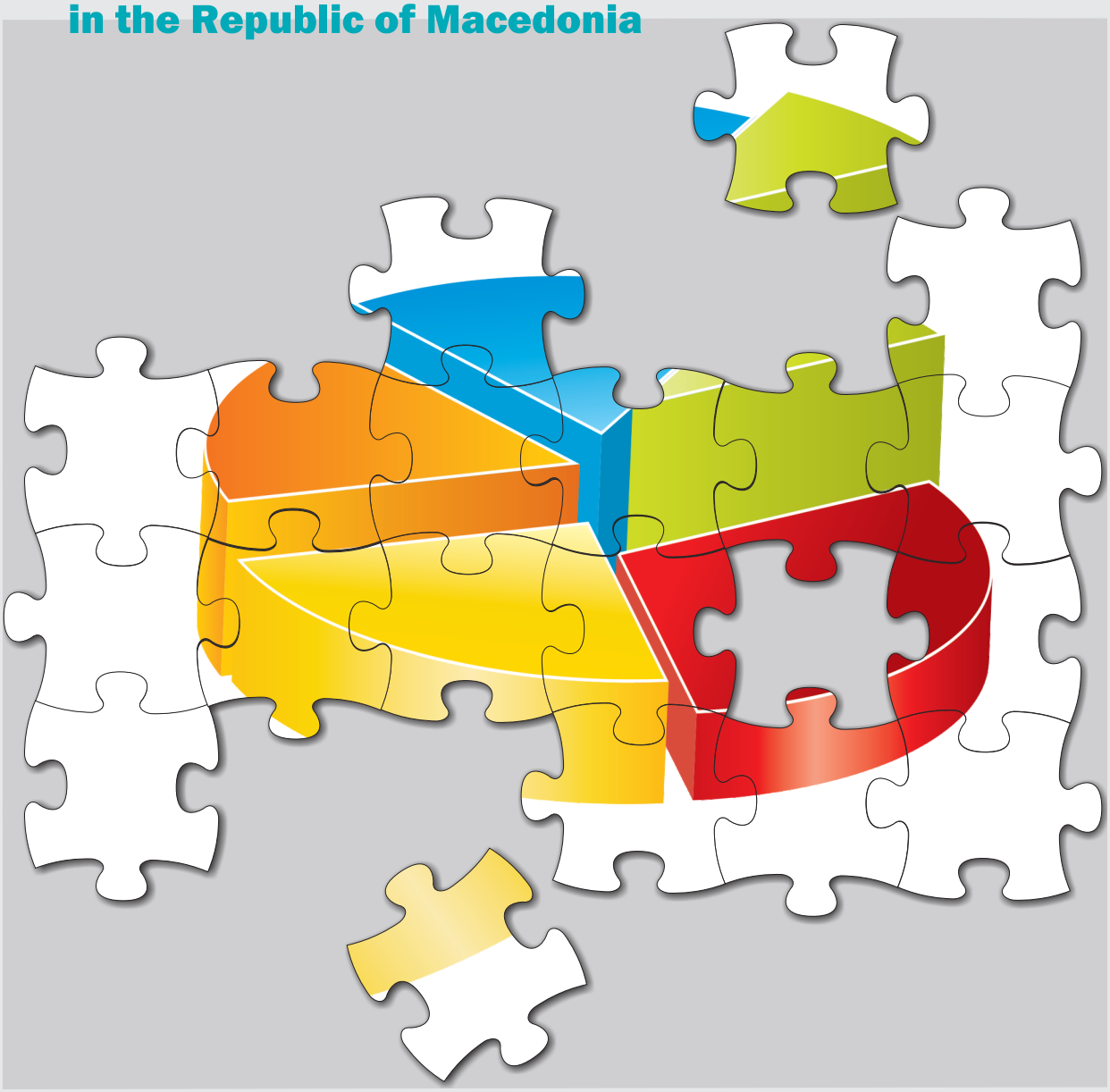
POLICIES, PRACTICES AND THEIR IMPACT ON THE QUALITY OF LIFE OF PEOPLE WITH RARE DISEASES

Comparative analysis and the situation in the Republic of Macedonia



ЖИВОТ СО ПРЕДИЗВИЦИ

Stefan Chichevaliev
Vesna Aleksovska

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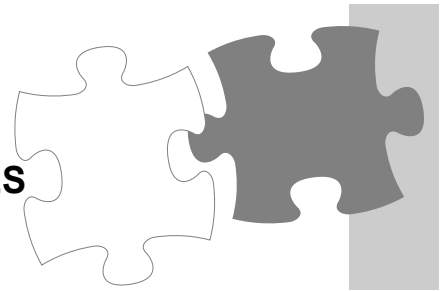

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FOREWORD

There are between 5,000-8,000 rare diseases, each of them with a prevalence of 0.1%, yet together they constitute a huge number affecting millions of lives globally.

The challenges posed by rare diseases are multiple and diverse and no single country, in particular smaller ones like Macedonia, can deal with these challenges independently. Yet, countries can and do join efforts and seize opportunities for addressing challenges of rare diseases so to gain benefits from global and regional efforts, especially in aspects of health, economic and social conditions, as well as quality of life and self-realization.

However, despite the recognizable progress in recent decades in improving the diagnosis, treatment and rehabilitation of rare diseases at national, regional and global levels, the need for better understanding of the unique challenges of rare diseases remains, especially in designing appropriate response measures in health and other sectors of social action.

This research is only a decimal piece of the big puzzle of life challenges posed by rare diseases, but it also applies to and draws lessons for all chronic diseases that affect the quality of life. Its purpose is to determine the situation, to explore opportunities and to make recommendations for achieving substantive improvements with the limited resources that every system is faced with.

We hope that this research will serve as a tool and a contribution in the dialogue on future research that should inform the policies for improvement of health and quality of life of people with rare diseases and those who care for them.

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LIST OF ABBREVIATIONS

EUROCAT	European Surveillance of Congenital Anomalies
EURORDIS	European Organization for Rare Disorders
HAE	Hunter syndrome, hereditary angioedema
HIFM	Health Insurance Fund of Macedonia
HP	Health professionals
ICD-10	International Classification of Diseases, 10th revision
MANU	Macedonian Academy of Sciences and Arts
NAHRB	National Alliance of People with Rare Diseases in Bulgaria
NARBM	National Alliance for Rare Diseases in Macedonia
NORBS	National Organization for Rare Diseases of Serbia
PCRD	Parents of children with rare disease/s
PRD	People with rare diseases
QoH	Quality of health
QoL	Quality of life
RD	Rare diseases
UC	University clinic
USA	United States of America
WHO	World Health Organization

EXECUTIVE SUMMARY

Conducted during 2015 and 2016, this study aims to understand the national situation and to respond to the challenges that the people with rare diseases are facing, as well as to create conditions for sustainable policy dialogue toward overcoming the main identified obstacles. The study brings into focus the people with rare diseases, their families and the health professionals whose opinions, experiences and suggestions (for improvement of the situation) were collected using quantitative (questionnaires) and qualitative (semi-structured questionnaires) methods. The obtained answers were analysed within the national context while taking into consideration the present sub-regional, regional and international relevant documents.

The study ascertains a degree of progress in regard to policies addressing rare diseases. However, it also indicates a series of weaknesses, particularly in the area of policy operationalization, primarily in terms of provision of an appropriate level of health service, which according to the respondents, is the key to maintaining high quality of life. On the other hand, they express a considerable level of satisfaction with their well-being and the wider societal environment (social skills, quality of life, psychological aspects, etc.), but there is room for improvement.

This study provides information on the five most important policy recommendations supported by the respondent groups:

1) Increasing financial support for medical treatment;
2) Awareness-raising among the professional community and the general public about the impact that rare diseases have on both the individual and the community;
3) Establishing international professional collaboration for the purpose of registering, monitoring, diagnosing, treating and research on rare diseases;
4) Operationalizing the definition, and introducing codification, classification and database of rare diseases;
5) Developing an integrated approach for detection, diagnostics, prevention and social integration for people with rare diseases and for their families at all levels of the health and social systems.

The recommendations point toward the need to initiate dialogue concerning the evidence-based policies and practices.

1. 1. INTRODUCTION

1.1. Definition, scope and challenges

Rare diseases are usually defined based on their prevalence.[1] They range from cystic fibrosis, haemophilia and Angelman Syndrome with an incidence of about 1 in 15,000 persons, to Opitz trigonocephaly syndrome, which is extremely rare with about one case in million people.[2]

A clear definition of the term "rare disease" is the basis for comprehensive understanding of the problem, of its essence and of the possibilities for effective action in the field. Article 3 of the Recommendation of the Council of the European Union[3] stipulates the definition of rare diseases adopted by the EU Member States, according to which rare disease is "any disease affecting fewer than 5 people in 10,000". This number may seem dismal but it translates into approximately 246 000 people throughout the EU's 28 member countries. Most patients suffer from even rarer diseases affecting 1 person in over 100,000. It is estimated that today in the EU, 5,000-8,000 distinct rare diseases affect 6-8% of the population i.e. between 27 and 36 million people.[4]

From a medical perspective, rare diseases often represent "chronic life-threatening conditions that affect multiple organs or organ systems and permanently weaken and disable the organism".[5] Hence, it is clear that under this approach, the term "rare disease" encompasses a wide range of clinical conditions classified in this group, in accordance with the epidemiological criterion of frequency, not solely on the basis of medical criteria. This represents a challenge not only for patients and those who care for them, but for the health system; rare occurrence of these diseases means that some of them are diagnosed in only a few thousands, hundreds or perhaps only several dozen people.

The myriad of challenges related to the rare diseases has been described in the academic and grey literature, drawing evidence from numerous empirical studies. For instance, the 2011 study of the Austrian Ministry of Health titled "Rare diseases

1 The number of cases of a disease existing in a given population at a specific period of time (period prevalence) or at a particular moment in time (point prevalence). Medical dictionary, Available: http://medical-dictionary.thefreedictionary.com/prevalence, Accessed: 06.12.2015

2 Bulletin of the World Health Organization, Coming together to combat rare diseases, Available: http://www.who.int/bulletin/volumes/90/6/12-020612/en/, Accessed: 06.12.2015

3 Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02), Available: http://ec.europa.eu/health/rare_diseases/policy/index_en.htm, Accessed: 06.12.2015

4 Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02), Available: http://ec.europa.eu/health/rare_diseases/policy/index_en.htm, Accessed: 06.12.201

5 Austrian National Action Plan for Rare Diseases 2014-2018, Available: http://www.europlanproject.eu/DocumentationAttachment/Austrian%20National%20action%20plan%20for%20rare%20diseases%20(2014-%202018)_Executive%20Summary-%20english%20(en).pdf, Accessed: 25.12.2015

in Austria"[6,7] indicates many complex challenges, such as the knowledge on rare diseases among HPs, the health policy and the general public sources of information; the existence of specialized institutions and clinical coordination among different care levels – especially among clinical practice and long-term care; a system of centralized data registry and collection; as well as, defining standards and provision of quality and efficiency in diagnostics, clinical treatment, therapy and rehabilitation.

One of the first challenges that patients with a rare disease face is diagnosis. The small number of patients and the similarity of symptoms in some rare diseases to other conditions complicate the timely accurate diagnosis.

Unlike for the more common diseases, health professionals have limited knowledge and skills for RD diagnosis and treatment. The low incidence of these disorders allows for a limited number of health professionals, most often in the specialized centres, to build their expertise in diagnosis and provision of adequate health care. Some countries are encouraging building expertise on certain rare diseases through specialized programs and strategic documents and financed by public funds.

After determining the correct diagnosis, the next challenge for patients is identifying opportunities for treatment. For many rare diseases, there is no specific therapy, primarily due to the lack of economic interest of the industry to develop such medicines, but also due to small size of patient cohorts, preventing full-scale clinical trials under the principles of good scientific practice.

A specific therapy has already been developed for the treatment of some rare diseases, falling into category of the so-called orphan drugs. According to the European Regulation on orphan medicinal products[8], an orphan drug is any drug intended for: a) a life-threatening or chronically debilitating condition; b) a condition affecting not more than 5 in 10,000 persons or as a medicinal product that is unlikely to generate sufficient return on investment without any incentives; and c) a condition for which there is no alternative method of treatment which provides satisfactory results or if such method exists, the medicinal product gives more benefit compared to the available alternative methods. Having in mind the research expenses and the good production practice standards, some countries allocate funds in their budgets for the purpose of stimulating such research and production.

To date, none of the 28 Member States of the European Union, regardless of the size and level of organization of their health systems, can cope with the issue of offering treatment for the entirety of the rare diseases spectrum. "Even in the UK [with a population of 62 million] some patients have to be sent overseas for treatment".[9]

This fact is supporting the claim that combined efforts for early detection and diagnosis, proper treatment and social support to improve and maintain the quality of life are needed; as well counselling as part of the activities for family planning, which would enable prevention of occurrence of new cases.

6 Voigtländer et al, Seltene Erkrankungen in Österreich", 2012), Available: http://bmgiis02.bmgfj.gv.at/BDBExtern/BrochureDownload.ashx?sel=WmR4NGlYdGVvY1VRV0RCSnpsWGxKQT090, Accessed: 25.12.2015

7 Austrian National Action Plan for Rare Diseases 2014-2018, Available: https://ec.europa.eu/health/rare_diseases/docs/national_plans_at_2014_2018_seltene_arkrankungen_sum_english.pdf, Accessed: 25.12.2015

8 Regulation (Ec) No 141/2000 Of The European Parliament And Of The Council of 16 December 1999 on orphan medicinal products), Available: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:en:PDF, Accessed: 06.12.2015

9 Bulletin of the World Health Organization, Coming together to combat rare diseases, Available: http://www.who.int/bulletin/volumes/90/6/12-020612/en/, Accessed: 06.12.2015

In addition, many European countries have endorsed strategies and plans that envisage:

- Mapping of rare diseases in health and social care systems;
- Promotion of medical/clinical treatment;
- Improvement of diagnostic practice, treatment and their access to patients;
- Promotion of research in the field, of the general knowledge and awareness, and epidemiology (registries of diseases);
- Collaboration between governmental and non-governmental sectors;
- Visibility of the problem;
- Prevention and early treatment, diagnostic standards, information system;
- The role of the primary health care as the point of first contact with health services;
- The safety of patients and the competence of health professionals to provide objective, quality and specific patient-focused information;
- Determining frameworks for monitoring and impacting assessment of policies and plans in practice.[10,11]

The national experience shows that a progress has been made since 2009 when the Ministry of Health introduced the Program for Treatment of Rare Diseases[12], based on the Law on Health Care.[13]

Initiated with the aim to understand the existing policies and practices in dealing with RD in the country as well as their impact on the quality of life for PRD, this study provides guidance and recommendations for action.

This study also contains a comparative analysis of policies and legislation in selected countries (Bulgaria, Serbia, Croatia and Slovenia), with the aim to provide information on the issue, policies and practices within similar socio-economic contexts and related to the activities of the European Union[14] for promotion of the current status of rare diseases, including:

1. Introduction of adequate codification and monitoring within the health information system;
2. Endorsement of national plans for rare diseases;
3. Creation of reference networks of specialized centres;
4. Collection and exchange of screening practices for rare diseases, and
5. Introduction of and keeping registries for rare diseases.

10 Patients' Priorities and Needs for Rare Disease Research 2014-2020, 2011, Available: http://www.eurordis.org/sites/default/files/publications/what_how%20_are_disease_research_0.pdf, Accessed: 02.03.2016

11 Overview of the National Rare Disease Policies, Available: http://www.eurordis.org/content/overview-national-rare-disease-policies, Accessed: 02.12.2015

12 Program for Treatment of Rare Diseases for 2009 in the Republic of Macedonia (Official Gazette No.45/09); Available: http://www.slvesnik.com.mk/Issues/0145DC355953F340BB9BD13F8D098B80.pdf, Accessed: 02.12.2015

13 Law on Health Care (Official Gazette of the Republic of Macedonia, No. 43/12, 145/12, 10/13), Available: http://www.fzo.org.mk/WBStorage/Files/3._ZAKON_ZA_ZDRAVSTVENATA_ZA[TITA_(PRE%5EISTEN_TEKST)_10_od_17.01.2013.pdf, Accessed: 25.12.2015

14 National plans or strategies for rare diseases), Available: http://ec.europa.eu/health/rare_diseases/national_plans/detailed/index_en.htm, Opened: 01.03.2016.

1.2. Basic epidemiologic data

To present day, there are between 5,000 and 8,000 rare diseases identified, the majority being genetic in origin. The rough estimate indicates that 1 in 15 people suffers from a rare disease i.e. 350 million people globally,[15] out of which 30 million live in Europe[16] and another 30 million in the USA.[17] With the above said, the rare diseases constitute a global health issue.

In the USA, in the last several decades, over 400 medicinal products have been approved as therapy for more than 200 symptoms related to rare diseases, and in EU over 70 products for around 45 indications[18] have been approved in the EU.

In the EU, nearly 246.000 people are diagnosed with a rare disease. The majority of patients suffer from diseases that affect 1 in 100.000 or more people. Considering the fact that 6-8% of the world population are affected by rare diseases[19], it is estimated that there are 27-36 million PRD living in Europe today. [20,21]

Scarce data on the epidemiology of rare diseases at national and global level is mostly due to the lack of records on a regional or national level, and indirectly to the incompleteness of the International Classification of Diseases - Tenth Revision (ICD-10), in which a huge number of rare conditions are not described and have no custom code.

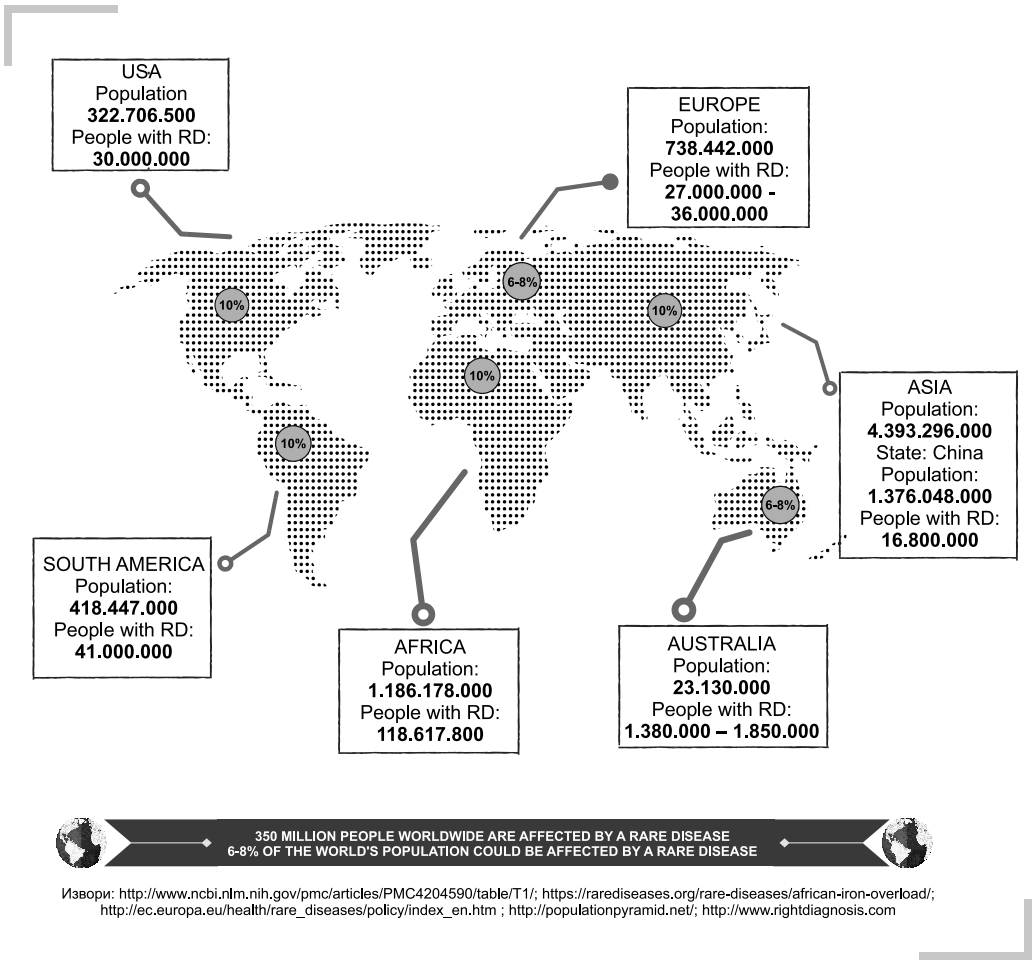
In recent years, there is and increased interest in RD, but there are still open questions about the lack of a unified and internationally recognized system of classification and codification, which will aid in the collection of the necessary epidemiological data that could be used for making evidence-based policies with the ultimate goal - improving the health and social status of the PRD.

1.3. Policies and legislation

During the last decade, the world has clearly understood the need of developing international mechanisms for addressing RD. According to the International Rare Diseases Research Consortium, the collaboration at international level stimulates, coordinates better and maximizes the rare disease research efforts around the world.[22] The European Union invests efforts in pooling the limited resources of some EU Member States to make it easier for PRD and health professionals to share information and expertise, particularly in the field of cross-border cooperation.[23]

15 RARE Diseases: Facts and Statistics, Available: https://globalgenes.org/rare-diseases-facts-statistics/, Accessed: 06.12.2015
16 RARE Diseases: Facts and Statistics, Available: https://globalgenes.org/rare-diseases-facts-statistics/, Accessed: 06.12.2015
17 RARE Diseases: Facts and Statistics, Available: https://globalgenes.org/rare-diseases-facts-statistics/, Accessed: 06.12.2015
18 Priority Medicines for Europe and the World "A Public Health Approach to Innovation" Update on 2004 Background Paper (2014)), Available: http://www.who.int/medicines/areas/priority_medicines/BP6_19Rare.pdf, Accessed: 06.12.2015
19 Quick facts on rare diseases, Available: http://www.health24.com/Medical/Genetics/Genes-and-disease/Quick-facts-on-rare-disease-20130228, Accessed: 26.12.2015
20 European Council, Available: http://ec.europa.eu/health/rare_diseases/policy/index_en.htm, Accessed: 28.12.2015
21 Priority Medicines for Europe and the World "A Public Health Approach to Innovation" Update on 2004 Background Paper (2014)), Available: http://www.who.int/medicines/areas/priority_medicines/BP6_19Rare.pdf, Accessed: 06.12.2015
22 Paul Lasko, International Rare Disease Research Consortium: State of the Art, 2014, Available: http://www.rare-diseases.eu/wp-content/uploads/2014/05/0301_Paul_Lasko.pdf, Accessed 01.03.2016
23 Identifying rare diseases, Available: http://ec.europa.eu/health/rare_diseases/orphanet/identification/index_en.htm,

Figure 1. Rare diseases at a global level: estimated size of the problem



Извори: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4204590/table/T1/; https://rarediseases.org/rare-diseases/african-iron-overload/; http://ec.europa.eu/health/rare_diseases/policy/index_en.htm ; http://populationpyramid.net/; http://www.rightdiagnosis.com

1.3.1. European Union

Overview

The increased interest in legal regulation of the diagnostics, treatment and provision of higher quality of life for PRD in the EU countries dates back to the last century. In 1994, the European Commission launched 23 projects within the BIOMED 2 Program, which included activities related to rare diseases as well.[24] The Commission made the

Accessed: 01.03.2016

24 Anton Leis Garcia, The Regulation of Orphan Drugs: a US – EU Comparative Perspective, This paper is submitted to satisfy both the academic requirements for the course "Food and Drug Law" of the Harvard Law School curriculum (Winter Semester 2004) and the Writing requirement of the LL.M. Program), March 2004, p.5, Available: leda.law.harvard.edu/leda/data/621/Orphan_Drugs_RTF.rtf, Accessed: 20.12.2015

next step by characterizing rare diseases as “a priority action area” for the European Union, which has resulted in submission of a proposal to the European Parliament and the European Council and ultimately, in the endorsement of the EU Program of Rare Disease Activities 1999-2003.[25] Every following action of the EU favoured determined and comprehensive regulation of the health care for PRD. These activities of the EU institutions – engaging national and regional organizations of patients and experts in the fields of health and social care – lead to the adoption of an important document of the Commission titled “European Challenges”, which is one of the most significant steps undertaken by the Commission.[26] Further on, the Commission submitted a proposal for adoption of an EU Recommendation for actions in the field of rare diseases, which was endorsed on 8 June 2009.[27] Nowadays, these two documents serve as an imperative for legal regulation in this area and as a legal basis for any subsequent joint strategy on rare diseases of the EU Member States, supporting the national health systems in the process of diagnosis, treatment and care for people with rare diseases.[28]

In addition, a three-year project in the field of public health titled “EUROPLAN – European Project for Rare Diseases National Plans Development” was implemented in the period 2008-2011, aiming at adopting the recommendations for difining national and regional rare diseases plans/strategies i.e. at promoting plans and at advising on their endorsement and implementation. This project resulted in the adoption of the document “EUROPLAN: Recommendations for the development of national strategies for rare diseases” which serves as a significant basis for adopting minimal standards for endorsement and implementation of national plans for rare diseases, as it builds upon the experience of a number of EU Member States.[29]

In 2012, the process of rare diseases research and regulation continues within a new three-year-long project EUROPLAN 2012-2015 in the previously defined directions: establishment of international network, promotion of collaboration and technical support of the participants in the process of health and social policy creation - to catalyse the process of endorsement and implementation of national plans/strategies with active involvement of the organizations for rare diseases. The final goal of these two projects is the adoption of a joint strategy for rare diseases that would refer to the entire European Union. However, such strategy has not yet been adopted.

In regard to rare diseases, the European Union has set out the following objectives: improving the recognition and visibility of rare diseases, supporting the development of national policies on rare diseases in its Member States and developing cooperation,

25 Anton Leis Garcia, The Regulation of Orphan Drugs: a US – EU Comparative Perspective), March 2004, p.5, Available: leda.law.harvard.edu/leda/data/621/Orphan_Drugs_RTF.rtf, Accessed: 20.12.2015

26 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), Available: ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf, Accessed: 20.12.2015

27 Council Recommendation on action in the field of rare diseases, Concil of the European Union, Brussels, 2009 Available: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF, Accessed: 26.12.2015

28 Sanja Stojkovic-Zlatanovic, National Plan For Rare Diseases – Comparative Legal Review, Available: https://www.researchgate.net/publication/259026326_Nacionalni_plan_za_retke_bolesti_-_uporednopravni_prikaz_Strani_pravni_zivot_br_12013_str_291-306, Accessed: 26.12.2015

29 Sanja Stojkovic-Zlatanovic, National Plan For Rare Diseases – Comparative Legal Review, Available: https://www.researchgate.net/publication/259026326_Nacionalni_plan_za_retke_bolesti_-_uporednopravni_prikaz_Strani_pravni_zivot_br_12013_str_291-306, Accessed: 26.12.2015

coordination and regulation for rare diseases at EU level.[30] For the purposes of achieving these objectives, the Council Recommendations on the implementation of EU activities in the field of rare diseases are as follows:

- Adoption of national plans for rare diseases in all Member States - to provide equal access to quality health care, including diagnosis, treatment and use of orphan drugs on the basis of equality and solidarity for all people affected by rare diseases across the entire EU;
- Introduction of both a common definition and an adequate codification of rare diseases for the purpose of visibility and recognition within the health system, as well as creation and organization of a unique dynamic list of rare diseases;
- Encouraging research of treatment options for rare diseases;
- Establishing centres for rare diseases and a European network of reference centres for rare diseases;
- Establishing common expertise in the field of rare diseases at European level;
- Strengthening organizations of people affected by rare diseases; and
- Ensuring sustainability of all planned activities in the field of rare diseases.

1.3.2. Addressing rare diseases in selected countries

Within the EU, all countries, through continued efforts give their contribution in realizing the common vision for RD, although the progress in dealing with RD is not the same in all Member States. Macedonia, through its strategic goal of EU membership is aspired towards achieving the given recommendations in this area.

To observe the developments in Macedonia in relation to the EU, it is necessary to make a comparative analysis of the policies and practices of the Member States, as well as with some of the candidate countries for membership, which would determine whether Macedonia is on the right discourse in the implementation of the EU recommendations, regarding the application of the established standards. To this end, four countries are selected for comparison: Bulgaria, Slovenia and Croatia as EU member states and Serbia as a candidate for EU membership. Despite this, several criteria were taken into account for selecting these countries: geographic position, similarity of health systems and specific focus on rare diseases.

30 Draft-National Program for Rare Diseases 2014-2019; 2014; Available: https://zdravlje.gov.hr/pristup-informacijama/savjetovanje-sa-zainteresiranom-javnoscu-1475/okoncana-savjetovanja/savjetovanja-u-2014-godini/nacrt-nacionalnog-programa-za-rijetke-bolesti-za-razdoblje-2014-2019-1712/1712, Accessed: 27.11.2015

Bulgaria

Bulgaria still lacks comprehensive health policy on rare diseases, which is responsibility of the Member States of the EU. Issues related to prevention, diagnosis and treatment of some rare diseases are partially represented in various national programs and laws, but without a comprehensive solution for many of the issues of medical, social and ethical nature.

