MINISTRY OF HEALTH
OF THE REPUBLIC OF CROATIA

NATIONAL PROGRAMME FOR RARE DISEASES 2015–2020

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Contents

1. Introduction

Rare diseases are a group of various diseases whose basic common characteristic is low prevalence. It is estimated that there are several thousand rare diseases which, although they are individually rare, collectively affect a large number of people. It is believed that there are 36 million people[1] suffering from rare diseases in Europe, which, in addition to the fact that these diseases are usually chronic and severe, indicates the importance of such diseases in terms of public health-related aspects.

In addition to low prevalence, rare diseases have many other common characteristics, and we can therefore regard them as a single group in the healthcare system. What is common to all of them is that they are usually diagnosed late, due to the insufficient knowledge of medical professionals and to the fact that diagnostics is often expensive and not easily accessible, which is particularly true for smaller countries that must rely on the diagnostics of foreign institutions to diagnose rare diseases. A late diagnosis can lead to unrecoverable consequences and complications of the underlying condition, which makes treatment more difficult and significantly affects the prognosis. In addition to the lack of diagnostics, the quality of healthcare services may vary or be inadequate, in both the care and treatment of patients. Since these are often complex diseases that affect several organs and organ systems, treatment must be multidisciplinary and well-coordinated. Healthcare services involved in the care of patients suffering from rare diseases are often poorly integrated and are not equally accessible in all regions. Drugs for rare diseases are more difficult to market, they can be very expensive and therefore are not easily available. Since rare diseases are often chronic and progressive, they lead to disability and a substantial decrease in the quality of life of patients and their families. In addition to the failure to identify problems and provide appropriate healthcare and treatment of patients, there is also the common problem of granting such patients social rights. Finally, there are no national or regional registries of patients suffering from rare diseases that could enable a more rational planning of healthcare services. All of the aforementioned results in families having to constantly struggle to obtain the necessary help and assistance. Much of their energy is expended in obtaining healthcare and social welfare rights that should be ensured and easily accessible in a well-organised system.

[1] Data source: Eurodis

2. Characteristics of Rare Diseases

According to the definition adopted by the European Union (hereinafter: EU), rare diseases are those that affect fewer than 5 people in 10,000 (1:2,000). Although it is estimated that there are around 7,000 rare diseases, their precise number is unknown and their inventorying is in progress. An accurate diagnosis may hide behind relatively common, but non-specific diagnoses (e.g. autism spectrum disorders, intellectual difficulties, epilepsy). It must be pointed out that rare diseases share many common characteristics: they are heterogeneous in regard to aetiology, time of onset, course of a disease, and affecting individual organs or organ systems. Most rare diseases are genetic or congenital, but malignant diseases, rare infections, allergies/autoimmune diseases, poisonings, and degenerative disorders can also be classified as rare diseases. The age at which rare diseases can occur varies. In fifty percent of patients, the first symptoms of a disease are present since childhood. The course of a disease can be fulminant or chronic, and the severity and prognosis can vary. Although they can affect only one organ (e.g. an eye or a muscle), most rare diseases affect a larger number of organs and organ systems. Due to their complexity, severity, and long duration, they can also lead to degenerative changes, disability, and a substantial decrease in the quality of life of patients. Physical, mental, intellectual, and sensory impairment can cause discrimination and affect equal opportunity access to education, and professional and social affirmation. The life expectancy of patients is often reduced. However, if detected in time, many of these diseases can be successfully treated and controlled.

3. European Union and Rare Diseases

Activities in the field of rare diseases have intensified at the EU level over the past decade. Rare diseases are among the priorities of the Third Programme for the Union's Action in the Field of Health 2014–2020. In November 2008 the European Commission adopted the document *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).* The document supports the Member States in organising and providing diagnostics, treatment and care for 36 million citizens suffering from rare diseases. In June 2009, the European Council adopted the *Council Recommendation of 8 June 2009 on an action in the field of rare diseases* that lays down the basic guidelines for the adoption of national plans for rare diseases for all Member States by 2013. The contents of these documents are derived from the recommendations of the Rare Diseases Task Force (RDTF) which was established via the European Commission Decision 2004/192/EC. The Decision 2009/872/EC on establishing the European Union Committee of Experts on Rare Diseases (EUCERD) ensures the continuous implementation of the initiatives that have been launched. This body regularly reports on the status in the field of rare diseases in Europe. The experts from the Orphanet portal, the largest European database of rare diseases and orphan drugs (www.orpha.net), as well as the members of the European Organisation for Rare Diseases (EURORDIS) (http://www.eurordis.org/) have actively participated in the drafting and adoption of these documents.

The main objectives of the European Union in the field of rare diseases are:

- to improve visibility and recognition of rare diseases;
- to support the development of national plans for rare diseases in Member States;
- to develop European cooperation, coordination, and regulation in the field of rare diseases.

The Council recommendations in the field of rare diseases include the following:

- adopting national plans for rare diseases in all Member States in order to ensure equal access

to high-quality healthcare, including diagnostics, treatment, use of orphan drugs, all based on the principle of equality and solidarity for all patients throughout the EU;
- establishing a common definition of rare diseases, ensuring appropriate codification of rare diseases in order for them to become traceable in healthcare systems, organising inventorying, and developing an inventory of rare diseases;
- fostering research into causes and treatment options for rare diseases;
- establishing a relevant healthcare organisation and a European network of reference centres for rare diseases;
- implementing joint expertise on rare diseases at the European level;
- empowering rare disease patient organisations;
- ensuring the sustainability of all planned activities in the field of rare diseases.

The implementation of the European Project for Rare Diseases National Plans Development (EUROPLAN) was ensured in order to ensure the development of guidelines and recommendations for drawing up national action plans for rare diseases under the Second Programme of Community Action in the Field of Health 2008–2013. In March 2010, EUROPLAN prepared the document entitled *Recommendations for the development of national plans for rare diseases*, followed by the document entitled *Selecting indicators to evaluate the achievements of RD initiatives* (www.europlanproject.eu). In the period from 2012 to 2015, EUROPLAN 2 continued its activities as part of the Joint Action EUCERD, Work Package4. By using these recommendations when implementing national plans for rare diseases, Member States can avail themselves of new information and communication technologies, as well as international diagnostics and treatment of rare disease patients, in those cases when appropriate care cannot be ensured domestically. This will also facilitate the inclusion in international clinical trials of new drugs. Unified protocols for screening methods, diagnostics, treatment, education, and the organisation of social services in the field of rare diseases could be ensured at European level. Research could be networked and treatment with orphan drugs could be harmonised (http://ec.europa.eu/health/rare_diseases/policy/index_en.htm). These activities will be implemented within the framework of the European Reference Networks (ERNs). The basis for the creation of the European Reference Networks for rare diseases is the EU Directive on the application of patients' rights in cross-border healthcare.

4. The Republic of Croatia and Rare Diseases

In the Republic of Croatia, the Croatian Society for Rare Diseases was established at the Croatian Medical Association in 2008. It was founded with the aim of promoting the knowledge of rare diseases and advancing medical practice, diagnostics, and treatment of such diseases. With the Society's encouragement, and in line with EU Recommendations, the Ministry of Health of the Republic of Croatia began to systematically address the issue of rare disease patients by creating a comprehensive framework that could ensure the highest level of modern healthcare, access to all rights, and the indiscriminate realisation of those rights. The Ministry of Health Commission for the Development and Monitoring of the National Programme for Rare Diseases (hereinafter the Commission) was established pursuant to the Health Minister's Decision of 24 May 2010, with the objective of implementing comprehensive activities for the promotion and protection of the rights of rare disease patients. The Commission is an advisory and expert authority tasked with the adoption of the National Programme for Rare Diseases 2015–2020 (hereinafter National Programme), which would summarise the problem of rare diseases from the viewpoints of the European Union and the Republic of Croatia and present the main strategic objectives and measures for improving healthcare in regard to rare diseases in the following period. Pursuant to the conclusions of the 1st National Conference on Rare Diseases that was held in Dubrovnik from 17th to 19th September 2010, organised by the Croatian Organisation of Rare Disease Patients and the European alliance of rare disease patient organisations EURORDIS, and

attended by the representatives of patient organisations, experts and the Government of the Republic of Croatia, as well as on the basis of the results of a survey conducted among the participants, the highlighted priorities of the National Programme for Rare Diseases are as follows:

Improving knowledge and the availability of information on rare diseases
Supporting the development of rare disease registries and their permanent financing
Supporting the activities and development of a reference centre network and relevant scientific organisations for rare diseases
Improving the availability and quality of healthcare (diagnostics, treatment, and prevention) for rare disease patients
Ensuring the availability of rare disease drugs
Improving the realisation of social rights for rare disease patients
Empowering rare disease patient organisations
Fostering scientific research on rare diseases
International networking and cooperation in the field of rare diseases

Once the National Programme is adopted, the Commission will continue to monitor its implementation through the implementation indicators for individual objectives and measures, and report on achieved results to the Ministry of Health once per year.

4.1. Definition, Classification, and Codification of Rare Diseases in the Republic of Croatia

The organisation and improvement of healthcare must be based on accurate epidemiological data that enables healthcare policy to be planned in accordance with a concrete picture of actual issues. Preliminary European reports reveal a lack of documented information on the epidemiology of rare diseases. Despite the fact that they significantly contribute to the morbidity and mortality of the population, rare diseases are invisible in the healthcare information system due to a lack of appropriate codification and classification. This emphasises the need to determine the number of patients, the prevalence, the natural course and characteristics of an individual rare disease, in order to be able to plan healthcare system interventions and enable improvements to healthcare monitoring and organisation.

At the joint meeting of the Croatian Society for Rare Diseases and the Croatian Society of Human Genetics at the Croatian Medical Association held in Cavtat on 15 May 2009, the professional community in the Republic of Croatia adopted the EU definition of rare diseases as those that affect fewer than 5 people in 10,000. At the workshop on the classification and codification of rare diseases held during the 1st National Conference, it was pointed out that a definition based on incidence should also be taken into account for certain severe diseases since they quickly lead to death and, although they are not objectively rare, they are rarely encountered (for example some severe tumours). The

important components in the classification of these disorders should also include the severity of a disease (for an individual, their family, and society) and the possibility of treatment (early diagnostics and faster familiarisation of experts with treatable diseases).

It is estimated that there are approximately 250,000 rare disease patients in the Republic of Croatia2. There is however no accurate and comprehensive epidemiological and/or statistical data on rare diseases in the country. In addition to patients remaining undiagnosed, the variety of locations and types of rare disease patient care (specialised centres, but also general practice surgeries, clinics and general hospitals) makes their prompt identification and monitoring even harder. The International Classification of Diseases 10 (ICD-10), which is in official use, does not have the appropriate codes for most rare diseases, so it is currently not possible to monitor the majority of rare diseases in the healthcare system. Hospital statistical data does not reflect the true morbidity due to the drawbacks of the ICD-10 classification and the use of DTS (Diagnostics and Therapy Groups) codes which favour those diseases/conditions that yield higher payments, and to the lack of awareness and knowledge of medical professionals on the importance of accurate codification and classification of rare diseases for public health, all of which results in superficial and inaccurate data.

4.2. Inventory and Registries of Rare Diseases

Rare diseases have been known to become misplaced in the healthcare information system due to the lack of an appropriate codification and classification system, and only an effective classification method can enable the obtaining of accurate epidemiological data for these entities. For more than a decade, many international organisations, led by the World Health Organisation (hereinafter WHO), and in particular the Rare Disease Task Force Working Group on Coding and Classification, have been exerting great efforts to create a classification of rare diseases that would be suitable for use by various users. They have encountered numerous problems: lack of accurate data; classification by aetiology or by the degree to which an individual organ or organ system is affected is rendered more difficult due to the heterogeneous nature of the diseases, whereby the same disease can originate from different causes and can affect multiple organs and systems (with a varying degree of severity); classification by disease groups is rendered more difficult; new entities are continuously being discovered, especially in the fields of syndromes, tumours and congenital metabolic diseases; establishing a final diagnosis often takes a long time. Finally, difficulties arise when attempting to compile an alphabetical classification due to numerous synonyms and varying medical terminology.

