State of the Art of Rare Disease – Activities in EU Member States and Other European Countries

Bulgaria Report

Definition of a Rare Disease

Bulgaria has adopted the European Commission definition of a rare disease and their National Plan espouses this definition.

Stakeholders in Bulgaria accept the definition of a prevalence of no more than 5 in 10,000 individuals. This definition is officially stated in the Bulgarian National Plan for Rare Diseases, and it is also included in the provisions of the Health Act.

Status Quo of any National Plan or Strategy for Rare Diseases

Bulgaria has adopted a National Plan in the past; however, this has now expired. On 27th November 2008, the Bulgarian Council of Ministers approved the National Plan for Rare Diseases – genetic disorders, congenital malformations and non-hereditary diseases (2009 – 2013). The Bulgarian National Plan for Rare Diseases began on 1st January 2009 and lasted for 5 years.
The plan consisted of nine priorities targeting all rare diseases, including the following:

- The collection of epidemiological data for rare diseases in Bulgaria through the creation of a national register;
- Improvement of the prevention of genetic rare diseases in Bulgaria through an expansion of the current screening programmes;
- Improvement of the prevention and diagnostics of genetic rare diseases by introducing new genetic tests, a decentralisation of laboratory activities and easier access to medico-genetic counselling;
- Integrative approach to the prevention, diagnostics, medical treatment and social integration of patients and their families;
- Promotion of the professional qualification of medical specialists in the field of early diagnostics and prevention of rare diseases;
- Feasibility study of the necessity, possibility and criteria for the creation of a reference centre for rare diseases of functional types;
- Organisation of a national campaign to inform society about rare diseases and their prevention;
- Support and collaboration with NGOs and patient associations for rare diseases;
- Collaboration with other EU Member States

The Plan officially ended on 31st December 2013. Prior to this the Ministry of Health had established a working group to prepare a draft for a Second National Plan. This Plan was expected to outline close collaboration with the National Rare Disease Registry and the Centres of Expertise for rare diseases, both of which were supposed to be operational by the end of 2014. However, no schedule for the adoption and implementation of the Second Plan was available by the end of 2013.

The Bulgarian Council of Ministers *did* approve a National Plan for Prevention of Non-communicable Chronic Diseases (2014-2020).

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Organisation of Rare Disease Health and Social Care (Centres of Expertise; ERNs; Integrated Care and Social Support)

Centres of Expertise

There is a national policy in place in Bulgaria regarding the designation of Centres of Expertise for rare diseases. Ministerial Ordinance No.16 was signed by the Bulgarian Minister of Health on 30th July 2014 and was promulgated in State Gazette on August 12th. This legislation was prepared by a Task Force at the Ministry of Health, established in 2013, which included health authorities, medical professionals and patient representatives.

The Task Force benefited from the extensive work of previous Task Forces, as well as the current EU recommendation on rare diseases. The Ordinance allows for the possibility of two or more medical institutions to apply as a single Centre of Expertise established on a base of functional cooperation. This is an important provision as expert centres are mandated to provide diagnosis, treatment, and follow up and rehabilitation of patients with rare diseases. Centres are explicitly required to bring together and to coordinate a multidisciplinary approach of a team of medical and non-medical specialists, in order to serve the specific medical, rehabilitation and palliative needs of rare disease patients and their families. Finally, all designated centres of expertise are required to participate to the National Registry for Rare Diseases. A period of designation lasts for up to 5 years and may be renewed. Designated centres are expected to put in place quality of care controls, including patient-reported outcomes. Centres are required to submit annual activity reports to a special Commission, which performs an external evaluation at the end of the designation period.

11 Centres comply with the national designation policy (equating to roughly 2 per million inhabitants)

European Reference Networks (ERNs)

Bulgaria has a formal process in place for the endorsement of Health Care Providers (HCPs) to participate as members or coordinators of an ERN. There are currently 6 HCPs participating as full members to 5 ERNs.