Definition

The country has accepted the EU definition for rare diseases: a rare disease is any condition that occurs in no more than 5 in 10,000 people.[31]

Classification and codification

The country is currently using the ICD-10. There is no separate system of classification and codification of rare diseases.[32]

Policies and regulation

National Program for Rare Diseases. The first National Program for Rare Diseases in Bulgaria[33] comes into force in 2009 along with a 2009-2013 Action Plan. The purpose of this program is to create an appropriate institutional framework and mechanisms for ensuring timely prevention, diagnosis, optimal treatment and rehabilitation of PRD (genetic, congenital malformations and non-heritable diseases) in Bulgaria. Furthermore, it indicates the need of establishing six reference-information centres on rare diseases, with a main objective - the creation of a national network.[34] The Network's principal functions are: data sharing and harmonization in relation to the implementation of the National Program for Rare Diseases, enabling functionality of the National Rare Diseases Registry, ensuring equal access to information and planning data collection at regional and national levels.

In accordance with the institutional framework for implementation of the National Program for Rare Diseases in Bulgaria shown in Figure 2, the National network of reference-information centres on rare diseases provides data to the National rare disease patient registry which serves the National Council for rare diseases as the basis for preparation and submission of proposals to the relevant authorities: the Ministry of Health in the context of implementation of the National Program for Rare Diseases in Bulgaria.

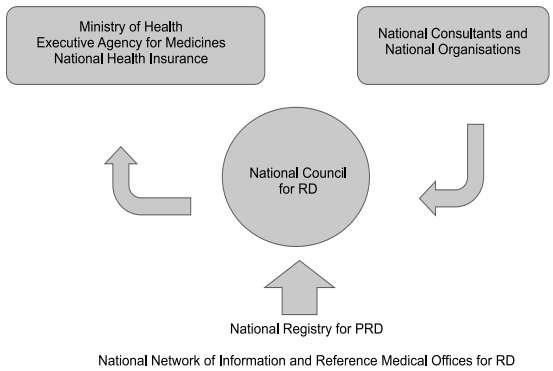
31 National Program for Rare Diseases 2009-2013 (in Bulgarian: Национална програма за редки болести 2009 – 2013, Р.Бугарија), Available: http://www.mh.government.bg/media/filer_public/2015/04/17/programa-redki-bolesti-2009-2013.pdf, Accessed: 27.12.2015

32 National Program for Rare Diseases 2009-2013 (in Bulgarian: Национална програма за редки болести 2009 – 2013, Р.Бугарија), Available: http://www.mh.government.bg/media/filer_public/2015/04/17/programa-redki-bolesti-2009-2013.pdf, Accessed: 27.12.2015

33 National Program for Rare Diseases 2009-2013 (in Bulgarian: Национална програма за редки болести 2009 – 2013, Р.Бугарија), Available: http://www.mh.government.bg/media/filer_public/2015/04/17/programa-redki-bolesti-2009-2013.pdf, Accessed: 27.12.2015

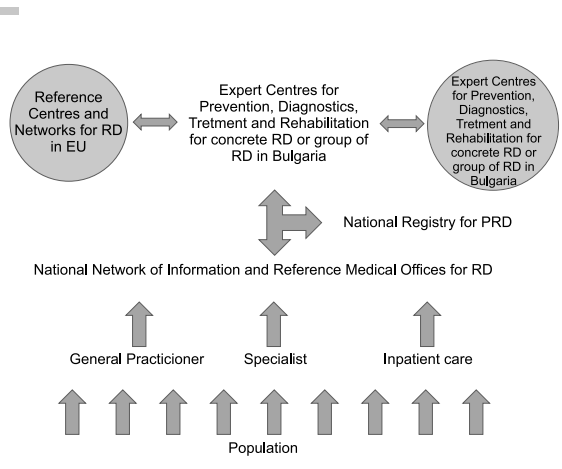
34 National Program for Rare Diseases 2009-2013 (in Bulgarian: Национална програма за редки болести 2009 – 2013, Р.Бугарија), Available: http://www.mh.government.bg/media/filer_public/2015/04/17/programa-redki-bolesti-2009-2013.pdf, Accessed: 27.12.2015

Figure 2. Institutional framework for implementation of the National Program for Rare Diseases in Bulgaria



Through primary health care, the patient is moved towards the secondary (specialist and hospital care) and tertiary (specialized centres) levels of care within the health care system. The relevant data is collected in the National rare disease patient registry, which gathers and shares information with Expert centres for prevention, diagnostic, treatment and rehabilitation of a particular rare disease or of a group of diseases in Bulgaria. After being diagnosed, PRD are referred to the Reference centre for rare diseases in the country and, if needed, to other Reference centres and networks for rare diseases in the EU. The path of the patient through the health system is shown in Figure 3.

Figure 3. Expected movement of the patients with rare diseases through the system



The National program has nine priorities:

1. Provision of epidemiological data on RDs in Bulgaria by establishing a National registry;
2. Improvement of genetic RDs prevention by expanding screening programs;
3. Improvement of genetic rare diseases prevention and diagnostic by introducing new genetic testing, decentralizing of laboratory testing activities and ensuring facilitated access to medico-genetic consultation;
4. Integrated approach in prevention, diagnostics, treatment and social inclusion of patients and their families;
5. Improvement of professional qualifications of practitioners in the field of early diagnosis and prevention of rare diseases;
6. Research on the need, possibility and criteria for establishment of a reference centre for rare diseases;
7. Launch of a national campaign for awareness-raising on rare diseases and their prevention;
8. Support and collaboration with CSOs and associations of PRD;
9. Close cooperation with other EU Member States regarding the objective of the program for cooperation with the expert group on rare diseases within the European Commission Directorate General Health and Consumers Affairs.

The Commission on rare diseases prepares a list of rare diseases and appoints hospital wards and units as centres of excellence for specific RD.

The results from the implementation of the National Programme for rare diseases is expected to contribute to improving the possibilities for timely diagnosis, treatment and rehabilitation. Although this program ended in 2013, Bulgaria has not yet adopted a new one. A positive development in addressing the rare diseases in the country can be noted in the work of the National Association of People with Rare Diseases, including representation and advocacy for patients as well as monitoring the procedures for obtaining treatment in the country or abroad.[35]

Financing

In 2004, with a Decree of the Council of Ministers,[36] the "Fund for Treatment of Children"[37] Centre was established as a separate legal entity. The Fund is an appellate

35 National Program for Rare Diseases 2009-2013 (in Bulgarian: Национална програма за редки болести 2009 – 2013, Р.Бугарија), Available: http://www.mh.government.bg/media/filer_public/2015/04/17/programa-redki-bolesti-2009-2013.pdf, Accessed: 27.12.2015

36 Decree No. 280/ 18.10.2004 establishing the center "Fund for Treatment of Children" which comes into force on 29.10.2014 (Official Gazette No.96, 29 October 2004, amended Official Gazette No.28, 4 April 2006, amended and complemented Official Gazette No.27, 9 April 2010. Amended and complemented Official Gazette No.38, 17 May 2011г., amended Official Gazette No. 70, 9 September 2011, amended Official Gazette No. 30, 17 April 2012) (In Bulgarian: Постановление № 280 от 18 октомври 2004 г. За създаване на център "фонд за лечение на деца" сила от 29.10.2004 г. (Обн. ДВ. бр.96 от 29 октомври 2004г., изм. ДВ. бр.28 от 4 април 2006г., изм. и доп. ДВ. бр. 27 от 9 април 2010г., изм. и доп. ДВ. бр.38 от 17 май 2011г., изм. ДВ. бр.70 от 9 септември 2011г., изм. ДВ. бр.30 от 17 април 2012г.)), Available: http://cfld-bg.com/new/document-1297, Accessed: 25.12.2015

37 Center "Fund for Treatment of Children" (In Bulgarian: **Център "Фонд за лечение на деца")** Available: http://cfld-bg.

body with earmarked budget operated by the Minister of Health. This body provides actions for organizational and financial support for children up to age of 18, in need of diagnostic and therapeutic procedures that are not available in the country; the Fund is especially supportive of children with extremely rare diseases. In March 2006, with the approval of the Government and modifications related to the Centre's activities, the right to financial support has been warranted to children up to the age of 18 for medicinal products that cannot be obtained in the country, or the available therapy does not give proper therapeutic response.

Registries and data

One of the priorities of the National Program for RD is the creation and maintenance of the National Registry. Within this priority, it is foreseen the establishment and maintenance of local registers of: PRD; the clinical trials of RD on the medical universities, colleges and institutions; and available diagnostic tests in the region.[38] The Information Centre on Rare Diseases and Orphan Drugs has published an overview of epidemiological data on rare diseases in Bulgaria. This report provides information on the development and cooperation in the area until 2014. While the development of the National Rare Diseases Registry is still ongoing, the country has joined the Orphanet registry and is currently developing a national Orphanet website.[39]

Health care services

The National Genetics Laboratory and the Centre for Molecular Medicine at the Medical University in Sofia have modern equipment and unique-for-Bulgaria robotic systems for major research in the field of genetic diagnostics. Also, as a result of the adopted Decree,[40] three expert centres for rare diseases were established in February 2016, in the areas of: hereditary neurological and metabolic diseases[41], primary immunodeficiency disorders[42] and for Fabry disease.[43]

The Centre for hereditary neurological and metabolic diseases covers 15 genetic diseases (progressive muscular dystrophy – types: Duchenne and Becker, myotonic, facioscapulo-humeral and limb-girdle dystrophies, distal myopathy, congenital myasthenia, familial amyloid polyneuropathy, spinal muscular atrophy, Gaucher's disease, Pompe

com/new/bg, Accessed: 06.12.2015

38 National Program for Rare Diseases 2009-2013 (In Bulgarian: Национална програма за редки болести 2009 – 2013, Р.Бугарија), Available: http://www.mh.government.bg/media/filer_public/2015/04/17/programa-redki-bolesti-2009-2013.pdf, Accessed: 27.12.2015

39 Rare diseases registries in Bulgaria (In Bulgarian: Регистри за редки болести в България), Available: http://www.raredis.org/?p=5998&lang=bg, Accessed: 24.03.2016

40 In accordance with the Decree No.16 adopted on 30 July 2014 regulating the conditions for rare diseases registration and the expert centers and reference networks for rare diseases (In Bulgarian: НАРЕДБА № 16 от 30 юли 2014 г. за условията и реда за регистриране на редките заболявания и за експертните центрове и референтните мрежи за редки заболявания), Available: http://dv.parliament.bg/DVWeb/showMaterialDV.jsp;jsessionid=DF2E8129D0E08EDA20B9BEF29C56A529?idMat=87157, Accessed: 24.03.2016

41 Under the guidance of Prof. Dr. Ivajlo Trnev

42 Under the guidance of Prof. Dr. Elisaveta Naumov

43 Under the guidance of Prof. Dr. Emil Paskalev

disease, Niemann-Pick disease types B and C and Wilson's disease) and provides prevention, diagnosis, treatment, monitoring and rehabilitation to patients affected by the aforementioned rare diseases coming from Bulgaria and the neighbouring countries.

The Centre for primary immunodeficiency disorders works by established algorithms for diagnosis and treatment of patients, developed on the basis of recommendations of the European Society for Immunodeficiency Disorders (ESID) and Pan-American Group of Immunodeficiency Disorders (PAGID).

The Centre for Fabry disease has an interdisciplinary team of nephrologists, neurologists, cardiologists, ophthalmologists, dermatologists, pulmonologists and gastroenterologists, which monitor the condition of patients suffering from Fabry disease.[44]

Orphan drugs and treatment

In 2005, the Decree no. 22[45] was adopted, which determines the conditions and the procedure for the use of drugs intended for treatment of rare diseases and the Decree on criteria, conditions and rules for inclusion of drugs in the positive list in the Republic of Bulgaria[46], which regulate the financing and use of medicines for treatment of rare diseases.

In relation to the regulatory framework, the Law on Medicines and Pharmacies regulates the regimen of drugs intended for the treatment of rare diseases and the so-called "orphan drugs", in compliance with both the Regulation No 141/2000/EU[47] and the Regulation 847/2000/EU.[48] These legal documents specify the criteria, conditions and procedure to determine the drugs intended for diagnostics, prevention and treatment of RD, as well as the conditions under which the holder of approval for use of such drug has the exclusive right in the market for a period of six or ten years.

The treatment for people with rare diseases is covered by the Ministry of Health as per the Decree No.34 which stipulates that the treatment of Bulgarian citizens suffering from certain diseases that do not fall into the mandatory health insurance are financed by the state budget.[49] such as: Thalassemia Major, congenital coagulopathy, Gaucher's disease, Wilson's disease, cystic fibrosis and other.

44 Three expert centers for rare diseases start operating within UMBAL "Aleksandrovska" (In Bulgarian: В УМБАЛ "Александровска" стартират три експертни центъра по редки болести), Available: http://alexandrovska.com/display.php?bg/%D0%B0%D0%BA%D1%82%D1%83%D0%B0%D0%BB%D0%BD%D0%BE/2422, Accessed: 24.03.2016

45 Decree No.22 adopted on 18 July 2015 on conditions and approval procedure for the use of medicines intended for treatment of rare diseases (Official Gazette No.62/05) (In Bulgarian: Наредба № 22 от 18 юли 2005 г. За условията и реда за разрешаване за употреба на лекарствени продукти, предназначени за лечение на редки заболявания (Обн. ДВ. бр.62 от 29 Юли 2005г.), Available: http://www.biomeda.biz/uploads/files/laws/Naredba.redki.zab.rtf, Accessed: 06.12.2015

46 Decree on criteria, conditions and rules for inclusion of drugs in the positive list in the Republic of Bulgaria (Official Gazette No.110/2007) (In Bulgarian: Наредба за критериите, условията и правилата за включване на лекарствени продукти в позитивния лекарствен списък в Република България (Отм. ДВ. бр.110/2007г.)), Available: http://econ.bg/Нормативни-актове/Наредба-за-критериите-условията-и-правилата-за-включване-на-лекарствени-продукти-в-позитивния-_l.l_i.127150_at.5.html, Accessed: 06.12.2015

47 Regulation (Ec) No 141/2000 of The European Parliament and of The Council), Available: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:en:PDF, Accessed: 06.12.2015

48 Commission Regulation (Ec) No 847/2000), Available: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:103:0005:0008:en:PDF, Accessed: 06.12.2015

49 Decree No. 34 adopted on 25 November 2005 on the payment of treatment for Bulgarian citizens from the State budget for diseases uncovered for by the compulsory health insurance (amended Official Gazette No. 95 from 18 November 2014) (In Bulgarian: Наредба № 34 от 25 ноември 2005 г. за реда за заплащане от републиканския бюджет на лечението на българските граждани за заболявания, извън обхвата на задължителното здравно осигуряване (изм. ДВ. бр.95 от 18 Ноември 2014г.)), Available: http://www.lex.bg/bg/laws/ldoc/2135513452, Accessed: 06.12.2015

Activism and support

National Alliance of People with Rare Diseases. The National Alliance of People with RD[50] was established in Bulgaria in 2007 to mediate between PRD and the health care system, and to advocate for the basic human right to equal and modern medical care.[51]

In Bulgaria, as in many countries around the world, PRD face a myriad of unsolved medical and social problems, which remain unknown and hidden from the public. These people are vulnerable and discriminated because they are denied one of the fundamental human rights i.e. the right of access to adequate health care and to information about their disease. The problems that PRD face also affect their loved ones and further burden their families, the community and the entire society.[52]

So far, the National Alliance of People with Rare Diseases has successfully helped three people who underwent lung transplantation in Vienna. Thanks to the efforts of the Alliance, the costs were covered by the State budget, which is considered a big victory and a big step forward in the fight against rare diseases. The last of the three cases was in July 2015 when the lung transplantation was done following a 6-month waiting period for a transplant.[53]

50 In original: Национален алианс на хората с редки болести

51 National Alliance of People with Rare Diseases (In Bulgarian: Национален алианс на хората с редки болести), Available: http://rare-bg.com/?page_id=2, Accessed: 06.12.2015

52 National Rare Diseases Program 2009-2013 (In Bulgarian: Национална програма за редки болести 2009 – 2013, Р.Бугарија), Available: http://www.mh.government.bg/media/filer_public/2015/04/17/programa-redki-bolesti-2009-2013.pdf, Accessed: 27.12.2015

53 News from the Sixth National Conference on Rare Diseases (In Bulgarian: новини от шестата национална конференция по редки болести пловдив 2015), Available: http://tinyurl.com/jyyxncl, Accessed: 27.12.2015

Serbia

Serbia has not yet developed and implemented a national program/strategy for rare diseases although it has been estimated that more than 400.000 of its citizens suffer from a rare disease.[54,55,56] In the past several years, certain initial steps have been undertaken towards solving the problems of people and families with rare diseases.

Definition

The country has accepted the EU definition of RD, according to which, a rare disease is any disease affecting fewer than 1 in 2000 people i.e. 5 in 10 000 people.[57]

Classification and codification

There is no separate system of classification and codification of rare diseases. The country is currently using the ICD-10. Due to the lack of adequate classification and codification, many rare diseases remain unrecognized by the health care system.[58]

Policies and regulation

With the Law on Alterations and Amendments of the Health Care Law,[59] the Serbian legislation recognizes the category of people with rare diseases for the first time, thus enabling these people to receive specific services within the health care system. According to this amendment (Article 11, paragraph 1, line 5) the health care in the country includes rare disorders together with more common ones i.e. "[…] malignant diseases, haemophilia, diabetes, psychosis, epilepsy, multiple sclerosis, stage 4 chronic kidney disease, cystic fibrosis, systemic autoimmune disease, rheumatic fever, addictions, provision of emergency medical care for sick or injured people, people with rare diseases… as well as services related to organ and tissue donation and transplantation".[60] These amendments also provide legal ground for establishment of

54 Sanja Stojkovic-Zlatanovic, National Plan For Rare Diseases – Comparative Legal Review), Available: https://www.researchgate.net/publication/259026326_Nacionalni_plan_za_retke_bolesti_-_uporednopravni_prikaz_Strani_pravni_zivot_br_12013_str_291-306, Accessed 25.11.2015

55 Article: Serbia still does not have a strategy for treating rare diseases (In Serbian: Srbija još bez strategije za lečenje retkih bolesti), Available: http://www.rts.rs/page/stories/sr/story/125/dru%c5%a1tvo/1891690/srbija+jo%c5%a1+bez+strategije+za+le%c4%8denje+retkih+bolesti.html, Accessed: 26.11.2015

56 Article: More than 400.000 Serbs suffer from rare diseases (In Serbian: Više od 400.000 srba boluje od retkih bolesti), Available: http://www.telegraf.rs/vesti/564516-vise-od-400-000-srba-boluje-od-retkih-bolesti, Accessed: 26.11.2015

57 National Organization for RD of Serbia (In Serbian: Национална организација за ретке болести Србије), Available: http://www.norbs.rs/, Accessed 02.03.2016

58 National Organization for RD of Serbia (In Serbian: Национална организација за ретке болести Србије), Available: http://www.norbs.rs/, Accessed 02.03.2016

59 Law of Alterations and Amendments of the Health Care Law, Official Gazette of the Republic of Serbia, Belgrade: No. 57/2011:2), Available: http://www.paragraf.rs/propisi/zakon_o_zdravstvenoj_zastiti.html, Accessed: 27.11.2015

60 Law of Alterations and Amendments of the Health Care Law, Official Gazette of the Republic of Serbia, Belgrade: No. 57/2011:2), Available: http://www.paragraf.rs/propisi/zakon_o_zdravstvenoj_zastiti.html, Accessed: 27.11.2015

centres for particular rare diseases within the health facilities at tertiary level, as well as the Fund for Rare Diseases within the Ministry of Health of Serbia.[61] Furthermore, the implementation, promotion and development of both activities and evaluation of programs for promotion of primary, secondary and tertiary prevention and control of rare diseases is recognized by the Public Health Law[62] as a health-related activity of public interest.[63]

Financing

The creation of the Fund for Rare Diseases could be interpreted as a step towards finding systematic solution to the problem with rare diseases. The Fund is envisaged to function through a Commission, which will meet as needed, on a case-by-case basis. The Fund is financed from donations[64] and earmarked share from the lottery games, however these funds are not sufficient to provide the necessary care for all patients. Therefore, the country has to continue the search for an appropriate way to allocate resources for the Fund for Rare Diseases.[65]

Despite these first steps, the development of a national program and a registry of rare diseases in Serbia remain of essential importance.

Registries and data

Currently, Serbia does not have precise statistical data on the number of people with RD, which hinders proper health care planning. At the end of 2014, the Government of the Republic of Serbia adopted the Law on Medical Documentation and Records in the Health System[66], which imposes the obligation to keep registries for 17 groups of diseases including RD. This law entered into force on 1 January 2016. In 2014, the Institute of Public Health of Serbia and the Expert Commission for Rare Diseases initiated the establishment of the Registry for Rare Diseases, that is expected to have a full-scale enforcement after the Law enters into force, and will include all available sources of information at all levels of the health care system.[67]

61 Sanja Stojkovic-Zlatanovic, National Plan For Rare Diseases – Comparative Legal Review, 2013), Available: http://www.researchgate.net/publication/259026326_Nacionalni_plan_za_retke_bolesti_-_uporednopravni_prikaz_Strani_pravni_ivot_br._12013_str._291-306, Accessed 25.11.2015

62 Health Care Law (Official Gazette RS, No.72/2009) (In Serbian: Zakonom o javnom zdravlju ("Sl. glasnik RS", br. 72/2009), Available: http://www.paragraf.rs/propisi/zakon_o_javnom_zdravlju.html#, Accessed: 28.11.2015

63 Health Care Law (Official Gazette RS, No.72/2009) (In Serbian: Zakonom o javnom zdravlju ("Sl. glasnik RS", br. 72/2009), Available: http://www.paragraf.rs/propisi/zakon_o_javnom_zdravlju.html#, Accessed: 28.11.2015

64 Article: Creation of the Fund for Rare Diseases, 2014 (In Serbian: Osnivanje fonda za lečenje retkih bolesti, 2014), Available: http://www.naslovi.net/2014-08-12/akter/osnivanje-fonda-za-lecenje-retkih-bolesti/11229619, Accessed: 27.11.2015

65 Article: More than 400.000 Serbs suffer from rare diseases (In Serbian: Više od 400.000 srba boluje od retkih bolesti), Available: http://www.blic.rs/Vesti/Drustvo/369597/U-Srbiji-od-retkih-bolesti-boluje-400000-do-450000-ljudi, Accessed: 27.11.2015

66 Law on medical records and records in health (Official Gazette RS, No. 123/14), (In Serbian: Закон о здравственој документацији и евиденцијама у области здравства, Сл.Гласник 123/14), Available: http://paragraf.rs/propisi/zakon_o_zdravstvenoj_dokumentaciji_i_evidencijama_u_oblasti_zdravstva.html, Accessed: 24.03.2016

67 National organization for RD in Serbia (на српски: Национална организација за ретке болести Србије), Available: http://www.norbs.rs/centri-za-retke-bolesti/, отворено на 02.03.2016 година

Health care services

In Serbia, the Centres for RD are health facilities at tertiary level that provide services for specific diseases, such as:

- Diagnosis;
- Prenatal and neonatal screening;
- Genetic counselling and keeping records of PRD in the country;
- Cooperation with international reference centres for RD diagnosis and treatment, as well as with the network of European and global organizations for RD;
- Continuous education in the field of RD and other activities aimed at promoting diagnosis and treatment of PRD.

The health institutions, including private practices and/or other entities providing health services, are obliged to report to the Centre for RD and to provide data on the number, type, diagnosed and treated PRD, and other data of importance for the Registry for RD. There are currently five centres for RD in the country: the Clinic Centre of Serbia in Belgrade, the "Dr. Vukan Cupic" Institute for Health Protection of Mother and Child in Belgrade, the University Children's Clinic in Belgrade, the Institute for Health Protection of Children and Youth of Vojvodina in Novi Sad and the Clinic for Neurology and Psychiatry for Children and Youth in Belgrade.[68]

Orphan drugs and treatment

In 2013, the orphan drugs entered the market in Serbia for the first time, as treatment for the following RD: Hunter syndrome, hereditary angioedema (HAE) in adults; drugs for improvement of the mobilization of hematopoietic stem cells into the peripheral blood for autologous transplantation in patients with lymphoma and myeloma, splenomegaly, hepatic porphyria, Cushing's disease in adults, renal angiomyolipoma associated with tuberous sclerosis (TSC), Pompe disease and ductus arteriosus persistens in preterm newborn born before 34 weeks of gestational age.[69] Out of 135 innovative medicines for RD treatment registered in Europe in the last four years, only one has been included in the positive drug list by the National Health Insurance Fund of Serbia. This is predominantly due to the long and intricate processes of drug registration and inclusion of drugs in the Fund's positive list.[70]

68 Results of the Agency for Medicines and Medical Devices of Serbia in 2013 (In Serbian: Резултати Агенције за лекове и медицинска средства Србије у 2013.години), Available: http://www.alims.gov.rs/ciril/files/2014/03/REZ-2014.pdf, Accessed: 24.03.2016

69 Rare diseases: Out of 135 drugs, only one in Serbia (In Serbian: Ретке болести: Од 135 лекова у Србији само један), Available: http://mondo.rs/a838124/Magazin/Zdravlje/Lekovi-za-retke-bolesti-u-Srbiji.html, Accessed: 24.03.2016

70 Rare diseases: Out of 135 drugs, only one in Serbia (In Serbian: Ретке болести: Од 135 лекова у Србији само један), Available: http://mondo.rs/a838124/Magazin/Zdravlje/Lekovi-za-retke-bolesti-u-Srbiji.html, Accessed: 24.03.2016

Activism and support

In 2010, the National Organization for Rare Diseases of Serbia (NORBS)[71] was established. This organization is a member of the European Organization for Rare Diseases (EURORDIS) and its primary goal is to improve the status and quality of life for this population in the country.

In 2011, NORBS organized the “National Plan for Rare Diseases - Real Perspectives in 2012” meeting with various stakeholders. Despite the assurancesof the Ministry of Health regarding undertaking actions in this field, no activities have been undertaken towards adopting such plan so far.

71 in Serbian: Национална организација за ретке болести Србије, НОРБС

Croatia

Although there are no accurate and comprehensive epidemiological and/or statistical data on rare diseases in the country, it is estimated that rare diseases affect approximately 250.000 people.[72,73,74] Despite the fact that PRD face similar difficulties as in other countries in terms of diagnosis, the greater number of institutions and types of services and care offered on all health care levels (through specialized centres, general practice, clinics and general hospitals) further complicate the timely diagnosis and disease monitoring.

Definition

At the joint meeting of the Croatian Society for Rare Diseases and the Croatian Society of Human Genetics held in May 2009, the professional community adopted the EU definition of rare diseases, according to which rare diseases are those that affect fewer than 5 in 10,000 people.[75]

Classification and codification

At the workshop on classification and codification of rare diseases held during the 1st National Conference in 2010, the important components of these disorders were pointed out: the severity of the disease and the possibility of treatment (early diagnostics and faster familiarization of experts with treatable diseases). The International Classification of Diseases 10 (ICD-10), which is in official use, does not have the appropriate codes for most rare diseases, which makes it impossible to monitor the majority of rare diseases in the health care system. The statistical data for hospital morbidity and mortality do not reflect the realistic scope due to the drawbacks of the ICD-10 classification, the lack of awareness and knowledge of medical professionals on the importance of this issue and the need for accurate codification and classification of rare diseases, which ultimately results in superficial and inaccurate data.[76]

72 Article: "Few patients are suffering from a rare disease, that is why the treatment is expensive", (In Croatian: Od rijetkih bolesti boluje nekoliko pacijenata pa je liječenje skupo), Availble: http://www.vecernji.hr/zdravlje/od-rijetkih-bolesti-boluje-nekoliko-pacijenata-pa-je-lijecenje-skupo-572841, Accessed: 02.12.2015

73 Article: In Croatia, 250,000 people suffer from rare diseases, (In Croatian: U Hrvatskoj 250.000 ljudi boluje od rijetkih bolesti!), 2013, Available: http://dnevnik.hr/vijesti/hrvatska/u-hrvatskoj-250-000-ljudi-boluje-od-rijetkih-bolesti---276628.html, Accessed: 02.12.2015

74 Article: 250,000 people suffer from rare diseases, (In Croatian: Od rijetkih bolesti boluje 250.000 ljudi), Available: http://www.jutarnji.hr/vijesti/hrvatska/od-rijetkih-bolesti-boluje-250.000-ljudi/3106373/, Accessed: 02.12.2015

75 National Program for Rare Diseases 2015-2020, 2015 (In Croatian: NACIONALNI PROGRAM ZA RIJETKE BOLESTI 2015. – 2020, 2015), Available: http://www.zdravlje.hr/content/download/13166/95892/file/NACRT%20-%20NACIONALNI%20PROGRAM%20ZA%20RIJETKE%20BOLESTI%20za%20nac%20dan.docx; Accessed: 02.12.2015

76 National Program for Rare Diseases 2015-2020, 2015 (In Croatian: NACIONALNI PROGRAM ZA RIJETKE BOLESTI 2015. – 2020, 2015), Available: https://zdravlje.gov.hr/programi-i-projekti/nacionalni-programi-projekti-i-strategije/ostali-programi/nacionalni-program-za-rijetke-bolesti-od-2015-do-2020/2190; Accessed: 02.12.2015

Policies and regulation

In September 2010, in Dubrovnik the first National Conference for RD was held, organized by the Croatian Association for Patients with Rare Diseases and the European organization for RD (EURORDIS). The following priorities of the National Program for Rare Diseases were presented:

- Improving knowledge and availability of information on RD;
- Supporting the development of RD registries and securing their sustainable financing;
- Supporting the development and activities of networks of reference centres and centres for RD;
- Improving the availability and quality of health care (diagnostics, treatment, and prevention) for PRD and ensuring availability of medicines for RD;
- Improving the implementation of social rights for PRD;
- Empowering organisations with PRD;
- Fostering scientific research on RD and international networking and cooperation.