There are currently two methods for classifying rare diseases. The first one is an alphabetical list of rare diseases, such as the one used by the Orphanet network. The advantage of this system is that it can be linked to other international codes (e.g. ICD, Online Mendelian Inheritance in Man, OMIM), which are used in most European countries as hospital discharge codes. The alphabetical system allows for each disease to be designated by a special code on a continuously updated list. The main drawback of this method is the fact that there are approximately 5,700 diseases registered in the Orphanet database, some of which are exceedingly rare, and that makes the system unsuitable for use in everyday codification. The Register of Persons with Disabilities at the Croatian National Institute of Public Health also tracks data regarding persons suffering from rare diseases who have developed a disability and who have been granted certain rights. The register lists approximately 3,000 rare disease patients, which makes the register important for future data linking.

The second classification method that is used by the WHO, the International Classification of Diseases, has several levels. The first one is nosological, for example, Diseases of the blood and blood-forming organs (D50-D89) are divided into various groups of diseases, e.g. coagulation defects, while the third level is a specific disease. This is the most frequently used classification method. It is used for the epidemiological monitoring of morbidity, mortality, and disability. The drawback of this system is that ICD9 and ICD10 do not include the majority of rare diseases. ICD11, which is being developed, is expected to have the appropriate codes for most rare diseases in its full electronic version.

Since information on rare diseases is fragmentary and expertise is limited, health registries are the key means of access to rare diseases. A health registry can be defined as a systematic, anonymous and continuous collection of data that is important for the health of a certain population.

Health registries require the collection of relevant and reliable data to facilitate decision making in prevention, treatment and research activities. The data that should be collected by a rare disease registry include incidence, spatial distribution, natural course and other clinical characteristics of a certain disease, treatment outcomes, as well as data on the availability and efficiency of healthcare services. Such a registry would enable the identification of existing and required resources, and would be an important planning and decision-making tool in the process of organising patient healthcare.

There is no comprehensive list or registry of rare diseases in the Republic of Croatia. The Registry for the Surveillance of Congenital Anomalies was introduced in the Republic of Croatia in1983 and, operating within the framework of the international network of registries of congenital anomalies – EUROCAT, it monitors deliveries in five Croatian regions (approximately 21% of deliveries per year). All congenital malformations, genetic syndromes, bone dysplasias, and chromosomal abnormalities (ICD10, Chapter 17, Q00-Q99), covering the majority of rare diseases, are entered in the registry. Since 2010 EUROCAT has been part of the Second Programme of Community Action in the Field of Health 2008–2013 implemented by Member States and the EU Commission. The Ministry of Health of the Republic of Croatia and the Reference Centre of the Ministry of Health of the Republic of Croatia for Monitoring Congenital Anomalies are involved in the implementation of this joint action as partners. The Republic of Croatia is also part of the network of European cystic fibrosis registries, EUROCARE-CF, the network of registries of patients suffering from rare neuromuscular diseases, NM -TREAT NMD and CARE NMD, the network of registries of patients suffering from primary immunodeficiencies, PID (with the European Society for Immunodeficiencies, ESID), and the European network of registries for intoxication type metabolic diseases. The reference centres for rare diseases enter their patients in international online registries for specific disorders (Fabry disease, mucopolysaccharidosis type I and II, Pompe disease).

4.3. Information and Education in the Field of Rare Diseases

Knowledge of rare diseases has grown exponentially in the last twenty years. However, access to information on specific rare diseases often continues to be poor, which emphasises the need for this knowledge not only among patients and their families, but also among experts and state administration bodies. Disseminating information on rare diseases is a complex task because the knowledge of their diagnosis, treatment, prevention, and available services is partial and fragmented. Collecting and

disseminating accurate information in a format adapted to the needs of experts, patients and their families is key for the advancement of healthcare for rare disease patients.

In the Republic of Croatia, public information on rare diseases can be obtained on the website of the Croatian Society for Rare Diseases at the Croatian Medical Association (www.rijetke-bolesti.org) and many Croatian rare disease patient organisations (rijetke-bolesti.hr; www.pws.hr;www.hull.hr; www.debra-croatia.com; www.cisticna-fibroza.hr; smk.mef.hr/osteogenesis; www.fenilketonurija.hr).

Information on certain rare disorders and initiatives in the field of rare diseases can also be found on the websites of non-governmental organisations devoted to healthcare issues (e.g. www.cybermed.hr; www.plivamed.net; zajednoprotivraka.org; www.centar-zdravlja.net; www.uppt.hr/index).

Within the scope of the EUROPLAN project and in cooperation with EURORDIS, the Croatian Alliance for Rare Diseases organised two national conferences on rare diseases[3] that attracted media interest and substantially contributed to the dissemination of information on rare diseases in the Republic of Croatia. The activities of patient organisations aimed at disseminating information on rare diseases also include Rare Disease Day activities (patients meeting with the President of the Republic of Croatia; promotional fairs; presentations by patient organisations; media appearances; roundtables, etc.).

Reference centres also provide information on rare diseases, be it for experts (by organising continuing education courses, professional and science conferences on rare diseases) or for patients and the general public (by preparing and publishing educational material). For example, the 8th Balkan Meeting on Human Genetics (Cavtat, 14–17 May 2009) featured the topic of rare diseases (Rare diseases - public policy, research, diagnosis and management). The 1st and 2nd Croatian Symposium on Rare Diseases, open to international participants, were held on 3 December 2010 and 24 February 2012 respectively, organised by the Croatian Society for Rare Diseases under the patronage of the Ministry of Health of the Republic of Croatia. A roundtable discussion on the topic "Rare diseases – achievements and challenges" was held at the 5th Congress of the Croatian Society of Human Genetics on 21 July 2011.

4.4. Reference Centres / Relevant Scientific Organisations

The Ministry of Health of the Republic of Croatia currently operates three large reference centres for rare diseases in the Republic of Croatia: the Reference Centre of the Ministry of Health of the Republic of Croatia for Monitoring Congenital Anomalies (Children's Hospital Zagreb), the Ministry of Health Reference Centre for Medical Genetics and Metabolic Diseases in Children (Department of Paediatrics, University Hospital Centre Zagreb), and the Reference Centre for Rare and Metabolic Diseases (Department of Internal Medicine, University Hospital Centre Zagreb). Furthermore, there are also reference centres dedicated to individual rare diseases or smaller groups of rare diseases (e.g. solid

[3] Report. 1st National Conference on Rare Diseases, Dubrovnik, 17-19 September 2010
Report. 2nd National Conference on Rare Diseases, Tuheljske toplice, 07-09 October 2011

tumours in children, hereditary epidermolysis bullosa). Reference centres are named in accordance with Article 7 of the Decree on criteria for assigning and renewing the name of a reference centre of the ministry competent for health (Official Gazette 77/2005), pursuant to which centres must meet the

stipulated conditions, demonstrating scientific and professional results in monitoring, studying and improving prevention, diagnostics and/or treatment and rehabilitation in the field of the medical profession for which they were established, and must meet stipulated conditions for their personnel and facilities. The existing regulations that were adopted for all diseases/groups of diseases and not only for rare diseases must be harmonised with the international recommendations issued by EURORDIS and EUCERD, where necessary. Furthermore, it is necessary to define the scope of activities of reference centres for rare diseases and improve them in regard to the personnel/facilities/equipment so that they can perform the tasks assigned to them. They should be networked with experts who operate from locations that do not meet the requirements for obtaining reference centre status, but are involved in the diagnostics and treatment of one rare disease or a group of rare diseases in Croatia. Moreover, it is necessary for such centres to join the European reference networks (ERNs) for rare diseases.

4.5. Rare Disease Diagnostics

One of the main difficulties encountered by rare disease patients is the lack of a prompt and accurate diagnosis. The repercussions of an inaccurate or late diagnosis can be very serious, which can lead to serious consequences for the physical and mental health of a patient. In cases of hereditary diseases, there can be a recurrence of the disease in a family, which might have been prevented had the accurate diagnosis been made promptly and had genetic counselling been given. In order to provide a prompt and early diagnosis of rare diseases, it is necessary to organise programmes for the early detection of impairments, promote research in the field of rare disease diagnostics, and provide equal access to sophisticated diagnostic tests. Since most rare diseases have a genetic basis, we will give special emphasis to the issue of the particularities of diagnosing hereditary/genetic disorders in the following chapters.

4.5.1. Genetic Counselling

Although around 80% of rare diseases are caused by genetic disorders, only a small number of patients receive appropriate genetic information from genetic counselling in the Republic of Croatia. This is because there are few organised services that employ experts educated for providing this type of healthcare service.

The European Convention on Human Rights and Biomedicine (Council of Europe, 1997), pursuant to Article 12, requires appropriate genetic counselling to be conducted prior to predictive (testing for genetic predisposition or susceptibility) and presymptomatic (testing for adult-onset monogenic diseases) testing, as well as prior to testing to identify a subject as a carrier of a genetic disorder. Pursuant to the recommendations of the European Society of Human Genetics, as well as the Croatian Society of Human Genetics at the Croatian Medical Association, due to the sensitivity of genetic information, genetic counselling should be conducted before each genetic test, and all findings should be presented to the subjects during a formal genetic counselling session. Pursuant to the

aforementioned recommendations, the information provided in this procedure should be presented by specially trained persons. In the Republic of Croatia, such persons are paediatric specialists, medical genetics subspecialists. With the development of a new medical specialty, clinical genetics, which already exists in all EU Member States, it is expected that more people will become able to provide high-quality information in this field, which will include providing detailed information on the nature of a disease, the ways it can be inherited, determining the likelihood of it reoccurring in a family (a priori, a posteriori, and the final or joint risk), test-related risks (e.g. various methods of prenatal and preimplantation diagnostics), restrictions in interpreting the results of specific genetic tests, possible restrictions/unknowns resulting from insufficient knowledge of certain issues related to a disease, and the need to inform and further test the family members who are at risk.

4.5.2. Diagnosing Genetic Disorders

4.5.2.1. Clinical Diagnosis

Clinical diagnostics is a process in which genetic testing is used to confirm or exclude suspicion of a certain genetic disorder based on medical history, clinical examination, laboratory testing and other tests. In most cases, this requires a detailed clinical evaluation of a patient, which is usually conducted during hospital treatment and polyclinic follow-ups by doctors who are medical genetics subspecialists with experience in clinical genetics, dysmorphology and metabolic diseases. Since genetic disorders are heterogeneous, clinical examination and processing can also be performed by doctors of all other medical specialties (e.g. optometry, dermatology, internal medicine, etc.), but they ultimately require that genetic testing be performed and its results interpreted by a specially trained person. The term genetic diagnosis indicates, therefore, a process of clinical intervention in the context of a relationship of a healthcare worker with a patient and his family. The term genetic testing, on the other hand, is used to refer to the methods and techniques used to analyse a genome (chromosomes/genes) or gene products (enzymes, hormones, etc.).

