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Rare Diseases and Orphan Drugs Accessibility in Bosnia and Herzegovina

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ABSTRACT

Introduction: Rare diseases are becoming more and more important since awareness is increasing. There are a lot of initiatives to ensure access to orphan drugs intended to treat these diseases but due to high price patients have low access and policy makers and payers are struggling with costs and assuring patient access rights to the available medication. **Aim:** Objective of this study is to assess current situation regarding rare diseases in Bosnia and Herzegovina (BiH) and availability of orphan drugs. Four domains are examined: legislation and policy, diagnostics and research, patient organizations and reimbursement and availability of medicines for rare diseases. **Results:** There are official programs and legislation ground for rare diseases in both entities of BiH: Republic of Srpska (RS) and Federation of BiH (FBiH). Diagnostic and genetic counseling are available but only for few rare diseases. Patient organizations are formed and active but still without engagement in some of international organizations. There are no special reimbursement criteria for orphan medicines. Number of reimbursed medicines is significantly lower than those on ORPHANET list, 67 and 26 in RS and FBiH respectively. Huge difference in number of reimbursed medicines within the country entities may be consequence of counting method. **Conclusion:** Even thou rare diseases in BiH are recognized in countries official programs and documents, with patients having their organizations, much more have to be done in availability of medicines and diagnostics in the rare disease field. Insufficient funds are huge obstacle toward this goal. New methods of medicine evaluation are need and recommended in order of better availability.

Key words: Rare diseases, orphan drug, health policy, pharmacoeconomic.

1. INTRODUCTION

Rare disease by its definition is a disease that affects less than 1 in 2000 people (1). Despite the fact relatively small number of patient for each of rare disease diagnosed, with the 6.000-8.000 known rare diseases, the number of patient in Europe reaches over 30 million by now or 6-8% of the total population (2). Most of those diseases are life threatening, debilitating, without proper cure and with demanding diagnostics. On the other hand, with small number of patients for each of diagnosis and a high costs for research and development of new treatments, there is a lack of interest from the commercial point of view. Generally there is a limited public awareness of rare diseases. In recent years, there are many initiatives on European and international level to foster and support research and development of medicines for rare diseases, as well as to establish proper legal framework enabling people suffering from those diseases better health care, following principles of quality and equality (1). Bosnia and Herzegovina is one of those countries trying to find its way to that common goal. BiH is low populated, low income and highly decentralize country. It constitutes of two entities, Republic of Srpska (RS) and Federation of Bosnia and Herzegovina (FBiH). Republic of Srpska has centralized health system with one Ministry of Health (MoH) and one Health Insurance Fund of Republic of Srpska (HIFRS). All drugs are reimbursed through HIFRS, by listing or individually reimbursement. On the other hand, FBiH has 10 cantons, each with its own MoH and HIF. Above them is Ministry of Health of Federation of Bosnia and Herzegovina (MoHFBiH). MoHFBiH adopts essential list of medicines, obligatory for each of cantons. Also, under MoHFBiH is Solidarity Fund. Solidarity Fund reimburses expensive and new therapies and medicines. Finally, on state level there is Council of Ministers where Minis-

try for Civil Affairs is responsible for health and supervises and controls the work of Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina (ALIMS BiH) (3). ALIMS BiH is the only focal point for health systems of two entities. In this quite complex health system (Figure 1) we will try to give an overview on current status of rare diseases. Because of simplicity and better understanding, situation will be separately explained for Republic of Srpska and Federation of Bosnia and Herzegovina. In two entities rare disease theme will be considered in four different domains: legislation and policy, diagnostics and research, patient organizations and reimbursement and availability of medicines.

2. METHODS

We have used different source of information to evaluate situation in the field of rare disease in Bosnia and Herzegovina. Literature review has been made for gathering already published information. Government's web-sites and official initiatives are also included in the search along with announcements published in Official Gazettes. To compare results with other countries and European legal framework, literature review has been made again. Web sites and documents of European Medicine Agency, ORPHANET and EURORDIS were searched also.

