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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;
- 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 National Conferences on Rare Diseases and Orphan Drugs since 2010;
- 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.

Contents

- Development and current trends in the field of epidemiological registries for rare diseases
- Summary presentation of the epidemiological registries for rare diseases, currently in place in Bulgaria

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Section 1

DEVELOPMENT AND CURRENT TRENDS IN THE FIELD OF EPIDEMIOLOGICAL REGISTRIES FOR RARE DISEASES

Until recently, epidemiological registries were considered as a research tool that is 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 on national and global level; 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 healthcare services for rare diseases and allocation of resources.

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 epidemiological data, because elaboration of standards for care and treatment is greatly facilitated in this way. 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 level.

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. 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 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 small number of cases and large geographic scope of data collection requires multiple collaborations and exchange of information, usually at international level, which is often constrained by legal frameworks;
- the need for resources to create and maintain registries for rare diseases that are almost equal to these for common diseases, but at the same time it is much more difficult to achieve long-term financial sustainability.

These barriers are the reason for the development and adoption of universal definitions, classifications and standards for rare disease data, as well as appropriate uniform policies and resources to create and maintain registries for rare diseases. In order to avoid fragmentation, inconsistency, lack of common standards and interoperability, the EU has made significant efforts in this area in recent years by funding a series of key projects:

- the international portal for rare diseases and orphan drugs Orphanet;

- the European project EUROPLAN elaborated recommendations for the establishment and implementation of national strategies for rare diseases;
- the European project EPIRARE laid down the foundations of a future European platform to support and facilitate the registration of patients with rare diseases by promoting standardisation of registration and quality control procedures;
- the European project RD-Connect aims to connect into a global infrastructure relevant research databases, registries and biobanks, creating a centralised resource platform for rare diseases research.

Recognising the currently existing rare disease registries, the results achieved by them, but also the problems encountered, the EU Committee of Experts on Rare Diseases (EUCERD) adopted at the end of its term recommendations for the development of registries for rare diseases, focusing on compatibility of the information and the use of common codification protocols. The European Commission, in its turn, is now seriously analysing the possibility of creating a platform for the development of registries for rare diseases in the EU by establishing a joint research centre.

Rare disease registries are also a popular topic in the USA, where the Office of Rare Diseases Research has recently launched a pilot project to launch the Global Rare Diseases Patient Registry and Data Repository (GRDR). The goal is to establish a data repository of de-identified patient data, aggregated in a standardised manner, using Common Data Elements (CDEs) and standardised terminology. This data will be available to all investigators to enable analyses across many rare diseases and to facilitate various biomedical studies, including clinical trials, in pursuit of developing drugs and therapeutics to improve the healthcare and the quality of life for the many millions of people who are diagnosed with rare diseases. De-identification of patient's data will utilize the Global Unique Identifiers (GUID) system which could also link patient's data to biospecimen data set. In an attempt to harmonise and provide standardisation among the different rare disease registries, ORDR has developed a number of resources, available to all. Among them are a set of CDEs that can serve groups establishing their patient registries and existing registries transferring their data to the GRDR repository and an informed-consent-document for participating in a patient registry.

Given the importance of registries, a number of steps for international coordination on 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 is a joint initiative of the European Commission and the US National Institutes of Health, launched in April 2011. IRDiRC is a long-term project, which aims to foster international collaboration in rare diseases research. It teams up researchers and organisations investing in rare diseases research in order to achieve two main objectives, namely to deliver 200 new therapies for rare diseases and means to diagnose most rare diseases by the year 2020. Despite this overall progress at international level, the support for the launch and development of rare disease registries at national level remains a crucial point. The aim of this report is to provide up-to-date and reliable information on the epidemiological registries for rare diseases in Bulgaria, thus to increase the visibility and awareness of these infrastructures in the country.

Section 2

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

The establishment of a national registry for rare diseases in Bulgaria was set as a priority objective in the country's National Plan for Rare Diseases (2009 – 2013), but its implementation has been repeatedly delayed over the time.

The idea re-emerged in 2013, because of the ongoing transposition of the EU Cross Border Healthcare Directive and the expected official designation of the centres of expertise for rare diseases in Bulgaria. On 30 July 2014 Ordinance № 16 of the Ministry of Health on the terms and procedure for registration of rare diseases and centres of expertise and reference networks for rare diseases was officially promulgated. The legal act contains provisions for the establishment of a national registry of patients with rare diseases. The registry will be managed by the National Center for Public Health and Analyses (NCPHA). The data set for registration shall include ID number and place of residence of the patient, as well as main and accompanying diagnoses. These data will be collected and submitted by centres of expertise and medical institutions that provide medical services to patients with rare diseases. Only anonymised data will be sent to the registry. This information will be updated every six months. Based on data from the national registry of patients with rare diseases, NCPHA will prepare and publish annual reports on the epidemiology of rare diseases in Bulgaria.