4.5.2.2. Genetic Tests

Genetic tests play an important role in the process of establishing a rare disease diagnosis. It is estimated that there are currently tests for more than a thousand genetic disorders, but their use is limited for a number of reasons. Since these are rare conditions, certain tests are performed only at certain centres in Europe/the world, which requires regulated cross-border cooperation. Moreover, in addition to creating a list of laboratories that perform certain tests, the Orphanet database being at the forefront of this activity, it is necessary to continuously work on the structure, harmonisation and quality of genetic tests, including their impact on economic policy in the sphere of healthcare, as well as legislative, ethical, and social issues. The EuroGentest project, launched under FP6 and continued under the FP7 programme, rose to prominence by organising external quality assessment (EQA) schemes for laboratories, as well as by publishing guidelines for the accreditation of genetic services with the aim of improving the quality of molecular, cytogenetic, biochemical and clinical procedures, and adopting a joint strategy for implementing such diagnostics in the European Union (www.eurogentest.org). Protocols and guidelines for best clinical practice are also issued by the

European Society of Human Genetics (www.eshg.org/), and, in the Republic of Croatia, by reference centres and the Croatian Society of Human Genetics (www.humana-genetika.org/).

Many laboratories in the Republic of Croatia perform genetic (cytogenetic, molecular, biochemical) diagnostics of rare diseases (www.rijetke-bolesti.org). Some laboratories conduct quality assurance on a voluntary basis within the framework of European institutions (EuroGentest, CEQUA, ECA, EMQN, ERNDIMQA). With the aim of achieving national harmonisation of laboratory methods and results in the field of general medical biochemistry, analytic methods and quality levels that must be met as a compulsory precondition for the application of unique age- and gender-dependent reference intervals were recommended for all medical biochemistry laboratories in the Republic of Croatia as of 1 January 2005. The number of initiatives for the harmonisation or verification of standards for cytogenetic and molecular tests is still insufficient at a national level. In addition to technical quality, it is also necessary to ensure high-quality interpretation of findings by specialists who are familiar with the disease that is being tested and who can provide comprehensive information, including genetic counselling. In the Republic of Croatia, this professional field is only partially regulated, by way of recommendations issued by the Croatian Society of Human Genetics (www.humana-genetika.org/).

The costs of genetic tests that are available in the Republic of Croatia are covered by the Croatian Health Insurance Fund under the mandatory health insurance scheme. For children under the age of 18, healthcare costs are fully covered by mandatory health insurance, while the healthcare costs of adults are partially covered by mandatory health insurance and partially by the insured persons themselves, unless they are also supplementary health insurance policy holders. Cases in which all healthcare costs are fully covered by mandatory health insurance (for example, malignant disease treatment) are an exception.

If a certain genetic test cannot be performed in the Republic of Croatia, the Croatian Health Insurance Fund, based on a request from an insured person, makes a decision based on appropriate medical documentation, and the mandatory recommendation for treatment abroad is issued by a council of reference centre medical specialists who are competent for the disease diagnosed to the insured person, or a medical specialist or a medical council at another healthcare facility that is a partner of the Croatian Health Insurance Fund, where the insured person is being treated. One or several international healthcare institutions that can perform the required treatment are recommended in the decision, and the latter also features the medical findings, opinions, and evaluations of the medical council of the Croatian Health Insurance Fund Directorate. The entire procedure is governed by relevant regulations. The decision is considered in relation to the impact the genetic test results may have on the further treatment of the patient, and therefore the requests that will have an impact on the treatment or improve the quality of life of the patient are generally approved. This prevents some patients from being diagnosed or having their diagnosis confirmed. Sending samples abroad, as well as receiving samples from foreign countries, is still often conducted outside an organised system, such as collegial assistance, international cooperation, ad hoc projects, etc.

4.5.2.2.1. Prenatal Diagnosis

Prenatal diagnosis (hereinafter PND) is defined as a series of ultrasound, cytogenetic, biochemical, and molecular techniques that are implemented in order to detect hereditary diseases and congenital

anomalies in a foetus. PND is performed for high-risk pregnancies and the indications for performing it are a family medical history that is positive for hereditary diseases and an increased risk of chromosomal abnormality related to the age of the mother and/or positive biochemical and ultrasound tests at screening or following exposure to teratogens. The objectives of a prenatal diagnosis are primarily to ensure the birth of a healthy child or the possibility of early treatment of the foetus. In the Republic of Croatia PND costs are covered by the Croatian Health Insurance Fund, when appropriately indicated.

4.5.2.2.2. Preimplantation Genetic Diagnosis

Today, assisted reproductive technology methods offer at-risk couples new possibilities for having healthy children, such as germ cell donation, preimplantation gender screening in cases of X-linked diseases, and preimplantation genetic diagnosis (hereinafter PGD), generally in cases when there is a risk of severe and rare genetic disorders, usually structural chromosomal abnormalities and monogenic diseases.

An analysis of PGD centres in Europe has shown that the standards for this test vary greatly throughout Europe, highlighting the problem of quality assurance control and accreditation procedures. PGD is not available in the Republic of Croatia, so there is no appropriate regulation for the use of these techniques, and the persons who require this service must obtain it abroad.

4.5.2.2.3. Presymptomatic and Predictive Diagnosis

Genetic tests can be used to establish a diagnosis before the onset of symptoms and signs of disease. Persons with a family history of disease are tested, and test results can indicate a high likelihood or increased risk of an onset of disease. Some of these diseases are preventable or treatable, while others are incurable. In Croatia, this type of testing is available for some neurological and psychiatric disorders (e.g. Huntington's disease, spinocerebellar ataxia, neurofibromatosis) and tumours (MEN, familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer), but is often conducted without appropriate genetic counselling.

4.5.2.2.4. Newborn Screening

The aim of newborn screening is to quickly diagnose and provide early/prompt treatment of newborns who are found to be suffering from a disease. For a disease to be included in the population screening programme, it must meet certain criteria. The classic Wilson and Jungner criteria from 1968, which were adopted by the WHO, have been modified in light of technological advances: a disease is treatable, an early clinical diagnosis of a disease cannot be established, there must be a reliable and financially acceptable test for the early detection of a disease. In the Republic of Croatia, newborn screening is a compulsory part of healthcare. It has been implemented for phenylketonuria since 1978, and for connatal hypothyroidism since 1985. Moreover, the National Programme for Early Detection of Hearing Impairment by Evaluating Evoked Otoacoustic Potentials was introduced in 2003. For a considerable time, newborn screening in some European countries has also included other more frequent diseases

for which effective treatment is available or those diseases for which it has been proven that early detection can significantly improve the prognosis, such as: congenital adrenal hyperplasia, disorders of breaking down fatty acids due to a medium-chain acyl-CoA dehydrogenase deficiency, cystic fibrosis. The spectrum of diseases that can be included in newborn screening is growing continuously thanks to new technologies. In the last 10-15 years an increasing number of countries have been using the tandem mass spectrometry technique, which is used to detect numerous organic acidurias, aminoacidopathies, carnitine cycle disorders, and fatty acid beta-oxidation disorders using a single test. A more recent screening programme is the detection of cyanotic heart defects by using pulse oximetry. In Europe, the number of diseases included in the screening varies from country to country and is dependent on the financial capacity and other circumstances of an individual country (e.g. higher incidence of hemoglobinopathies in Mediterranean countries or in certain ethnic groups), as well as on the ethical implications of the screening programme. Due to the benefits it has and the numerous requirements that have already been met, newborn screening should be expanded in Croatia by introducing the tandem mass spectrometry technique and other tests, and the selection and order of the inclusion of diseases in the screening should be harmonised with existing capacities, professional criteria and European recommendations.

4.6. Rare Disease Treatment

Treatment options for rare diseases are often scarce and not very effective. One of the crucial problems in treating rare disease patients is achieving equality of treatment, since there is a tendency for healthcare funds to be allocated more to treating common diseases, and drugs for rare diseases are often expensive or do not exist, and are therefore known as orphan drugs. The development of orphan products (that include drugs, gene and cell therapy) requires special incentives that take into account the low interest of the pharmaceutical industry and scientists, as well as the difficulties, challenges and complications related to determining the effectiveness and safety of treating a small number of patients.

There have been significant improvements in this regard in recent years, with more rare disease drugs becoming available on the market thanks to European incentives. In 1999 the European Parliament adopted Regulation (EC) no 141/2000 (the so-called "Orphan Regulation") that established incentives for the development of orphan drugs. For all EU Member States, the evaluation process for orphan drugs is coordinated by the European Medicines Agency (EMA: www.ema.europa.eu), and legally binding decisions are issued by the European Commission. There are two committees involved in the evaluation process for orphan drugs at the EMA: the Committee for Orphan Medicinal Products (COMP) and the Committee for Medicinal Products for Human Use (CHMP).

The COMP issues an opinion on whether a certain drug can be approved for orphan status and the CHMP issues an opinion on whether a certain drug can be granted an EU-wide marketing authorisation. The EMA submits the opinions of both committees to the European Commission, which adopts a legally binding decision that pertains to all EU Member States.

A drug can be approved for orphan status if it meets the following criteria:

- the drug is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10,000 persons in the EU; or
- the drug is intended for the diagnosis, prevention or treatment of a life-threatening, chronically debilitating, or chronic and serious condition, whereby it is unlikely that the

marketing of the drug would generate a sufficient return on investment to justify the development costs of the drug; and

- no satisfactory method of diagnosis, prevention or treatment of that condition is available in the EU or, if such method exists, the new drug will be of significant benefit to the persons affected by that condition.

The List of Particularly Expensive Drugs, which also lists expensive drugs for some rare diseases, was established in the Republic of Croatia in 2006. Since 15 November 2010 the Agency for Medicinal Products and Medical Devices of Croatia has been publishing the list of medicinal products for treating rare and severe diseases which have been authorised in the Republic of Croatia, and approved for orphan status in the EU and granted the European marketing authorisation on its website (www.halmed.hr). A detailed procedure has been laid down for the inclusion of a drug on the List of Particularly Expensive Drugs. The decision-making authority for the inclusion is the Board of Governors of the Croatian Health Insurance Fund, and the proposal for inclusion on the List is considered by the Drug Committee.

From its overall budget, the Croatian Health Insurance Fund allocates a certain amount of funding for the drugs on the List of Particularly Expensive Drugs. The Croatian Health Insurance Fund introduced a regulatory method to control the increase in drug consumption. Maximum consumption is contractually defined in financial terms. Contracts are entered into with marketing authorisation holders, and consumption is monitored to prevent abuse, which has allowed savings and the introduction of new drugs on the list. Since the contractual amounts are fixed annually, problems can arise with newly diagnosed patients starting treatment. In order to shorten the administrative procedure, the expert evaluation by the Croatian Health Insurance Fund was abolished, and insured persons can be granted the right to particularly expensive drugs pursuant to the authorisation of the drug committee of the hospital at which they are receiving treatment. However, this introduces the issue of competence of hospital committees in deciding on treatment for rare diseases for which they lack expertise. Treatment by donation is also possible (so-called compassionate use), from the establishment of a diagnosis to the moment the drug is approved. Drugs that are not on the list are covered by hospital costs, which can be a great financial burden for hospital institutions. Hospital drug committees decide on the treatment of patients with drugs which are not on the list of essential drugs of the Croatian Health Insurance Fund, as well as with drugs used to treat some rare diseases, in cases when the recommendation for use of a drug is not approved by the competent regulatory authority and contained in the Summary of Product Characteristics (so-called off-label use). The importing of relatively inexpensive drugs required to treat some rare diseases is sometimes hindered by the fact that companies have no interest in starting an import procedure for a small market.

Certain medicinal products and medical services (drugs, medical equipment, orthopaedic devices, specialist treatments) are not reimbursed by the Croatian Health Insurance Fund, and the offer of medical services at healthcare institutions can vary. The availability of orphan drugs depends on two factors – the import approval procedure and the method for settling treatment costs – wherein lies the possibility of procedural improvements. On the other hand, a rational application of expensive drugs must be ensured. The approval to start and continue treatment with expensive drugs is not related to reference centres/relevant healthcare organisations; rather, it is left to the judgement of individual hospitals and hospital committees that lack sufficient expertise, which can lead to expensive therapy being uncritically prescribed.