HCP Members	European Reference Networks (ERNs)
MHAT “Sveta Marina”	Endo-ERN
USHATE “Acad. Ivan Penchev”	Endo-ERN
Expert Center on coagolopathias and Congenital Anemias	ERN EuroBloodNet ERN EURO-NMD
University Hospital “Alexandrovska”	MetabERN
University Neurological Hospital “ST. Naum” Sofia	ERN-RND
Varna Expert Center of coagulopathies and rare anemias	ERN EuroBloodNet

Integration of Rare Diseases into Social Policies and Services

Specific actions exist to enable people with rare diseases to access general social/disability programmes; for example, training guidelines for social workers etc. There are specific actions undertaken by different stakeholders, mainly patient organisations, to provide information and training for patients, their families and caregivers. Various ‘daily life assistance’ programmes are available, for patients, family and carers. These programmes are organised at the municipal level and vary significantly across the country. Most importantly, they are not rare disease specific, they are general programmes which aim to support patients with disabilities and/or chronic conditions.

The officially designated Centres of Expertise for rare diseases -11 centres as of October 2016- are expected to facilitate multidisciplinary, holistic, continuous health care provision to rare disease patients and their families.

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Rare disease patients and their families can benefit from the ongoing programmes to support integration of people with disabilities and/or chronic conditions.

Rare Disease Registration

Bulgaria has neither national nor regional registries for rare diseases; however, specific disease registries do exist.

Despite the strong support of the European Commission and the adoption of a targeted national policy for the creation of national registries for rare diseases, a national registry for rare diseases does not yet exist in Bulgaria. One of the priorities of the Bulgarian National Programme for Rare Diseases (2009 – 2013) was the collection of epidemiological data for rare diseases in Bulgaria through the creation of a National registry. Ministerial Ordinance No.16 was signed by the Bulgarian Minister of Health, in regard to the acceptance of several sets of EU Committee of Experts on Rare Diseases (EUCERD) recommendations, namely on quality criteria for Centres of Expertise for rare diseases in Member States (adopted in October 2011), on informed decisions based on the clinical added value of orphan medicinal products (adopted in September 2012), on ERNs for rare diseases (adopted in January 2013), on rare disease patient registration and data collection (adopted in June 2013), and on the core indicators for rare diseases national plans and strategies (adopted in June 2013).

The information Centre for Rare Diseases and Orphan Drugs gathered information on the existence and functioning of epidemiological registries for rare diseases in Bulgaria. Consent forms and accompanying information was provided by 13 registries (list alphabetically below):

- National registry of adult patients with chronic myeloid leukaemia;
- 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.

Genetic Testing and Neonatal Screening

National guidelines for the performance of **genetic testing** in Bulgaria are regulated by the Health Act and the National Medical Genetics Standard. Genetic tests for the diagnosis of rare diseases are mainly provided by the National Genetic Laboratory (NGL). The NGL is a national reference laboratory which provides methodological guidance and control over the activities of the genetic laboratories and performs centralised specialist tests. It was established more than 35 years ago, through the initiation of biomedical analysis of various rare disorders and mass neonatal screening for PKU. At the moment, NGL provides routine diagnosis with DNA analysis (including prenatal and evaluation of carrier status) for many disorders: cystic fibrosis, phenylketonuria, Wilson disease, neuromuscular disorders, Niemann–Pick (in target population), beta thalassemia, galactokinase deficiency (in target population), microdeletions and microduplications syndromes, inborn hypothyroidism and others. The NGL also has the capacity to perform routine enzymatic analysis and GS/MS analysis for diagnosis of

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many rare disorders (Krabe, Pompe, MPS). In 2010 the laboratory introduced MS/MS analysis for the metabolic study of inherited disorders.

The government supports genetic testing by financing diagnostic kits and consumables. Genetic testing abroad is possible for diseases for which genetic tests are not available in Bulgaria, following commission approval (although there is no dedicated policy to facilitate cross-border genetic testing). Furthermore, clinical centres and individual research teams have the opportunity -through research projects funded by relevant universities and the Ministry of Education's Research Fund- to apply for routine implementation of molecular genetic diagnosis of certain rare diseases. In these cases, patient diagnosis is provided free of charge. According to the Orphanet database, genetic tests are available in Bulgaria for 34 genes and an estimated 84 diseases (Information extracted from the Orphanet database in Feb 2014).

