151
Distribution by sex	Male – 131; Female – 119; Anonymous – 5
Territorial scope	Nationwide
Coordinator	Dr. Tsonka Miteva, DD Information Centre for Rare Diseases and Orphan Drugs, Plovdiv
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NATIONAL REGISTRY OF ADULT PATIENTS CML

Rare disease's name (ICD-10 code)	Chronic myeloid leukemia (C92.1)
Year of launch	2010
Year of latest update	2012
Number of patients from latest update	328
Distribution by age	Adults – 328
Distribution by sex	Male – 163; Female – 165
Territorial scope	Nationwide
Coordinator	Dr. Tsonka Miteva, DD Information Centre for Rare Diseases and Orphan Drugs, Plovdiv
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NATIONAL REGISTRY OF PATIENTS WITH PID

Rare disease's name (ICD-10 code)	Primary immunodeficiencies (D80, D81, D82, D83, D84, D89)
Year of launch	2010
Year of latest update	2012
Number of patients from latest update	109
Distribution by age	N/A
Distribution by sex	Male – 56; Female – 53
Territorial scope	Nationwide
Coordinator	Prof. Elisaveta Naumova, MD, DSc, PhD Alexandrovska University Hospital, Sofia
Bibliography	N/A

NATIONAL REGISTRY OF PATIENTS WITH CROHN DISEASE

Rare disease's name (ICD-10 code)	Crohn disease (K50)
Year of launch	2010
Year of latest update	2012
Number of patients from latest update	191
Distribution by age	Children (under 18) – 1; Adults – 190
Distribution by sex	Male – 84; Female – 107
Territorial scope	Nationwide
Coordinator	Dr. Tsonka Miteva, DD Information Centre for Rare Diseases and Orphan Drugs, Plovdiv
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NATIONAL REGISTRY OF PATIENTS WITH GAUCHER DISEASE

Rare disease's name (ICD-10 code)	Gaucher disease (E75.2)
Year of launch	2011
Year of latest update	2011
Number of patients from latest update	13
Distribution by age	Children (under 18) – 1; Adults – 12
Distribution by sex	Male – 8; Female – 5
Territorial scope	Nationwide
Coordinator	Dr. Tsonka Miteva, DD Information Centre for Rare Diseases and Orphan Drugs, Plovdiv
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NATIONAL REGISTRY OF PATIENTS WITH MPS2

Rare disease's name (ICD-10 code)	Mucopolysaccharidosis type II (E76.1)
Year of launch	2011
Year of latest update	2011
Number of patients from latest update	7
Distribution by age	Children (under 18) – 7; Adults – 0
Distribution by sex	Male – 7; Female – 0
Territorial scope	Nationwide
Coordinator	Dr. Tsonka Miteva, DD Information Centre for Rare Diseases and Orphan Drugs, Plovdiv
Bibliography	1. Miteva Ts, Iskrov G, Popova L, Stefanov R. Epidemiological registries for rare diseases. 2nd National conference for rare diseases and orphan drugs – conference proceedings book, 2011; p. 149.

NATIONAL REGISTRY OF PATIENTS WITH WILSON DISEASE

Rare disease's name (ICD-10 code)	Wilson disease (E83.0)
Year of launch	2011
Year of latest update	2011
Number of patients from latest update	162
Distribution by age	Children (under 18) – 14; Adults – 148
Distribution by sex	Male – 90; Female – 72
Territorial scope	Nationwide
Coordinator	Dr. Tsonka Miteva, DD Information Centre for Rare Diseases and Orphan Drugs, Plovdiv
Bibliography	1. Miteva Ts, Iskrov G, Popova L, Stefanov R. Epidemiological registries for rare diseases. 2nd National conference for rare diseases and orphan drugs – conference proceedings book, 2011; p. 149.

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