4.7. Rare Disease Prevention

Although primary prevention is possible only for a limited number of rare diseases, it is known that some external factors such as, for example, the mother's chronic disease or inadequate nutrition, can cause congenital anomalies, teratogenic effects and tumours. In order to have a preventive effect, measures must be taken even before conception by living a healthy lifestyle, taking folic acid and vitamin preparations during the periconceptional period and the first trimester of pregnancy, and by avoiding the intake of harmful substances such as alcohol, illegal drugs and nicotine, especially during pregnancy. The implementation of the strategy for the primary prevention of congenital malformations must follow new scientific findings on risk factors, and information must be made available to experts and the general public.

4.8. Social Services and Rare Diseases

Many rare diseases carry a heavy health, economic and social burden. Although this is common for many chronic diseases, there are some characteristics that set rare diseases apart. To wit, many rare diseases have onset as early as in childhood or adolescence, which means that the burden for the patient, their family and the society is almost lifelong. Physical, mental, intellectual, and sensory impairment sets an individual apart at a very early time. Therefore, patients suffering from rare diseases have specific social needs during a long period of time, and this requires planned, continuous activity.

There are currently no social services dedicated to providing services to rare disease patients. The needs of such patients are catered to by the social welfare system, in the same manner as those of all other chronic patients and persons with disabilities. The state provides financial support for the integration and employment of disabled persons. The National Strategy of Equal Opportunities for Persons with Disabilities 2007–2015 was adopted in order to regulate services and social services to facilitate the integration of persons with disabilities in the education system, as well as facilitate their employment and everyday life activities. The programme of counselling centres for parents of children with developmental disabilities and disabled persons, the personal assistant project, and other projects specified in the aforementioned strategy are a significant contribution to the social protection of children with developmental disabilities and their families, among whom there is a substantial number of rare disease patients, therefore these and similar programmes must be supported and improved, and their practical application monitored.

The social welfare system in the Republic of Croatia is regulated by the Social Welfare Act (Official Gazette 157/13 and 152/14). The implementation of social welfare activities at a national level is monitored and improved by the Ministry of Social and Youth Policies. The social welfare system is based on the subsidiarity principle, which implies that individuals and families are responsible for their own social security, and the role of the state is to assist them in their endeavour, with the objective of preventing, mitigating, and alleviating social disadvantage, by providing a broad spectrum of rights in terms of financial assistance and social services. Some of the social welfare beneficiaries are children with developmental disabilities and disabled adults who, pursuant to the aforementioned Act, may be granted some of the following material rights: right to benefits for personal needs, e.g. accommodation; a single benefit payment; education-related benefits; personal disability benefits; allowance for assistance and care; parent-caregiver status or caregiver status; benefits until employment; other extra-institutional services: primary social services; counselling and assistance; household assistance; psychosocial support; early intervention; assistance in entering regular education programmes (integration); day care and assisted living and accommodation services as an institutional form of care, offered at social welfare homes, centres for providing community services, or other service providers in accordance with the aforementioned Act, and extra-institutional care in foster families or foster homes. The role of extra-institutional services has been growing in importance in recent years, and the number

of service providers has grown, allowing beneficiaries a greater choice of options for services which are endeavouring to meet their needs (customisation). In order to be granted the aforementioned rights and services, a beneficiary must contact a social welfare centre that is competent for issuing decisions on the relevant issues, according to the applicant's place of residence.

The amount of all social welfare financial benefits is calculated as a percentage of a base sum determined by the Government of the Republic of Croatia in a Decision on the base sum for social welfare benefits. The funds for financing social welfare activities are allocated from the budget of the Republic of Croatia, the budgets of local and regional self-government units, and the City of Zagreb, revenues generated from the participation of beneficiaries and their caregivers in social service funding, own revenues, donations, aid, and other earmarked revenues.

In accordance with the European Commission proposal, social services for rare disease patients should be organised at a national level in order to observe the national culture and way of life as much as possible, and those services should include: a) respite care services; b) information services and helplines; c) therapy programmes for children and adolescents; d) financial and psychological support. In addition to patients and medical staff, social workers, educators, teachers, etc. should also be educated on rare diseases.

4.9. Rare Disease Patient Organisations

The Croatian Alliance for Rare Diseases (hereinafter the Alliance) has evolved from the Croatian Organisation of Rare Disease Patients and is the umbrella organisation for rare diseases in the Republic of Croatia. It groups together other rare disease organisations (epidermolysis bullosa, cystic fibrosis, osteogenesisimperfecta, phenylketonuria, Prader-Willi syndrome, haemophilia, scleroderma, collagenosis, myotoniacongenita, myasthenia gravis, multiple myeloma, Wolf-Hirschhorn syndrome) and individual members. Since its establishment, the Alliance has been working on raising awareness and improving knowledge about rare diseases, among both healthcare workers and government institutions that can influence the treatment, care and quality of life of patients, and among the general public. Cooperation with the Ministry of Health and the Croatian Health Insurance Fund is of particular importance. The Alliance endeavours to help patients and their families by providing information, assistance, and lobbying for rights in the field of healthcare, social welfare, legal assistance, and other types of care. The Alliance also cooperates with similar international organisations, primarily EURORDIS and Orphanet. Every year, on the last day of February, the Alliance celebrates international Rare Disease Day. In 2013, the Alliance membership was comprised of 16 member organisations, 286 individual members and over 1,500 members with more than 400 different rare diagnoses. The Croatian Rare Disease Helpline project, which is part of the European helpline network, has been implemented since late 2010. In early 2013 the Alliance introduced a toll-free number (0800-99-66) for all callers.

Members of the Alliance were involved in the preparation of the National Programme for Rare Diseases 2015–2020 and the activities of the Croatian Society for Rare Diseases at the Croatian Medical Association. Although certain results are evident, the activities of rare disease patient organisations should be empowered financially and in other ways, in order to aid them in providing education, fighting for the quality of care and treatment, involving interested experts, raising funds for projects that benefit the treatment of patients, and linking and networking with similar international organisations.

4.10. Research in the Field of Rare Diseases

In the Republic of Croatia scientific research in the field of rare diseases is conducted within the framework of projects of the Ministry of Science, Education and Sports and individual international projects. Only around 1% of the projects[4] of the Ministry of Science, Education and Sports are focused on research into rare diseases, including basic research and clinical studies.

Clinical trials are limited by the small number of patients, so clinical studies are mostly organised at an international level. According to the clinical study database, out of 355 trials in the Republic of Croatia, only four pertain to rare diseases http://www.regpok.hr.

Trials in the field of rare diseases are few, disjointed and fragmented, thus they require special incentives, networking and coordination at a national and international level.

4.11. International Networking and Cooperation in the Field of Rare Diseases

The Republic of Croatia participates in several international projects in the field of rare diseases, such as:

1. ECORN (www.ecorn-cf.eu), specialised e-Health information system for patients suffering from cystic fibrosis.
2. Euro Care CF (www.eurocarecf.eu), involved in research in the field of diagnostics and treatment for cystic fibrosis, including the creation of the European registry of CF patients.
3. EUROCAT (www.eurocat-network.eu), network of registries for the surveillance of congenital anomalies.
4. Euro Gentest (www.eurogentest.org), whose objective is to harmonise and standardise genetic diagnostic services related to rare diseases in Europe.
5. EUROPLAN (www.europlanproject.eu), a project that aims to support the adoption of national plans for rare diseases in EU Member States.
6. Orphanet (www.orpha.net), database of rare diseases in Europe intended for doctors, patients and their families.
7. E-IMD – European Registry and Network for Intoxication Type Metabolic Diseases (www.eimd-registry.org), network of registries for intoxication type metabolic diseases.
8. EPIRARE (European Platform for Rare Disease Registries) (www.epirare.eu/project.html), network that is working on a common platform for rare disease registries.

International cooperation should be further improved by activating a larger number of experts from the Republic of Croatia in these and other organisations, networking relevant scientific organisations with similar international institutions, and joining new European initiatives/projects in the field of rare diseases. Particular consideration should be given to the participation of Croatian scientists in E-Rare projects (www.e-rare.eu), and cooperation with the International Rare Diseases Research Consortium (IRD and RC) and the European Research Infrastructure Consortium (ERIC).

[4] Data source: Ministry of Science, Education and Sports

5. Priorities in the Field of Rare Diseases in the Republic of Croatia and Proposed Measures

5.1. Improving Knowledge and the Availability of Information on Rare Diseases

Objective

To improve the availability of information on rare diseases and healthcare options for patients, all types of healthcare workers, as well as other experts involved in the treatment of rare disease patients and their families.

Recommendations

- Support information sources available to experts and patients.
- Identify, coordinate and support existing sources of information on rare diseases.
- Encourage academic institutions, professional associations, scientific and research centres, and patient organisations to work together to promote and spread knowledge of available rare disease information sources.

5.1.1. Measure – Continuing Education of Experts

Implementing organisations: professional associations, reference centres, universities that offer healthcare studies, Faculty of Pharmacy and Biochemistry at the University of Zagreb, Faculty of Education and Rehabilitation Sciences at the University of Zagreb, Croatian Society for Rare Diseases at the Croatian Medical Association, Croatian National Institute of Public Health.

Co-implementing organisations: Ministry of Health, Ministry of Social and Youth Policies, Ministry of Science, Education and Sports, the Commission.

Activities:

1. Support the development and maintenance of the website of the Croatian Society for Rare Diseases at the Croatian Medical Association.

2. Create a guidebook for rare diseases with existing ICD10 codes.

3. Foster the inclusion of topics on rare diseases in undergraduate and postgraduate studies at universities that offer healthcare studies.

4. Foster the inclusion of topics on rare diseases in undergraduate studies at other faculties and universities for healthcare and non-healthcare professionals involved in the treatment of rare disease patients.

5. Symposiums/courses/workshops/roundtables on the topic of rare diseases.

6. Disseminate information about the National Programme to the general public and the media, European bodies.

Timeframe:

1. Continuous

2. Task duration: two years

3. - 6. Continuous

Implementation indicators:

1. Report on the continuous development of the website (www.rijetke-bolesti.org).

2. Completed guidebook with information on rare diseases with ICD10 codes, disease descriptions, diagnostic techniques, treatment and prevention options, information on social services and organisations (as a printed publication and a digital version for the website).

3. Subjects in undergraduate and postgraduate studies that include topics on rare diseases at universities that offer healthcare studies.

4. Subjects in undergraduate studies that include topics on rare diseases at other universities and colleges.

5. Annual reports on the number of symposiums/courses/workshops/roundtables.

6. Annual reports on the development of the National Programme and on the monitoring of its implementation.

Funding: activities will be conducted within the framework of regular business activities; a portion of the funds will be ensured through sponsorship and from EU programme funds, from registration fees, and Ministry of Health resources (A734211 Improving healthcare service quality, accounting item 323: HRK 30,000 for 2015 and accounting item 321: HRK 30,000 for 2016 and 2017; A803005 Cooperation with citizens' associations, accounting item 381: HRK 50,000 – for 2015, 2016 and 2017).

5.1.2. Measure – Continuous Information to and Education of Patients and the General Public on Rare Diseases

Implementing organisations: Croatian Alliance for Rare Diseases, reference centres, Croatian Society for Rare Diseases at the Croatian Medical Association, the Commission.

Co-implementing organisations: Ministry of Health, Ministry of Social and Youth Policies, Ministry of Science, Education and Sports, Education and Teacher Training Agency, independent experts, Croatian National Institute of Public Health, Croatian Health Insurance Fund.

Activities:

1. Support the websites of Croatian rare disease patient organisations.

2. Celebrate Rare Disease Day (last day of February).

3. Print brochures, leaflets and posters that disseminate general information on rare diseases.

4. Create written informational and educational materials aimed at rare disease patients and their families.

5. Organise educational meetings, courses, workshops and roundtables on topics that deal with medical, ethical, legal, and social aspects of rare diseases for patients and the general public (including schools), advocating the use of the HON certificate.