With the adoption of the National Programme,[77] a Commission to monitor the implementation of the relevant indicators for individual targets and measures was established, responsible for regular monitoring and reporting to the Ministry of Health and the government on the progress of the objectives.

Given the fact that there is insufficient information on RD in common person language, Croatia is in the process of developing the Croatian Rare Disease Helpline Project, aimed at providing information on diagnosis and treatment options to PRD through a helpline.[78]

Financing

The financial means for the implementation of the National Program for Rare Diseases 2015-2020 are secured from the budgets of the Ministry of Health of Croatia and the Croatian Health Insurance Fund. The total amount for program implementation for 2015 was 360 million kuna (approximately 48 million Euros), and for 2016 and 2017 the planned amounts are 362 million kuna (approximately 48.2 million Euros) and 364 million kuna (approximately 48.6 million Euros), respectively. The funding is allocated for improvement of the quality of health care, cooperation with citizens' associations, support of the establishment and maintenance of RD registries, and support of research on rare diseases.[79]

77 DECISION to adopt National Program for Rare Diseases for the period 2015-2020, 2015 (In Croatian: O D L U K U o donošenju Nacionalnog programa za rijetke bolesti za razdoblje 2015. – 2020, 2015), Available: https://vlada.gov.hr/UserDocsImages//Sjednice/2015/214%20sjednica%20Vlade//214%20-%207.pdf, Accessed: 02.12.2015

78 Croatian Symposium on Rare Diseases, 2012 (In Croatian: Hrvatski simpozij o rijetkim bolestima, 2012), Available: http://www.rijetke-bolesti.org/docs/47.pdf, Accessed: 27.11.2015

79 National Program for Rare Diseases 2015-2020, 2015 (In Croatian: NACIONALNI PROGRAM ZA RIJETKE BOLESTI 2015. – 2020, 2015), Available: http://www.zdravlje.hr/content/download/13166/95892/file/NACRT%20-%20NACIONALNI%20PROGRAM%20ZA%20RIJETKE%20BOLESTI%20za%20nac%20dan.docx; Accessed: 02.12.2015

Registries and data

Croatia still does not have a registry for RD. Established in 1983, the Registry for congenital anomalies functions as a part of the International Network of Registries for Congenital Anomalies (EUROCAT) and monitors the births in five regions of Croatia (about 21% of all births annually). In 2010, EUROCAT joined the EU Second Health Program for 2008-2013, the member-states and the European Commission. The implementation process is jointly coordinated by the Ministry of Health of the Republic of Croatia and the Ministry's Reference Centre for monitoring of congenital anomalies. Croatia is also a part of the European Cystic Fibrosis Registry (EUROCARE-CF), the Network of registries for people affected by rare neuromuscular diseases (NM-TREAT NMD) and its project on Duchenne disease (CARE-NMD); the Network of registries for people with primary immunodeficiency of the European Society for primary immunodeficiency (ESID) and the European network of registries for poisonings caused by metabolic diseases (EIMD). The reference centres for RD enlist their patients in the international online registries for specific diseases, such as Fabry disease, Pompe diseases, Mucopolysaccharidosis type I-II and others.

Health care services

Reference centres for RD. Currently, three reference centres for RD function within the Croatian Ministry of Health: Reference Centre for monitoring of congenital anomalies (Clinic for Paediatrics, Zagreb), Reference Centre for medical genetics and metabolic diseases in children (Department of Paediatrics at the University Hospital Centre, Zagreb) and Reference Centre for rare and metabolic diseases (Department of Internal medicine at the University Hospital Clinic, Zagreb). Further, there are reference centres that treat certain RDs or small groups of RDs (e.g., solid tumours in children).[80]

In 2015, using the allocated budget for the National Program for Rare Diseases, the Croatian Union for Rare Diseases provided services to 1500 PRD and their families. A portion of the funds was used as a separate fund for expensive medicines, in order to prevent overburden to the budgets of respective health facilities.[81]

Orphan drugs and treatment

In 2006 the country introduced a "List of especially expensive medicines" which also includes the drugs for certain RDs. In 2010, the Agency for Medicines and Medical Devices (HALMED) published on its website a list of medicines for treatment of rare and other serious diseases which are approved for use in Croatia and which have the status of orphan drugs in the EU, along with the approval for their distribution. The List

80 National Program for Rare Diseases, 2015-2020, 2015 (In Croatian: NACIONALNI PROGRAM ZA RIJETKE BOLESTI 2015. – 2020, 2015), Available: http://www.zdravlje.hr/content/download/13166/95892/file/NACRT%20-%20NACIONALNI%20PROGRAM%20ZA%20RIJETKE%20BOLESTI%20za%20nac%20dan.docx; Accessed: 02.12.2015

81 Article: For patients in 2015, 360 million kuna, 2015 (на хрватски: Za oboljele u 2015. 360 milijuna kuna, 2015, Available: http://www.vecernji.hr/hrvatska/za-oboljele-u-2015-360-milijuna-kuna-993312, Accessed: 02.12.2015

of especially expensive medicines is extended according to a procedure determined by the Governing Council of the Croatian Health Insurance Fund. Any proposal to add certain medicines to the list is decided upon by the Committee for Medicinal Products.

Activism and support

The Croatian Association for Rare Diseases was established in 2008, as part of the Croatian Medical Association with the aim to promote recognition of RD and to improve the medical practice, diagnosis and treatment in this field. Upon the request of the Association and in line with the EU recommendations, the Ministry of Health introduced a systematic approach to solving the issues faced by PRD, through creating a comprehensive framework in order to assure the highest standard of protection and implementation of all rights, without any discrimination.[82]

In May 2010, the Minister of Health adopted a Decision establishing the Commission on Rare Diseases within the Ministry of Health. Its objective is to develop and monitor the implementation of the National Program for Rare Diseases which would summarize the problems and challenges related to these diseases, as seen from the perspective of the EU and the Republic of Croatia. The Commission also maintains the dialogue of relevant stakeholders, which the Government and the Ministry have already launched with the citizens' organizations active in the field. The Commission consists of 11 members, three of whom represent the associations of PRD and the remaining eight are representatives of the state administration or experts in the field.

82 National Program for Rare Diseases 2015-2020, 2015 (In Croatian: NACIONALNI PROGRAM ZA RIJETKE BOLESTI 2015. – 2020, 2015), Available: http://www.zdravlje.hr/content/download/13166/95892/file/NACRT%20-%20NACIONALNI%20PROGRAM%20ZA%20RIJETKE%20BOLESTI%20za%20nac%20dan.docx; Accessed: 02.12.2015

Slovenia

Definition

The National Plan for RD in Slovenia uses the definition of the EU, according to which rare diseases are those that affect fewer than 5 in 10,000 people.[83]

Classification and codification

The ICD-10 diagnosis codes and the portal for rare diseases and orphan drugs Orphanet will remain in use until the new edition of the International Classification of Diseases - ICD-11[84] is released, following the ongoing revision process.[85]

The proper classification of rare diseases requires the involvement of both competent institutions of Slovenia and Slovenian representatives in international organizations, particularly in the EU and the World Health Organization (WHO).[86]

Regulation and policies

In 2012, the Health Council of Slovenia adopted a National Plan for Rare Diseases, with an action plan designed to serve as a roadmap until 2020 and is characterized as "an opportunity to better coordinate the efforts of all involved partners and to establish a comprehensive, accessible, timely health care focused on patients". The main objectives of the Plan are:

- Identification and monitoring of RD;
- Improvement of early diagnosis and access to adequate medical interventions;
- Mechanisms for improvement of the integrated approach toward RD;
- Promotion of access to information for patients, general public and experts.

83 Work plan in the field of RD of the Republic of Slovenia (In Slovenian: Načrt dela na področju redkih bolezni v Republiki Sloveniji), Available:http://www.mz.gov.si/fileadmin/mz.gov.si/pageuploads/redke_bolezni_2012_-_nacrt_dela/Nacrt_dela_na_podrocju_redkih_bolezni.pdf, Accessed: 02.03.2016

84 The International Clasification of Diseases 11, Available: http://www.who.int/classifications/icd/revision/en/, Accessed: 02.03.2016

85 ICD-11 Update, Available: http://www.who.int/classifications/icd/revision/2015_11_ICD11_Newsletter.pdf, Accessed: 02.03.2016

86 Work plan in the field of RD of the Republic of Slovenia (In Slovenian: Načrt dela na področju redkih bolezni v Republiki Sloveniji), Available: http://www.mz.gov.si/fileadmin/mz.gov.si/pageuploads/redke_bolezni_2012_-_nacrt_dela/Nacrt_dela_na_podrocju_redkih_bolezni.pdf, Accessed: 02.03.2016

The defined activities include:

- Establishing of a National RD Registry;
- Creation of national reference centres linked to international networks;
- Identifying opportunities for cross-border cooperation in the field of genetic testing and other services;
- Introduction of evidence-based clinical guidelines;
- Defining policies in relation to medicines for RD and preparation of guidelines for competent authorities;
- Finding additional financial resources to meet the needs for orphan drugs;
- Creation of an umbrella organization of patients' groups;
- Establishing a national centre for rare diseases in the country.[87]

Financing

The implementation of activities in the field of RD is financed through various sources. There are no specific financing guidelines at national level regarding genetic testing, but the testing considered necessary, is financed by the Health Insurance Institute of Slovenia.

The work of professional associations for PRD is financed by the Government/the public and the private sector (sponsorships and donations). The Ministry of Health also provides financial support to certain programs of these associations through calls for proposals that have a different scope and purpose, depending on the identified needs.[88]

Registries and data

Currently, there is still no unique national RD registry in this country. The new Law on Health Care, which is in the process of adoption, is expected to provide legal basis in accordance with the current National plan. Slovenia contributes to the European registries EUROCARE-CF and RARECARE.[89]

87 Work plan in the field of RD of the Republic of Slovenia (In Slovenian: Načrt dela na področju redkih bolezni v Republiki Sloveniji), Available: http://www.mz.gov.si/fileadmin/mz.gov.si/pageuploads/redke_bolezni_2012_-_nacrt_dela/Nacrt_dela_na_podrocju_redkih_bolezni.pdf, Accessed: 02.03.2016

88 2014 Report on the State of the Art of Rare Diseases in Slovenia, Available: http://www.eucerd.eu/upload/file/Reports/2014ReportStateofArtRDActivitiesSI.pdf, Accessed: 24.03.2016

89 Work plan in the field of RD of the Republic of Slovenia (In Slovenian: Načrt dela na področju redkih bolezni v Republiki Sloveniji), Available: http://www.mz.gov.si/fileadmin/mz.gov.si/pageuploads/redke_bolezni_2012_-_nacrt_dela/Nacrt_dela_na_podrocju_redkih_bolezni.pdf, Accessed: 02.03.2016

Health care services

To present day, there are still no official specialized centres for RD, although the National Plan envisages their establishment. The majority of PRD gets the needed health services at the University Medical Centre in Ljubljana, being referred from other levels of care for treatment of genetic, endocrine, metabolic and neurodegenerative disorders. In addition, a Centre for Fabry disease is established in Slovenj Gradec.

PRD often use health care services in other EU countries, enabled through the Directive for Cross-border Cooperation (telemedicine, mobile experts, mobile patients[90] and other).

Orphan drugs and treatment

The specific treatment that exists for some RD is not yet available in the country, which suggests necessity for improving the support services and quality of network for rehabilitation.

Also, for effective treatment and rehabilitation, it is important to establish a system of evidence-based clinical guidelines, which will describe the indications for use of orphan drugs. The criteria for classification of new drugs that need to be introduced in the services provided under the compulsory and supplementary health insurance are constantly changing. Since medicines for treating RD are quite expensive, there is a need for additional sources of funding that would allow equitable access to health services for PRD as a fundamental principle of the Slovenian health care system.[91]

Activism and support

Slovenia still does not have a national alliance, union or umbrella organization for uniting the organizations for PRD. Existing organizations are financing their activities from diverse sources, mainly through sponsorships, donations and grants from the Government/the public and the private sector.

The role of the patients' organizations is recognized in the National Plan, which ensures their involvement in the legislative consultation process, as well as in the processes of policy making and programming.

The main source of information on RD at national level is the Orphanet Team, established in 2006 and officially recognized and designated by the Ministry of Health in 2010. This team is responsible for data collection (specialized clinics, medical laboratories, current research, registries, clinical trials and organizations of PRD) and entry into the Orphanet database. A national version of Orphanet platform was developed in 2011.

90 The term "mobile experts" refers to health professionals who can provide health services in cross-border cooperation, while "mobile patient" refers to patients who may receive health services in cross-border cooperation in the framework of their health insurance.

91 Work plan of the Republic of Slovenia in the field of RD (In Slovenian: Načrt dela na področju redkih bolezni v Republiki Sloveniji), Available: http://www.mz.gov.si/fileadmin/mz.gov.si/pageuploads/redke_bolezni_2012_-_nacrt_dela/Nacrt_dela_na_podrocju_redkih_bolezni.pdf, Accessed: 02.03.2016

The country has initiated the procedure for appointment of National Contact Point for PRD, responsible for providing information to health professionals regarding rare diseases, diagnosis and treatment. Until the determination of its suitable place within the system, the function of the National Contact Point is carried out by the Centre for Undiagnosed Rare Diseases, organized as a medical unit at the Clinical Institute of Medical Genetics and financed through the Program for Genetics.[92] The help line to inform PRD is not yet available, but it is envisaged within the responsibilities of the National Contact Point.

92 National Program for Rare Diseases 2009-2013, Republic of Bulgaria (In Bulgarian: Национална програма за редки болести 2009 – 2013, Р.Бугарија), Available: http://www.mh.government.bg/media/filer_public/2015/04/17/programa-redki-bolesti-2009-2013.pdf, Accessed: 02.12.2015

Macedonia

Definition

The country has adopted the definition according to which RDs are diseases that affect fewer than 1 in 2.000 people, but not more than 20 patients at national level.[93]

Classification and codification

There is no standardized approach for rare diseases. Additional burden is the lack of appropriate classification and codification of rare diseases at national level. The ICD-10 is in official use in the country.

Policies and regulation

Program for RD. The first Program for Rare Diseases in Macedonia was adopted in 2009, and subsequently new programs are adopted every year. The program objectives include raising awareness and expertise of RDs aimed at achieving the level of organization, implementation and results attained by the EU Member States.

Strategy and plan for RD. In addition to the Program for Rare Diseases in the country, the National Alliance for Rare Diseases in Macedonia (NARBM) proposed a National Strategy and Plan for Rare Diseases 2014-2020, which covers all significant issues relating to RD in the country, and whose objectives are:

- Prevention;
- Early recognition and diagnosis;
- Access to adequate health care;
- Treatment for PRD;
- Improving registries in accordance with the international classification;
- Increasing awareness on rare diseases among health professionals and the general public;
- Coordination at national and international levels with reference health and scientific research institutions and associations for PRD.[94]

93 Program for the treatment of rare diseases in 2016 in the Republic of Macedonia (Official Gazette No.192/15); Available: http://www.fzo.org.mk/WBStorage/Files/PROGRAMA_ZA_LEKUVANE_NA_RETKI_BOLESTI_VO_REPUBLIKA_MAKEDONIJA_ZA_2016_GODINA.pdf, Accessed 01.03.2016

94 National plan and strategy for rare diseases 2014-2020; Available: http://challenges.mk/wp-content/uploads/2014/02/Nacionalen-plan-za-retki-bolesti.docx, Accessed: 02.12.2015

The Strategy is based on the Recommendations of the European Commission and the European Parliament (2009, 2010 and 2011), which are particularly focused on the support of health policies for RD and the application of modern scientific knowledge for improving the treatment of RD, pooling resources, solidarity and development of an international strategy.

The Strategy also considers the challenges in the approach and care for RD, namely:

- Lack of relevant epidemiological data;
- Lack of experience and interest among HPs;
- Lack of systematic approach and opportunities for treatment;
- Significant costs for treating a small number of diseases, mostly abroad;
- Uncertain progress of the disease and inability for relevant cost estimate for the total treatment of RD;
- Lack of specifically planned budget funds for treatment;
- Lack of legislation regarding RD.

This Strategy has not yet been adopted.

Financing

For the implementation of the 2015 Program for Rare Diseases, a total of 90 million denars were allocated from the Central Budget of the country. The financial support for the treatment of PRD can be allocated regardless of their insurance status. For 2016, 203 million denars have been allocated for the Program from two sources: 80 million from the state budget and 123 million from the revenues of the Ministry of Health. Funds are allocated for three groups of activities: treatment of PRD regardless of their health insurance status (197 million denars), provision of equipment for the diagnosis and treatment of RDs (4 million denars) and education and training of health professionals (2 million denars).

Registries and data

There is still no systematic and standardized approach for codification, hindering the understanding of the complete epidemiological situation with RDs. If the EU estimation is extrapolated (6-8%) in its most conservative scenario, it can be assumed that there are around 120,000 patients with RD in the country.

The Program provides grounds for establishment of a National Registry of RD, concordant with the data protection and other relevant national regulations.[95] The

95 Program for the treatment of rare diseases in 2011 in the Republic of Macedonia (Official Gazette No.06/11); Available: http://www.slvesnik.com.mk/Issues/595CF4961E57714C93E86B782BFDF26D.pdf, Accessed: 02.12.2015

registry will enable exchange and comparison of data at sub-regional, regional and global levels, as well as gathering data from the individual records of clinics, the Health Insurance Fund (HIF) and the Ministry of Health. Since 2015, the Ministry of Health is actively working on completing the Registry of PRB (mostly children), including information on diagnosis, treatments and therapeutic requirements with medicines that are not on the positive list. The initial classification in the registry applies to two types of diseases in accordance with Orphanet: (a) diseases that can be treated with medications, and (b) rare diseases for which there is no treatment, but are important for diagnostic and planning purposes.

So far, although it is still not completely regulated, the Registry has 460 registered patients. Novelty associated with the registry keeping is the establishment of one instead of two commissions - National Expert Commission composed of doctors from various specialties, which confirms the diagnosis and therapy for each PRD and gives opinion on the PRD registration into the Registry, subject to confirmation of their diagnosis. Further, the Commission submits information to the Ministry of Health for procurement of the designated treatment. The Program for RD ensures funds for procurement of medicines for treatment of RDs that are the only treatment option but are not in the positive list.[96]

Health care services

Reference centres for RD. There are still no specialized centres in Macedonia, but the majority of patients with rare diseases are registered at the University clinic for children's diseases since these diseases are commonly detected and manifested at early age i.e. immediately after birth, by the age of 5 or by the age of 15.

Given that PRD have an equal right to quality and accessible health care as other patients, Macedonia has been set exactly in this direction: equal acesss to early diagnosis, quality treatment and rehabilitation services, in accordance with the majority of countries worldwide and almost every European country which have been working on the promotion of health care quality and availability as well as on promotion of research, early detection and prevention of RDs.

Orphan drugs and treatment

Early diagnosis of RDs, which are commonly of genetic origin, is the best warranty for effective treatment from both therapeutic and financial aspects. However, the available treatment is very often not curative, but rather offers limited to extensive symptomatic relief.[97,98,99]

96 Program for the treatment of rare diseases in 2016 in the Republic of Macedonia (Official Gazette No.192/15); Available: http://www.fzo.org.mk/WBStorage/Files/PROGRAMA_ZA_LEKUVANE_NA_RETKI_BOLESTI_VO_REPUBLIKA_MAKEDONIJA_ZA_2016_GODINA.pdf, Accessed 01.03.2016

97 Program for the treatment of rare diseases in 2012 in the Republic of Macedonia (Official Gazette No.08/12); Available: http://www.slvesnik.com.mk/Issues/FCD4ECEFD36AB24480FCB4631FE35EA2.pdf, Accessed: 02.12.2015

98 Program for the treatment of rare diseases in 2013 in the Republic of Macedonia (Official Gazette No.04/13); Available: http://www.slvesnik.com.mk/Issues/4810E889FE587743A5A17DD577000C0B.pdf, Accessed: 02.12.2015

99 Program for the treatment of rare diseases in 2014 in the Republic of Macedonia (Official Gazette No.19/14); Available: http://www.slvesnik.com.mk/Issues/6c208badae664d3f924c715e992e003f.pdf, Accessed: 02.12.2015

The treatment for PRD is provided through the Program, based on the diagnosis confirmed by the Commission, which further gives its opinion and recommendation to the Ministry of Health for procurement of medicines and orphan-drugs.

Activism and support

In 2014, the "Life with Challenges" Citizens' Association for RD in collaboration with the "HEMOLOG" Association for people with haemophilia, rare coagulopathies and von Willebrand and the Association for Emancipation, Solidarity and Equality of Women of the Republic of Macedonia – ESE organized a conference, which resulted in establishment of the National Alliance for Rare Diseases in the Republic of Macedonia (NARBM).[100] Their goal was to gather associations working in the field of RDs and other organizations working in similar areas towards joint action, encouragement and support of health care system reforms in the field of RDs.

In this process, the preparation of the National Plan for Rare Diseases was pinpointed as a priority since it would provide long-term solutions to issues and challenges faced by the PRD and their families. NARBM developed and proposed a National Strategy and a Plan for rare diseases for the period 2014-2020.

NARBM has been actively working on improving the quality of life for PRD and their families. Through its 13 member organizations, the Alliance is currently covering over 50 rare diseases. Its activities are designed to raise the general and institutional awareness, provide counselling and support to families as well as to provide education to health professionals, activate and train volunteers, and ensure cooperation with international and national organizations in addressing the issues and challenges posed by rare diseases.

NARBM has analysed the collected requests from PRDs over the past year, and has identified the problems with which they are faced, including: 1) difficulties of registering new PRDs in the Registry and of providing additional quantities of medicines; 2) insufficient quantities of medicines available to already registered PRDs; 3) lack of combination of adequate medicines for registered PRDs; 4) administration of medicines; 5) suspicious quality of medicines procured as a result of the price being the main procurement criterion in tender procedures; 6) the limitation of RDs covered through the Program to only those that affect a maximum number of 20 PRDs; 7) lack of funds for diagnosis of RDs; 8) problem of coverage of patients with rare forms of malignant diseases; 9) inappropriate conditions for disease monitoring/control; 10) lack of necessary supplements and additional orthopaedic devices; and 11) assignment of personal assistants to people with severe disability.

Civil society organisations working on improving the condition of PRDs and their families are the strongest driving force making remarkable efforts to bring PRDs in the focus of public policies, especially in the social and health sectors. Their main area of operation is explicitly in the domain of improving the quality of health and the quality of

100 Национална алијанса за ретки болести во Македонија (НАРБМ)

life of PRDs, through various activities, including: sending information to/for patients, linking patients with same RD, informing HPs through education events and lectures, and raising awareness about the existing Registry and Program for RD; all of the above constitutes the civil society organisations as the true representatives and advocates of PRD before the public sector and institutions of the system.

1.4. Comparative analysis of policies and legislations in the European Union and in selected countries

The comparative analysis of policies and legislations in the selected countries from the Balkan Region (Bulgaria, Serbia, Croatia and Slovenia) aims to provide overview of the situation in these countries as well as to provide information on possible solutions to issues related to RD, in accordance with the EU policies to act in the field:

1. Provision of adequate codification and registration within the health information system;
2. Adoption of national plans for rare diseases;
3. Creation of reference networks of specialized centres;
4. Introduction of screenings for RDs;
5. Development of registries for RDs;
6. Research and development;
7. Increasing the visibility of the issue from health and social perspective.

All EU member states and candidate countries for EU accession use the International Classification of Diseases, 9th or 10th revision, in which not all rare diseases are listed. Recently, some EU member states introduced the ORPHA codes, which represent a codified system of rare diseases developed by the Orphanet initiative. ORPHA codes are used combined with the ICD classification or separately as pilot projects.

A National Plan and/or a Strategy for Rare Diseases have been adopted in the following EU member countries: Belgium, Cyprus, Czech Republic, France, Germany, Greece, Hungary, Lithuania, Portugal, Romania, Slovakia, Slovenia, Spain and the United Kingdom. Strategic documents are in advanced stage of adoption in Austria, Croatia, Denmark, Finland, Ireland, Italy and Poland. From within the countries selected for this analysis, only Slovenia has an adopted Strategy and Plan for RD, while Croatia is in an advanced stage of adoption. Bulgaria, Macedonia and Serbia are still behind in this respect; Bulgaria and Macedonia have an adopted national program for RD, while in Serbia such a program is still not available.

Although officially still unrecognized, specialized centres for rare diseases have been established in a great number of EU member states: Austria, Belgium, Croatia, Czech Republic, Cyprus, Germany, Greece, Ireland, Hungary, the Netherlands, Slovenia, and Sweden. Other countries like Bulgaria, Estonia, Finland, Latvia, Lithuania, Portugal, Poland, Romania and Slovakia have addressed this issue by designating already existing healthcare institutions as specialized centres for RDs.

In addition, the EU introduced a pilot Network of reference centres for RD to provide support to PRDs.

List of pilot European reference networks for rare diseases

1. **DYSCERNE:** Dysmorphology
2. **ECORN CF**: Cystic Fibrosis
3. **PAAIR**: Patient Associations and Alpha1 International Registry,
4. **EPNET**: European Porphyria Network,
5. **EN-RBD**: Rare Bleeding Disorders, Paediatric Hodgkins Lymphoma Network
6. **NEUROPED**: Rare Paediatric Neurological Diseases
7. **EURO HISTIO NET**: Langerhans cell histiocytosis and associated syndrome in EU
8. **TAG**: Together Against Genodermatoses
9. **CARE NMD**: Dissemination and Implementation of the Standards of Care for Duchenne muscular Dystrophy in Europe

Source:http://ec.europa.eu/health/rare_diseases/docs/2014_rarediseases_implementationreport_en.pdf

Table 1. Review of activities in areas determined by the EU for promotion of the situation with rare diseases in Bulgaria, Serbia, Croatia, Slovenia and Macedonia

Elements of comparison	Bulgaria	Serbia	Croatia	Slovenia	Macedonia
National strategy and plan	No	No	No	National Plan for Rare Diseases 2012-2020	No
National program	2009-2013	No	2015-2020	No	2009-2015
National registry	Orphanet Joint Action - ongoing	Orphanet Joint Action	Orphanet Joint Action	Orphanet Joint Action	Yes
Coding/ Monitoring	ICD-10	ICD-10	ICD-10	ICD-10	ICD-10
Financing	Fund for Treatment of Children	Fund for Rare Diseases	The Croatian Association for Rare Diseases manages the funds provided through the Program for Rare Diseases	Health Insurance Fund	Health Insurance Fund and Program for Rare Diseases
Specialized centre	Yes	Yes	Yes	No	No
Reference centre	No	No	Yes	No	No
National information centre	Yes	Yes	Yes	No	No
Screening	Yes	Yes	Yes	Yes	Yes
National alliance of organizations for PRDs	**NAHRB**	NORBS	Croatian Association for Rare Diseases	No	NARBM
Research	No	No	It is estimated that nearly 4% of the current research projects could be related to rare diseases	No	No

**Извор:http://ec.europa.eu/health/rare_diseases/docs/2014_rarediseases_implementationreport_hr.pdf*

Screening of newborn (NBS), according to Wilson and Jungner (Wilson & Jungner, 1968) as a measure for early detection of a rare disease, is available in health systems in all EU member-states, candidate countries and members of the European Free Trade Association (EFTA), as well as in most of the potential candidate countries. In the national screenings, of diseases, between 2 and 29 disorders are rare diseases.

Due to the substantial number of inaccurate diagnoses and information, the control is mainly focused on the laboratory results rather than on the process patients go through. The procedures and information about the disease and the treatment provided to parents are not subject to strict control and monitoring.[101]

At EU level, collection and accessibility of information regarding RDs is provided through the European Commission supported Orphanet Joint Action.

The Orphanet Joint Action strives to collect and interlink information regarding 6,000 diseases and to enable search by disease name and characteristics (e.g. prevention, statistics, and so forth).[102] All countries of the comparative analysis have developed a national Orphanet web page in their language with exception to Macedonia.