However, the current absence of a national registry for rare diseases in Bulgaria does not mean that local stakeholders are not working on these issues. The Bulgarian rare disease stakeholders have greatly realised the importance and benefits of this epidemiological tool. A number of such databases exist as a result of joint activities between scientific societies, clinical centers, patient organisations and NGOs.

The Information Centre for Rare Diseases and Orphan Drugs has called for taking part in this survey the known functioning in Bulgaria epidemiological registries for rare diseases. Consent forms and date information have been provided by 14 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 Crohn disease;
- 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.

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 ADULT PATIENTS WITH CHRONIC MYELOID LEUKEMIA

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 Information Centre for Rare Diseases and Orphan Drugs, Plovdiv
Bibliography	1. Stefanov R, Mihaylov G, Gercheva L, Hadzhiev E, Marinova-Goranova V, Tsvetkov N, Bogdanov L, Raynov J. Epidemiology of CML in Bulgaria – a pilot study (in Bulgarian) . Social Med and Health Management, 2010; 1:7-13. 2. Miteva Ts, Iskrov G, Popova L, Stefanov R. Epidemiological registries for rare diseases. 2 nd National conference for rare diseases and orphan drugs – conference proceedings book, 2011; p. 149.

NATIONAL REGISTRY OF PATIENTS WITH BECKER MUSCULAR DYSTROPHY

Rare disease's name (ICD-10 code)	Becker muscular dystrophy (G71.0)
Year of launch	2008 – 2010
Year of latest update	2013
Number of patients from latest update	33
Distribution by age	Children (under 18) – 30; Adults – 3
Distribution by sex	Male – 31; Female – 2
Territorial scope	Nationwide
Coordinator	Prof. Ivailo Tournev, Assoc. Prof. Velina Guergueltcheva Alexandrovskia University Hospital, Sofia
Bibliography	1. Todorova A, Todorov T, Georgieva B, Lukova M, Guergueltcheva V, Kremensky I, Mitev V (2008). MLPA analysis/complete sequencing of the DMD gene in a group of Bulgarian Duchenne/Becker muscular dystrophy patients. Neuromuscul Disord; 18(8):667-70.

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 Information Centre for Rare Diseases and Orphan Drugs, Plovdiv
Bibliography	1. Miteva Ts, Iskrov G, Popova L, Stefanov R. Epidemiological registries for rare diseases. 2 nd National conference for rare diseases and orphan drugs – conference proceedings book, 2011; p. 149.

NATIONAL REGISTRY OF PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY

Rare disease's name (ICD-10 code)	Duchenne muscular dystrophy (G71.0)
Year of launch	2008 – 2010
Year of latest update	2013
Number of patients from latest update	87
Distribution by age	Children (under 18) – 67; Adults – 20
Distribution by sex	Male – 87; Female – 0
Territorial scope	Nationwide
Coordinator	Prof. Ivailo Tournev, Assoc. Prof. Velina Guergueltcheva Alexandrovskaya University Hospital, Sofia
Bibliography	1. Todorova A, Todorov T, Georgieva B, Lukova M, Guergueltcheva V, Kremensky I, Mitev V (2008). MLPA analysis/complete sequencing of the DMD gene in a group of Bulgarian Duchenne/Becker muscular dystrophy patients. <i>Neuromuscul Disord</i> ; 18(8):667-70.

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	2014
Number of patients from latest update	17
Distribution by age	Children (under 18) – 1; Adults – 16
Distribution by sex	Male – 9; Female – 8
Territorial scope	Nationwide
Coordinator	Dr. Tsonka Miteva Information Centre for Rare Diseases and Orphan Drugs, Plovdiv
Bibliography	1. Miteva Ts, Iskrov G, Popova L, Stefanov R. Epidemiological registries for rare diseases. 2 nd National conference for rare diseases and orphan drugs – conference proceedings book, 2011; p. 149.

NATIONAL REGISTRY OF PATIENTS WITH MPS2 MUCOPOLYSACCHARIDOSIS TYPE II

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 Information Centre for Rare Diseases and Orphan Drugs, Plovdiv
Bibliography	1. Miteva Ts, Iskrov G, Popova L, Stefanov R. Epidemiological registries for rare diseases. 2 nd National conference for rare diseases and orphan drugs – conference proceedings book, 2011; p. 149.