Timeframe:

1. Continuous, annual reports

Implementation indicators:

1. Report on the continuous development of websites of rare disease organisations.

2. Celebration of international Rare Disease Day (media appearances, organised public events, organised roundtables, etc.).

3. Number and scope of printed materials for patients and their families.

4. Number and scope of printed materials for the public.

5. Number of educational meetings, courses, workshops, and roundtables.

Funding: activities will be conducted within the framework of regular business activities; funds will be ensured through sponsorship, from EU programme funds, registration fees, and Ministry of Health resources (A734211 Improving healthcare service quality, accounting item 323: HRK 20,000; and A803005 Cooperation with citizens' associations, accounting item 381: HRK 20,000 – for 2015, 2016 and 2017).

5.2. Supporting the Development of Rare Disease Registries and Their Permanent Financing

Objective

To cooperate with the development of a classification and codification system for rare diseases, which would enable the coordination and comprehensiveness of patient healthcare at the national level. This system must be easily upgradeable to the future International Classification of Diseases (ICD11).

To analyse existing systems for rare disease data collection, and promote their operation, development and coordination through Commission activities.

Recommendations:

- work on improving the classification and codification of rare diseases by aligning with international guidelines;
- define quality criteria for rare disease registries;
- establish a monitoring and evaluation method for existing rare disease data collection models;
- examine the possibilities of basic data collection at a national level in cooperation with international projects (EPIRARE, EU Rare Diseases Repository Platform*).*

5.2.1. Measure: Improve Knowledge on Rare Disease Epidemiology

Implementing organisations: Croatian National Institute of Public Health, reference centres, rare disease experts.

Co-implementing organisations: Ministry of Health, Croatian Health Insurance Fund.

Activities:

1. List of rare diseases featured in the ICD10 and its analysis for the Republic of Croatia.

2. Customise information systems for rare disease codification.

3. Develop a system for monitoring rare diseases in the national healthcare system until the application of the ICD11 (obligatory use of ICD10 codes for rare diseases or Orphanet codes) and connect healthcare service payments with the appropriate codes for these diseases.

4. Education and training of healthcare workers on rare disease codification.

5. Support protocols and participate in the activities of codification and classification groups at an international level (e.g. EUROCAT Coding and Classification Committee, etc.).

6. Adopt rare disease nomenclature and classification in accordance with WHO ICD11.

Timeframe:

1. One year after the adoption of the National Programme

2. One year after the adoption of the Ministry of Health decision

3. 6 months after information system customisation

4. Continuous

5. Continuous

6. After the publication of WHO ICD11

Implementation indicators:

1. List of rare diseases featured in the ICD10 is compiled and published on the website of the Croatian Society for Rare Diseases, and the Guidebook for Rare Diseases Registered in ICD10 is published in the Republic of Croatia.

2. Information system for rare disease codification is customised.

3. Annual reports on rare disease codification monitoring via the Croatian Health Insurance Fund system following the decision of the Ministry of Health.

4. Number of organised courses/lectures on rare disease codification.

5. Working group documents.

6. Adoption of regulations.

Funding: activities will be conducted within the framework of regular business activities; funds will be ensured through sponsorship, from EU programme funds, registration fees, and Ministry of Health resources (A788002 Programme of Community Action in the Field of Health, accounting item 371: HRK 50,000 – for 2015, 2016 and 2017; and A A884001 Croatian National Institute of Public Health, 37: HRK 100,000 for 2015, HRK 20,000 for 2016, and HRK 20,000 for 2017).

5.2.2. Measure: Supporting the Development of Rare Disease Registries and Their Financing

Implementing organisations: reference centres, Ministry of Health, Croatian National Institute of Public Health.

Co-implementing organisations: relevant scientific organisations and rare disease organisations, Croatian Society for Rare Diseases at the Croatian Medical Association, Croatian Alliance for Rare Diseases, Croatian Health Insurance Fund.

Activities:

1. Support existing rare disease registries:

    a) mandatory registration of congenital anomalies at all Croatian maternity hospitals (EUROCAT);

    b) Rare Tumour Registry – mandatory registration of rare tumours in the registry.

2. Participate in EU projects – EPIRARE, EURD Registration Repository Platform. Adopting guidelines for the development of a rare disease registry and selection of common data to be collected for all rare diseases at a European level, and registry quality assurance.

3. Regulate financial, ethical and legislative issues related to the functioning of registries – identification of the current status and issues, drawing up proposals.

4. Support new rare disease registries (the establishment of new registries must be preceded by a pilot study and a transparent financial structure that will ensure system sustainability, logistics, and other assistance).

5. Consider the need to create a National Rare Disease Registry.

Timeframe:

1. Continuous

    a) Gradual expansion of registration to all maternity hospitals; coverage of entire territory of the Republic of Croatia (approximately 45,000 births per year) in the three years following the adoption of the regulation

    b) Gradual expansion of registration; coverage of entire territory of the Republic of Croatia in the three years following the adoption of the regulation, gradual networking with compatible European networks

2. In accordance with international project flowcharts

3. Continuous

4. Continuous

5. Issue an opinion three years after the adoption of the National Programme

Implementation indicators:

1. Supporting existing rare disease registries:
    a) Adopting regulations on mandatory registration with existing registries referred to under a) and b);
    b) EUROCAT Croatia – annual reports + % of monitored births in the Republic of Croatia;
    c) Involvement of institutions that monitor and treat patients suffering from rare tumours;
    d) Number of rare tumour patients registered in the Rare Tumour Registry;
    e) Involvement in the international registry network.

2. International project reports, prepared document on the possible establishment of the rare disease registry in the Republic of Croatia, including the financial structure which will ensure its sustainability.

3. Annual reports.

4. New registries for individual groups of rare diseases.

5. Opinion on the need to create a National Rare Disease Registry.

Funding: activities will be conducted within the framework of regular business activities; funds will be ensured through sponsorship, from EU programme funds, registration fees, and Ministry of Health resources (A788002 Programme of Community Action in the Field of Health, accounting item 371: HRK 250,000 – for 2016 and 2017; A A884001 Croatian National Institute of Public Health, 37: HRK 80,000 – for 2016 and 2017).

5.3. Supporting the Activities and Development of a Reference Centre Network and Relevant Scientific Organisations for Rare Diseases

Objective

To improve healthcare services for rare disease patients by ensuring the comprehensiveness, multidisciplinary approach and coordination of those services within the healthcare system.

Recommendations

Due to the low incidence of rare diseases, there are few experts who specialise in them in the Republic of Croatia. The overall knowledge of epidemiology, prevention, diagnostics and treatment options for rare diseases is generally insufficient due to a lack of individual experience. It is therefore necessary to direct both experts and patients to certain reference centres, approved as such by the Ministry of Health pursuant to existing regulations, or to centres that employ experts for treating a specific rare disease or a group of rare diseases.

5.3.1. Measure: Organising and Improving the Activities of Reference Centres and Centres that Employ Rare Disease Experts

Implementing organisations: Ministry of Health.

Co-implementing organisations: Croatian Health Insurance Fund, reference centres and rare disease experts, relevant professional associations at the Croatian Medical Association.

Activities:

1. Appoint a coordinator at the Ministry of Health, and analyse and compile a list of reference centres. Adopt criteria for awarding the title of a rare disease expert – an individual specialising in certain rare diseases which are not treated within the framework of existing reference centres – and compile a list of such experts. Make the list of reference centres and rare disease experts available to the public (on the website of the Ministry of Health, the Croatian Health Insurance Fund, professional associations, and healthcare institutions).

2. Improve the capabilities of human resources and the facilities of reference centres, as well as the equipment for rare disease diagnostics and treatment:

a) Identify HR requirements that can vary from centre to centre, with the option of adopting POLKA project recommendations (Second Programme of Community Action in the Field of Health 2008–2013), as well as EUCERD recommendations (www.eucerd.eu/?post type=document&p=1224).

b) Reference centres must be special units with staff that provide multidisciplinary care to patients.

c) The structure of human resources and the equipment must ensure diagnostics and/or treatment without hindering: education and training at all levels, research, data collection, cooperation with relevant organisations, contact with primary healthcare and social services (HR plans must also include non-healthcare professionals, e.g. social workers, psychologists at genetic counselling centres, etc.).

d) An education and training plan must be drawn up to provide professional training to personnel, which includes education at foreign centres that operate in the same area of expertise.

3. Identify spatial requirements; centres must not be "over-medicalised", and the specific requirements of patients (accessibility for persons with disabilities, adaptation of waiting rooms and treatment facilities, etc.) must be taken into account when organising the centre:

a) Identify further equipment required for high-quality diagnostics of the rare diseases in which the reference centres specialise.

b) Analyse the quality of existing equipment; compile a list of equipment that should be upgraded and draw up a procurement plan for new equipment. Motivate the justifiability of equipment procurement for centres, i.e. the justifiability of conducting diagnostics abroad.

c) Implement the finalised and approved plans for human resources, facilities and equipment.

4. Devise and draw up a plan for the exchange of data on biological samples, visuals and other diagnostic materials between national reference centres for individual rare diseases, and between relevant scientific organisations in other countries. The need for the adoption of relevant regulations should be analysed to that effect.

5. Regularly confer with reference centres on issues related to rare diseases when issuing decisions at the Ministry of Health and the Croatian Health Insurance Fund, especially in cases of treatment with expensive drugs.

Timeframe:

1. Appoint a coordinator at the Ministry of Health, analyse and compile a list of reference centres. Draw up the criteria for awarding the title of an expert for a particular rare disease or group of diseases. Based on clearly specified criteria, compile a list of rare disease experts 12 months after the start of programme implementation.

2. Within 3 months of compiling the list of rare disease reference centres, the reference centres must submit their proposals for human resources, facilities and equipment with relevant justifications. The HR capacities, facilities and equipment of reference centres for the diagnostics and treatment of rare diseases should be gradually upgraded over the following five years, whereby an implementation plan should be drawn up within six months.

3. A system protocol should be drawn up within one year, which would enable the exchange of biological samples, visuals and other diagnostic materials between national reference centres for individual rare diseases, and between them and relevant scientific organisations in other countries. Consider the need to adopt relevant regulations.

4. Within one year, draw up a proposal regulating the obligation of the Croatian Health Insurance Fund to regularly confer with reference centres and centres of expertise when issuing decisions pertaining to rare diseases, their treatment and care.

Implementation indicators:

1. The coordinator at the Ministry of Health has been appointed, and the list of reference centres and rare disease experts has been published.

2. The implementation plan for monitoring HR, facility and equipment upgrades of reference centres for the diagnostics and treatment of rare diseases has been drawn up.

3. A protocol for establishing a system that enables the exchange of biological samples, visuals and other diagnostic materials between national reference centres for individual rare diseases, and between them and relevant scientific organisations in other countries has been adopted.

4. Regulations laying down the obligation of the Ministry of Health and the Croatian Health Insurance Fund to regularly confer with reference centres and centres of expertise when issuing decisions pertaining to the treatment and care of rare disease patients have been adopted.

Funding: within the funding framework for regular business activities.

5.3.2. Measure: Improving the Activities of Rare Disease Reference Centres and Centres of Expertise

Implementing organisations: reference centres, Ministry of Health.

Co-implementing organisations: relevant scientific organisations, Croatian Health Insurance Fund.

Activities:

Reference centres should implement the following activities:

1. Organise the education and training of healthcare and non-healthcare professionals involved in the treatment of rare disease patients. Reference centres should be hubs for meeting and educating patients on rare diseases, as well as for raising awareness of the general public on rare diseases and possibilities for their diagnostics and treatment. Reference centres have an important role in the coordination and networking with primary healthcare services (see priority 5.1.).

2. Tracking rare disease registry data relevant to the disease in which an individual reference centre specialises (see priority 5.2.).