3. RESULTS

LEGISLATION AND POLICY

Republic of Srpska

Republic of Srpska program for rare diseases for period 2015-2020 was written by the Ministry of Health and Social Welfare (4). Legal ground for the Program is based on Council of Europe (CE) Recommendations from 2009 on an action in the field of rare diseases (1). Recommendations of the CE are based on the documents and recommendations they have adapted: European Multidisciplinary Group Commission, the DG SANCO Task Force on Rare Diseases,ORPHANET project and EURORDIS (5, 6, 7). Wider initiatives includes European project for development of national programs for rare diseases (EUROPLAN) which is part of European Community Action in the field of rare diseases (7). Legal framework in RS includes Health Protection Law, Health Insurance Law and Policy of improving people health status in Republic of Srpska until 2020 (8-14). Within the Program Minister of Health appoints Coordinator for rare diseases in RS. Committee for rare diseases is also appointed by Minister and coordinates all activities in the field of Program. Coordinator and Committee are appointed on the four year period. Implementation of the program includes further activities: planning and allocation of financial recourses for the purpose of early detection, prevention, treatment and rehabilitation of persons with rare disease; advancing the level of knowledge and professional capacities of medical doctors in the field of prevention and early diagnostics of rare diseases; creation of network for rare diseases; establishing register of patients with rare disease; establishing and/or advancing screening for risk for rare disease; monitoring of treatment success, increasing the number of highly specialized personnel in the field of clinical genetics; to ensure valid pre-testing information about genetic testing; to establish and timely refresh the list of expert medical centers for rare diseases; to support work of non-government and other patient organizations in the field of rare disease; to provide participation in the project European network for rare diseases; to establish close international cooperation with other expert and research centers outside the country (4). Realization of the Program goals is very much depending on the available financial resources, and due budget constrains in recent years, some of the goals are left unrealized so far or are falling behind planed schedule.

In October 2017, a proposal of Law on Solidarity Fund for diagnosis and treatment of diseases, conditions and injuries of children abroad was adopted in the National Assembly of the Republic of Srpska. This law established a Solidarity Fund for the purpose of treating ill children abroad who are unable to receive adequate health care services in the RS to countries with health facilities where treatment is possible. Also, this law could be of importance in the treatment and diagnostics of rare diseases (15).

Federation of Bosnia and Herzegovina

The commitment of BiH or its Entities to accession to the European Union (EU) *inter alia* implies the adoption of a legal framework that treats rare diseases in a special way. Thus, the Strategy for rare disease in Federation of Bosnia and Herzegovina (2014-2020) was adopted in 2014, based on the principles, goals, regulations and instruments applicable in the European Union area. The strategic framework for rare diseases of the FBiH is a clear commitment of the competent authorities to address the need for action in the field of rare diseases, defining the priority objectives and actions (20). As noted, there are no adequate epidemiological data on rare diseases in the FBiH due to the inadequate application of the International Classification of Diseases (MK-10) and the lack of systematic access to these diseases. Until the adoption of this document, the Federation of B&H did not have a strategic document as well as an action plan for rare diseases, and consequently no special, planned budget for the overall treatment of people with rare diseases.

Also, there is no uniform system for the registration of rare diseases, nor list or register of rare diseases. The existing legal framework needs to be further improved in order to ensure adequate access to rare diseases, and the mentioned Strategy is an important part of this framework. Current legislation, that could be solid base for further development includes:

The Strategic Health Development Plan of the Federation B&H 2008 - 2018. The overall strategic goal is to improve the accessibility, quality and efficiency of health care of the population, driven by increased solidarity and reducing inequalities (21).

The Strategy for Sexual and Reproductive Health and Rights in the Federation of Bosnia and Herzegovina, adopted by the Government of the Federation of Bosnia and Herzegovina. In postpartum protection, it is important to provide prevention, early detection and treatment of complications of both mothers' and children's diseases.

Strategic Plan for Promoting Early Growth and Development of Children in the Federation of B&H 2013-2017 aims at an integrated approach to the health, education and