NATIONAL REGISTRY OF PATIENTS WITH MYOTONIC DYSTROPHY TYPE I

Rare disease's name (ICD-10 code)	Myotonic dystrophy type I (G71.1)
Year of launch	2008 – 2010
Year of latest update	2013
Number of patients from latest update	47
Distribution by age	Children (under 18) – 3; Adults – 44
Distribution by sex	Male – 23; Female – 24
Territorial scope	Nationwide
Coordinator	Prof. Ivailo Tournev, Assoc. Prof. Velina Guerguelcheva Alexandrovskia University Hospital, Sofia
Bibliography	–

NATIONAL REGISTRY OF PATIENTS WITH MYOTONIC DYSTROPHY TYPE II

Rare disease's name (ICD-10 code)	Myotonic dystrophy type II (G71.1)
Year of launch	2008 – 2010
Year of latest update	2013
Number of patients from latest update	3
Distribution by age	Children (under 18) – 0; Adults – 3
Distribution by sex	Male – 0; Female – 3
Territorial scope	Nationwide
Coordinator	Prof. Ivailo Tournev, Assoc. Prof. Velina Guerguelcheva Alexandrovskia University Hospital, Sofia
Bibliography	–

NATIONAL REGISTRY OF PATIENTS WITH NEUROENDOCRINE TUMORS

Rare disease's name (ICD-10 code)	Neuroendocrine tumors (K50)
Year of launch	2013
Year of latest update	2013
Number of patients from latest update	127
Distribution by age	Children (under 18) – 4; Adults – 123
Distribution by sex	Male – 57; Female – 70
Territorial scope	Nationwide
Coordinator	Dr. Tsonka Miteva Information Centre for Rare Diseases and Orphan Drugs, Plovdiv
Bibliography	–

NATIONAL REGISTRY OF PATIENTS WITH PHENYLKETONURIA

Rare disease's name (ICD-10 code)	Phenylketonuria (E70.0)
Year of launch	1977
Year of latest update	2014
Number of patients from latest update	171
Distribution by age	Children (under 18) – 95; Adults – 76
Distribution by sex	Male – 87; Female – 84
Territorial scope	Nationwide
Coordinator	Assoc. Prof. Alexey Savov National Genetic Laboratory, Sofia
Bibliography	1. Kremensky I, Jordanova A, Todorova A, Savov A, Iankova S, Georgieva B, Zaharova B, Kaneva R, Petkova R, Andonova S, Ivanova M, Michaylova E, Ivanova N, Klaydjieva L. Mutation profile of the most common genetic disorders in Bulgaria. Balkan journal of Medical genetics vol 3 (4) 3-12, (2000) 2. I. Kremensky, A. Todorova, A. Jordanova, A. Savov, I. Tournev, S. Iankova, B. Georgieva, B. Zaharova, R. Kaneva, R. Petkova, S. Andonova, M. Ivanova, R. Rainova, and L. Klaydjieva. Spectrum of mutations of the most common genetic disorders in Bulgaria. The Official International E.C. Qual. L. Journal for Quality of the Research. Vol1 Issue2 p. 172-185 March-April (2003).

NATIONAL REGISTRY OF PATIENTS WITH PRIMARY IMMUNODEFFICIENCIES

Rare disease's name (ICD-10 code)	Primary immunodeficiencies (D80, D81, D82, D83, D84, D89)
Year of launch	2010
Year of latest update	2014
Number of patients from latest update	131
Distribution by age	N/A
Distribution by sex	Male – 66; Female – 65
Territorial scope	Nationwide
Coordinator	Prof. Elisaveta Naumova Alexandrovska University Hospital, Sofia
Bibliography	–

NATIONAL REGISTRY OF PATIENTS WITH SPINAL MUSCULAR ATROPHY

Rare disease's name (ICD-10 code)	Spinal muscular atrophy (G12.2)
Year of launch	2008 – 2010
Year of latest update	2013
Number of patients from latest update	52
Distribution by age	Children (under 18) – 31; Adults – 21
Distribution by sex	Male – 29; Female – 23
Territorial scope	Nationwide
Coordinator	Prof. Ivailo Tournev, Assoc. Prof. Velina Guerguelcheva Alexandrovska University Hospital, Sofia
Bibliography	–

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 Information Centre for Rare Diseases and Orphan Drugs, Plovdiv
Bibliography	1. Miteva Ts, Iskrov G, Popova L, Stefanov R. Epidemiological registries for rare diseases. 2 nd National conference for rare diseases and orphan drugs – conference proceedings book, 2011; p. 149.