With regards to the funding, except Serbia and Macedonia, all other analysed countries have established funds for rare diseases. In these two countries, the funding for rare diseases is ensured through the health insurance and the Program for rare diseases of the Ministry of Health.

Regarding visibility of rare diseases in the society, there are no documents in these countries that were identified to confirm that any particular attention was given to this issue. Bulgaria, Serbia, Croatia and Macedonia have national-level alliances for rare diseases, while in Slovenia visibility and advocacy activities are pursued by specialized civil society organizations.

As in the other analysed countries, in Macedonia, PRD face numerous challenges as well, beginning from the diagnosis, treatment and rehabilitation as well as enabled social integration. Hence, the need for this research, aiming at identifying challenges and opportunities posed by RD, through direct contact and interaction with key stakeholders, analysing the situation and proposing recommendations for improvement.

101 New Born Screening in Europe Opinion of the EUCERD on Potential Areas for European Collaboration), Available: http://www.eucerd.eu/wp-content/uploads/2013/07/EUCERD_NBS_Opinion_Adopted.pdf, Accessed: 06.12.2015

102 Orphanet Joint Action, Available: http://www.orpha.net/consor/cgi-bin/ResearchTrials_Networks.php?lng=EN&data_id=99707&title=EUCERD-Joint-Action--Working-for-rare-diseases&search=Directory_Institutions_Simple, Accessed: 06.12.2015

2. METHODOLOGY

2.1. Chosen methods

For the purpose of this study, a mixed method approach was chosen, integrating quantitative and qualitative methodological tools through questionnaires and semi-structured interviews with three groups of respondents: 1) persons with rare disease(s) (PRD), 2) parents of children with rare disease(s) (PCRD), and 3) health professionals (HP). Prior to data collection, all research instruments were validated through piloting with representatives of all three groups of respondents. The choice for applying a mixed methodological approach was made in accordance with the purpose of the research- to compare the legal instruments and policies in the country, to understand the experiences and practices of PRD, PCRD and HP and see if and how rare diseases affect the quality of life of PRD.

Additionally, desktop research and comparative analysis of national, European and other relevant documents was conducted, to better understand the broader context of RD and to showcase specific good practices relevant to the recommendations of this research.

2.2. Instruments and sampling

For the purpose of this research, questionnaires and semi-structured interviews were used. Separate questionnaires were prepared for each of the three groups of respondents: PRD, PCRD and HP. The questionnaire for the first two groups of respondents was structured into the following topics: socio-demographic characteristics, familiarity with the disease, leisure time, attitude towards the disease, perception of the quality of life, psychological aspects of life, response in stressful situations, social skills and satisfaction with health care services. The questionnaire for the third group - the health professionals, consisted of questions regarding the institution where the respondents work, their experience, education and the services they offer within their institutions.

The validation of the structured questionnaires was performed with 7 PRDs, 6 HPs and two associations of citizens; it allowed for correction and adjustment of the preciseness of the questions and answers, and it also allowed for addition of questions that were not anticipated in the original design, but were considered useful to include as they might gather significant insights and perspectives from the respondents.

Several sampling strategies were considered, and finally a purposive sample and a snowball sample were chosen. Questionnaires were distributed to the sample group both in hard copy and in online-based electronic form, by providing link via e-mail (Appendices 3, 4 and 5).

Interview guide with specific questions was prepared for each group of respondents. The interviews were conducted at a location chosen by the respondent, and audio recorded, based on received informed consent. The audio recordings were transcribed verbatim, and the transcripts were used for the thematic analysis of the answers.

Each of the three interview guides was designed to direct the conversation with the respondent about PRD, their relationship to health facilities, health professionals, cooperation with professional associations, and the impact of RDs on their quality of life. Introducing open questions in the guides allowed for in-depth examination of contextual circumstances, experiences, attitudes and opinions of the respondents. Each of the interviewed groups was chosen to give a different perspective on the issue, while at the same time increasing the possibility to generalize the conclusions (Appendices 6 and 7).

Since in qualitative research it is not common to determine sample size, the so-called rule of "sample saturation" was applied, reached when the new interviews are not giving any new information and perspectives on the issue of interest. Sample saturation was achieved with the following number of interviewed persons in each of the groups: PRD – 16 respondents, PCRD – 10 respondents and HP – 15 respondents. The sample was considered sufficient and valid for the following steps of data analysis. The persons involved in the validation process were not considered as part of the main sample.

2.3. Analysis

In order to assess whether policies and practices for RD in Macedonia exist and wheter RD's affect the quality of life of PRDs, an analysis of the collected primary and secondary data was conducted.

The desktop research consisted of analysing national, sub-regional (South-Eastern Europe), European and other relevant documents in order to provide comparative analysis of the policies and practices of the SEE countries.

Given the size of the sample, the data obtained from the structured questionnaire survey were analysed using descriptive statistics, using the Microsoft Excel software program, while those obtained from the interviews were analysed by the method of thematic analysis.[103]

The data were organized based on the primary sources and theoretical literature. The data were analysed and categorized in terms of agreement-disagreement points among interviewees. The points of agreement were used for drawing conclusions, whereas the points of disagreement reflect questions that require further research. In

103 Bryman A., Social Research Methods, Fifth edition, Available: https://books.google.mk/books?id=N2zQCgAAQBAJ&printsec=frontcover&source=gbs_vpt_buy#v=onepage&q&f=false, Accessed: 15.05.2016

this way, the interview data served to confirm and supplement the already available data, to draw conclusions and make recommendations for further action.

The data obtained from the questionnaires were analysed first, followed by an analysis of the interviews to get the entire picture of the situation and the alternatives to address RDs in the country. Finally, a triangulation of the results was performed, to verify the theses, to check for validity and to identify the possibilities for generalization of the conclusions and recommendations.

2.4. Threats to validity

One of the threats to the validity of this study is the relatively small number of PRD in the Registry. Taking into account the nature and size of the target group, this sample can be taken as valid for the initial implementation of this kind of research, aimed at determining the future needs for research in this area.

Another threat to validity considered was the availability of interviewees, but this challenge was overcomed by applying self-interviewing (in electronic and in hard copy) and choice of target (purposive sample) and/or snowball sample, with all the disadvantages posed by this type of interviewing.

3.RARE DISEASES, COMMON QUESTIONS: STUDY FINDINGS

3.1. Introduction: Aspects of the quality of life

When quality of life (QoL) is discussed in the context of health and disease, the term health-related quality of life (QoH) is more often used to distinguish it from the other aspects of quality of life. Since health is a multidimensional concept, QoH is a complex issue as well, related to one's physical, psychological, emotional and social functioning.[104]

Researching and evaluating the quality of life of PRD can contribute to identifying their health-related and other needs.[105] In most cases, rare diseases are life-threatening and chronically debilitating, requiring long-term treatment by specialists, as well as expensive medical and other care.

In the past several years, the number of methods for measuring QoL i.e. QoH has been exponentially growing. Although former definitions of QoH are rather limited and refer to satisfying daily needs and activities, the expansion of methodology allowed for QoH to grow into a concept that encompasses physical, psychological and social aspects of health. Consequently, the main objectives of modern methods are to assess the extent to which the disease and its treatment influence these aspects, considering patients' experiences, beliefs, expectations and viewpoints as well.[106]

The analysis results show that PRD face complex challenges regarding their familiarity with the disease, the physical and psychological aspects of their life as well as the health system response. Their perception of QoL is of great importance to decision makers, as decisions should be focused on the individual and his/her real needs. The study results are given through five investigated points:

1. Familiarity with and sources of information on RDs;
2. Diagnosis, treatment and follow-up;

104 Ferrans CE. Definitions and conceptual models of quality of life. In: Lipscomb J, Gotay CC, Snyder C, editors. Outcomes assessment in cancer. Cambridge, England: Cambridge University; 2005. p. 14–30, Available: http://ebooks.cambridge.org/chapter.jsf?bid=CBO9780511545856&cid=CBO9780511545856A010, Accessed: 23.11.2015

105 Luis Rajmil , Lilisbeth Perestelo-Pérez, Michael Herdman: Quality of Life and Rare Diseases, Available: http://www.researchgate.net/publication/46171155_Quality_of_Life_and_Rare_Diseases, пристапено на 23.11.2015

106 Solans M, Pane S, Estrada MD, et al (2008) Health-related quality of life measurement in children and adolescents: a review of instruments. Value Health 11:742–764, Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4140509/, Accessed: 10.12.2015

3. Obstacles in the process of treatment and care within the system;
4. Satisfaction with health and other types of care;
5. Impact of the disease on the QoL.

3.2. Awareness, sources of information and education on rare diseases

3.2.1. Awareness and sources of information on rare diseases

According to the results, the condition with the awareness among PRDs and PCRDs is satisfactory because of availability and accessibility of plentiful of information. The Internet is the main source of information, although other important sources quoted by the respondents are leaflets, medical handbooks as well as associations and specialists (Figures 4 and 5).

Health professionals confirm that for them the Internet is the main source of information as well, mostly because of the availability of latest information. Most often, they inquire the necessary information by themselves and sometimes they get informed through trainings organized by their institution (Figure 6).

Figure 4. Most common sources of information on RD, PRD, (n=16)

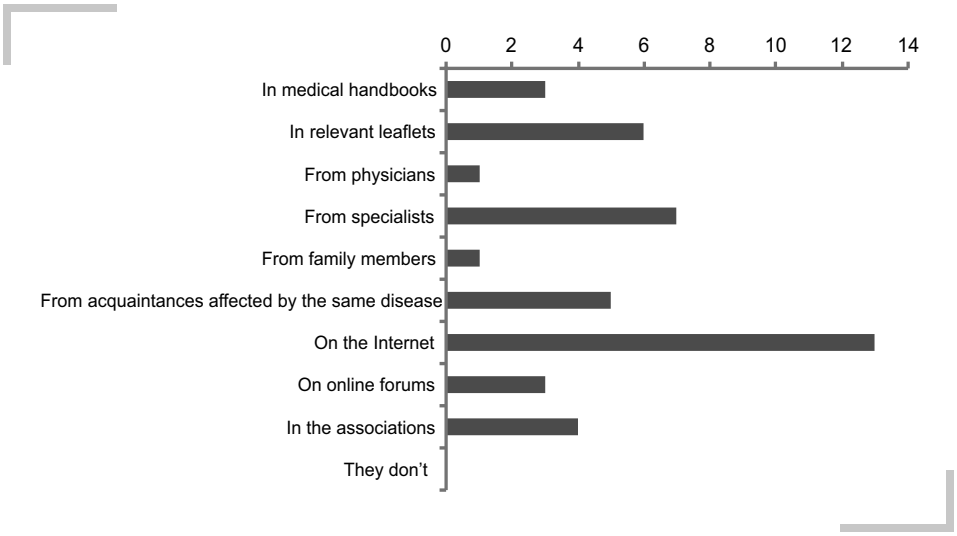


Figure 5. Most common sources of information on RD, PCRD, (n=10)

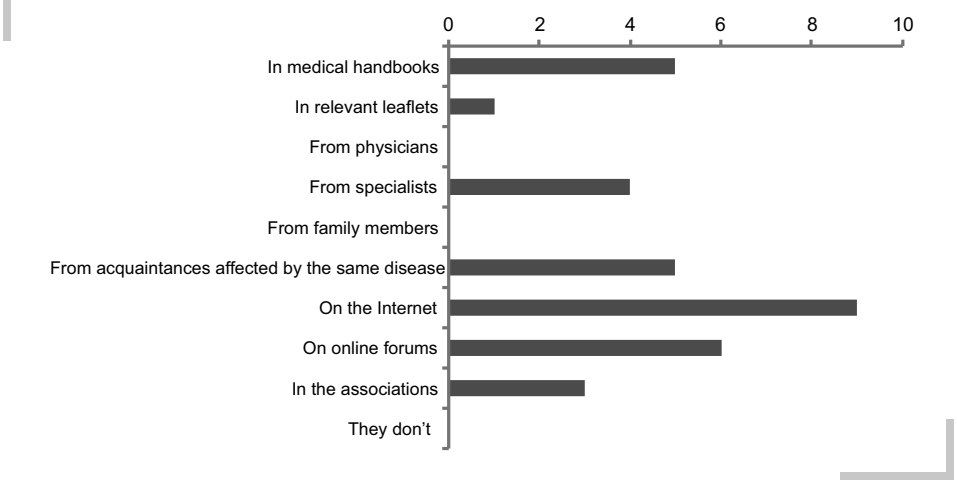
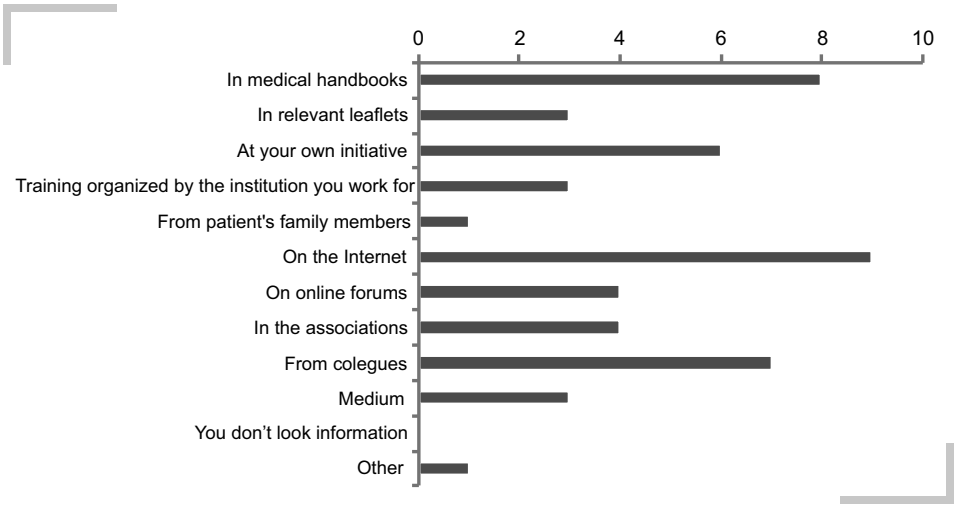


Figure 6. Most common sources of information on RD, HP, (n=15)



The study shows that it is not always possible to obtain the required information; in other words, great effort is needed to find such information; even if found, the information can be difficult to understand. Still and by far in highest percentage, according to PRD and PCRD, the most clear and understandable information with suitable explanation is obtained from health professionals (Figure 7 and Figure 8).

Figure 7: Access to information on RD, PRD, (n=16)

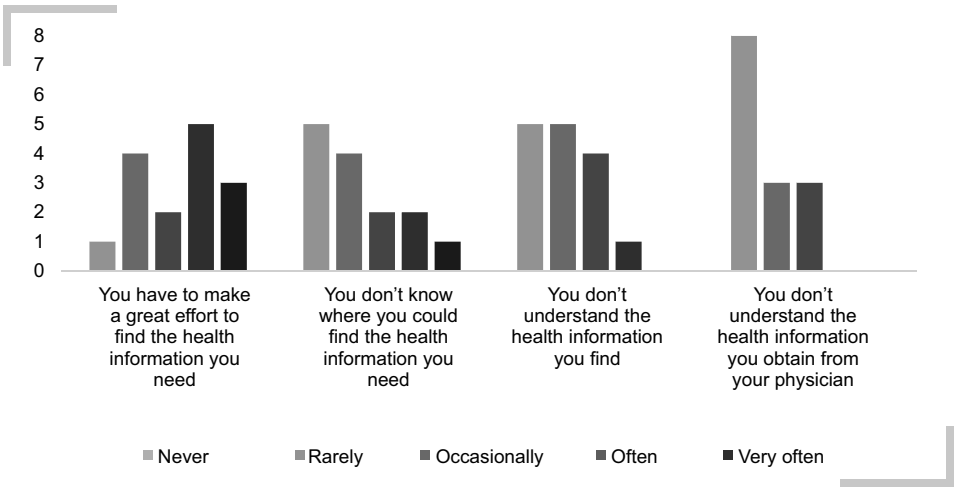
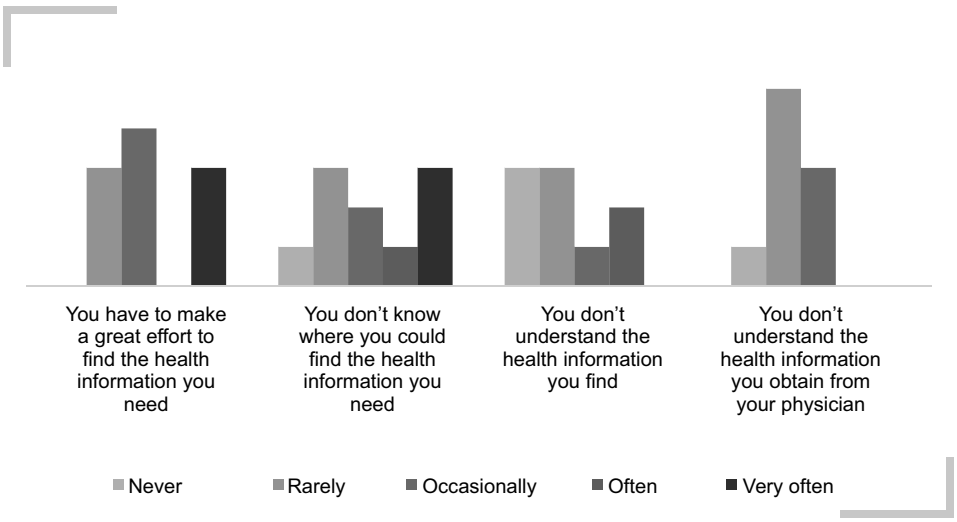


Figure 8: Access to information on RD, PCRD, (n=10)



To PRD, it is important to be informed about their disease and the possible complications. They want to share and exchange their experience with other persons suffering from the same disease and believe that the more they know, the greater the control they have over symptoms and treatment (Figure 9). It is equally important to PCRD to be informed about the disease of their child and the possible complications; they want to be able to share their experiences with other people affected by the same disease. Parents, too, believe that the more they know about the disease of their child, the greater the control they will have over it (Figure 10).

Figure 9: Importance of being informed about RD, PRD, (n=16)

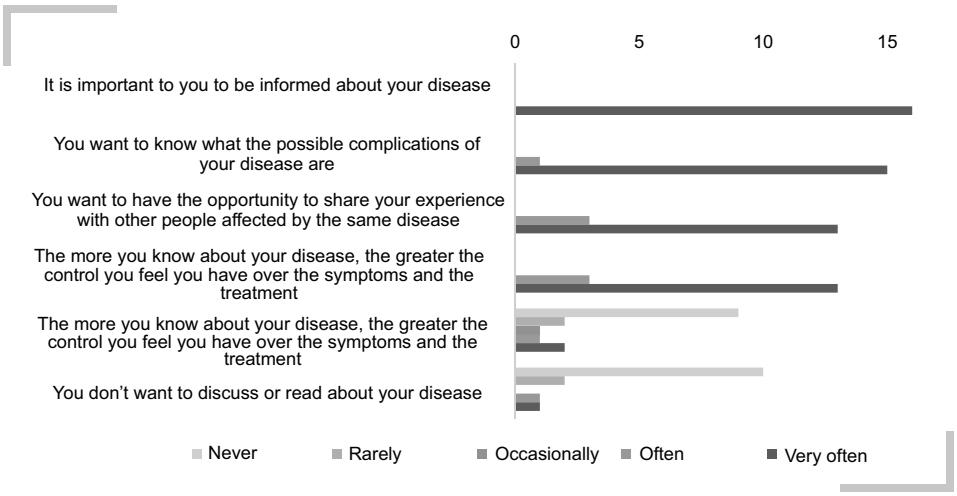
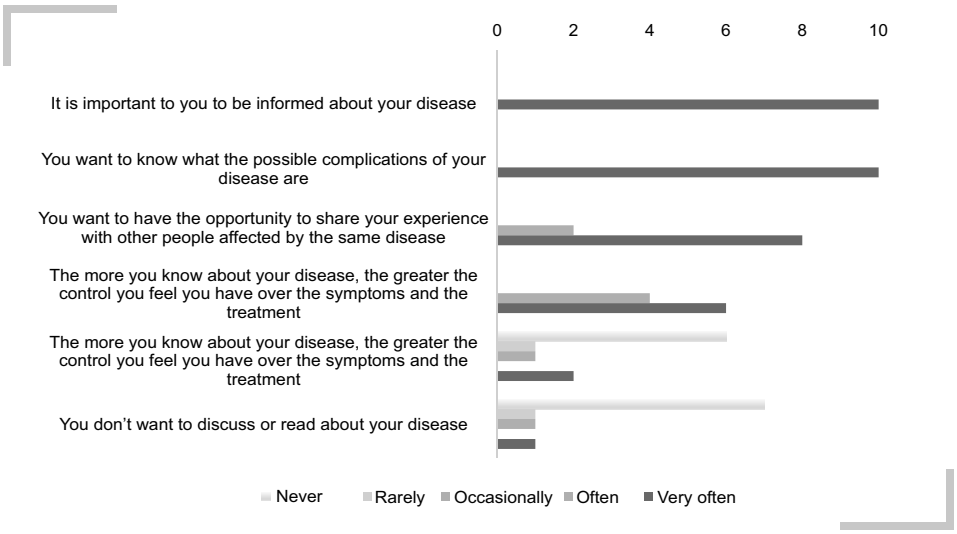


Figure 10: Importance of being informed about RD, PCRD, (n=10)



For those reasons, PRD would like to obtain more information also related to the latest studies, causes of disease, treatment options and side effects, interpretation of results and self-help methods (Figure 11). In addition, PCRD would like to learn more about the alternative ways of treatment and the possibility to participate in clinical trials (Figure 12). Health professionals, too, find it important to know more about various types of treatment, the latest research findings, as well as about the possibility to participate in clinical trials (Figure 13).

Figure 11: RD-related information of importance to PRD, (n=16)

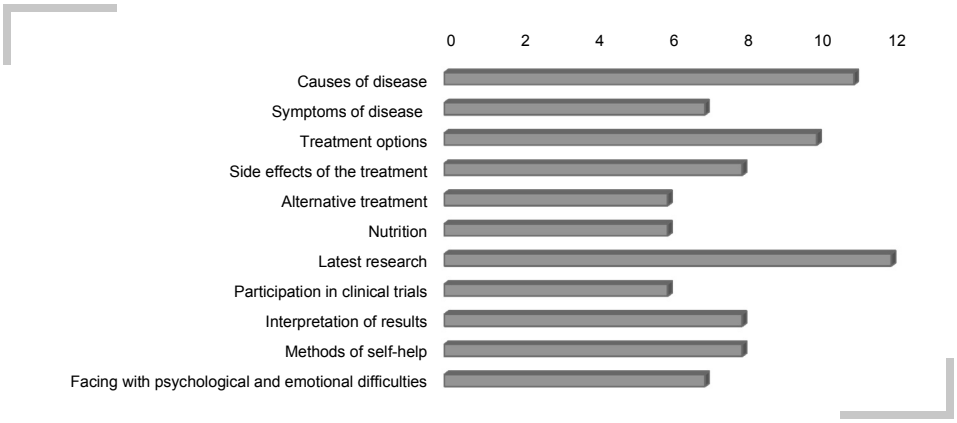


Figure 12: RD-related information of importance to PCRD, (n=10)

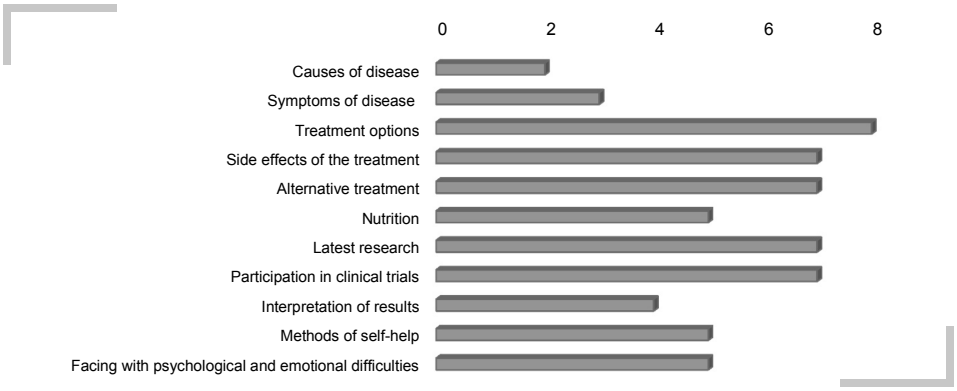
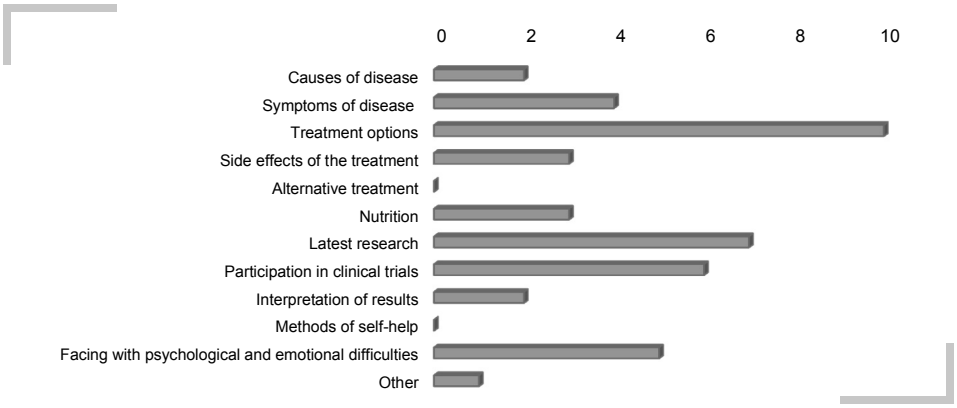
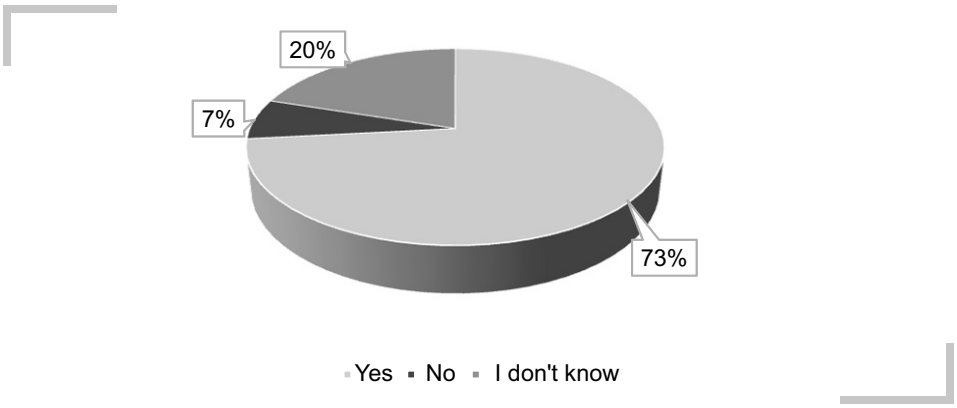


Figure 13:RD-related information of importance to HP, (n=15)



In terms of existing policies, there are HPs who are not yet acquainted with the existence of the Program for treatment of RD (Figure 14).

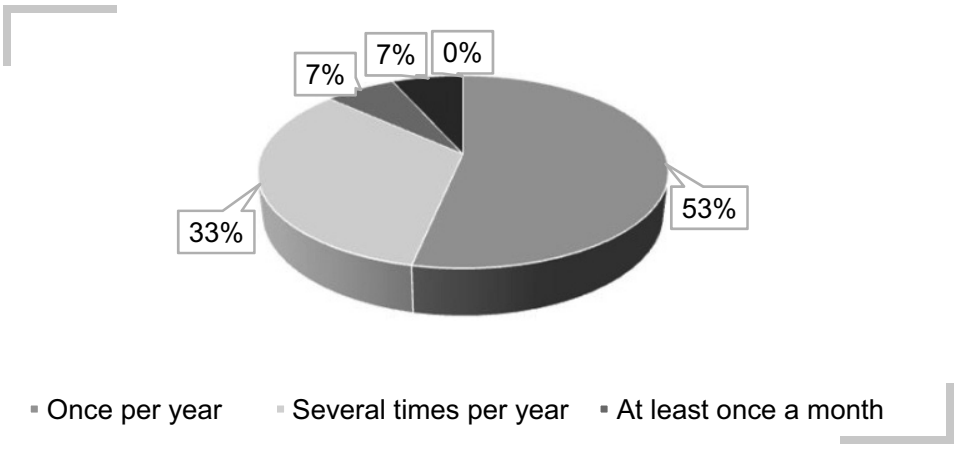
Figure 14: Familiarity of HPs with the Program for treatment of RD, (n=15)



3.2.2. Education and experience of health professionals

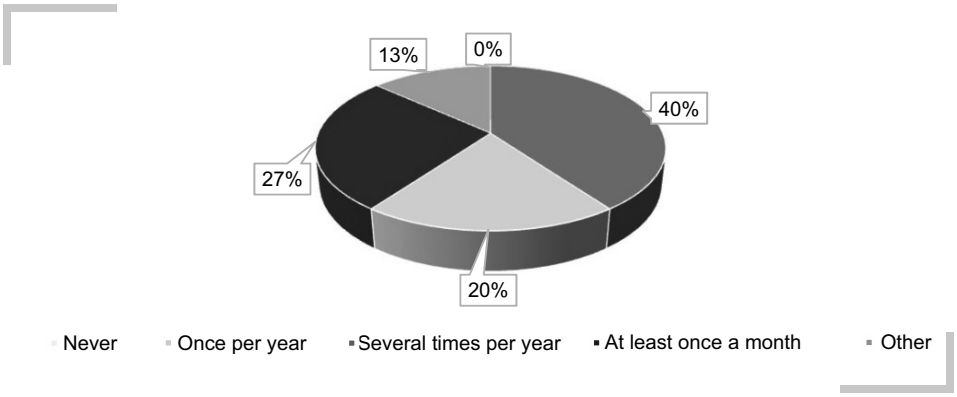
Most HPs who participated in the research indicated that education regarding RD is on their own initiative, either through searching the Internet or through educational lectures organized by the employing institution. Fifty-three per cent of respondents said they attend educational lectures for RD several times during the year, and 33% attend these lectures only once a year (Figure 15).