3. Diagnostics and multidisciplinary treatment of rare diseases, whereby one reference centre or centre of expertise can also monitor a group of related rare diseases (for example, rare solid tumours) or larger groups of rare diseases (for example, inherited metabolic diseases in children or adults). Reference centres or centres of expertise should issue decisions on the start of treatment for rare disease patients and conduct regular monitoring of those patients (between follow-up visits, treatment can also be conducted at hospitals closer to a patient's place of residence, in cooperation with experts from the reference centre or centre of expertise). That would put treatment know-how to maximum use and limited financial resources would be spent in the best and most effective ways (see priorities 5.4. and 5.5.).

4. Draw up guidelines and protocols for the treatment and monitoring of rare disease patients.

5. Draw up a proposal for a national rare disease screening programme for the entire population, not just newborns (reference centres and the Ministry of Health – under priority 5.4.3.).

6. Scientific research in the field of rare diseases (also see priority 5.8.).

7. Identify relevant scientific organisations in other countries, especially those in geographical proximity, as complementary partner institutions for Croatian reference centres, and build up close cooperation with them, especially with those specialising in rare diseases about which our reference centres do not have much experience, and join the ERN in accordance with EU recommendations and directives (see priority 5.9.).

Timeframe:

1. Continuous
2. Establish a registry within one year (for <100 cases per year); further development – continuous.
3. Continuous
4. Continuous
5. The outline for the national population screening programme should be drawn up within two years, and its implementation, and monitoring thereof, should start within three years.
6. Continuous
7. Relevant scientific organisations in other countries, especially those in geographical proximity, as complementary partner institutions for Croatian reference centres, should be identified within one year, and close cooperation with them established within two years.

Implementation indicators:

1. Reference centre reports on conducted education and training (i.e. number of lectures, courses, etc.) of healthcare and non-healthcare professionals involved in the treatment of rare disease patients have been published. Reference centre reports on the conducted education of patients (i.e. the number of lectures, courses, etc.) have been published, as well as reports on the number of newspaper articles, radio and television features, websites, articles on web portals, etc. aimed at introducing the general public to rare diseases and possibilities for their diagnostics and treatment (see 5.1.).
2. Data tracking systems/registries of individual rare diseases or groups of rare diseases have been established.
3. Annual reference centre reports on the number of diagnosed, monitored and treated rare disease patients, number of expert opinions issued, etc. have been drafted.
4. The guidelines and protocols for the treatment and monitoring of rare disease patients have been designed in cooperation with relevant professional associations at the Croatian Medical Association and have been published on the website of the Croatian Medical Association, the website of the Croatian Society for Rare Diseases, and in scientific journals.
5. The proposal for the national population screening programme for selected rare diseases (extending beyond newborn screening) has been drawn up.
6. The number of research papers on rare diseases published in one year, the response to journals featuring such papers, and the number of citations of those papers.
7. Annual reference centre reports on cooperation with relevant scientific organisations in other countries have been published.

Funding: activities will be implemented within the framework of regular business activities of reference centres.

5.4. Improving the Availability and Quality of Healthcare (Diagnostics, Treatment and Prevention) for Rare Disease Patients

Objective 1

To provide rare disease patients with quick and easy access to specialist services in order to improve diagnostics and early detection of rare diseases.

Recommendations

- Education and training of family doctors and general practitioners, paediatricians, gynaecologists, medical experts and others on recognising the clinical signs and symptoms of rare diseases and their characteristics.
- Encourage the creation of a list of service providers that offer rare disease treatment, in order to provide general practitioners with clear instructions.
- Improve the scope and quality of national rare disease diagnostics and provide easily accessible international diagnostic routes, if testing cannot be performed in the Republic of Croatia. Improve cross-border cooperation in rare disease diagnostics with the objective of improving diagnostics and reducing costs.
- Ensure genetic counselling for persons suffering from genetic disorders before and after genetic testing.

Objective 2

To improve the diagnostics and treatment of rare diseases that were diagnosed prenatally.

Recommendations

- Adopt prenatal screening guidelines for congenital anomalies.
- Refer pregnant women whose foetus is at risk of developing a rare disease (e.g. suspected bone dysplasia, metabolic disorder, malformation syndrome, etc.) to tertiary centres that offer advanced methods of prenatal diagnosis and treatment, surgical and intensive care departments, and other services that specialise in high-risk newborns, in cooperation with relevant reference centres and genetic counselling centres.

Objective 3

To improve newborn screening programmes and other rare disease screenings.

Recommendations

- Expand newborn screening by introducing the tandem mass spectrometry method and other tests that can detect rare congenital diseases.
- In order to be functional, newborn screening performed in the Republic of Croatia by blood sample analysis needs to continue to be performed centrally, as organised by the Department

for Newborn Screening at the Ministry of Health Reference Centre for Medical Genetics and Metabolic Diseases in Children, part of the Department of Paediatrics at the University Hospital Centre Zagreb, with the aims of ensuring the highest possible quality and curbing costs.

- As proposed by members of the profession, i.e. the Ministry of Health Commission for Newborn Screening, a proposal will be outlined regarding which diseases should be included in the screening and how the screening should be organised. The final decision will be made by the Ministry of Health.
- After the adoption of the Newborn Screening Programme, the Ministry of Health Commission for Newborn Screening will monitor its implementation and publish annual reports and recommendations.
- Newborn screening should be conducted in accordance with the recommendations of EU experts, as specified in the documents "Newborn Screening in Europe - Expert Opinion Document" and "Executive Report to the European Commission on Newborn Screening in the European Union", and in accordance with future European recommendations.
- Adopt a national population screening programme for rare diseases in other age groups.

Objective 4
To improve the availability of drugs and the comprehensiveness of medical care for rare disease patients.

Recommendations

- Involve reference centres and professional associations within the Croatian Medical Association in the process of adopting positions on the availability of rare disease drugs on the Croatian Health Insurance Fund lists.
- Find ways of importing drugs that are not produced in the Republic of Croatia, regardless of profitability for the importer/supplier.
- Ensure treatment abroad for rare disease patients if such treatment is not possible in the Republic of Croatia. Involve reference centres in the assessment of the need for treatment abroad and respect the opinion of those centres.
- Systematically develop rare disease treatment options and the detection of treatable rare diseases as early as possible.

Objective 5

To implement measures and intervention in the field of primary prevention of rare diseases.

Recommendations

- Adopt primary prevention measures that can decrease the incidence of rare diseases, in accordance with international recommendations.

- Prepare and disseminate information on the teratogenic effect of certain substances such as medications, alcohol, cosmetic preparations, and other harmful environmental factors.
- Support existing and develop new programmes for the education of women suffering from chronic diseases such as epilepsy, diabetes and obesity before conception and during pregnancy.
- Support the dissemination of information and performance of interventions aimed at preventing congenital anomalies (e.g. pre-conception administration of folic acid in order to reduce the incidence of neural tube defects and other malformations).
- Foster cooperation with the implementation of international projects on the prevention of congenital anomalies.

5.4.1. Measure: Improving the Availability and Quality of Rare Disease Diagnostics

Implementing organisations: Ministry of Health, Croatian Health Insurance Fund, reference centres, centres of expertise, Croatian National Institute of Public Health, Agency for Quality and Accreditation in Healthcare and Social Welfare, clinical institutes for laboratory diagnostics, Croatian Society for Rare Diseases and other professional associations at the Croatian Medical Association, Croatian Chamber of Medical Biochemists.

Co-implementing organisations: laboratories and other diagnostic centres that perform rare disease diagnostics and are not part of rare disease reference centres or clinical hospitals.

Activities:

1. Education and training of doctors and other experts specified under priority 5.1.1.
2. Develop a database of laboratories that perform cytogenetic, genetic and biochemical diagnostics of rare diseases in Croatia – available on the website (5.2.1.).
3. Include information on Croatian diagnostic laboratories, clinical departments, research centres, and patient organisations in the Orphanet database.
4. Improve diagnostics through a harmonised introduction of diagnostic methods in the Republic of Croatia, where organisationally and economically feasible.

   a) Publish a call for interest for rare disease diagnostics and treatment, with the aim of harmonising the organisation of healthcare in that field.

   b) In cooperation with reference centres, establish a commission at the Croatian Society of Human Genetics that will examine the possibility of expanding the scope of genetic (cytogenetic/biochemical/genetic) testing available in Croatia and, based on the analysis of existing resources and needs, issue a recommendation for future development.

   c) Ensure procedures for the introduction of new tests by the Croatian Health Insurance Fund.

5. Accreditation of laboratories that perform rare disease diagnostics, and quality assurance at a national and (when necessary) international level.

a) Analyse existing laboratories and existing accreditations.

b) Analyse human resources, equipment and facilities of existing diagnostic units, and identify the shortcomings that must be remedied in order for the laboratories to become accredited.

c) Adopt regulations that will lay down the obligation of national and, when necessary, international accreditation of laboratories, and ensure their financing.

6. Ensure that certain tests that are not available in the Republic of Croatia can be performed abroad and ensure that their costs be covered by the Croatian Health Insurance Fund. In consultation with the Croatian Health Insurance Fund, amend the decision-making process on conducting tests and treatment for rare diseases abroad:

a) If a reference centre has indicated a certain test that is performed abroad, the approval procedure must be simplified (no additional expert opinions, since in cases of rare diseases the expertise outside reference centres and centres of expertise is questionable).

b) Analyse and propose the adoption of regulations pursuant to which the Croatian Health Insurance Fund could approve all tests to be performed abroad at a level accessible in clinical practice in other EU Member States, and not just those tests that have an immediate effect on treatment. The position that each patient has the right to the most accurate diagnosis would thereby be adopted. Monitor all activities within the implementation framework of the EU directive on cross-border healthcare.

7. Ensure a valid interpretation of diagnostic test results and, in cases of genetic disorders, ensure mandatory genetic counselling. Genetic counselling must be conducted by educated and trained staff, ideally medical genetics subspecialists, and if such a professional is unavailable, counselling must be conducted in accordance with the recommendations of the Croatian Society of Human Genetics.

a) Analyse the method of issuing diagnostic tests for rare diseases in institutions specified in the list compiled under measure 5.2.1.

b) Include the requirement for an expert interpretation of diagnostic test results and, in cases of genetic disorders, genetic counselling in the national accreditation procedure.

8. Conduct a survey on healthcare services among rare disease patients (the survey would include diagnostics and treatment).

Timeframe:

1. See 5.1.1.

2. See 5.2.1.

3. Continuous

4. Collecting data for the database of rare disease diagnostics and treatment centres within 6 months of the National Programme coming into force, followed by continuous monitoring by way of annual Commission reports.

5. Analysis of the accreditations of existing laboratories and the requirements of diagnostic units in regard to human resources, equipment and facilities – 18 months after the Programme's entry into force; adoption of regulations that will lay down the framework of national accreditation and, when necessary, laboratory accreditation.

6. Under item:

a) Analyse and, when required, adopt appropriate regulations within one year, followed by their continuous implementation.

b) Continuously monitor implementation.

7. Under item:

a) Within one year of compiling the list referred to under measure 5.2.1.

b) When adopting regulations within the framework of a national or international accreditation procedure for a certain genetic laboratory.

8. At the start of National Programme implementation and after 5 years.

Implementation indicators:

1. See 5.1.1.

2. See 5.2.1.

3. Number of laboratories, clinical departments, research centres and organisations included in the Orphanet database.

4. Report of the Commission of the Croatian Society of Human Genetics and reference centres; the number of new diagnostic tests for rare diseases introduced in Croatia, and the number of services approved by the Croatian Health Insurance Fund.

5. Status report on laboratory accreditation and, when necessary, additional harmonisation of regulations on laboratory accreditation.

6. Analysis and harmonisation of amendments to regulations that lay down the decision-making method of the Croatian Health Insurance Fund for covering the costs of diagnostic tests for rare diseases that must be performed abroad.