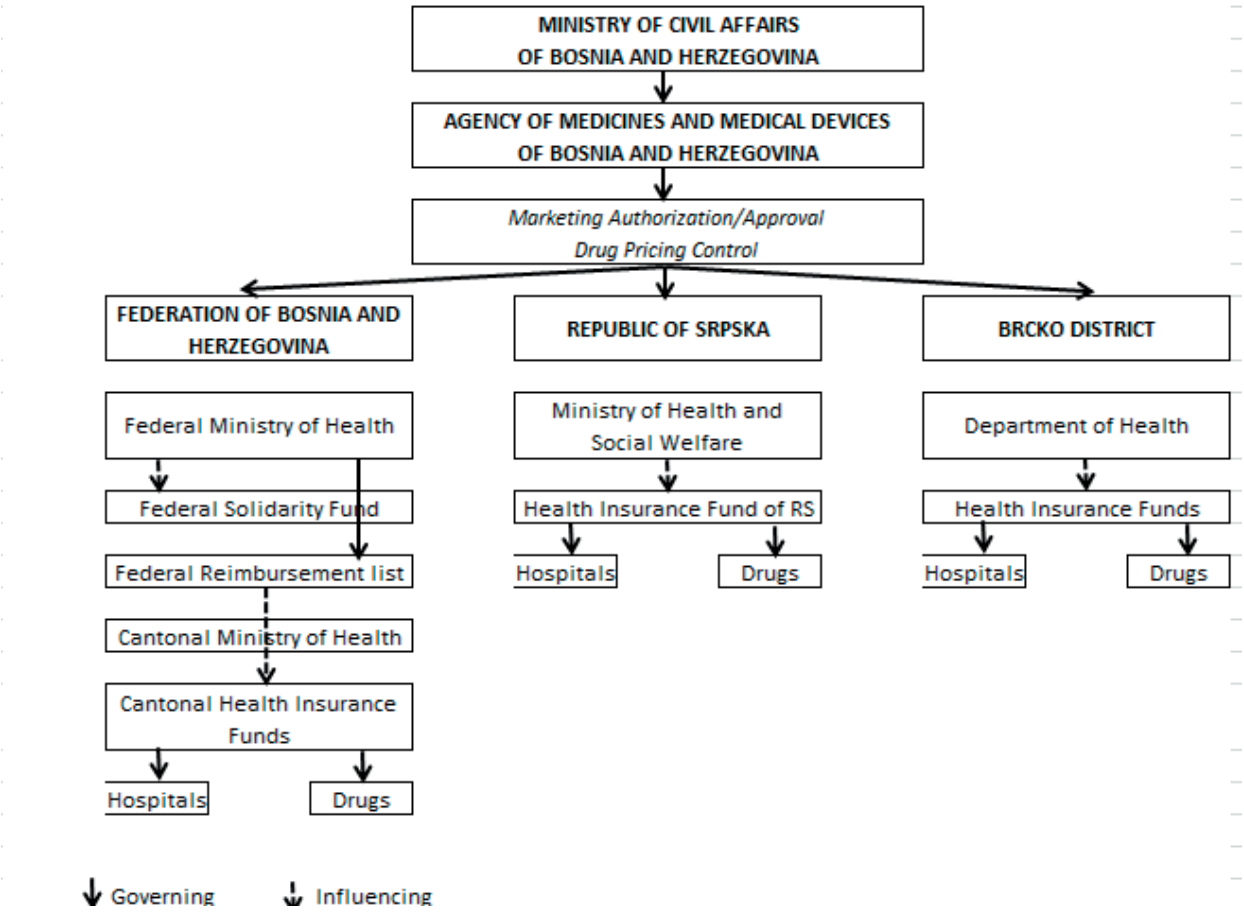

Figure 1. Overview of main stakeholders in healthcare system in Bosnia and Herzegovina

social protection sectors, among other things, to improve accessible and quality services for future parents, during pregnancy and childbirth, newborns, and to stimulate the proper growth and development of children, with special emphasis on children up to three years as well as early detection and intervention.

Within the health system reform, and based on the Strategic Health Development Plan for the period 2008-2018, a whole series of laws and regulations have been adopted that represent a significant step forward in terms of improving health care.

According to the Law on Health Records, there are clear legal grounds for the establishment of special registers in the field of rare diseases and according to the needs of the FBiH.

DIAGNOSTICS AND RESEARCH

Republic of Srpska

In past 30 years in RS there is diagnostics of chromosome anomalies and screening on phenylketonuria (first occasionally than regularly). Since 2004 there is screening of hearing in newborns, and since 2007 neonatal screening on hypothyroidism. Genetic counseling department is opened 2009 in University clinical center of Republika of Srpska (UKCRS) and prenatal diagnostic of chromosome anomalies has started. Biochemistry screening of pregnant woman on most common chromosome anomalies and search for the risk of congenital anomalies and genomic diseases in pregnancy are conducted since 2010 (4). The Center for Rare Diseases is opened in 2015 and 330 patients has been registered so far and 130 different diseases have been identified. Unfortunately, a large number of rare diseases we cannot confirm in our diagnostic center and such patients are sent abroad. The European Association for Hemophilia and Blood Coagulation Disorders at the end of June 2017 awarded a certificate to the Department of Children's Hematooncology of UKCRS, which is now included in the European map of the centers for the treatment of hemophilia and is the only such center in B&H (16).

Federation of Bosnia and Herzegovina

The Federation of B&H does not own a specialized center for rare diseases, but within certain healthcare facilities, however, there are provided conditions for risk search and diagnostics for a smaller number of rare diseases, especially at tertiary level of health care.

The Federation of B&H, in clinical healthcare facilities, has medical and technical conditions for screening for congenital hypothyroidism, phenylketonuria and adrenal hyperplasia, cystic fibrosis, Pompea's disease, screening of fruits on chromosomal aneuploids, as well as the possibility of prenatal and postnatal standard karyotyping.