Figure 15: How often do HPs attend lectures on RDs, (n=15)



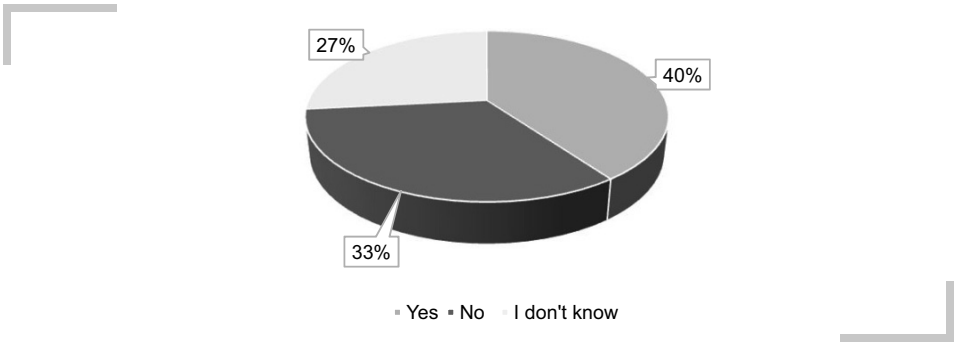
The work experience of the respondents spans from one to 40 years and involves various specialties at different work positions. Throughout their careers, the health professionals have come across and treated the following diseases: Gaucher disease, Beta thalassemia, Cystic fibrosis, Leucodystrophy, Tuberous sclerosis complex, Wilson's disease and Spinal muscular atrophy. Some of them reported to come in contact with PRD at least once per month while others - once per year (Figure 16).

Figure 16: How often do HPs meet PRD in the course of their work, (n=15)



Regarding the availability of a specialist in RD at their clinic, 40% of responding HPs gave positive answer, 33% gave a negative answer and 27% did not know. (Figure 17).

Figure 17: Are there specialists in RD at the clinics of haematology and children's diseases, (n=15)



Respondents indicated availability of specialists for cystic fibrosis, muscular dystrophy and Gaucher's disease.

Regarding the types of services provided at institutional level, health professionals working at the University clinic of haematology and the University clinic for children's diseases explained that for PRD, these health institutions provide diagnosis, treatment, supportive treatment, treatment follow-up and complete health care.

3.3. Diagnosis, treatment and follow-up

Respondents from the PRD group have responded to have one of the following diseases: mastocytosis, idiopathic pulmonary hypertension, Wilson's disease, Gaucher's disease, Non-Hodgkin's lymphoma, Crohn's disease, amyotrophic lateral sclerosis, Von Willebrand disease, acute intermittent porphyria, etc. In the PCRD group the parents reported metabolic and genetic disorders of their children: dextrocardia with situs inversus, Kartagener syndrome, Rett syndrome, juvenile dermatopolymyositis – M33,[107] hereditary angioedema, congenital aganglionic megacolon (Q43, A41, E86),[108] dermatitis herpetiformis in coeliac disease, mucopolysaccharidosis type IVa, Morquio syndrome, adrenomyeloneuropathy and carnitine-palmitoyltransferase-II deficiency (CPT-II).

According to respondents, the time of first occurrence of symptoms is very variable, ranging from birth up to 50 years of age. Moreover, respondents stated that the period between the onset of symptoms and the diagnosis varies greatly and depends on both the disease and the overall health condition. Within responses, this period ranged from one month to several years for the correct diagnosis to be determined. During this period, PRD live with the symptoms and without treatment, which may have negative effects on the course of the disease and on their overall health condition.

For the PRD, the diagnostic process involves finding their way through the labyrinth of the health care system: examination of their condition by different health institutions and contact with various HPs. Unfortunately, inaccurate diagnosis is common outcome in a number of cases and is therefore, the main obstacle to adequate and timely treatment. The survey results indicate that nearly 50% of PRD have had an inaccurate diagnosis (Figure 18). The same was reported by PCRD, where 60% of the children had such situation (Figure 19).

107 ICD-10 codes
108 ICD-10 codes

Figure 18: Accuracy of the first diagnosis, PRD, (n=16)

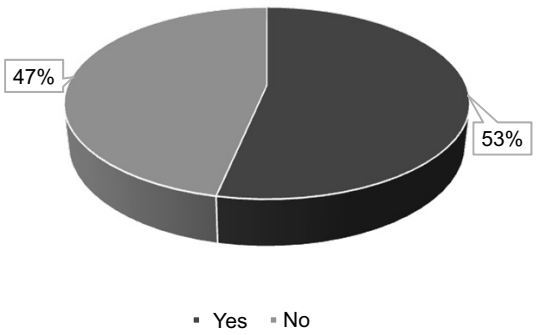
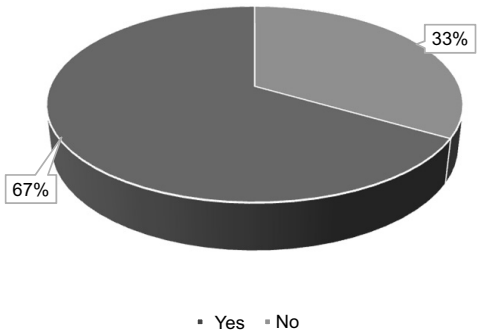


Figure 19: Accuracy of the first diagnosis, PCRD, (n=10)



In some cases, PRD have been diagnosed with more than two diagnoses; the most extreme examples showcased by some PRD are as high as over 10 different diagnoses. This period is extremely difficult for PRD as their symptoms continue and might even get exacerbated, but due to unspecified diagnosis, they cannot receive treatment and therefore face physical, psychological as well as financial difficulties. During this period, they consult many doctors – sometimes even more than 10 (Figure 20) to get the accurate diagnosis. Similar situation was reported by PCRD (Figure 21).

Figure 20: Number of consultations before the final diagnosis, PRD, (n=16)

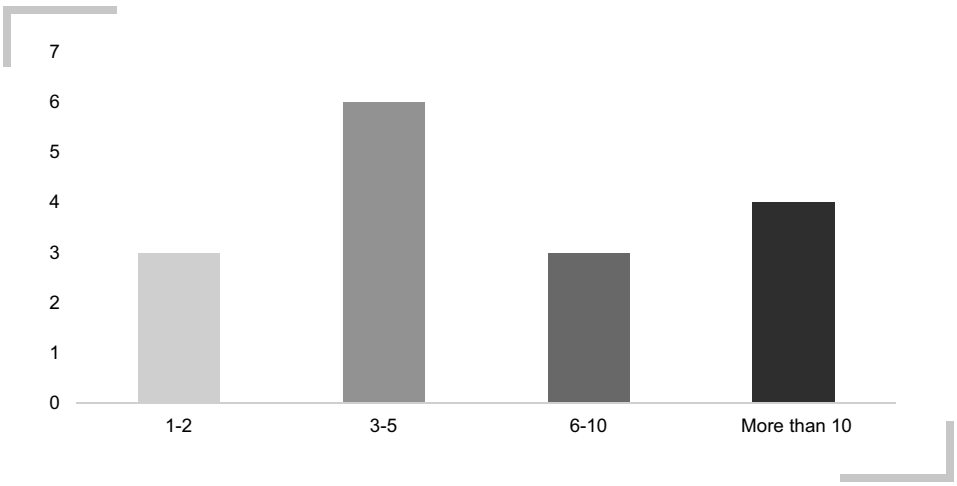
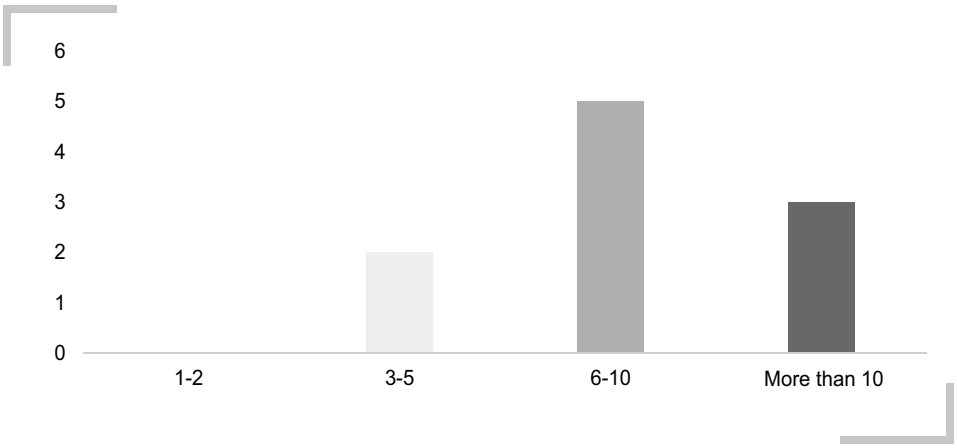


Figure 21: Number of consultations before the final diagnosis, PCRD, (n=10)



Depending on the disease, the accurate diagnosis of the respondents was established by different health institutions in the country such are the university clinics of children's diseases, neurology, cardiology, dermatology, gastroenterohepatology and the Centre for haemophilia.

In Macedonia, the treatment and monitoring of PRD is carried out in several clinics: university clinics (UC) of children's diseases (departments of rheumatology, immunology, gastroenterohepatology), immunology, haematology, dermatology (department of skin diseases), gastroenterohepatology, , rheumatology, , neurology (department of neuromuscular diseases), Centre for haemophilia, Institute of Immunobiology and

Human Genetics, Institute for respiratory diseases – Kozle, Institute of Physical Medicine and Rehabilitation in Kozle, as well as "Filip Vtori" Private Hospital. PRD who undergo medical treatment abroad referred to "Dr. Apostolski" Outpatient Neurological Clinic in Belgrade, "AKN Vienna"[109] and the Great Ormond Street Hospital in London. As much as 50% of the respondents think that there is no specialist in the country to give information, diagnosis or treatment for their specific condition (Figure 22). Even greater percentage of parents (70%) think that there is no specialist in Macedonia for their child's disease (Figure 23).

Figure 22: Access to an adequate institution for RD treatment in the country, PRD, (n=16)

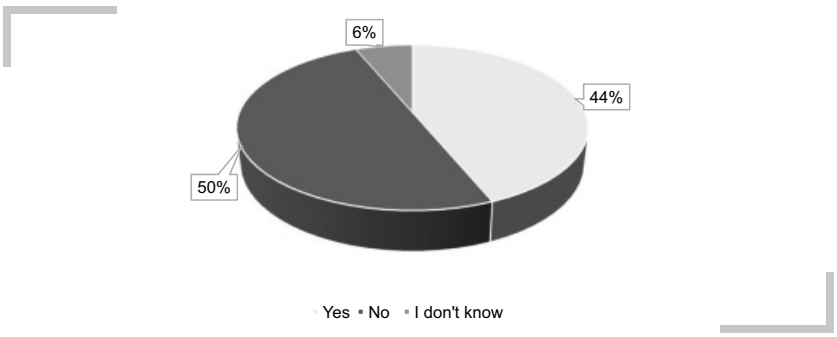
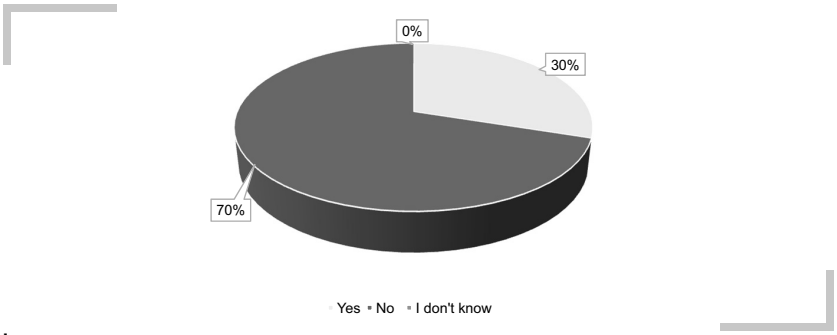


Figure 23: Access to an adequate institution for RD treatment in the country, PCRD, (n=10)



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Respondents in their answers indicated the names of specialists they have consulted and who are treating them.[110]

After diagnosis is established and treatment is commenced (if available), PRD stated that it is necessary to regularly go to check-ups and follow-up laboratory testing, in accordance with the dynamics dictated by their disease and overall health condition.

109 Alternativgemeinschaft Körperbehinderter und Nichtbehinderter (Alternative community for physically disabled and non-disabled)

110 See Appendix no. 2

For some conditions, check-ups are performed every two weeks, while for others once a year or once every two years.

The follow-up of the condition of PRD mostly consists of biochemical testing. As much as 81% of the respondents specified the need of this type of examination (Figure 24), followed by functional and radiological examinations (Figures 25 and 26).

Figure 24: Types of examinations needed for RD monitoring, (n=16)

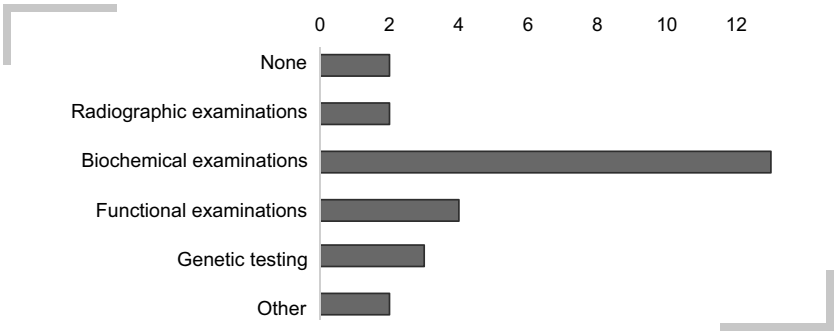


Figure 25: Types of diagnostic examinations performed, PRD, (n=16)

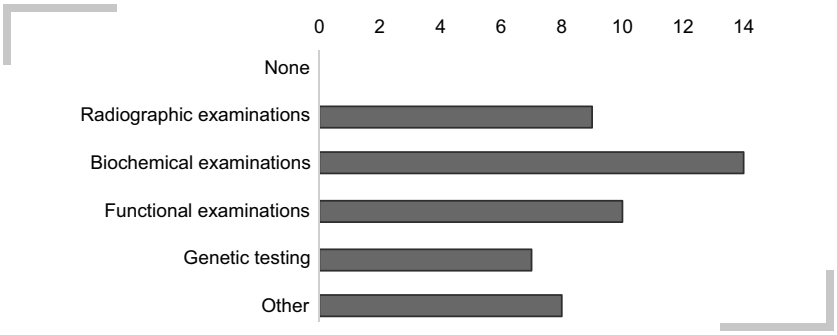
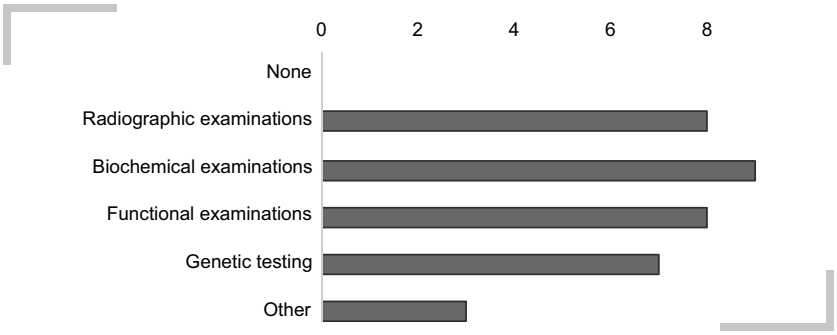


Figure 26: Types of diagnostic examinations performed, PCRD, (n=10)



3.4 Quality of health care

3.4.1 Access to treatment and care

In terms of health care, PRD point to the various challenges: setting wrong and/or delayed definitive diagnosis; delayed or inappropriate treatment; unavailability of medicines, medical devices and additional treatment (e.g. physical therapy) and so forth. (Table 2).

The most common difficulties indicated by PRD and PRCD in the study are shown in Figure 27 and Figure 28. In addition, for children with rare diseases, access to surgical services is also hindered.

Figure 27: Access to services in the system, PRD, (n=16)

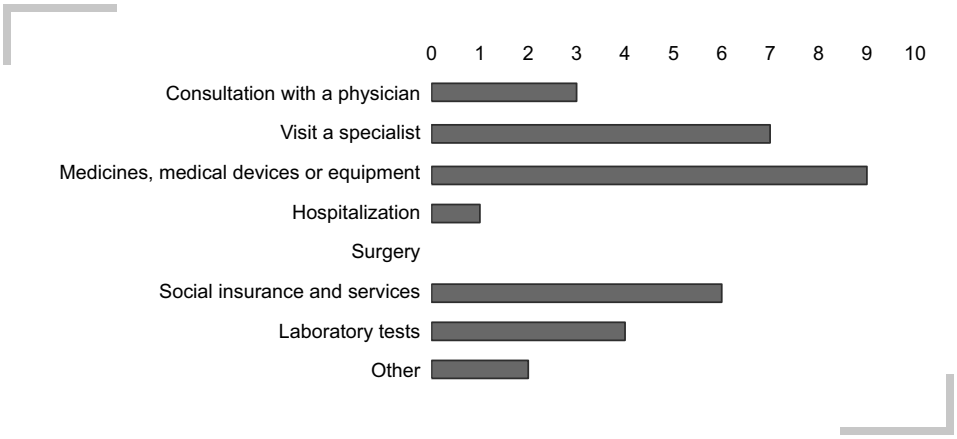


Figure 28: Access to services in the system, PCRD, (n=10)

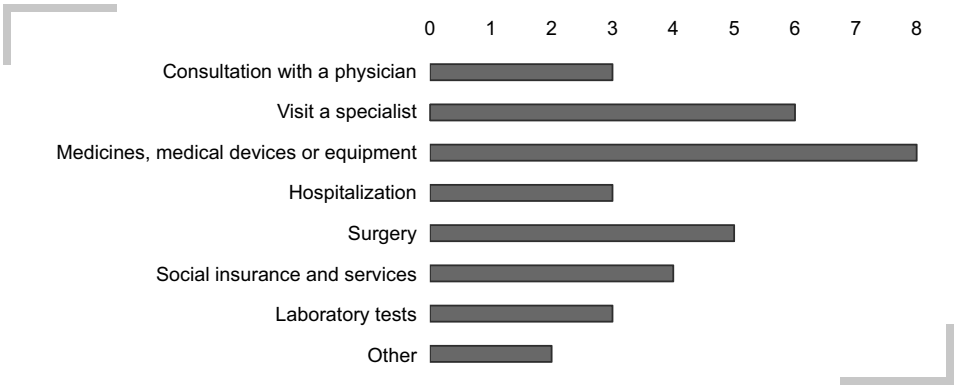


Table 2: Barriers to treatment and care within the system (PRD and PCRD)

Identified obstacles	Reasons given by the respondents
DIAGNOSING	
Inaccurate diagnosis	• Non-recognition of the disease by several specialists • Lack of equipment for diagnosis • Doctors are not sufficiently informed about rare diseases • Arrogant doctors • Problem in the educational process (misdiagnosis of autism) • Misdiagnosis of psychogenic illness
Lack of final diagnosis	• Non-recognition of the disease by several specialists • Lack of equipment for diagnosis • Doctors have no experience • Doctors are not sufficiently informed about rare diseases • Indifference of doctors
CARE and TREATMENT	
Untimely treatment	• Expensive medicines • Unavailable medicines for the disease in Macedonia • The first symptoms are vague for doctors to make diagnosis • Lack of qualified medical staff • Referring patients to wrong clinics • Referral from one specialist to another for years • No medicine on the positive list • Due to untimely treatment, people with RD have faced the following conditions: chronic bronchitis, epilepsy, delayed speech, several-hour-long clinical placement, onset of symptoms and progression of the disease, toxic enterocolitis and life-threatening condition.
Inadequate treatment	• Receiving wrong treatments • Combination of drugs that can have opposite effect if used together • Insufficient knowledge among doctors due to the low incidence and the small number of patients affected by the disease • Giving contraindicated therapy • Untimely diagnosis • Insufficient dosage monitoring
AVAILABILITY of MEDICINES, MEDICAL DEVICES and OTHER TYPE of TREATMENT	
Availability of medicines	• Not imported in the country • Using old-fashioned treatment with cryoprecipitate • Medicines are not on the positive list of HIFM • Due to unavailability of medicines, people with RD faced the following conditions: severe dehydration, intoxication and several-day-long supervised clinical placement
Availability of medical devices	• Oxygen concentrator • Wheelchair • Catheters for rectal irrigation • Reagents
Availability of other type of therapy	• Personal assistant for disabled people • Immunotherapy • Visit by nurse • Supplements for daily maintenance of condition • Special dietary supplements

Regarding the treatment and needed care, PRD and PCRD point to a wide range of issues shown in Figure 29 and Figure 30, respectively.

Figure 29: Issues within the system of treatment and care, PRD, (n=16)

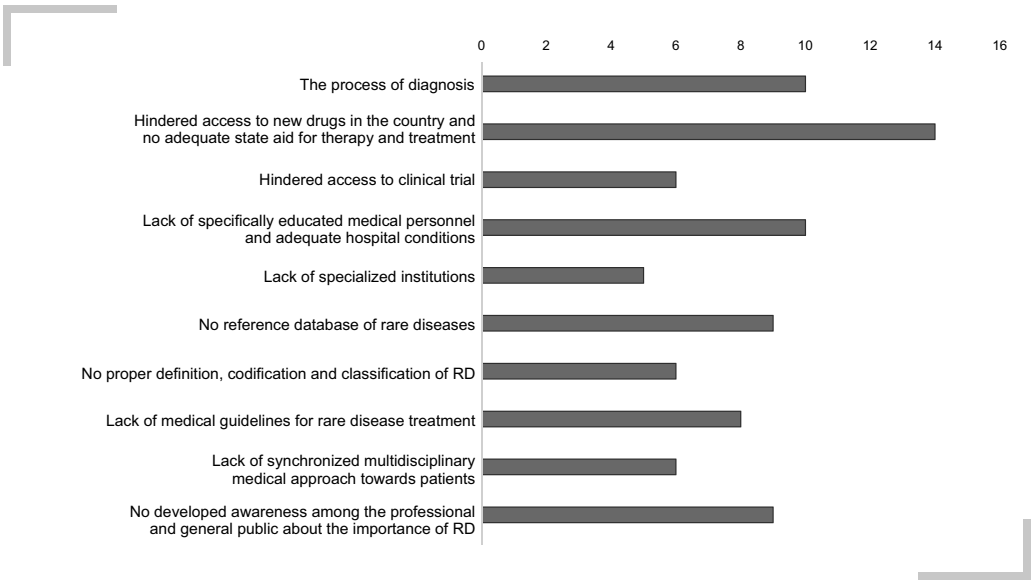
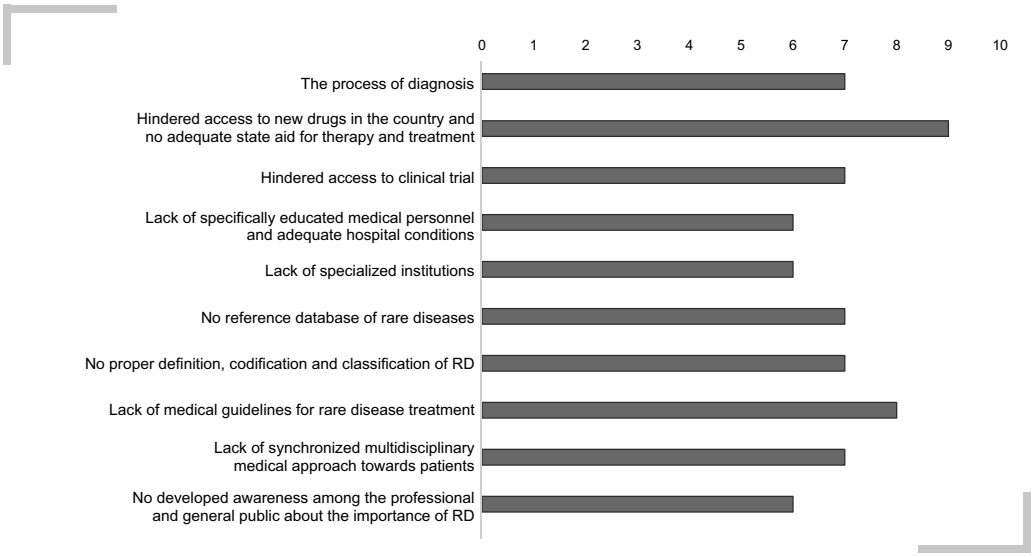


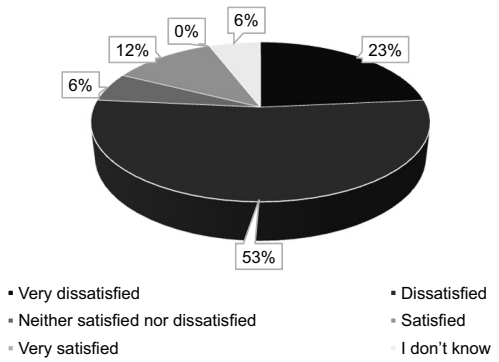
Figure 30: Issues within the system of treatment and care, PCRD, (n=10)



3.4.2. Satisfaction with health care

Respondents expressed dissatisfaction with the health care; 53% of them are dissatisfied with the cooperation and support they receive from the Ministry of Health, in contrast to 12% who are satisfied and 6% who don't have an opinion (Figure 31).

Figure 31: Support from and cooperation with the Ministry of Health, PRD, (n=16)



Approximately 60% of the respondents are dissatisfied or very dissatisfied with the support and cooperation with the HIFM, as opposed to 13% who are satisfied (Figure 32). The percentage is even higher in the PRCD group (Figure 33).

Figure 32: Support from and cooperation with HIFM, PRD, (n=16)

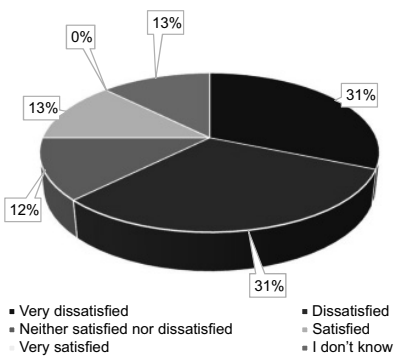
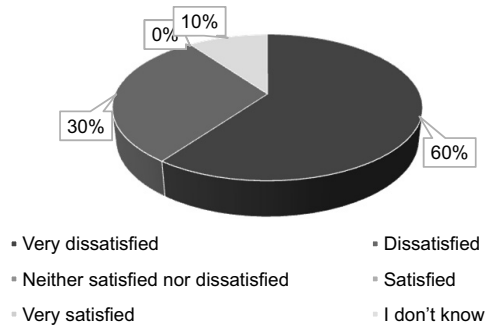


Figure 33: Support from and cooperation with HIFM, PCRD, (n=10)



When asked about their experience with the support and cooperation with health care institutions in the country, many of the respondents are neither satisfied nor dissatisfied (Figure 34 and Figure 35).