7. Harmonising regulations on national and international laboratory accreditation.

8. Survey results.

Funding: activities will be conducted within the framework of regular business activities; funds will be ensured through sponsorship, from EU programme funds, registration fees, and Ministry of Health resources (A734211 Improving healthcare service quality, accounting item 323: HRK 100,000 for 2016, and HRK 100,000 for 2017), and by allocation from the Croatian Health Insurance Fund resources.

5.4.2. Measure: Improving the Diagnostics and Treatment of Prenatally Diagnosed Rare Diseases

Implementing organisations: reference centres, centres of expertise, Croatian Society for Rare Diseases and other professional associations at the Croatian Medical Association, Croatian Health Insurance Fund, Ministry of Health.

Co-implementing organisations: laboratories and other diagnostic centres that perform prenatal diagnostics and are not part of rare disease reference centres.

Activities:

1. Develop guidelines for prenatal screening methods that detect congenital diseases. In cooperation with the relevant professional associations at the Croatian Medical Association, adopt guidelines for screening methods and algorithms for processing pregnant women, including biological sampling protocols, when there is suspicion of a particular group of rare genetic disorders.

2. Among relevant professional associations at the Croatian Medical Association, and in cooperation with the Croatian Health Insurance Fund, consider the need to introduce preimplantation genetic diagnostics in the Republic of Croatia.

Timeframe:

1. Continuous

2. Two years after the adoption of the National Programme.

Implementation indicators:

1. Protocols/guidelines for processing and monitoring pregnant women who are at risk of a particular group of rare genetic disorders have been adopted and published on the website of the Croatian Society for Rare Diseases and other relevant associations at the Croatian Medical Association, and have been published in scientific journals.

2. Commission report.

Funding: activities will be conducted within the framework of regular business activities of professional associations at the Croatian Medical Association.

5.4.3. Measure: Improving Newborn Screening with the Aim of Prompt Detection of Rare Diseases

Implementing organisations: Ministry of Health, Croatian Health Insurance Fund, Ministry of Health Reference Centre for Medical Genetics and Metabolic Diseases in Children at the Department of Paediatrics, and the Clinical Institute of Laboratory Diagnosis at the University Hospital Centre Zagreb.

Co-implementing organisations: Croatian Society for Rare Diseases, Croatian Paediatric Society, Croatian Society of Human Genetics and other relevant professional associations at the Croatian Medical Association, Croatian Alliance for Rare Diseases.

Activities:

1. Start of operations of the Ministry of Health Commission for Newborn Screening that will oversee all aspects of the expansion of newborn screening, its implementation and organisation. The activities of the Commission for Newborn Screening would include:

a) gathering relevant documentation, analysis and response on each disease for which screening is conducted or is under consideration, cost-benefit analysis of all aspects of the screening programme;

b) analysis of the relevant bioethical and legal framework of this activity in the Republic of Croatia, in accordance with European recommendations (*Newborn Screening in Europe, Expert Opinion Document, final draft* 3 July 2011; Loeber JG et al. J Inherit Metab Dis, 2012; DOI 10 1007/s10545-012-0483).

2. Adoption of and amendments to regulations on conducting newborn screening in the Republic of Croatia in accordance with the cost-benefit analysis, with the ability to ensure financing for the expanded newborn screening programme.

3. After the adoption of regulations on conducting newborn screening in the Republic of Croatia, the Commission for Newborn Screening will monitor its implementation and publish annual reports and recommendations.

4. Draw up documents to inform the public, maternity hospital staff, pregnant women, mothers, and other interested parties about newborn screening.

5. Publish all screening information on the website in order to make information widely available.

6. Education and training of the staff that will be involved in programme implementation.

7. Analyse the need to employ a medical biochemist and a senior medical biochemistry technician/engineer to work on improving metabolic screening, and their education and training.

8. Networking and aligning screening in the Republic of Croatia with other European and non-European countries, with the aim of establishing mutual assistance in improving the quality of newborn screening.

9. Develop confirmatory tests for positive screening results (second degree tests from the first sample, as well as from subsequent samples).

10. Analyse the need and financing framework for the procurement of another tandem mass spectrometer, which would enable newborn screening to be performed continuously and could also be used for numerous other tests.

Timeframe:

1. In progress

2. After the Commission has issued its opinion and financing has been secured

3. Continuous

4. Continuous

5. Continuous

6. Continuous

7. After the adoption of the expanded programme for newborn screening

8. Continuous

9. Continuous

10. Within 6 months

Implementation indicators:

1. Regular operation of the Commission for Newborn Screening; analyses completed.

2. The regulation on the implementation of newborn screening in the Republic of Croatia has been drawn up and adopted.

3. In accordance with the analysis and the adopted regulation, monitor the implementation of newborn screening

(number of detected patients, number of false positives, number of false negatives, positive predictive test value, estimated decrease in mortality and morbidity) and annual Commission reports.

4. Number and scope of printed materials.

5. Report on the continuous development of the website.

6. Report on conducted education and training.

7. In accordance with the analysis results, meet possible staffing needs.

8. Degree of alignment with other European centres for newborn screening.

9. Second degree tests have been developed.

10. Depending on the analysis, meet the possible need to procure another tandem mass spectrometer; a financing plan has been drawn up in accordance with the analysis.

Funding: Within the funding framework for regular business activities.

5.4.4. Measure: Improving the Availability and Quality of Rare Disease Treatment

Implementing organisations: Ministry of Health, Croatian Health Insurance Fund, Agency for Medicinal Products and Medical Devices, reference centres.

Co-implementing organisations: Croatian Society for Rare Diseases and other professional associations at the Croatian Medical Association, various associations.

Activities:

1. Regulate treatment methods for rare disease patients by making it mandatory, especially in cases involving expensive therapy, to start treatment at reference centres in which the course of the treatment will be periodically followed up and evaluated by a multidisciplinary team of experts with experience in treating rare diseases.

2. Ensure that educated and trained teams of specialists are available at reference centres to implement all measures of patient treatment and rehabilitation (under priority 5.3.).

3. Draw up a proposal for the adoption of a special list of rare disease drugs, providing such drugs would be funded from the budgets of healthcare institutions, in order to make them more available.

4. Monitor healthcare costs related to rare diseases in order to optimise the allocation of available financial resources.

5. Conduct a survey on healthcare services among rare disease patients (the survey would include diagnostics and treatment) (see 5.4.1.8.).

6. Other activities under 5.5.

Timeframe:

1. Adopt the relevant regulation during the first year of programme implementation.

2. Check within the framework of reference centre verification.

3. Adopt the relevant proposal one year after the start of programme implementation.

4. Continuous

5. At the start and at the end of National Programme implementation (see 5.4.1.8.).

6. See 5.5.

Implementation indicators:

1. The relevant regulation has been adopted.

2. This requirement should be featured in the reference centre verification procedure. Thereby, every reference centre that had its status approved would also have had this requirement implemented.

3. The relevant proposal has been adopted.

4. Annual reports.

5. Survey results (see 5.4.1.8.).

6. See 5.5.

Funding: within the funding framework for regular business activities and by allocation from the Croatian Health Insurance Fund resources.

5.4.5. Measure: Improving Rare Disease Prevention

Implementing organisations: Ministry of Health, Croatian Health Insurance Fund, Croatian National Institute of Public Health, reference centres, Croatian Society for Rare Diseases and other professional associations at the Croatian Medical Association.

Activities:

1. Determine the current status of primary prevention of congenital anomalies by joining the international research "Survey of policies in EU Member States on primary prevention of Congenital Anomalies (CA)" - *WP7 Joint Action EUROCAT*.

2. Based on the analysis of results, and in cooperation with professional associations, define the measures for improving primary prevention of rare disorders.

3. Determine the extent of knowledge and the opinions of pregnant women/women in general regarding the possibilities of preventing malformations.

4. Draw up written informational and educational materials on the possibilities of primary prevention of rare disorders.

5. Organise educational meetings, courses, workshops with topics about the possibilities of rare disease prevention for experts and the general public (including schools).

Timeframe:

1. First year of programme implementation.

2. Within two years of obtaining the results of the research referred to in item 1.

3. By the end of 2015

4. Continuous

5. Continuous

Implementation indicators:

1. The results of the research have been published in a report on the international research project.

2. Working group report.

3. The survey has been conducted and its results published.

4. Number of printed informational and educational materials.

5. Number of educational meetings, courses, workshops have been held.

Funding: EU funding (WP7 *Joint Action EUROCAT)*

5.5. Ensuring the Availability of Rare Disease Drugs

Objective

To facilitate the availability of rare disease drugs.

Recommendations

- Make the information on rare disease drugs available to experts and patients.
- Enable new drugs to be administered to rare disease patients in the Republic of Croatia as soon as possible.
- Simplify the procedure of emergency importing of unapproved drugs to the Republic of Croatia, as well as mechanisms that would ensure that the procedure is quick and unobstructed.

5.5.1. Measure: Improving the Availability of Information on Orphan Drugs

Implementing organisations: Agency for Medicinal Products and Medical Devices, Croatian Health Insurance Fund.

Co-implementing organisations: Ministry of Health.

Activities:

1. Create a list of drugs for the treatment of rare and severe diseases, approved in the Republic of Croatia, which have been approved for orphan status in the EU and granted the EU-wide marketing authorisation in the centralised procedure. This list would enable access to information on approved drugs in the Republic of Croatia, as well as access to information on an individual approved drug (Summary of Product Characteristics, Patient Information Leaflet) (www.halmed.hr).

2. Regular monitoring of newly approved drugs and updating of information on the approved drug (Summary of Product Characteristics, Patient Information Leaflet).

3. Monitoring of newly approved drugs and informing the public about them.

4. Cooperation with representatives or applicants in order to establish better communication between the parties concerned (associations – reference centres – applicants – Agency for Medicinal Products and Medical Devices – Croatian Health Insurance Fund).

Timeframe:

From the day of accession of the Republic of Croatia to the EU, all marketing authorisations granted in the centralised procedure for authorising medicinal products in the European Union have automatically become valid for the marketing of those products in the Republic of Croatia, which implies that the European Commission will authorise, publish and update all drug information (EMA).

Implementation indicators:

1. The data in the drug database on the Agency website are regularly updated (www.halmed.hr).

2. The information about the drug approved in the Republic of Croatia is regularly updated (Summary of Product Characteristics, Patient Information Leaflet).

3. Implementation is monitored via database records and annual reports.

Funding: within the funding framework for regular business activities.

5.5.2. Measure: Improving the Availability of Orphan Drugs on the Croatian Market

Implementing organisations: Agency for Medicinal Products and Medical Devices.

Co-implementing organisations: Ministry of Health, reference centres and relevant scientific organisations.

Activities:

1. Give priority to the processing of applications submitted by marketing authorization holders or other natural/legal persons authorised by the marketing authorization holders to be exempt from the obligation of publishing the product identification and patient information leaflet in the Croatian language for the Republic of Croatia. This is implemented for EU-approved orphan drugs when a drug is not

available in packaging in the Croatian language, with the aim of ensuring the availability of the drug for patients.

2. Give priority to the processing of applications for emergency importing of a drug on the basis of a statement issued by a non-EU (third country) hospital. This is implemented when an orphan drug is not approved in the EU, but has been approved in a third country, in order to ensure appropriate availability of the drug for patients.

Timeframe:

1. Continuous

2. Continuous

From the day of accession of the Republic of Croatia to the EU, all marketing authorisations granted in the centralised procedure for authorising medicinal products in the European Union have automatically become valid for the Republic of Croatia.

Implementation indicators:

1 and 2 – implementation is monitored by keeping records of the time required to process a marketing authorisation application/market a drug/process an emergency import application.

Funding: within the funding framework for regular business activities.