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	2012
Number of patients from latest update	270
Distribution by age	Children (under 18) – 105; Adults – 165
Distribution by sex	Male – 141; Female – 129
Territorial scope	Nationwide
Coordinator	Dr. Tsonka Miteva Information Centre for Rare Diseases and Orphan Drugs, Plovdiv
Bibliography	1. Miteva Ts, Kaleva V, Stefanov R. National registry of patients with thalassemia in Bulgaria. 4 th Eastern European conference for rare diseases and orphan drugs – conference proceedings book, 2009: p. 143. 2. Miteva Ts, Stefanov R, Kaleva V, Rangelova M, Stoyanova D, Manoilova K, Stoyanova A, Kostova S, Kostova D, Chakarov I, Georgieva R, Ribov D. National registry of thalassemia major patients – pilot study's results from 2010. 1 st EUROPLAN National conference for rare diseases and orphan drugs – conference proceedings book, 2010: p. 142. 3. Kaleva V, Stefanov R, Semova G, Miteva Ts. National registry of patients with thalassemia in Bulgaria – results of the second survey made in October 2010. Abstracts of the 12th International Conference on Thalassemia and the Haemoglobinopathies, 2011. 4. Miteva Ts, Stefanov R, Kaleva V, Rangelova M, Stoyanova D, Manoilova K, Stoyanova A, Kostova S, Kostova D, Chakarov I, Georgieva R, Ribov D. National registry of thalassemia major patients – results by June 2011. 2 nd National conference for rare diseases and orphan drugs – conference proceedings book, 2011; p. 148.

REFERENCES

- Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products
http://ec.europa.eu/health/files/eudralex/vol-1/reg_2000_141/reg_2000_141_en.pdf
- Directive 2011/24/EU of the European Parliament and of the Council on the application of patients' rights in cross-border healthcare
<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:EN:PDF>
- 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
http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf
- Council Recommendation (2009/C 151/02) on an action in the field of rare diseases
<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF>
- EUCERD Recommendations on Rare Disease Patient Registration and Data Collection (5 June 2013)
http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_RDRegistryDataCollection_adopted.pdf
- The international portal for rare diseases and orphan drugs Orphanet
<http://www.orpha.net/consor/cgi-bin/index.php>
- European project for rare diseases national plan development (EUROPLAN). Recommendations for the development of national plans for rare diseases
http://www.euoplanproject.eu/_newsite_986987/Resources/docs/2008-2011_2.EUROPLANGuidance.pdf
- European project for rare diseases national plan development (EUROPLAN). Selecting indicators to evaluate the achievements of rare diseases initiatives
http://www.euoplanproject.eu/_newsite_986987/Resources/docs/2008-2011_3.EUROPLANIndicators.pdf
- European Platform for Rare Disease Registries (EPIRARE)
<http://www.epirare.eu/>
- RD-CONNECT – an integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research
<http://rd-connect.eu/>
- Posada de la Paz M, Groft S C (Eds.) Rare Diseases Epidemiology. Springer's Advances in Experimental Medicine and Biology, Vol. 686, 2010
- Orphanet. Rare Disease Registries in Europe, Orphanet Report Series, Rare Diseases collection, January 2014
<http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf>
- Ministry of Health. National programme for rare diseases (2009 – 2013) (unofficial translation in English)
<http://www.raredis.org/pub/events/NPRD.pdf>
- Ministry of Health. Ordinance № 16 of 30 July 2014 on the terms and procedure for registration of rare diseases and centers of expertise and reference networks for rare diseases
<http://dv.parliament.bg/DVWeb/showMaterialDV.jsp;jsessionid=7F3346719F17C9EB71FB6A59F7ADFEF9?idMat=87157>
- 2nd National conference for rare diseases and orphan drugs – conference proceedings book, 2011 (in Bulgarian)
http://raredis.org/pub/Newsletter/Conference_Book_2011.pdf
- 3rd National conference for rare diseases and orphan drugs – conference proceedings book, 2012 (in Bulgarian)
http://raredis.org/pub/Newsletter/Conference_Book_2012_LQ.pdf
- 4th National conference for rare diseases and orphan drugs – conference proceedings book, 2013 (in Bulgarian)
http://raredis.org/pub/Newsletter/Book_2013_LQ.pdf