Figure 34: Support from health care institutions, PRD, (n=16)

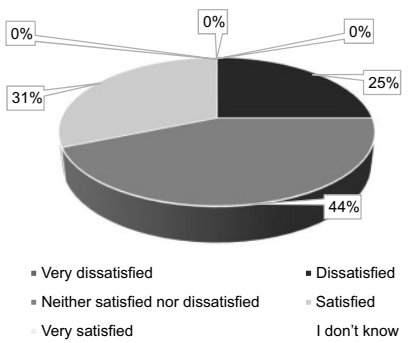
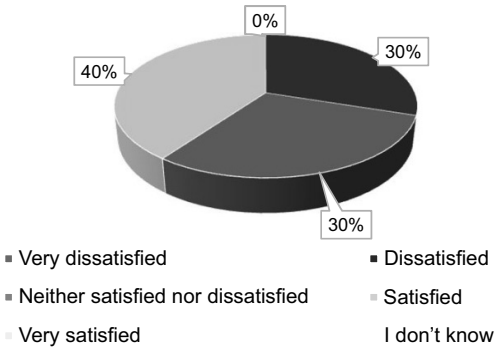


Figure 35: Support from health care institutions, PCRD, (n=10)



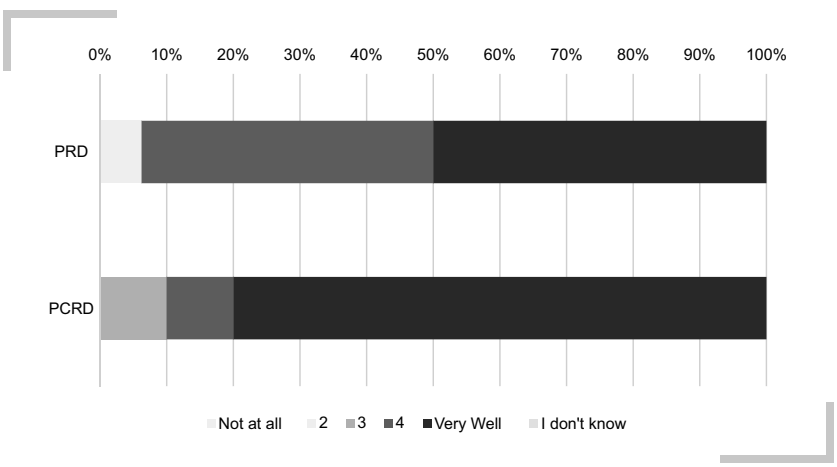
3.5 Impact of the disease on the quality of life for people with rare diseases

Like any long-term and incapacitating condition, rare diseases, too, have an essential impact on the quality of life. Understanding the disease and the attitude towards it, the concern about the condition, emotional stability, the control over the disease and the treatment process are only some of the factors affecting the quality of life. This study investigated four elements of influence: the attitude towards the disease, the social life, the psychological aspect and the perception of quality of life.

3.5.1 Attitude towards the disease

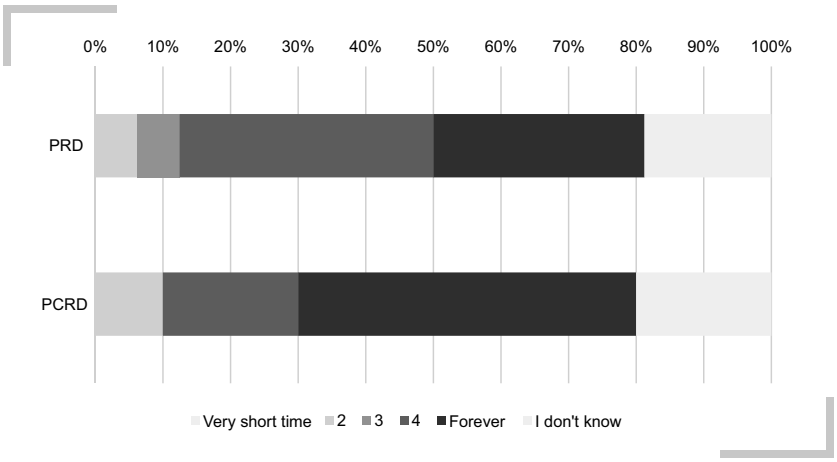
When asked how well they understand and accept the condition they have, as much as 50% of respondents said they understand it very well, 44% that they understand it well understood and 6% did not understand their disease. The majority of PCRD (80%) also said they understand the disease of their child very well (Figure 36).

Figure 36: Understanding of the disease by PRD and PCRD, on a scale of 1-6 (1 Not at all, 5 – Very well and 6 – I don't know)



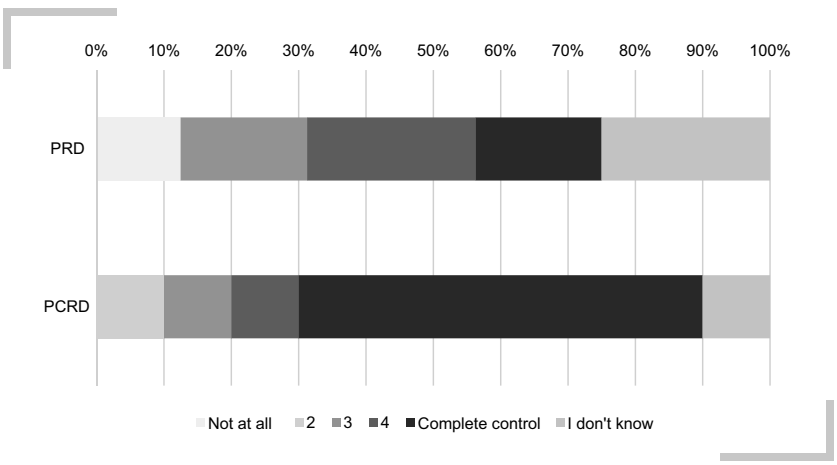
In terms of their understanding and acceptance of the disease duration, 50% of the respondents answered that it was life-long condition, 25% that would last long time, 19% didn't have an opinion and 6% answered that their disease is a short-term condition. The majority of PCRD (70%) also think that their child's disease is long-term or life-long disease (Figure 38).

Figure 37: Duration of the disease according to PRD and PCRD on a scale of 1-6 (1 Very short time, 5 – Forever and 6 – I don't know)



In relation to the control over the disease, answers were diverse: 25% of the PRD did not know how much control they have, about 45% have partial or complete control, while 12% said they didn't have any control over their disease. Unlike PRD, PCRD believe that they have greater control over their child's disease (Figure 38).

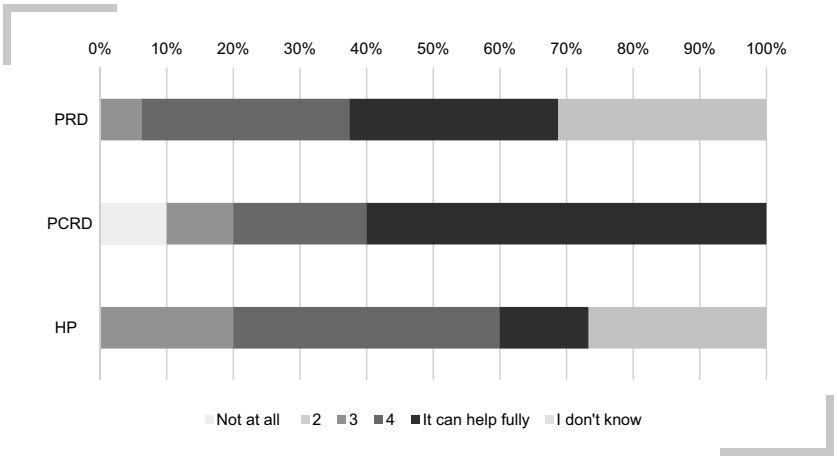
Figure 38: Control over the disease according to PRD and PCRD on a scale of 1-6 (1 Not at all, 5 – Complete control and 6 – I don't know)



The opinion of the respondents about effectiveness and benefit of the treatment for their disease is almost evenly divided: 31% think that it can entirely be of help, 31% that can help a lot, 31% have not formed an opinion, while 7% think the treatment will

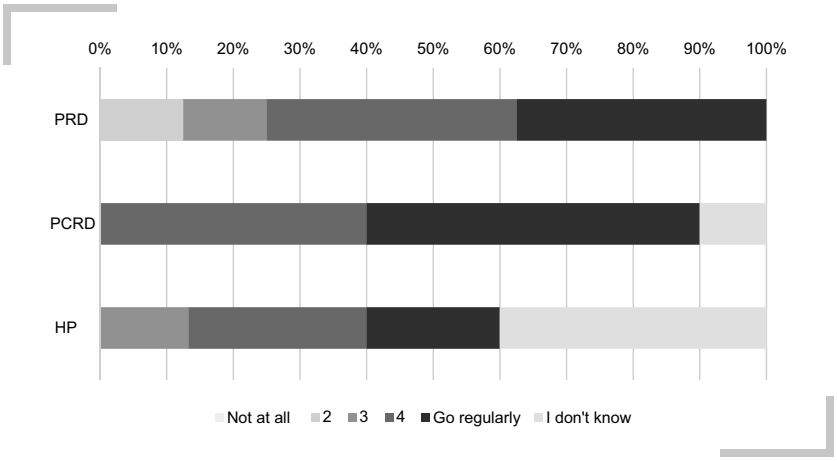
help somehow. The responses of PCRD are quite similar, with an exception that 10% of parents think that the treatment would not help their child. Along these lines, 73% of the HPs have an opinion that PRD believe the treatment could be entirely of help (Figure 39).

Figure 39: Can treatment help, according to PRD, PCRD and HPs, on a scale of 1-6 (1 Not at all, 5 – Fully and 6 – I don't know)



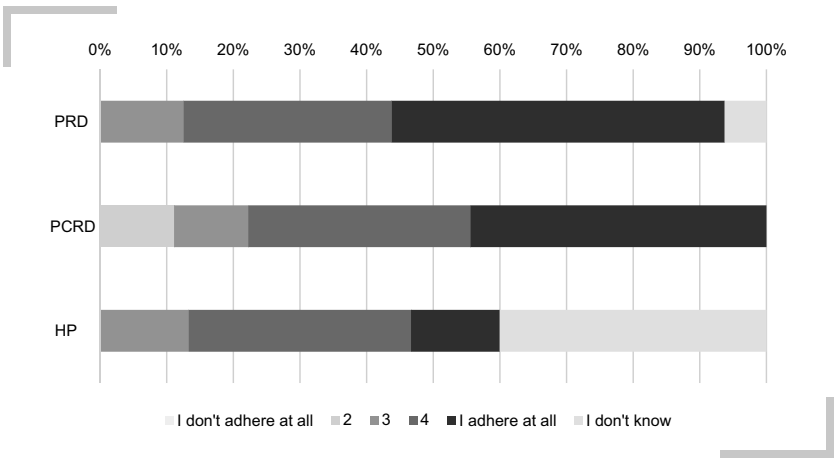
The expressed belief in a positive outcome of the treatment, contributes to the regularity of medical check-ups and interest in monitoring one's own condition or disease. Most health professionals (60%) believe that the PRD regularly go to check-ups (Figure 40).

Figure 40: Frequency of health check-ups, on a scale of 1-6 (1 No check-ups at all, 5 – Regular check-ups and 6 – I don't know)



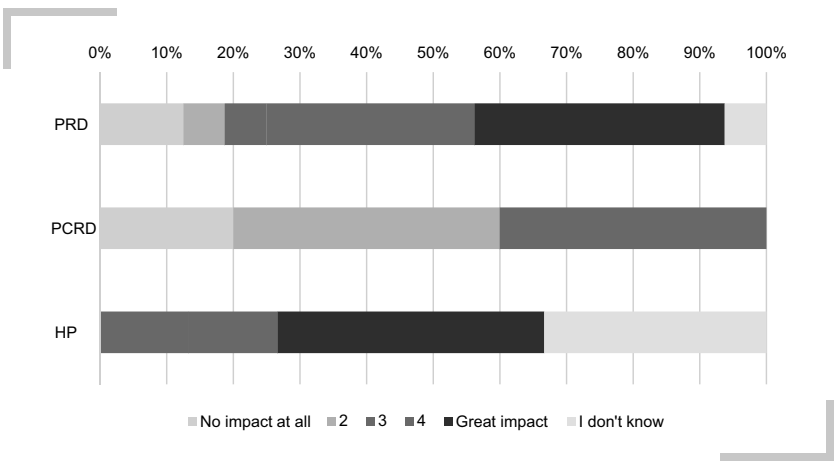
In terms of trust and adherence to medical advice, PRD and PRCD believe in health professionals, especially doctors and specialists, and therefore most of them adhere to the advice given. Health professionals are less sure whether patients adhere to their advice (Figure 41).

Figure 41: Adherence to medical advice, on a scale of 1-6 (1 I don't adhere at all, 5 – I adhere fully and 6 – I don't know)



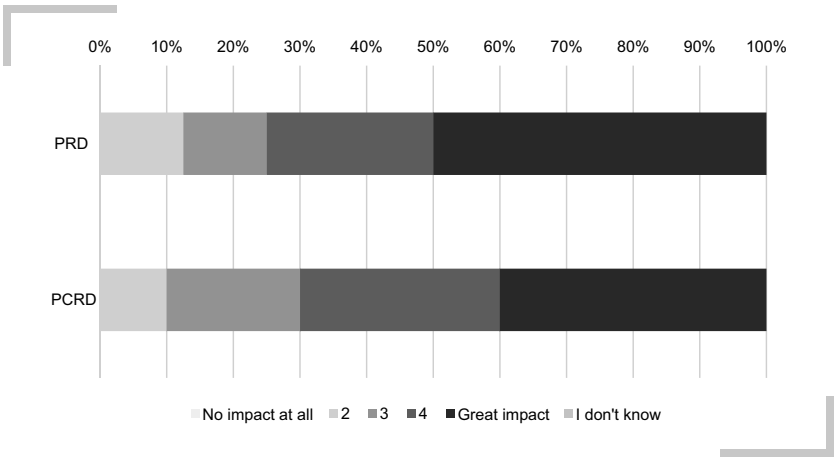
From the respondents' answers, it seems that the disease greatly affects their emotional state, since only 6% of them said that RD had no impact. Unlike PRDs, PCRDs believe that the disease does not play a major role in the emotional state of their child. Health professionals, as well consider that the disease has a major impact on the emotional state of the patient (66%), (Figure 42).

Figure 42: Emotional effect of RD, on a scale of 1-6 (1 No impact at all, 5 – Great impact and 6 – I don't know)



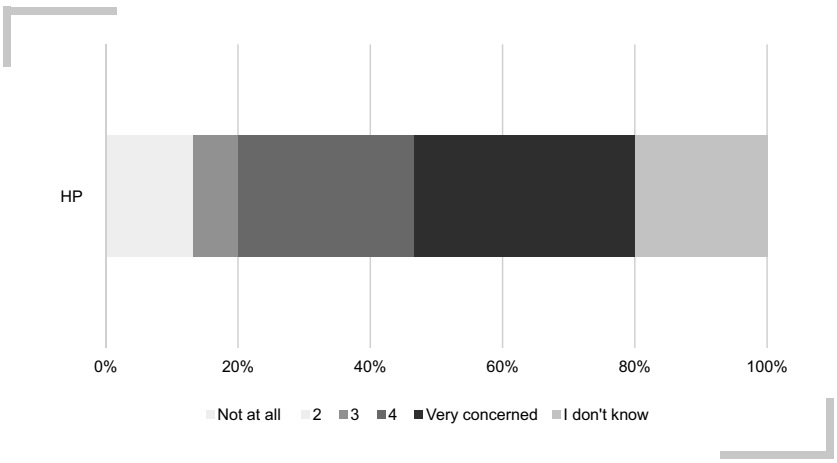
The research shows that RDs have strong impact on life overall: 88% of the respondents in PRD group consider that RD affects their life considerably; very similar responses were observed in the PCRD group (Figure 43).

Figure 43: Impact of RD on life according to PRD and PCRD, on a scale of 1-6 (1 No impact at all, 5 – Great impact and 6 – I don't know)



On the other hand, HPs provided various opinions on the extent to which PRD are concerned with their disease; although the majority believe that PRD are very concerned (67%), some of them still think that there are PRD who aren't concerned about their condition at all (13%), (Figure 44).

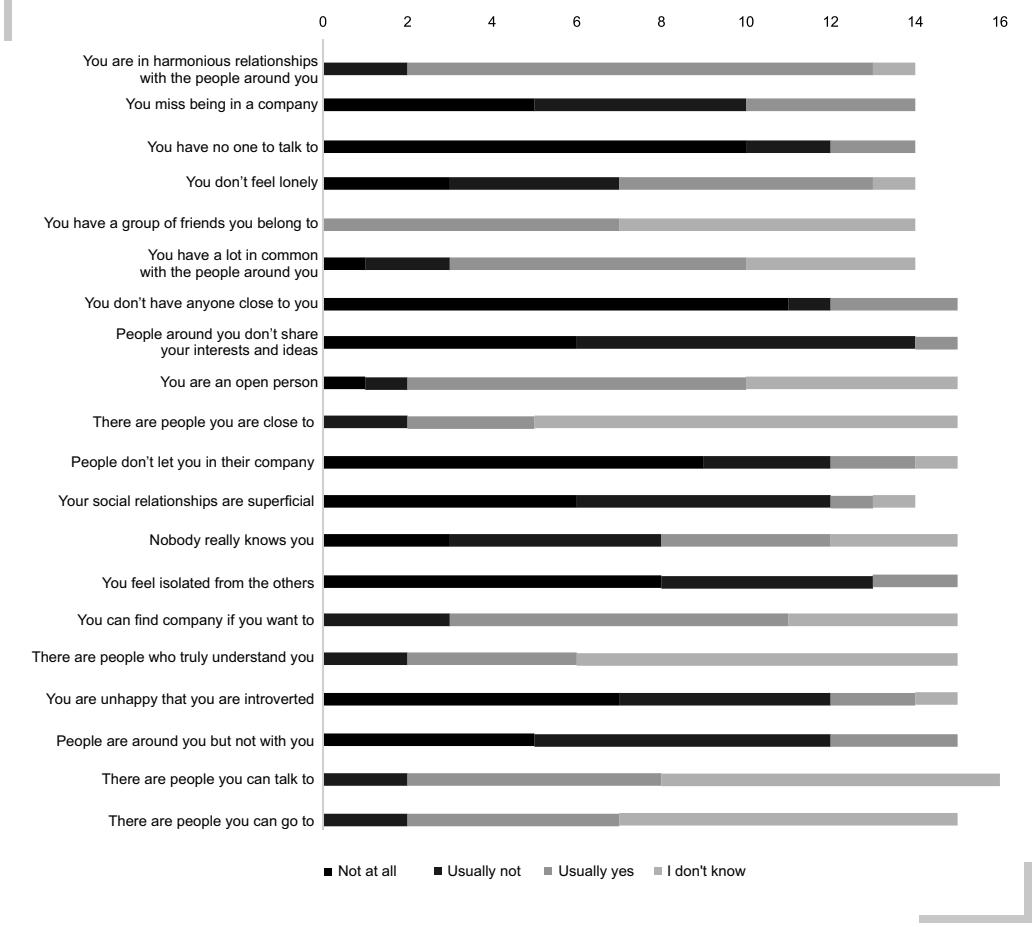
Figure 44: Opinion among HPs about the concern of PRD with their disease, (n=15)



3.5.2 Social life

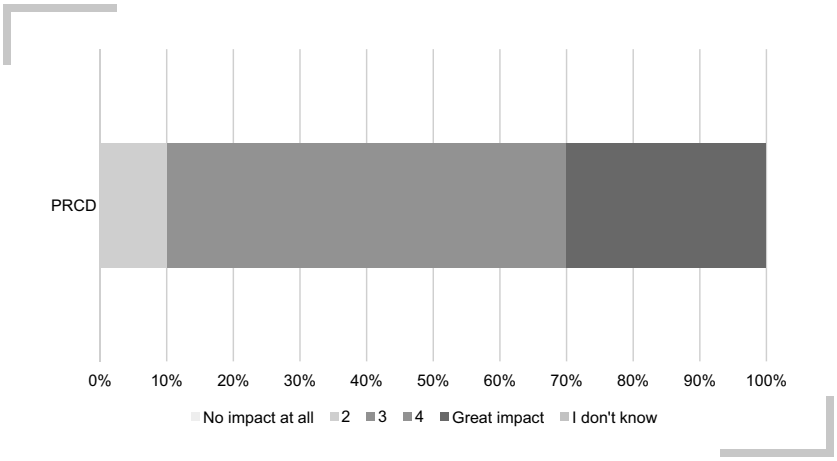
Social life is an interaction of complex relations that every individual has with their surroundings, community and society i.e. the people with whom they live, work, socialize or meet. According to the PRDs, the disease significantly affects their social life, particularly the relations with the surrounding. Answers reveal that the disease affects PRDs differently; some tend toward introversion and have a reduced sense of belonging and friendship, while others believe they are surrounded by close friends, a group to which they belong, that the environment accepts them and they do not feel isolated (Figure 45).

Figure 45: The social life of PRD, (n=16)



PCRD, too, responded that the disease affects their child's socialization (90%), (Figure 46).

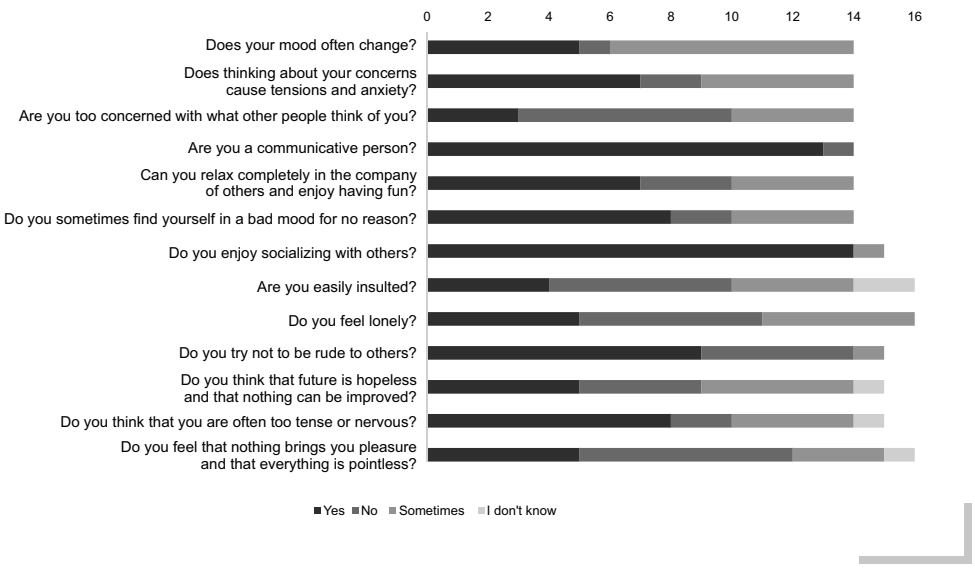
Figure 46: Impact of the disease on socialization of children with RD, (n=10)



3.5.3 Psychological aspects of life

According to the respondents' answers, PRDs seem like communicative people with occasional mood swings, who sometimes find it difficult to relax in the company of others because the disease can cause anxiety and tension (Figure 47).

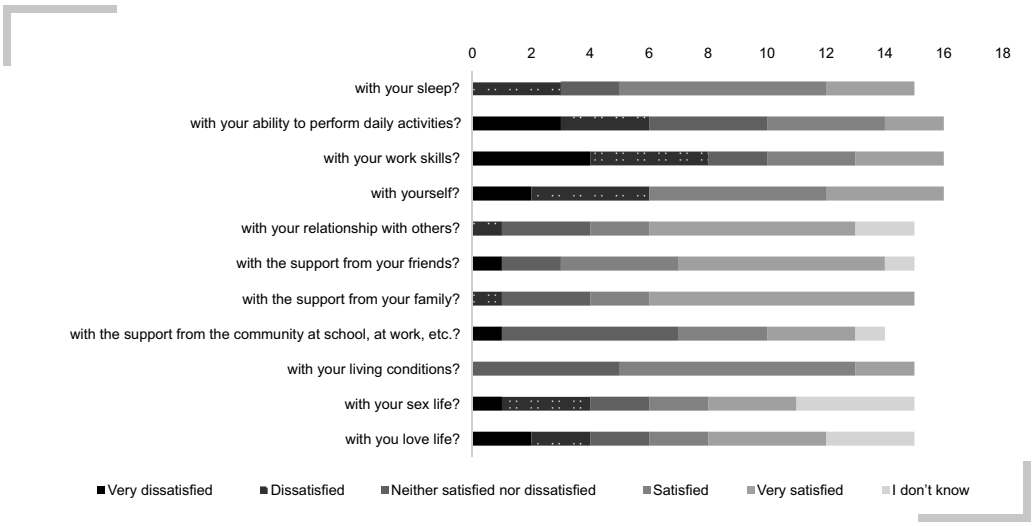
Figure 47: Psychological aspects of life for PRD, (n=16)



3.5.4 Perception of quality of life by people with rare diseases

PRDs expressed feeling of support mostly from their families and close friends. Their dissatisfaction is mainly related to their working skills and activities of daily living (Figure 48).

Figure 48: Self-perception of the quality of life, PRD, (n=16)

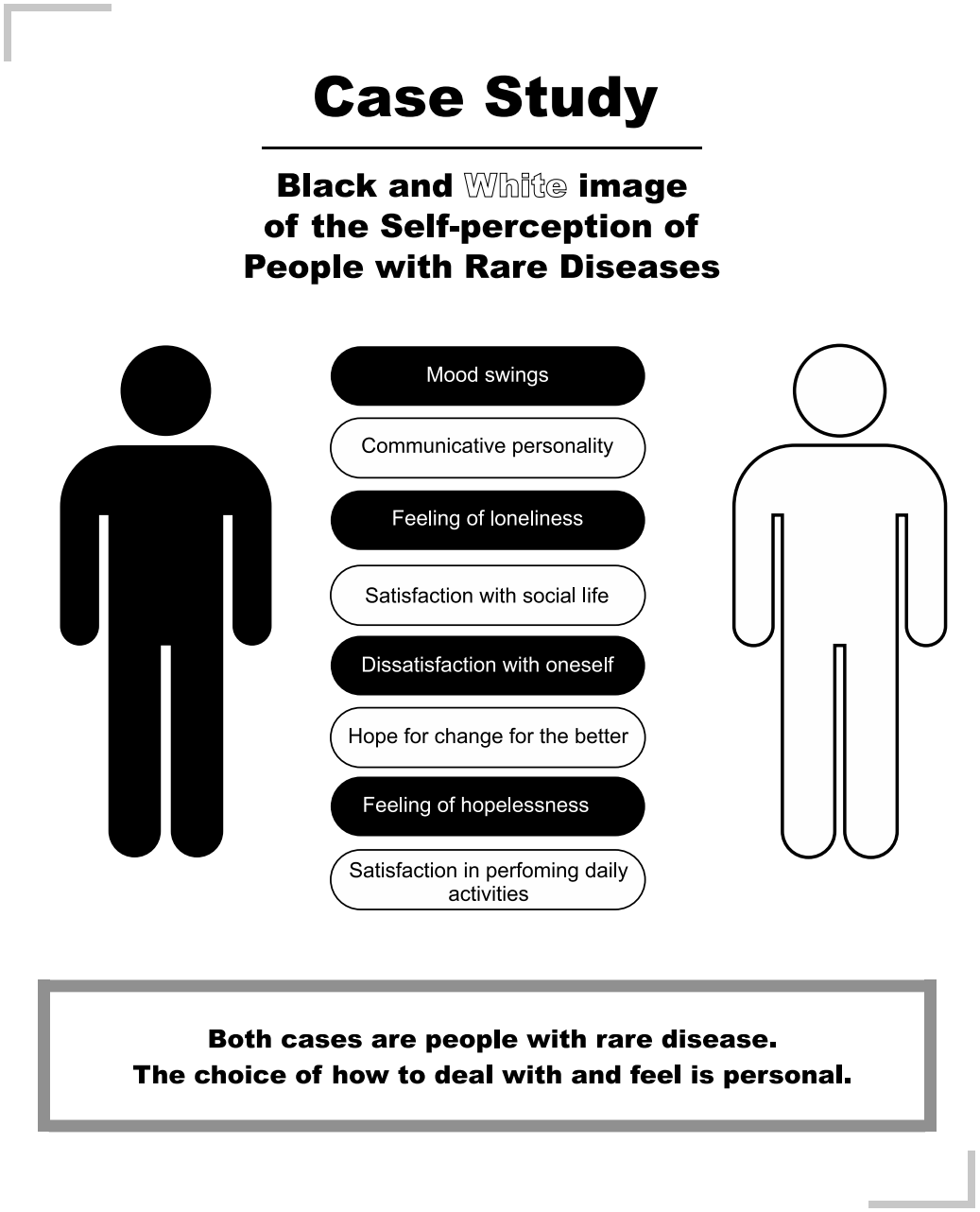


The self-perception of PRD depends on several factors:

- The time between the first occurrence of symptoms and the final diagnosis;
- The process of diagnosis and experienced problems during that process;
- The process of finding the adequate institution for treatment, regular check-ups and follow up examinations;
- The frequency of regular check-ups and laboratory examinations;
- The type of treatment they receive;
- The diversity of social life;
- The support from family and friends;
- The familiarity with the disease;
- The personal characteristics;
- The perception of the quality of life, and other.

The case study presented in the following infographic vividly presents the complex milieu of factors that affect the quality of life of each patient with a long-term, disabling disease, which characteriaes of most of the rare diseases as well.

Figure 49: Black and white image of self-perception among PRDs



3.6. The way forward

As already described, the challenges that life brings with any long-term, disabling and life-threatening disease, as most rare diseases, are really complex, multi-layered and multi-faceted, and include the response of the health care system, the social and psychological aspects of the disease, full social integration and so forth - all as part of the overall quality of life.

Finding new ways of diagnosing, revision of ICD, improving the encoding, increased co-operation at national, regional and international levels, education of health professionals, increased availability of information, the implementation of programs, strategies and plans, are just some of the ways of dealing with RD in terms of the response of the health system. But after the diagnosis and appropriate treatment are established, new challenges are surfacing, such as social interaction and integration, enabling active participation in society and self-realization.