5.6. Improving the Obtainability of Social Welfare System Rights for Rare Disease Patients

Implementing organisations: Ministry of Labour and Pension System, Ministry of Social and Youth Policies.

Co-implementing organisations: Croatian Alliance for Rare Diseases, reference centres and centres of expertise, social welfare centres.

Activities:

1. Inform rare disease patients about the conditions and methods for obtaining social welfare system rights.
2. Develop support services in local communities.
3. Include rare disease experts in the list of experts for first-degree expert evaluation authorities.
4. Participate in the education and training of experts/members of first-degree expert evaluation authorities and employees of social welfare centres.
5. Ensure the active participation of patient organisations in the adoption of decrees and acts.

Timeframe: continuous.

Implementation indicators:

1. Availability of information; number of workshops, seminars, education and training courses that were held.

2. Number of requests for assistance granted and services provided.

3. The proposal for appointing rare disease experts to be included in the list of experts for first-degree expert evaluation authorities has been submitted.

4. Report on conducted education and training of experts/members of first-degree expert evaluation authorities and employees of social welfare centres.

5. A questionnaire has been given to patients; new decrees and acts have been adopted in cooperation with patients and the Croatian Alliance for Rare Diseases.

Funding: within the framework of regular business activities.

5.7. Empowering Rare Disease Patient Organisations

Objective

1. To inform patients and their families, raise awareness and improve knowledge about rare diseases, and provide assistance to patients and their families.

2. Cooperate with reference centres and participate in the implementation of National Programme activities.

3. Assist and inform patients about healthcare, social welfare, and psychological care rights.

Recommendations

– Pursuant to the conclusions of the 1st and 2nd National Conference on Rare Diseases (2010 and 2011), organised under the EUROPLAN project and EURORDIS (a member of which, the Croatian Alliance for Rare Diseases, is the umbrella organisation for rare diseases in the Republic of Croatia), the key role of patient organisations in resolving the specific needs of rare disease patients and their families has been established. The conclusions highlight the need for cooperation and networking of organisations, specialist doctors, and reference centres.

Implementing organisations: Croatian Alliance for Rare Diseases.

Co-implementing organisations: Ministry of Health, Ministry of Social and Youth Policies, Ministry of Science, Education and Sports, faculties of medicine.

Activities:

1. Bringing together rare disease patient organisations and rare disease patients.

2. Cooperation and partnership with reference centres and the network of rare disease specialists.

3. Cooperate with rehabilitation centres to ensure inclusion of rare disease patients.

4. Cooperate with social welfare centres to ensure the rights of rare disease patients.

5. Organise the programme for the accommodation and transport of patients and their families for the purpose of visiting reference centres, if distant from the place of residence.

6. In cooperation with the Croatian National Institute of Public Health, compile a list of rare disease registries.

7. Launch the Croatian Helpline, in cooperation with reference centres and EURORDIS.

8. Organise the certification of the Helpline, in cooperation with the Centre for Palliative Medicine, Medical Ethics and Communication Skills (CEPAMET) at the University of Zagreb School of Medicine.

9. Education and training of member organisations/patients to enable them to get actively involved in the decision-making processes related to rare disease issues.

10. Participate in the implementation of measures planned under the National Programme.

11. Gather experiences acquired and issues encountered by patients and their families.

12. Organise psychological help in cooperation with reference centres, and

13. Cooperation with the Office of the Ombudsman for Persons with Disabilities.

14. Socialisation of patients through patient organisation programmes.

15. Raise public awareness:

- Introducing patients and their families, as well as the general public, to the National Programme.

- Celebrating Rare Disease Day and organising the annual conference.

- Creating educational materials and therapy tools in cooperation with experts.

- Expanding the website with a database of reference centres and specialists to facilitate the referral of patients to certified centres.

- Expanding the web portal www.rijetke-bolesti.hr – healthcare professionals and patients by way of targeted public health campaigns.

- Presenting the National Programme at an international level, in cooperation with EURORDIS and other international rare disease organisations.

16. International cooperation: Orphanet, EURORDIS, cross-border cooperation with organisations and institutions.

Timeframe: continuous.

Implementation indicators:

1. Annual reports that will include:
   - an overview of the number of organisations and projects;
   - the number of signed partnership agreements;
   - web portal news.
2. The Helpline has been launched.
3. The number of education and training courses/lectures held in cooperation with institutions and organisations (national and international).
4. Rare Disease Day has been organised.
5. The annual conference has been organised.

Funding: within the funding framework for regular business activities, from EU programme funds, from budget funds allocated for calls for tenders published by organisations (A 803005 Cooperation with citizens' associations, accounting item 381: HRK 30,000 – for 2015, 2016 and 2017).

5.8. Fostering Scientific Research of Rare Diseases

Objective

To foster research in the field of rare diseases and the quick transfer of knowledge and findings into clinical practice with the aim of improving diagnostics and patient treatment.

Recommendations

- Foster initiatives for epidemiological, clinical, basic and translational research in the field of rare diseases.
- Give priority to rare disease research and foster national and international projects in that field.
- Improve and maintain the necessary infrastructure for rare disease research.
- Stimulate reference centre networks and relevant scientific organisations to research rare diseases and coordinate their efforts in that field.

Implementing organisations: Ministry of Science, Education and Sports, Ministry of Health.

Co-implementing organisations: Croatian National Institute of Public Health, Croatian Science Foundation, reference centres and relevant scientific organisations.

Activities:

1. Create a national network of scientists working on rare disease issues (identify and list scientific teams and projects).

2. Identify existing national research programmes in the field of rare diseases – basic, translational, clinical, public health, and social research.

3. Ensure that the scientific programmes on rare diseases can be easily identifiable in wide-ranging national programmes.

4. Regularly update the list of existing and new scientific programmes on rare diseases.

5. Assist the Ministry of Science, Education and Sports in equipping reference centres and other research centres that conduct rare disease research.

6. Specific programmes of financing and/or including young scientists/junior research assistants in rare disease projects.

7. Coordination of rare disease research programmes at a national level and networking with other national programmes in the EU.

8. Initiatives for supporting international scientific projects on rare diseases (E-rare, Rare Connect, IRDiRC, Horizon2020, ERIC).

Timeframe:

1. Establish a national network of scientists involved in rare disease research one year after the adoption of the National Programme.

2. Compile a list of existing national research programmes on rare diseases one year after the adoption of the National Programme, evaluate them, and adopt a plan for their financing within the following 6 months.

3. 6 months after compiling the list of research programmes on rare diseases.

4. Continuous

5. Within one year of compiling the list of national research programmes on rare diseases, draw up a plan for financing scientific equipment in accordance with the recommendations of programme managers.

6. Draw up a programme for financing and including young scientists in rare disease projects one year after compiling the list of national research programmes.

7. 18 months after compiling the list of national research programmes.

8. Draw up a proposal for initiatives 18 months after the adoption of the National Programme.

Implementation indicators:

1. The list of scientists involved in rare disease research has been compiled.

2. The list of research projects/programmes on rare diseases has been compiled.

3. The system for the identification of rare disease projects within national programmes has been created.

4. Lists referred to in items 1 and 2 are updated annually.

5. The plan for including and financing young scientists/doctoral candidates in projects/programmes from the list referred to in item 2 has been drawn up.

6. Annual reports of the coordination committee.

7. The proposal for initiatives has been drawn up.

Funding: from regular funds.

5.9. International Networking and Cooperation in the Field of Rare Diseases

Objective

– To network with other European countries in the professional field, in scientific research and in the activities of rare disease patient organisations.

Recommendations

- Cooperation in the professional field;

- Cooperation between organisations;

- Cooperation in scientific research.

Implementing organisations: Ministry of Health, Ministry of Science, Education and Sports, reference centres and relevant scientific organisations, Croatian Alliance for Rare Diseases, the Commission.

Co-implementing organisations: Croatian Health Insurance Fund, Croatian National Institute of Public Health.

Activities:

1. Bring the National Plan into line with European recommendations and documents (EUROPLAN, EPIRARE, EUCERD).

2. Maintain existing networks and cooperation in the field of rare diseases (see 4.10.), as well as inclusion in other European networks (ERN, IRDiRC, ECRIN, www.ecrin.org/,etc.).

3. Cooperate with other countries (at the level of ministries, reference centres and centres of expertise, associations) in order to maintain a common infrastructure, share expenses, ensure maximum efficiency.

Timeframe: continuous.

Implementation indicators:

1. Adoption of the National Programme in line with the guidelines of the EUROPLAN I and II projects, alignment with the recommendations of the EPIRARE project, adoption of EUCERD guidelines (reports by Croatian representatives, to be reviewed by the Commission).

2. Drawing up of a list of existing cooperation networks; annual reports on international cooperation issued by reference centres, relevant scientific organisations, and associations. Periodic review of the list of international networks and its expansion (the Commission).

3. Ministerial initiatives and reports by reference centres and centres of expertise on the establishment and development of cooperation.

Funding: within the funding framework for regular business activities.

6. Funding

The funds for the implementation of the National Programme for Rare Diseases 2015–2020 have been allocated in Division 096, Title 05 – Ministry of Health: for activities A734211 – Improving healthcare service quality (HRK 50,000 for 2015; HRK 150,000 per year for 2016 and 2017), for activities A803005 – Cooperation with citizens' associations, expenditure group 38 – other expenditures (HRK 100,000 per year from 2015 to 2017), for activities A788002 Programme of Community Action in the Field of Health, expenditure group 37 – benefits to citizens and households on the basis of insurance and other benefits (HRK 50,000 for 2015, HRK 300,000 per year for 2016 and 2017); and in Division 096, Title 25 – Institutes, agencies and other budget beneficiaries, RKP 26346 – Croatian National Institute of Public Health: for activities A884001 – Croatian National Institute of Public Health, expenditure group 37 – benefits to citizens and households on the basis of insurance and other benefits (HRK 100,000 per year from 2015 to 2017) for the activities of the Croatian National Institute of Public Health in this field. The Ministry of Health will also allocate the funds required for Programme implementation in Division 096 for the period from 2018 to 2020.

The funds for the implementation of the National Programme for Rare Diseases 2015–2020 have been allocated under the Financial Plan of the Croatian Health Insurance Fund, as an extra-budgetary beneficiary, for the 2015–2017 period as follows: HRK 360,389,000 for 2015, HRK 362,190,945 for 2016, and HRK 364,001,900 for 2017.

The total funds for the implementation of the National Programme for Rare Diseases 2015–2020 amount to HRK 360,689,000.00 for 2015, HRK 362,840,945.00 for 2016, and HRK 364,651,900.00 for 2017.

7. Conclusion

Although they have low prevalence, rare diseases have a significant impact on the quality of life of individuals and their families and, in overall terms, on the morbidity and mortality of the population, which is why they are classified as healthcare priorities at both EU and national levels.

The high level of complexity of these disorders requires a global approach, which includes well-coordinated actions at European, national and regional levels, as well as joint efforts to foster the spreading of knowledge, diagnostics, prevention and treatment and research options in the field of rare diseases. Furthermore, due to the high social burden they entail, rare diseases require coordinated activities and the development of social services and patient organisations.

With the National Programme, the Ministry of Health – in cooperation with other state administration bodies, healthcare institutions, the Croatian Health Insurance Fund, in partnership with the medical profession and civil society organisations – seeks to meet the needs of rare disease patients in the Republic of Croatia, in accordance with EU recommendations. This Programme integrates nine strategic activity areas, including the education and information of experts, patients and the general public, prevention and early detection of rare diseases, integrated healthcare and social welfare, and fostering research in the field of rare diseases.

The document presents a series of objectives and recommendations on how to contribute to the improvement of healthcare service quality in the field of rare diseases with a rational use of resources. It is based on available information and scientific advances in the field, clinical expertise and ethical principles for ensuring equal healthcare levels for all citizens of the Republic of Croatia.