One of the priorities of the National Plan was to improve the availability and accessibility of the current **screening** programmes. In 1979, mass neonatal screening was introduced in Bulgaria for phenylketonuria, galactosaemia (discontinued in 1993), congenital hypothyroidism and congenital adrenal hyperplasia. Today, newborn screening remains available for these 3 conditions…

- Phenylketonuria
- congenital hypothyroidism
- congenital adrenal hyperplasia

… through screening programmes coordinated by the University Maternity Hospital National Genetic Laboratory in Sofia for the metabolic screening programmes (phenylketonuria), and the University Paediatric Hospital in Sofia for the endocrine screening programmes (congenital hypothyroidism and congenital adrenal hyperplasia). These programmes cover the entire country, with more than 130 neonatal structures carrying out blood sampling 3-5 days after birth. Over 90% of neonates are included at present. Ordinance 26 of the Ministry of Health provides equal access to the neonatal screening programmes. However some problems remain, for instance the postponed mailing of screening cards to centralised labs, and the need for technological upgrades. It is expected that with the implantation of the Ministry of Health regulation on Centres of Expertise for rare diseases, the neonatal screening laboratories will be designated as Centres of Expertise as well, and they will be organised into a reference network.

Clinical Practice Guidelines and Training Activities

Clinical Practice Guidelines (CPGs)

There is no national policy to develop CPGs or Implement CPGs. There *is* a policy for adopting CPGs.

Ministerial Ordinance No.16 placed a substantial emphasis on the organisation of collaboration between medical treatment facilities to ensure the continuity of care between childhood, adolescence and adulthood, as well as the continuation of care between all stages of a rare disease. Applying institutions are scrutinised to demonstrate their high level of expertise and experience, documented by the volume of referrals, second opinions, peer-reviewed publications, grants, teaching and training activities.

Training and Education

In May 2016, the National Alliance of People with Rare Diseases (NAPRD), together with medical students, organised a one-day rare diseases training seminar. The seminar allowed medical students and specialists to become more familiar with key rare disease concepts, for example the definition of a rare disease, major issues and important initiatives. Topics such as transplantation and organ donation (in Bulgaria and abroad) were also discussed. Similar events have been planned by various patient organisations during the year, as patients try to raise awareness and improve knowledge of rare diseases among students.

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Information Resources for Rare Diseases

Orphanet Activities

Bulgaria has an operational National Orphanet team, currently hosted by the Bulgarian Association for Promotion of Education and Science, BAPES, and its project Information Centre for Rare Diseases and Orphan Drugs, ICRDOD. There was no dedicated funding in the national plan to support the functioning of the Orphanet team.

The team produces documents in the Bulgarian national language, and is in charge of collecting data on rare disease related services, i.e. specialised clinics, Centres of Expertise, medical laboratories, ongoing research, registries, clinical trials and patient organisations, which are entered into the Orphanet database.

National Helplines for Rare Disease

A helpline is in place in Bulgaria which is dedicated to rare diseases. It is funded through a mixture of private and public funding and is available for both patients and professionals. The Information Centre for Rare Diseases and Orphan Drugs, ICRDOD (2004) is specifically designed to meet the needs of rare disease patients, providing them with reliable information and opportunities to receive adequate diagnosis, treatment and follow-up and rehabilitation. A volunteer team, comprised of more than 20 leading medical professionals, supports the efforts of ICRDOD which has created an extensive rare disease open access online library in the Bulgarian language.

Official Information Centres

The Information Centre for Rare Diseases and Orphan Drugs, ICRDOD, is a project and activity of the Bulgarian Association for the Promotion of Education and Science (BAPES). It is a non-governmental, non-profit organisation, registered under the Bulgarian law on non-profit legal in 2003. ICRDOD is a free educational and informative service, providing information in both Bulgarian and English, which delivers personalised responses to requests from patients, families and medical professionals. It operates a bilingual website (www.raredis.org) and a rare disease helpline (+359) 32 57 57 97. The ICRDOD also provides a bi-monthly newsletter entitled “Rare Diseases & Orphan Drugs” which is distributed free of charge. The newsletter is published in two versions, Bulgarian (ISSN 1314-3581) and English (ISSN 1314-359X). The ICRDOD also provides an online registry of rare disease patients, and a rare diseases library in Bulgarian.