The EU is working on pooling limited resources to support national efforts and a joint answer to the aforementioned problems, and on improving research on RD.[111]

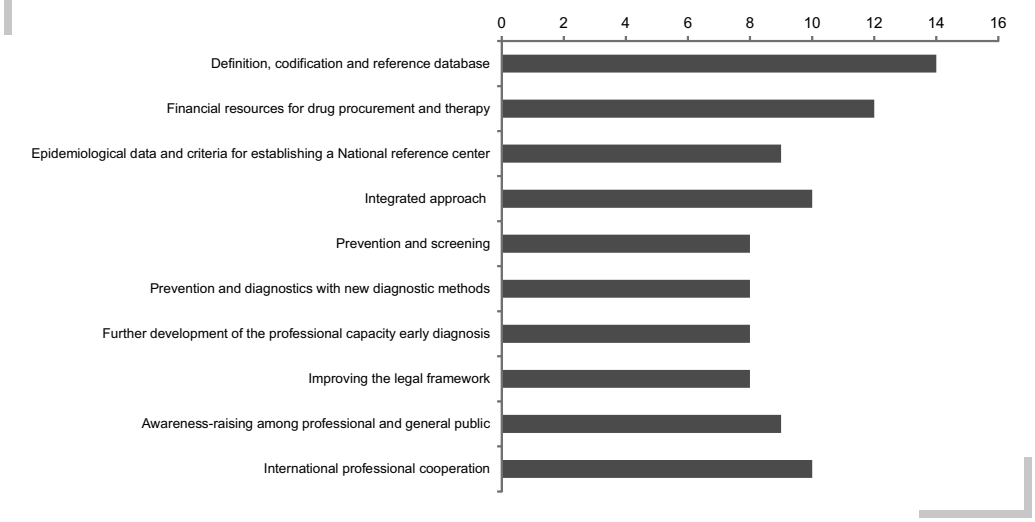
In Macedonia, the current efforts are directed at establishing a Registry of RD, securing funding for treatment and training of HPs. In the future, the focus should additionally be placed on adoption and implementation of the National Strategy for RD, involving PRD and all other stakeholders: patients' associations, the Ministry of Health, the Health Insurance Fund, MANU, health institutions at all levels of care (primary, secondary and tertiary) and other sectors through line ministries and institutions: Ministry of Labour and Social Policy, Ministry of Economy, Employment Service Agency, and so forth. The already made step forward in financing the Program for RD is to be commended, but the need to adopt criteria for allocation of funds remains i.e. introducing transparent waiting list, as well as constantly finding new sources of funding, especially in the segment of education of HPs, expanding the positive list of medicines and new medical devices for PRD.

111 What is EU doing?, Available: http://ec.europa.eu/health/rare_diseases/policy/index_en.htm, Accessed: 29.03.2016

Additionally, a huge benefit for decision-makers but also for HPs may be the improvement of cooperation at national, regional and international levels for sharing good practices with countries that have positive results from implementation. In this regard, a huge benefit for the PRD and PCRD may be the inclusion of the country in the Orphanet network and creating national page within the Orphanet platform, which would increase access to information on rare diseases in Macedonian language.

According to health professionals who participated in the research, the situation can be improved through multiple activities, depicted in Figure 50.

Figure 50: Opinion of HPs on the improvement of the quality of treatment for PRD, (n=15)



4. CONCLUSIONS AND RECOMMENDATIONS

4.1. Conclusions

1. Holistic approach
    a. Macedonia, as many countries in the region and in the EU, faces a number of systemic challenges in terms of prevention, early detection, timely diagnosis, treatment, care and rehabilitation of PRD.
    b. The national policies, strategies and plans of the country do not yet have a holistic approach to this issue, which would mean addressing it through measures in all relevant sectors (social, health, educational and financial).
    c. Evidence gathered by different sectors, particularly health, social and educational sectors, do not yet have the possibility for systemic monitoring of the situation, which is feasible on the basis of relevant and sufficient data (e.g. epidemiological and other data).
2. Inclusion of PRD and the civil society
    a. The specificity of certain rare diseases requires the need for involvement of PRD in the planning and decision-making processes regarding their needs, not only in relation to their health, but also from social and wider societal aspects.
    b. Although cooperation has been established, the civil society isn't yet sufficiently included in the dialogues on development and implementation of policies, strategies and plans to overcome the challenges in the field.
3. Impact on the quality of life
    a. Like other chronic and debilitating diseases, rare diseases, too, considerably affect the quality of life for PRDs. Understanding the disease and the attitude towards it, the concern about one's own condition, the emotional state, the control over the disease, the process of treatment and other integral elements of the condition greatly influence the quality of life, and should be taken into consideration when addressing the issue of social integration and quality of life of these persons.

Table 3. The challenges faced by PRD in the health system

Area	*Challenges*
Legislation	• There is no standardized approach towards RD in Macedonia. The lack of both adequate classification and registration of RD at national level and a well-organized approach towards the PRD present an additional burden. • There is neither uniform system for registration of RDs, nor a uniform list, both of which are necessary to understand the overall situation and to establish bodies and structures to improve the health and quality of life for the people and families affected by RDs.
Health data and health information system	• There is a lack of adequate, accurate and sufficient information available to PRD (website, leaflets and other informative materials). • The analysis results show that people with rare diseases face complex problems related to their familiarity with the disease, the physical and psychological aspects of their life, as well as the health care system response. • Their perception of the quality of life is of crucial importance for the decision-makers focused on the patient and his/her real needs. • The Internet is the main source of information about PRD, PCRD and HPs. Other significant sources are: brochures about the disease, medical guidelines, associations and medical specialists. Clearest health information is obtained from doctors. It rarely happens for someone not to get an explanation for the information received. • PRD and PCRD would like to know more about the disease, and to have the opportunity to share and exchange experiences with other patients or parents of children with the same disease and believe that the more they know about their illness, the more control they have over the symptoms and treatment; they would like to learn more about the latest research, the cause of the disease, types of treatment, side effects of treatment and interpretation of the results and methods of self-help.
Human resources in the health system	• The lack of experience and interest among HPs derives from their insufficient education of a certain rare disease that prevents the provision of adequate professional assistance. An interesting finding is that the time between the first occurrence of the symptoms and the establishment of diagnosis varies greatly and depends on both the disease and the condition. It might take from one month to several years for the diagnosis to be specified. During that time, PRD live with these symptoms without treatment, which can have negative effects on the development of the disease and their overall health. Unfortunately, inaccurate diagnosis is made in a number of cases and is therefore, the main obstacle to adequate and timely treatment. In some cases, patients received two or more diagnoses; some of them have consulted with more than ten medical specialists before they get a final diagnosis. Half of the respondents believe that there is no specialist in the country from which they can receive information, diagnosis and treatment for their condition.
Access to health services	• The Newborn Screening should be offered as a measure for early detection of RDs in the public health care system. • The high cost of the treatment for small number of patients and diseases, mostly abroad, clearly indicates the unaffordability of health care. • The inability to accurately assess the costs of total treatment for rare diseases leads - due to other factors as well as to the uncertain course of the disease - to inadequate planning and realization of health care funds for PRD
Satisfaction with treatment and care	• PRD and PCRD are dissatisfied with the cooperation and support of the Ministry of Health and the Health Insurance Fund, while their opinion on the health facilities were diverse, with the majority of respondents neither satisfied nor dissatisfied.

Table 4. Recommendations of PRD, PCRD, representatives of associations for RD and HP for promoting and better addressing the challenges of RD

Area	*Recommendations*
Legislation and policies	• Improvment of legislation and policies using a holistic cross-sectoral approach; • Integrating RDs in the legislation to protect PRD as a vulnerable group; • Improvment of policies on quality and safety assurance of the procured medicines; • Defining additional criteria for procurement of medicines, besides the price as the main criterion set in the public procurement notices;
Definition and codification	• Introducing definition, codification, classification and database for RD; • Developing an integrated approach for detection, diagnosis, prevention and social intervention of PRD and their families at all levels of the health system;
Financing	• Continuing efforts to increase financial support for the purchase of medicines; • Continuing efforts to increase financial support for for diagnosis and treatment of RD; • Continuing efforts to increase the funds for education of health professionals who diagnose/treat PRD;
Access to treatment and care	• Introducing new drugs for RD in the positive drug list of HIFM to ensure facilitated access to treatment; • Improving the cooperation and support from national institutions and health care institutes for PRD; • Promoting the access to health care for PRD; • Eliminating the obstacles in the process of treatment and care that these people face and introducing newborn screening practice;
Information	• Creating an Info-centre about RD to better inform PRD and PCRD and to facilitate the access to information for RD; • Designing the national Orphanet website to follow the latest research, codes and information related to early detection, treatment and rehabilitation for PRD;
Visibility and Awareness-raising	• Raising awareness among HPs and the general public about the impact of RD on the health of the individual, family and community;
Education	• Introducing additional RD-related education as part of the continuing medical education of doctors in order to increase the interest and experience in the field of RD;
International cooperation	• Establishing an international professional collaboration for the purpose of registering, monitoring, diagnosis, treatment and research of RD.

4.2. Recommendations

PRDs have an equal right to quality and access to health care and a decent quality of life as everyone else. Although the Constitution guarantees the right to health, it is not fully and appropriately operationalized throughout the legislation and health and related policies.

The global experiences clearly show that the advance in early detection and treatment of RD is achievable, realistic and possible.

This study also informs about the need to strengthen the social response to the challenges of RD, both in terms of health care by investing in the health system focused on the individual and in other sectors such as social care, education and the labour market, whose policies inevitably have a role and impact on health, quality of life and self-fulfilment of these individuals. In addition, the findings and the conclusions of the research may propose numerous measures and activities, whose implementation in the short- and long-term would contribute towards gradual improvement of the situation of the PRDs.

These recommendations point to the need for initiating evidence-based policy dialogue, involving all sectors and stakeholders, for an effective planning and use of resources at national level but also of information and experience in the region and beyond, to achieve optimal results in improving the health and quality of life of PRDs.

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APPENDICES

Appendix 1. Rare diseases that affect the respondents of this study

List of rare diseases

People with rare diseases	Parents of children with rare diseases
Acute intermittent porphyria	Adrenomyeloneuropathy
Amyotrophic lateral sclerosis	Carnitine palmitoyltransferase II deficiency
Crohn disease	Dermatitis herpetiformis in coeliac disease
Gaucher disease	Dextrocardia with situs inversus
Idiopathic pulmonary hypertension	Hereditary angioedema
Non-Hodgkin lymphoma	Juvenile dermatopolymyositis - M33[112]
Pempigus vulgaris mucocutaneus	Kartagener syndrome
Rippling muscle disease	Mucopolysaccharidosis type IV – Morquio syndrome
von Willebrand disease	Rett syndrome
Wilson disease	Total colonic aganglionosis Q43, A41, E86[113]

112 ICD-10 codes
113 ICD-10 codes

Appendix 2. National and foreign institutions and specialists

Institutions offering RD treatment	Specialists for RD treatment
University clinic (UC) for Children's diseases (departments of rheumatology, immunology, gastroenterohepatology)	Prof. Dr. Zoran Guchev Dr. Biljana Choneska
UC for Haematology	Dr. Marica Pavlovikj Dr. Violeta Dejanova Ilijevska
UC for Gastroenterohepatology	Dr. Vladimir Avramovski
UC for Dermatology (department of skin diseases)	Dr. Vesna Grivcheva Panovska Dr. Nina Caca Biljanovska
UC of Neurology (department of neuromuscular diseases)	Dr. Igor Petrov
Institute of immunology and human genetics	
Institute for respiratory diseases – Kozle	
Institute of physiotherapeutic medicine and rehabilitation - Kozle	
Private hospital "Filip Vtori"	
UC of rheumatology	
Foreign institutions for RD treatment	
Outpatient neurological clinic "Dr. Apostolski" in Belgrade	
"AKN Vienna" in Vienna	
Great Ormond Street Hospital in London	

Appendix 3. Questionnaire for people with rare diseases

This questionnaire is **ANONYMOUS**. It will not be possible you to be identified throughout the survey.

There are no right or wrong answers to the following questions. Write down only what you feel or what you believe is correct.

Take your time and fill out the questionnaire carefully and thoughtfully. Please provide as much information as possible, or explanations to the questions that require a detailed answer.

Answer the questions by following the instructions and check the box next to the answer. **If you fill out the questionnaire ELECTRONICALLY, please note that the box to the answer is checked automatically when you click on it.**

Thank you in advance for your cooperation!

SOCIO-DEMOGRAPHIC CHARACTERISTICS

You are filling out the questionnaire

1. By yourself	☐
2. By yourself in the presence of your parent or your guardian	☐
3. By the parent	☐
4. By the guardian	☐

1. Sex

1. Male	☐
2. Female	☐

2. Place of residence

3. How old are you?

4. Highest level of education completed:

1. Several grades of elementary education	☐
2. Completed elementary education	☐
3. Completed secondary education	☐
4. Completed college or faculty	☐
5. Postgraduate studies	☐

5. What is your status?

1. Pupil	☐
2. Student	☐
3. Employed	☐
4. Unemployed	☐
5. Retired	☐
6. Other:	☐

6. How do you ensure your monthly income? More answers are possible.

1. You are employed	☐
2. You are supported by your parents	☐
3. Your friends help you	☐
4. Your relatives help you	☐
5. You receive social security benefits	☐
6. You receive a pension	☐
7. You receive social security disability benefits	☐
8. Other (indicate):	☐

7. How many members does your household have?

8. What is the total income of all household members including your income as well?

Amount in MKD:	MKD

INFORMATION ON YOUR HEALTH CONDITION

9. Have you been diagnosed with a rare disease?

1. Yes	☐
2. No	☐

10. What is your diagnosis? FILL OUT WITH BLOCK LETTERS

11. If your disease has NOT been diagnosed yet, what is the reason?

12. How old were you when your disease was diagnosed?

13. How long did the time lag last from the first apperence of symptoms to the final diagnosis?

14. Was your disease diagnosed with the first diagnosis?

1. Yes	☐
2. No	☐

15. If NO, how many diagnoses have you had so far?

16. In which institution/clinic was your diagnosis made?

_____

_____

17. In which institution/clinic and in which department do you get your treatment? (Name of the institution and the department, city and country if it is abroad)

_____

_____

18. How often do you do health check-ups and laboratory testing?

19. What kind of treatment do you need?

1. Medicines	☐
2. Physical therapy	☐
3. Psychiatric help	☐
4. Other: (indicate)	☐

20. What kind of examinations are needed for disease monitoring?

1. None ☐
2.Radiographic examinations ☐
3. Biochemical examinations ☐
4. Functional imaging ☐
5. Genetic testing ☐
6. Other (indicate): ☐

21. Can these examinations be provided in the country and are they covered by HIFM?

1. Yes and they are covered by HIFM ☐
2. Yes, but they are not covered by HIFM ☐
3. No ☐
4. I don't know ☐

22. How many doctors have you consulted before the final diagnosis was made?

1. 1-2 ☐
2. 3-5 ☐
3. 6-10 ☐
4. More than 10 ☐

23. What kind of examinations did you do?

1. None ☐
2. Radiographic examinations ☐
3. Biochemical examinations ☐
4. Functional imaging ☐
5. Genetic testing ☐
6. Other (indicate): ☐

24. Is there a specialist for your disease in Macedonia?

1. Yes ☐
2. No ☐
3. I don't know ☐

25. If there is, what is his/her name, institution affiliated and specialty?

26. Have you faced any systemic obstacles during the treatment process?

A. Untimely treatment

Explain: _____

B. Inadequate treatment

Explain: _____

C. No final diagnosis was made

Explain: _____

D. Inaccurate diagnosis

Explain: _____

E. Unavailability of medicines

Explain: _____

F. Unavailability of medical devices

Explain: _____

G. Unavailability of other type of treatment (e.g. physical therapy)

Explain: _____

27. How do you obtain your medicines and treatment?

1. Health institutions provide them ☐
2. I buy them myself in the country ☐
3. I buy them myself from abroad ☐
4. As a donation from pharmaceutical companies ☐
5. Other (indicate): ☐

28. Is the treatment covered by the health insurance i.e. is it included in the positive list of HIFM or some other program of the Ministry of Health?

1. Yes ☐
2. No ☐

29. If your treatment is not covered by the health insurance, how much would it cost you on a monthly basis?

Amount in MKD:..... MKD

30. Can you afford to buy this therapy?

1. Yes ☐
2. Yes, but not fully ☐
3. No ☐

31. In your opinion, what are the most important problems that people with rare diseases face? More answers are possible.

1. The process of diagnosis ☐
2. Hindered access to new drugs in the country and no adequate state aid for therapy and treatment ☐
3. Hindered access to clinical trials ☐
4. Lack of specifically educated medical personnel and of adequate hospital conditions ☐
5. Lack of specialized institutions ☐
6. No reference database for rare diseases ☐
7. No proper definition, codification and classification of rare diseases ☐
8. Lack of medical guidelines for rare disease treatment ☐
9. Lack of synchronized multidisciplinary medical approach towards patients ☐
10. Lack of developed awareness among the professional and general public about the importance of RD ☐

32. Please indicate the types of care to which you had hindered access. More answers are possible.

1. Consultation with a general practitioner ☐
2. Visiting a specialist ☐
3. Medicines, medical devices or equipment ☐
4. Hospitalization ☐
5. Surgery ☐
6. Social care and services ☐
7. Laboratory examinations ☐
8. Other:_____ ☐

33. Are you a member of an association for people with rare diseases?

1. Yes ☐
2. No ☐

34. Are you satisfied with the work of the association?

Not satisfied			Very satisfied		I don't know
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

35. Do you have a suggestion on how to improve the working of the association?

_____

AWARENESS ABOUT THE DISEASE

36. Answer to each statement by selecting only one answer. Some statements are similar but please answer to each one.

	(1) Never	(2) Rarely	(3) Occasionally	(4) Often	(5) Very often
1. You have to make a great effort to find the health information you need	☐	☐	☐	☐	☐
2. You don't know where you could find the health information you need	☐	☐	☐	☐	☐
3. You don't understand the health information you find	☐	☐	☐	☐	☐
4. You don't understand the health information you obtain from your physician	☐	☐	☐	☐	☐

37. To what extent do these statements refer to you?

	(1) Not at all	(2) Mostly no	(3) Yes and no	(4) Mostly yes	(5) Absolutely
1. It is important to you to be informed about your disease	☐	☐	☐	☐	☐
2. You want to know what the possible complications of your disease are	☐	☐	☐	☐	☐
3. You want to have the opportunity to share your experience with other people affected by the same disease	☐	☐	☐	☐	☐
4. The more you know about your disease, the greater the control you feel you have over the symptoms and the treatment	☐	☐	☐	☐	☐
5. You prefer not to be informed about the possible complications of your disease	☐	☐	☐	☐	☐
6. You don't want to discuss or read about your disease	☐	☐	☐	☐	☐

38. Where do you usually look for information about your disease? More answers are possible.

1. In medical handbooks ☐
2. In relevant leaflets ☐
3. From general practitioners ☐
4. From specialists ☐
5. From family members ☐
6. From acquaintances affected by the same disease ☐
7. On the Internet ☐
8. On online forums ☐
9. In the association ☐
10. You don't look ☐

39. Please select the topics related to your disease for which you would like to learn more. More answers are possible.

1. Cause of the disease ☐
2. Symptoms of disease ☐
3. Treatment options ☐
4. Side effects of the treatment ☐
5. Alternative treatment ☐
6. Nutrition ☐
7. Latest research ☐
8. Possibility to participate in clinical trials ☐
9. Interpretation of results ☐
10. Methods of self-help ☐
11. Dealing with psychological and emotional difficulties ☐

LEISURE TIME

40. To what extent are the following activities included in your leisure time?

	(1) Never	(2) Rarely	(3) Occasionally	(4) Often	(5) Very often
1.Sport events	☐	☐	☐	☐	☐
2.Culture events	☐	☐	☐	☐	☐
3.Socializing with friends	☐	☐	☐	☐	☐
4.You have a hobby	☐	☐	☐	☐	☐
5.Time spent with your family	☐	☐	☐	☐	☐
6.You are mostly alone at home	☐	☐	☐	☐	☐
7. You volunteer in the community	☐	☐	☐	☐	☐

41. When you think about how you spend your leisure time, you think that:

1. You spend it usefully ☐
2. There should be a possibility of greater choice ☐
3. You spend it uselessly ☐
4. You spend it mostly boring ☐

ATTITUDE TOWARDS THE DISEASE

42. To what extent does your disease influence your life?

It does not				It influences greatly	I don't know
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

43. How well do you understand your disease?

Not at all			Very well		I don't know
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

44. How concerned are you about your disease?

Not at all			Very concerned		I don't know
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

45. In your opinion, how much control do you have over your disease?

No control at all			Full control		I don't know
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

46. In your opinion, how long will your disease last?

Very shortly			Forever		I don't know
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

47. In your opinion, how much can the treatment help you?

Not at all			Can help me fully		I don't know
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

48. How satisfied are you with the availability of health services?

Not at all			Very satisfied		I don't know
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

49. How regularly do you go for check-ups?

Not at all				Regularly	I don't know
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

50. To what extent do you adhere to medical advice?

I don't adhere at all				I adhere fully	I don't know
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

51. To what extent does your disease affect your emotional state? (e.g. Do you feel angry, gloomy, depressed, etc.?)

No impact at all				Great impact	I don't know
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

PERCEPTION OF THE QUALITY OF LIFE

52. Answer to each statement by selecting only one answer. Some statements are similar but please answer to each one.

How satisfied are you with:	(1) Very dissatisfied	(2) Dissatisfied	(3) Neither dissatisfied nor satisfied	(4) Satisfied	(5) Very satisfied	(6) I don't know
1. Your sleep?	☐	☐	☐	☐	☐	☐
2. Your ability to perform daily activities?	☐	☐	☐	☐	☐	☐
3. Your work skills?	☐	☐	☐	☐	☐	☐
4. Yourself?	☐	☐	☐	☐	☐	☐
5. Your relationship with other close people?	☐	☐	☐	☐	☐	☐
6. The support from your friends?	☐	☐	☐	☐	☐	☐
7. The support from your family?	☐	☐	☐	☐	☐	☐
8. The support from the community at school, at work?	☐	☐	☐	☐	☐	☐
9. Your living conditions?	☐	☐	☐	☐	☐	☐
10. Your sex life?	☐	☐	☐	☐	☐	☐
11. Your love life?	☐	☐	☐	☐	☐	☐

53. As far as your physical health is concerned, how many days in the last 30 days did you feel bad physically? Select only one answer.

1. Number of days .....
2. None ☐
3. I don't know/I am not sure ☐

54. In the past 30 days, approximately for how many days were you not able to perform your daily activities due to bad physical or mental health (e.g. Self-care, work, recreational activities, etc.)?

1. Number of days .....
2. None ☐
3. I don't know/I am not sure ☐

PSYCHOLOGICAL ASPECTS OF LIFE

55. Please answer to each question by selecting only one answer.

	(1) Yes	(2) No	(3) Sometimes	(4) I don't know
1. Does your mood often change?	☐	☐	☐	☐
2. Does thinking about your concerns cause tensions and anxiety?	☐	☐	☐	☐
3. Are you too concerned with what other people think of you?	☐	☐	☐	☐
4. Are you a communicative person?	☐	☐	☐	☐
5. Can you relax completely in the company of others and enjoy having fun?	☐	☐	☐	☐
6. Do you sometimes find yourself in a bad mood for no reason?	☐	☐	☐	☐
7. Do you enjoy socializing with others?	☐	☐	☐	☐
8. Are you easily insulted?	☐	☐	☐	☐
9. Do you feel lonely?	☐	☐	☐	☐
10. Do you try not to be rude to others?	☐	☐	☐	☐
11. Do you think that the future is hopeless and that nothing can be improved?	☐	☐	☐	☐
12. Do you think that you are often too tense or nervous?	☐	☐	☐	☐
13. Do you feel that nothing brings you pleasure and that everything is pointless?	☐	☐	☐	☐

REACTION TO STRESSFUL SITUATIONS

56. People differ in the ways they deal with everyday stressful situations.

Although various events provoke different reactions in the same individual, please think of various unpleasant/stressful situations and of your MOST COMMON reactions.

	(1) Never	(2) Sometimes	(3) Usually	(4) Very often	(5) Always	(6) I don't know
1. You tend to turn such situations into valuable life experiences	☐	☐	☐	☐	☐	☐
2. You are disturbed, but give your best to hide your feelings	☐	☐	☐	☐	☐	☐
3. You turn to somebody for advice	☐	☐	☐	☐	☐	☐
4. You try with all your strength to do something in such situations	☐	☐	☐	☐	☐	☐
5. You convince yourself that it is not true, that such thing is not possible	☐	☐	☐	☐	☐	☐
6. You believe in God	☐	☐	☐	☐	☐	☐
7. You tend to look for humour in such situations	☐	☐	☐	☐	☐	☐
8. You admit to yourself that you cannot solve the problem and stop trying	☐	☐	☐	☐	☐	☐
9. You want to be alone	☐	☐	☐	☐	☐	☐
10. You try to get emotional support from your friends and relatives	☐	☐	☐	☐	☐	☐
11. You avoid your friends and any relevant discussion to think about the situation/problem yourself	☐	☐	☐	☐	☐	☐
12. You consider various ways to solve the situation	☐	☐	☐	☐	☐	☐
13. You hope that someone else will solve the situation	☐	☐	☐	☐	☐	☐

SOCIAL SKILLS

57. Answer to each statement by selecting only one of the four offered answers. Some statements are similar but please answer to each one.

	(1) Not at all	(2) Mostly not	(3) Mostly yes	(4) Absolutely
1. You are in harmonious relationships with the people around you	☐	☐	☐	☐
2. You miss being in a company	☐	☐	☐	☐
3. You have no one to talk to	☐	☐	☐	☐
4. You don't feel lonely	☐	☐	☐	☐
5. You have a group of friends you belong to	☐	☐	☐	☐
6. You have a lot in common with the people around you	☐	☐	☐	☐
7. You no longer have anyone close to you	☐	☐	☐	☐
8. People around you don't share your interests and ideas	☐	☐	☐	☐
9. You are an open person	☐	☐	☐	☐
10. There are people you are close to	☐	☐	☐	☐
11. People don't let you in their company	☐	☐	☐	☐
12. Your social relationships are superficial	☐	☐	☐	☐
13. Nobody really knows you	☐	☐	☐	☐
14. You feel isolated from the others	☐	☐	☐	☐
15. You can find company if you want to	☐	☐	☐	☐
16. There are people who truly understand you	☐	☐	☐	☐
17. You are unhappy that you are introverted	☐	☐	☐	☐
18. People are around you but not with you	☐	☐	☐	☐
19. There are people you can talk to	☐	☐	☐	☐
20. There are people you can turn to	☐	☐	☐	☐

SATISFACTION WITH HEALTH CARE

58. Please answer to each question by selecting only one option.

	(1) Yes	(2) No	(3) Sometimes	(4) I don't know
1. Does your doctor spend enough time with you?	☐	☐	☐	☐
2. Does your doctor know what disease you are suffering from?	☐	☐	☐	☐
3. Does your doctor show interest in your personal problems?	☐	☐	☐	☐
4. Does your doctor listen to what you are saying?	☐	☐	☐	☐
5. Does your doctor inform you on everything you want to know about your symptoms and disease?	☐	☐	☐	☐
6. Are you satisfied with the explanation of the reason for the requested examinations and the intended method of treatment?	☐	☐	☐	☐
7. Is there a possibility to consult with your doctor by telephone?	☐	☐	☐	☐
8. Does your doctor help you overcome the emotional problems related to your health condition?	☐	☐	☐	☐
9. Does your doctor help you address your disease-related worries?	☐	☐	☐	☐
10. Does your doctor help you understand the importance of adherence to advice?	☐	☐	☐	☐
11. Does your doctor explain to you and prepare you for the specialist examination or the hospital treatment?	☐	☐	☐	☐

59. How satisfied are you with the cooperation with health institutions in the Republic of Macedonia?

1. Very dissatisfied ☐
2. Dissatisfied ☐
3. Neither satisfied nor dissatisfied ☐
4. Satisfied ☐
5. Very satisfied ☐
6. I don't know ☐

60. How satisfied are you with the cooperation and support from the Ministry of Health?

1. Very dissatisfied ☐
2. Dissatisfied ☐
3. Neither satisfied nor dissatisfied ☐
4. Satisfied ☐
5. Very satisfied ☐
6. I don't know ☐

61. How satisfied are you with the cooperation and support from the Health Insurance Fund?

1. Very dissatisfied ☐
2. Dissatisfied ☐
3. Neither satisfied nor dissatisfied ☐
4. Satisfied ☐
5. Very satisfied ☐
6. I don't know ☐

62. In your opinion, what should be done to improve the quality of your treatment?

More answers are possible.

1. Introduction of adequate definition, codification and cataloguing of RD and establishing a reference database for RD ☐
2. Provision of financial resources for drug procurement and better access to medicines and treatment for rare diseases in our country ☐
3. Provision of epidemiological data on RD and preparation of guidelines and criteria for establishing a National reference centre for RD ☐
4. Integrated approach toward detection, prevention and social integration of people with RD and their families ☐
5. Improving the prevention of RD of genetic origin and organization of extensive screenings ☐
6. Improving the prevention and diagnostics of RD of genetic origin by introducing new diagnostic technologies and improving the availability to genetic information and consultations ☐
7. Improving the professional capacity of health professionals and collaborators in terms of timely detection and early diagnosis of RD ☐
8. Improving the legal framework for the treatment of people with RD ☐
9. Facilitate the procedure for regular disease monitoring (biochemical and other laboratory analyses) ☐
10. Awareness-raising among the professional and general public about the importance of RD and their impact on population health ☐
11. Establishing international professional cooperation in the field of registering, monitoring, diagnosis, treatment and research of rare diseases. ☐
12. Other (please indicate): ☐

Appendix 4. Questionnaire for parents of children with rare diseases

This questionnaire is **ANONYMOUS**. It will not be possible you to be identified throughout the survey.

There are right or wrong answers to the following questions. Write down only what you feel or what you believe is correct.

Take your time and fill out the questionnaire carefully and thoughtfully. Please provide as much information as possible, or explanations to the questions that require a detailed answer.

Answer the questions by following the instructions and check the box next to the answer. **If you fill out the questionnaire ELECTRONICALLY, please note that the box to the answer is checked automatically when you click on it.**

Thank you in advance for your cooperation!

SOCIO-DEMOGRAPHIC CHARACTERISTICS

1. Your child's sex

   1. Male ☐
   2. Female ☐

2. Place of residence

   ☐

3. How old is your child?

   ☐

4. Your highest level of education completed:

   1. Several grades of elementary education ☐
   2. Completed elementary education ☐
   3. Completed secondary education ☐
   4. Completed college or faculty ☐
   5. Postgraduate studies ☐

5. How do you ensure your monthly income? More answers are possible.

1. You are employed ☐
2. You are supported by your parents ☐
3. Your friends help you ☐
4. Your relatives help you ☐
5. You receive social security benefits ☐
6. You receive a pension ☐
7. You receive social security disability benefits ☐
8. Other (indicate): ☐

6. How many people live in your household?

7. What is the total income of all household members including your income as well?

Amount in MKD: MKD

8. In the past 30 days, approximately for how many days were you not able to perform your daily activities due to bad physical or mental health of your child (e.g. work, recreational activities, etc.)?

1.Number of days .....

2.None ☐

3.I don't know/I am not sure ☐

9. In the past 30 days, approximately for how many days were you not able to perform your daily activities (e.g. work, recreational activities, etc.) due to regular medical check-ups or therapy?

1.Number of days .....

2.None ☐

3.I don't know/I am not sure ☐

10. Have your child been diagnosed with a rare disease??

1. Yes ☐
2. No ☐

11. What is your child's diagnosis? FILL OUT WITH BLOCK LETTERS

12. If your child's disease has NOT been diagnosed yet, what is the reason?

_____

_____

13. How old was your child when his disease was diagnosed?

14. How long did the time lag last from the first appearance of symptoms to the final diagnosis?

15. Was your child's disease diagnosed with the first diagnosis??

1. Yes ☐
2. No ☐

16. If NO, how many diagnoses have your child had so far?

17. In which institution/clinic was your child's diagnosis made?

_____

18. How many doctors have you consulted before the final diagnosis was made?

1. 1-2 ☐
2. 3-5 ☐
3. 6-10 ☐
4. More than 10 ☐

19. What kind of examinations did your child do? More answers are possible.

1. None ☐
2. Radiographic examinations ☐
3. Biochemical examinations ☐
4. Functional imaging ☐
5. Genetic testing ☐
6. Other (indicate): ☐

20. Is there a specialist for your child's disease in Macedonia?

1. Yes ☐
2. No ☐
3. I don't know ☐

21. If there is, what is his/her name, institution affiliated and specialty?

_____

22. Have your child faced any other health issues during the treatment process:

A. Untimely treatment
Explain: _____

B. Inadequate treatment
Explain: _____

C. No final diagnosis was made
Explain: _____

D. Inaccurate diagnosis
Explain: _____

E. Unavailability of medicines
Explain: _____

F. Unavailability of medical devices
Explain: _____

G. Unavailability of other type of treatment (e.g. physical therapy)
Explain: _____

23. How do you obtain your child's medicines, treatment, orthopaedic aids, food supplements and therapy?

1. Health institutions provide them ☐
2. I buy them myself in the country ☐
3. I buy them myself from abroad ☐
4. As a donation from pharmaceutical companies ☐
5. Other (indicate): ☐

24. Is the treatment covered by the health insurance i.e. is it included in the positive list of HIFM or some other program of the Ministry of Health?

1. Yes ☐
2. No ☐

25. If your treatment is not covered by the health insurance, how much would it cost you on a monthly basis?

1. Amount in MKD: ..... MKD.
2. The child is not treated; we cannot afford the treatment ☐

26. In your opinion, what are the most important problems that people with rare diseases face? More answers are possible.

1. The process of diagnosis ☐
2. Hindered access to new drugs in the country and no adequate state aid for therapy and treatment ☐
3. Hindered access to clinical trials ☐
4. Lack of specifically educated medical personnel and of adequate hospital conditions ☐
5. Lack of specialized institutions ☐
6. No reference database for rare diseases ☐
7. No proper definition, codification and classification of RD ☐
8. Lack of medical guidelines for rare disease treatment ☐
9. Lack of synchronized multidisciplinary medical approach towards patients ☐
10. Lack of developed awareness among the professional and general public about the importance of RD ☐

27. Please indicate the types of care to which you had hindered access. More answers are possible.

1. Consultation with a general practitioner ☐
2. Visiting a specialist ☐
3. Medicines, medical devices or equipment ☐
4. Hospitalization ☐
5. Surgery ☐
6. Social care and services ☐
7. Laboratory examinations ☐
8. Other: ☐

28. Are you a member of an association for people with rare diseases??

1. Yes ☐
2. No ☐

29. Are you satisfied with the work of the association?

    1. Yes ☐
    2. No ☐

30. If you are not satisfied with their work, in your opinion, what should the association change?

    _____

AWARENESS ABOUT THE DISEASE

31. Answer to each statement by selecting only one answer. Some statements are similar but please answer to each one.

	(1) Never	(2) Rarely	(3) Occasionally	(4) Often	(5) Very often
1. You have to make a great effort to find the health information you need	☐	☐	☐	☐	☐
2. You don't know where you could find the health information you need	☐	☐	☐	☐	☐
3. You don't understand the health information you find	☐	☐	☐	☐	☐
4. You don't understand the health information you obtain from your physician	☐	☐	☐	☐	☐

32. To what extent do these statements refer to you?

	(1) Not at all	(2) Mostly no	(3) Yes and no	(4) Mostly yes	(5) Absolutely
1. It is important to you to be informed about your child's disease	☐	☐	☐	☐	☐
2. You want to know what the possible complications of your child's disease are	☐	☐	☐	☐	☐
3. You want to have the opportunity to share your experience with other parents of children affected by the same disease	☐	☐	☐	☐	☐
4. The more you know about your child's disease, the greater the control you feel you have over the symptoms and the treatment	☐	☐	☐	☐	☐
5. You prefer not to be informed about the possible complications of your child's disease	☐	☐	☐	☐	☐
6. You don't want to discuss or read about your child's disease	☐	☐	☐	☐	☐

33. Where do you usually look for information about your child's disease? More answers are possible.

1. In medical handbooks ☐
2. In relevant leaflets ☐
3. From general practitioners ☐
4. From specialists ☐
5. From family members ☐
6. From acquaintances affected by the same disease ☐
7. On the Internet ☐
8. On online forums ☐
9. In the association ☐
10. You don't look ☐

34. Please select the topics related to your disease for which you would like to learn more. More answers are possible.

1. Cause of the disease ☐
2. Symptoms of disease ☐
3. Treatment options ☐
4. Side effects of the treatment ☐
5. Alternative treatment ☐
6. Nutrition ☐
7. Latest research ☐
8. Possibility to participate in clinical trials ☐
9. Interpretation of results ☐
10. Methods of self-help ☐
11. Dealing with psychological and emotional difficulties ☐

ATTITUDE TOWARDS THE DISEASE

35. To what extent does your child's disease influence your child's life?

It does not				It influences greatly	I don't know
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

36. To what extent does your child's disease influence your child's socialisation?

It does not				It influences greatly	I don't know
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

37. How well do you understand your child's disease?

Not at all ☐1 ☐2 ☐3 ☐4 ☐5 Very well ☐6 I don't know

38. How concerned are you about your child's disease?

Not at all ☐1 ☐2 ☐3 ☐4 ☐5 Very concerned ☐6 I don't know

39. In your opinion, how much control do you have over your child's disease?

No control at all ☐1 ☐2 ☐3 ☐4 ☐5 Full control ☐6 I don't know

40. In your opinion, how long will your child's disease last?

Very shortly ☐1 ☐2 ☐3 ☐4 ☐5 Forever ☐6 I don't know

41. In your opinion, how much can the treatment help your child?

Not at all ☐1 ☐2 ☐3 ☐4 ☐5 Can help my child fully ☐6 I don't know

42. How satisfied are you with the availability of health services?

Not at all ☐1 ☐2 ☐3 ☐4 ☐5 Very satisfied ☐6 I don't know

43. How often do you go to regular check-ups with your child?

I don't go at all ☐1 ☐2 ☐3 ☐4 ☐5 I regularly go ☐6 I don't know

44. To what extent do you adhere to medical advice?

I don't adhere at all ☐1 ☐2 ☐3 ☐4 ☐5 I adhere fully ☐6 I don't know

45. To what extent does your child's disease influence your child's emotional state?

No impact at all ☐1 ☐2 ☐3 ☐4 ☐5 Great impact ☐6 I don't know

SATISFACTION WITH HEALTH CARE

46. Please, based on your experiences, answer these questions pertaining to the relations of the doctor towards you and your child.

	(1) Yes	(2) No	(3) Sometimes	(4) I don't know
1. Does your doctor spend enough time with you?	☐	☐	☐	☐
2. Does your doctor know what disease your child is suffering from?	☐	☐	☐	☐
3. Does your doctor show interest in your personal problems?	☐	☐	☐	☐
4. Does your doctor listen to what you are saying?	☐	☐	☐	☐
5. Does your doctor inform you on everything you want to know about your child's symptoms and disease?	☐	☐	☐	☐
6. Are you satisfied with the explanation of the reason for the requested examinations and the intended method of treatment for your child?	☐	☐	☐	☐
7. Is there a possibility to consult with your doctor by telephone?	☐	☐	☐	☐
8. Does your doctor help you overcome the emotional problems related to your child's health condition?	☐	☐	☐	☐
9. Does your doctor help you address your child's disease-related worries?	☐	☐	☐	☐
10. Does your doctor help you understand the importance of adherence to advice?	☐	☐	☐	☐
11. Does your doctor explain to you and prepare you for the specialist examination or the hospital treatment?	☐	☐	☐	☐
12. Does your doctor provide you with answers for the questions related to your child?	☐	☐	☐	☐

47. How satisfied are you with the cooperation with health institutions in the Republic of Macedonia?

1. Very dissatisfied ☐
2. Dissatisfied ☐
3. Neither satisfied nor dissatisfied ☐
4. Satisfied ☐
5. Very satisfied ☐
6. I don't know ☐

48. How satisfied are you with the cooperation with and support from the governmental institutions?

1. Very dissatisfied ☐
2. Dissatisfied ☐
3. Neither satisfied nor dissatisfied ☐
4. Satisfied ☐
5. Very satisfied ☐
6. I don't know ☐

49. In your opinion, what should be done to improve the quality of your treatment? More answers are possible.

1. Introduction of adequate definition, codification and cataloguing of RD and establishing a reference database for RD ☐
2. Provision of financial resources for drug procurement and better access to medicines and treatment for rare diseases in our country ☐
3. Provision of epidemiological data on RD and preparation of guidelines and criteria for establishing a National Reference Centre for RD ☐
4. Integrated approach toward detection, prevention and social integration of people with RD and their families ☐
5. Improving the prevention of RD of genetic origin and organization of extensive screenings ☐
6. Improving the prevention and diagnostics of RD of genetic origin by introducing new diagnostic technologies and improving the availability to genetic information and consultations ☐
7. Improving the professional capacity of health professionals and collaborators in terms of timely detection and early diagnosis of RD ☐
8. Improving the legal framework for the treatment of people with RD ☐
9. Facilitate the procedure for regular disease monitoring (biochemical and other laboratory analyses) ☐
10. Awareness-raising among the professional and general public about the importance of RD and their impact on population health ☐
11. Establishing international professional cooperation in the field of registering, monitoring, diagnosis, treatment and research of rare diseases. ☐
12. Other (please indicate): ☐

Appendix 5. Questionnaire for health professionals

This questionnaire is **ANONYMOUS**. It will not be possible you to be identified throughout the survey.

There are no right or wrong answers to the following questions. Write down only what you feel or what you believe is correct.

Take your time and fill out the questionnaire carefully and thoughtfully. Please provide as much information as possible, or explanations to the questions that require a detailed answer.

Answer the questions by following the instructions and check the box next to the answer. **If you fill out the questionnaire ELECTRONICALLY, please note that the box to the answer is checked automatically when you click on it.**

Thank you in advance for your cooperation!

QUESTIONNAIRE

1. Name of the institution you work for:

   _____

2. Location of the institution you work for (city, muncipality):

   _____

3. Type of the institution you work for:

   1. General practice (primary HC) ☐
   2. General/Clinical hospital ☐
   3. Specialised hospital ☐
   4. University Clinic ☐
   5. Health Centre ☐
   6. Other (indicate): ☐

4. Your sex

   1. Male ☐
   2. Female ☐

5. What is your age?

   ☐

6. Your specialty:

   _____

7. On what position do you work within the institution you work for
   (Director, Head of Department, Departmental doctor, Health Centre doctor etc.)

   _____

8. How many years of experience do you have?

   ☐

9. How many years do you work on this position?

   ☐

10. How often you attend lectures and seminars in the field of rare diseases?

    1. Never ☐
    2. Few times a year ☐
    3. Once a year ☐
    4. At least once a month ☐
    5. Other (indicate): ☐

11. How often do you encounter PRD within your work?

    1. Never ☐
    2. Few times a year ☐
    3. Once a year ☐
    4. At least once a month ☐
    5. Other (indicate): ☐

12. To what extent the mentioned situations that occur on your job, make you feel stressed?

	(1) It's not stressful at all	(2) It's rarely stressful	(3) Sometimes it's stressful	(4) Stressful	(5) Extremely stressful
1. Inadequate salaries	☐	☐	☐	☐	☐
2. Inadequate work space	☐	☐	☐	☐	☐
3. Small opportunity for advancement	☐	☐	☐	☐	☐
4. Poor organization of work	☐	☐	☐	☐	☐
5. Administrative work	☐	☐	☐	☐	☐
6. Heavy workload	☐	☐	☐	☐	☐
7. Threats of law suits and procedures	☐	☐	☐	☐	☐
8. Inadequate expectations from the patients and their families	☐	☐	☐	☐	☐
9. Exposure to inappropriate public criticism	☐	☐	☐	☐	☐
10. Wrongfully informing the patient by the media and other sources	☐	☐	☐	☐	☐
11. Conflicts with patients and members of their families	☐	☐	☐	☐	☐
12. Inability to separate private and professional life	☐	☐	☐	☐	☐
13. Lack of adequate continuous education	☐	☐	☐	☐	☐
14. Limited time for examination of patients	☐	☐	☐	☐	☐

13. Have you collaborated with Citizens' Associations for rare diseses, within your work?

1. Yes ☐
2. No ☐
3. I don't know ☐

14. How satisfied are you with the collaboration?

1. Very dissatisfied ☐
2. Dissatisfied ☐
3. Nether satisfied nor dissatisfied ☐
4. Satisfied ☐
5. Very satisfied ☐
6. I don't know ☐
7. Other: ☐

15. Please indicate types of services that the institution you work for can provide for PRD?

_____

16. Are there any special programs for treatment of rare diseases in Macedonia?

1. Yes ☐
2. No ☐
3. I don't know ☐

17. If there are, have you referred some patients towards the program?

1. Yes ☐
2. No ☐
3. I don't know ☐

18. Are there any specialists for some rare disease in your clinic?

1. Yes ☐
2. No ☐
3. I don't know ☐

19. If there is, who is he/she, what is his/her speciality and for which rare disease?

_____

20. Which rare diseases and number of people with rare diseases have you encountered within your work? FILL OUT WITH BLOCK LETTERS

Disease: _____ No.of persons: _____

Disease: _____ No.of persons: _____

I have not met _____

21. From which sources do you get information on rare diseases? More answers are possible.

1.In medical handbooks ☐
2.In relevant leaflets ☐
3.Own initiative ☐
4.Through training organised from the institution I work for ☐
5.Family members of the patient ☐
6.Internet ☐
7.On online forums ☐
8.From Citizen's Association for rare diseases ☐
9.From colleagues ☐
10. From media ☐
11. You don't look ☐
12. Other (indicate): ☐

22. Please select the topics related to your disease for which you would like to learn more. More answers are possible.

1. Cause of the disease ☐
2. Symptoms of disease ☐
3. Treatment options ☐
4. Side effects of the treatment ☐
5. Alternative treatment ☐
6. Nutrition ☐
7. Latest research ☐
8. Possibility to participate in clinical trials ☐
9. Interpretation of results ☐
10. Methods of self-help ☐
11. Dealing with psychological and emotional difficulties ☐
12. Other (indicate): ☐

23. In your opinion, what are the most important problems that people with rare diseases face? More answers are possible.

1. The process of diagnosis ☐
2. Hindered access to new drugs in the country and no adequate state aid for therapy and treatment ☐
3. Hindered access to clinical trials ☐
4. Lack of specifically educated medical personnel and of adequate hospital conditions ☐
5. Lack of specialized institutions ☐
6. No reference database for rare diseases ☐
7. No proper definition, codification and classification of RD ☐
8. Lack of medical guidelines for rare disease treatment ☐
9. Lack of synchronized multidisciplinary medical approach towards patients ☐
10. Lack of developed awareness among the professional and general public about the importance of RD ☐

24. In your opinion, how much support do PRD have from their families?

Not at all — They have fully — I don't know

☐1 ☐2 ☐3 ☐4 ☐5 ☐6

25. In your opinion, how much PRD think that the treatment can help? (this question is referring to the opinion of the person who is filling the questionnaire)

Not at all — Can help them fully — I don't know

☐1 ☐2 ☐3 ☐4 ☐5 ☐6

26. Do PRD go to health check-ups regularly?

Not at all — Yes — I don't know

☐1 ☐2 ☐3 ☐4 ☐5 ☐6

27. To what extent PRD adhere to medical advice?

They don't adhere at all — They adhere fully — I don't know

☐1 ☐2 ☐3 ☐4 ☐5 ☐6

28. How concerned are the patients about their disease?

Not at all — Very concerned — I don't know

☐1 ☐2 ☐3 ☐4 ☐5 ☐6

29. To what extent does the disease affect their emotional state (e.g. Do you feel angry, gloomy, depressed, etc.?)

No impact at all			Great impact		I don't know
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

30. Please, based on your experience, answer the questions pertaining to your relations with the PRD.

	(1) Yes	(2) No	(3) Soometimes	(4) I don't know
1. Do you spend enough time talking to PRD?	☐	☐	☐	☐
2. Do you think that patients think that you spend enough time talking to them?	☐	☐	☐	☐
3. Do you show interest for their personal problems?	☐	☐	☐	☐
4. Do the patients think that you pay attention to what they talk about?	☐	☐	☐	☐
5. Do you inform patients for all the symptoms related to their disease?	☐	☐	☐	☐
6. Do you think that patients think that you have informed them for all the symptoms related to their disease?	☐	☐	☐	☐
7. Are patients satisfied with the explanation of the reasons for the requested examinations and the intended method of treatment?	☐	☐	☐	☐
8. Is there a possibility for the patients to consult with the doctors by telephone?	☐	☐	☐	☐
9. Do you help in overcoming their emotional problems related to their health?	☐	☐	☐	☐
10. Do you help in overcoming their concern related to their disease?	☐	☐	☐	☐
11. Do you help them understand the importance to adhere to medical advices?	☐	☐	☐	☐
12. Do you explain and prepare the patients for the specialist examination or the hospital treatment?	☐	☐	☐	☐
13. Do you think that patients share the same opinion that you are helping them?	☐	☐	☐	☐
14. In your practice you don't have contact with PRD.	☐	☐	☐	☐

31. In your opinion, what should be done to improve the quality of your treatment? More answers are possible.

1. Introduction of adequate definition, codification and cataloguing of RD and establishing a reference database for RD ☐
2. Provision of financial resources for drug procurement and better access to medicines and treatment for rare diseases in our country ☐
3. Provision of epidemiological data on RD and preparation of guidelines and criteria for establishing a National reference centre for RD ☐
4. Integrated approach toward detection, prevention and social integration of people with RD and their families ☐
5. Improving the prevention of RD of genetic origin and organization of extensive screenings ☐
6. Improving the prevention and diagnostics of RD of genetic origin by introducing new diagnostic technologies and improving the availability to genetic information and consultations ☐
7. Improving the professional capacity of health professionals and collaborators in terms of timely detection and early diagnosis of RD ☐
8. Improving the legal framework for the treatment of people with RD ☐
9. Awareness-raising among the professional and general public about the importance of RD and their impact on population health ☐
10. Establishing international professional cooperation in the field of registering, monitoring, diagnosis, treatment and research of rare diseases. ☐
11. Other (please indicate): ☐

Appendix 6. Questionnaire for interviews with decision and policy makers, experts and academic community

QUESTIONNAIRE

(Decision and policy makers, experts and academic community)

[Policies and programs]

1. Are there any policies for dealing with RD? Which are they?
2. Are there any programs for RD?
   I. Were you involved in the creation of programs for the treatment of rare diseases in Macedonia? In which way?
3. Are you familiar with the procedure and implementation of programs for treatment of rare diseases in the country?
4. Do you know who was involved in the development and implementation of programs for RB?
5. In your opinion, who should be involved in the preparation and implementation for treatment of rare diseases?
6. Do you have information or have you participated in other policies which are mentioned or processed rare diseases (social protection, employment, etc.)?
7. In your opinion, what are the main goals of the program for treatment of rare diseases?
   I. Are these goals achieved? If not, what is the reason?
8. Do you think the program is sufficient to improve the quality of life for people with rare diseases? Why?

[General: Strategy and Plan for Rare Diseases 2014 - 2019]

9. The National Alliance for RD in Macedonia, in 2014, prepared Draft-National strategy and plan for RD that would set a framework for action until 2019.
   I. Did you know that there is such a document?
   II. Do you think it's prepared well? Why?
   III. In your opinion, why Macedonia has no strategy and plan for RD?
   IV. In your opinion, do you think that the Strategy should be adopted? Why?
10. In your opinion, who should be involved in the development and implementation of a Strategy and Plan for RD? Why?

11. In your opinion and experience, are these strategy and plan sufficient to progress in the fight against rare diseases? Why?
12. What would you do in addition to these documents and policies?

REGISTRY, CRITERIA, PROCEDURE

13. In the Program for Treatment of Rare Diseases in Macedonia in 2016, the definition of rare diseases has been cited and the registry of rare diseases.

    I. Do you know how it came to that definition?

    II. Could you explain the definition, what does it mean?

    III. When was the registry created? What is registered in it?

    a. Do you know how many PRD are registered until now?

    IV. What is the procedure for entering the registry for RD?

    V. What are the criteria for entering the registry for RD? Who operates/manages this registry?

    VI. What should PRD do to apply for funding from the Program?

    VII. How do they choose the persons who will receive funds for treatment?

    VIII. Can you explain the whole process?

DOCTORS AND THEIR RESPONSIBILITIES

14. In your opinion, what are the obligations of doctors according to the Program for treatment of RD for 2016?

    I. Do doctors have an obligation to register the PRD in separate registry?

    II. Do doctors refer PRD to the Program for treatment of RD in Macedonia?

    III. Is there a need for registry of specialists for RD?

    IV. How often doctors attend trainings for RD?

    V. Is there a need for introducing of additional trainings in the continuous medical education?

    VI. Is there a need in the country for exchange of practices and experiences for RD?

ROADMAP FOR PRD

15. How do you know that it is a RD?
16. Is there a universal approach for PRD to receive diagnosis?

I. What would you consult me if you think that I have received misdiagnosis and inadequate therapy?

II. What examinations would you recommend?

III. What would you consult me if the therapy is unavailable in Macedonia?

17. How often do you meet PRD in your practice?

I. Is there an increase of PRD in Macedonia i.e. do you meet PRD more regularly than before?

II. What is your experience with RD? With PRD?

III. Which RD have you meet until now?

18. In your opinion, are there specialists for RD in Macedonia?

I. Could you indicate who are they, their speciality and in which health institution they work in?

II. What do you think about creating a special team of specialists for RD?

III. What do you think about establishing specialised centres for RD?

PERCEPTION OF PRD

19. If you put yourself in a position of PRD, would you think that the programs are: fair, motivational or regressing?

a. Would you change something? If yes, what? If not, why not?

20. How is the quality of life of PRD? Why?

21. Can PRD complete their daily activities?

22. Do you think that PRD are satisfied with their ability to work? Why?

FINAL QUESTIONS

In your opinion:

23. How can the diagnosis of RD in Macedonia be improved?

24. How can the access to therapy for RD in Macedonia be facilitated?

25. How can PRD help to improve the system and their condition?

26. What would you recommend to people who still don't have diagnosis?

27. What is your advice for PRD?

28. Do you have other suggestions or information that you would like to share?

Thank you for your time.

Appendix 7. Questionnaire for interviews with representatives from citizen's associations for rare diseases

QUESTIONNAIRE

(Representatives of Citizens' associations for Rare Diseases)

[Policies and programs]

1. Are there any policies for dealing with RD? Which are they?
2. Are there any programs for RD in the country?
3. Were you involved in the creation of programs for the treatment of rare diseases in Macedonia? In which way?
4. Do you know who was involved in the development and implementation of programs for RB?
5. In your opinion, who should be involved in the preparation and implementation for treatment of rare diseases?
6. Do you think the program is sufficient to improve the quality of life for people with rare diseases? Why?

[General: Strategy and Plan for Rare Diseases 2014 - 2019]

7. The National Alliance for RD in Macedonia, in 2014, prepared Draft-National strategy and plan for RD that would set a framework for action until 2019. Did you know that such a document exist?
8. Do you think that the Strategy should be adopted? Why?
9. In your opinion, who should be involved in the development and implementation of a Strategy and plan for RD? Why?
10. In your opinion and experience, are these strategy and plan sufficient to progress in the fight against rare diseases? Why?
11. What would you do in addition to these documents and policies?

REGISTRY, CRITERIA, PROCEDURE

12. In the Program for treatment of rare diseases in Macedonia in 2016, the definition of rare diseases and the registry of rare diseases have been cited. What is your opinion about the definition?
13. Is the Registry for RD functional? Are you satisfied with the Registry for RD?

14. In your opinion, what could be improved?
15. How do your Association and NARBM help to improve the registry?
16. Do you know how many PRD are registered in the Registry? What are the benefits for PRD from the Registry?

CITIZENS' ASSOCIATION AND NARBM

17. What does your Association do for PRD?
18. How many PRD are members of your association? How many diseases does the association cover?
19. What activities are implemented?
20. Is your association a member of NARBM?
21. What does NARBM do for PRD? How many diseases does the aliance cover?
22. Are you satisfied with what have you done so far?
23. What activities are planned for the future?

ROADMAP FOR PRD

24. Is there a universal approach for PRD to receive diagnosis?
25. What examinations are usually done?
26. What PRD mostly need?
27. What is needed for more accessible diagnosis for PRD?
28. Do PRD have sufficient access to therapy? If not, what is missing, for how many PRD and how can be improved?
29. How can the diagnosis of RD in Macedonia be improved?
30. How your association helps in the process of obtaining a definitive diagnosis? Therapy?
31. How can the access to therapy for RD in Macedonia be improved?

PERCEPTION OF PRD

32. You are PRD. Do you think that the programs are: fair, motivational or regressing? Why?
33. In your opinion and experience, how is the quality of life for PRD? Why?
34. Can PRD fulfil their daily activities?
35. Do you think that PRD are satisfied with their work abilities? Why

FINAL QUESTIONS

36. How can PRD help to improve the system and their condition?
37. What would you recommend to people who still don't have diagnosis?
38. What is your advice for PRD?
39. Do you have other suggestions or information that you would like to share?

Thank you for your time.






НАЦИОНАЛНА АЛИЈАНСА
ЗА РЕТКИ БОЛЕСТИ
НА Р МАКЕДОНИЈА

ЖИВОТ
ПРЕПОЗНАЕНИ

BIOMARIN

Celgene

genzyme

Pfizer