In 2010 ICRDOD started publishing papers which reviewed rare disease topics. The objective of these papers is to summarise topics in the field of rare diseases and to present complex medical information in a reader-friendly format. An example of the types of papers the ICRDOD publishes can be found in a report issued in July 2013, which reviewed access to medicines for rare diseases in Bulgaria. The report was divided into 4 sections:

- Orphan medicinal product designation and market authorisation
- Pricing, Inclusion in the Positive Drug list and reimbursement
- Mechanisms for accelerated access to Innovative medicines
- Conclusions

The Bulgarian Information Centre for Rare Diseases and Orphan Drugs (ICRDOD) released a report in 2012 listing and providing up to date information on the epidemiological registries for rare diseases in Bulgaria.

Rare Disease Research Activities

Bulgaria does not have any specific programmes or projects to fund or facilitate rare disease research. At present Bulgaria participates in neither E-Rare no IRDiRC.

The Bulgarian Association for the Promotion of Education and Science (BAPES) is a non-profit organisation which was established in 2003. The aim of the organisation is to raise awareness of rare diseases among the medical

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community and society as a whole. **BAPES helps to stimulate fundamental, clinical and public health research on rare diseases in Bulgaria** as well as promoting the development and provision of care and services for people with rare diseases and their families. BAPES is an active participant in all major European public health projects in the field of rare diseases, for instance RD PORTAL, EUROPLAN, EPIRARE, BURQOL-RD, RARE BESTPRACTICES, STORE and ASDEU.

BAPES has consecutively launched the Information Centre for Rare Diseases and Orphan Drugs, ICRDOD in 2004, the "RareDis" Medical Centre in 2009 and the Centre for Health Technology Assessment and Analysis CAHTA in 2013. The project activities are explicitly designed to meet the needs of rare disease patients and provide them with reliable information and opportunities for adequate diagnosis, treatment, follow-up and rehabilitation. Since 2013 ICRDOD, "RareDis" and CAHTA have been united in territory and function within a single institution, the Institute for Rare Diseases (IRD). IRD is one of the very first interdisciplinary and multifunctioning rare disease platforms in Eastern Europe. The Institute gives a comprehensive and coherent framework for rare diseases and orphan drugs in Bulgaria, helping to achieve the most important of BAPES objectives, to provide modern, accessible and quality care for peoples with rare diseases.

National Alliance of Patient Organisations and Patient Representation

Bulgaria has a national alliance for rare disease patient organisations: the National Alliance of People with Rare Diseases (NAPRD) is a non-governmental organisation bringing together patient organisations and individuals with rare diseases. It aims to create a link between the people with rare diseases and the representatives of the social and healthcare systems. NAPRD advocates for the right to timely and equal medical care, as well as the creation of adequate laws in the field of the protection of the rights of peoples with rare diseases. A NAPRD representative is also a member of the National Consulting Council on Rare Diseases within the Ministry of Health.

Orphan Medicinal Products (OMPs)

Approximately 20 OMPs with a European Union marketing authorisation are available in Bulgaria. There are *some* measures in place to facilitate access to OMPs for patients: the Institute for Rare Diseases has researched and elaborated a multi-criteria decision analysis value measurement model to access and appraise orphan drugs. This was achieved through the exploration of the preferences on the criteria's weights and performance scores through a stakeholder-representative survey and a focus group discussion that were both organised in Bulgaria (Iskrov G, Miteva-Katrandzhieva T and Stefanov R (2016) Multi-Criteria Decision Analysis for Assessment and Appraisal of Orphan Drugs. Front. Public Health 4:214.doi: 10.3389/fpubh.2016.00214). The model has been submitted to the Bulgarian Health authorities for consideration and implementation in cases of orphan drug assessment appraisal.

Rare Disease Day

The Institute for Rare Diseases hosted an event to celebrate Rare Disease Day in Plovdiv. Patients, doctors and volunteers gathered on 28 February in MC Raredis. Annually, there are several conferences, meetings and workshops which are focussed on rare diseases and designed for students, specialists and patients. The largest of these is the Conference for Rare Diseases and Orphan Drugs, which is held every year at the beginning of September. The conference aims to provide information about expert centres and reference networks, registries and epidemiological survey, health technology assessments for rare diseases and personalised care for rare disease patients.

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