At major clinical centers there is genetic information services (counseling) introduced. However, there are no laboratories for diagnosing or screening metabolic disorders, as well as routine diagnostics of micro delivery syndromes and molecular genetics diagnosis. Although there are resources and professional staff, the introduction of new diagnostic methods is limited by the lack of development plans and programs, based on the real needs and financial

INN	List of medicines Federal Solidarity fund	Orphan designation in EU	Without orphan designation but intended for orphan diseases in EU
temozolomide	X		X
mercaptopurine	X		X
capecitabine	X		X
docetaxel	X*		X
imatinib mesilate	X		X
filgrastim	X		X
rituximab	X		X
trastuzumab	X		X
bevacizumab	X*		X
erlotinib	X*		X
sunitinib malate	X		X
sorafenib tosylate	X	X	X
pemetrexed	X		X
nilotinib	X	X	X
everolimus	X	X	X
octocog alpha	X		X
eptacog alpha	X		X
adalimumab	X		X
bosentan	X		X
azacitidine	X	X	X
paclitaxel	X		X
brentuximab	X	X	X
pazopanib	X		X
axitinib	X		X
bortezomib	X		X
lenalidomide	X	X	X

*not indicated for orphan disease

Table 1. Overview of orphan drugs reimbursed in Federation of Bosnia and Herzegovina with or without orphan designation in EU. Cross comparison with Orphanet list 2017

estimates of the health system in the Federation of B&H. It is important to emphasize that there are institutions in the Federation of Bosnia and Herzegovina that have developed infrastructure in the technical and personnel sense for the implementation of genetic diagnostics, which are not part of the health system, and are therefore not financed from the mandatory health insurance funds. The services of such institutions are, for the aforementioned reasons, difficult to access or unavailable to patients.

PATIENT ORGANIZATIONS

Republic of Srpska

Alliance for rare diseases of Republic of Srpska (Alliance) is founded in April 2015. Initial financial recourses are gathered via charity auction organized by Prime Minister of Republic of Srpska. Later, next year, another charity has been organized to raise funds to treat rare diseases and to support the work of the Alliance. This time the initiator of the event was President of the Republic of Srpska. Alliance gathers 185 families with rare and ultra-rare diseases and four patient's societies: societies of patients with cystic fibrosis, phenylketonuria and hyperamoniemia, hemophilia and mucopolisaharidosis. They are also founding societies of the Alliance. Work and goals of the Alliance are very much based on the Program for rare diseases. So far there is no adequate register of patients with rare disease, nor the register of so far diagnosed rare diseases. So, the Alliance creates its own database of patients and diagnosed rare disease which is supposed to rely on official register when it becomes fully operational according to Program goals. It operates on whole territory of RS giving the patients opportunity for networking, information exchange and mutual support. One of the activities is to organize campaigns and raise awareness in general population about rare diseases, change the attitude of society toward patients with rare disease. In 2016 it was granted status of ''Society of Public Interest''. Alliance started to publish its own educational journal about rare diseases in January 2017. Along with similar societies in nearby countries, Serbia and Croatia, it organizes different events during the ''Rare Disease Week'' in February. So far, Alliance, neither any of its Societies, is not the member of any European or International society in the field of rare diseases (17).

Federation of Bosnia and Herzegovina

Patient organizations play important role in Federation of Bosnia and Herzegovina, as well as on the national level as shown in a study conducted by Nongovernmental organization Asocijacija XY in 2013 and supported by EU Commission fund (22). This study showed that the cooperation of user associations with relevant health institutions in B&H with a view to improving the provision of support to affected persons and their families in exercising the rights from the scope of health and social protection is particularly important. Patient organizations through their work provide support and assistance to the patients and their informing and sensitizing the public about rare diseases, etc. They have organized their own ways of working and acting in accordance with the health care system, and operate at the following levels: state, entity, cantonal and local. The research has shown that patient organizations in FBiH have more organized organizational potentials than the associations from the RS, in terms of defined long-term and short-term goals, mission and clear division of work and responsibilities within the association, so they have greater opportunities to help their members. More importantly, it has a role to play cooperation with related associations in the country and abroad, that usually has more developed program of their work and represent a significant source of experience and good practice. This also points to the usefulness of networking on the state and international level, in order to systematically address the problems of this population, focusing on advocacy at all levels of government in B&H.

REIMBURSEMENT AND AVAILABILITY OF MEDICINES

Republic of Srpska

We have crossed-over HIFRS medicines lists with ORPHANET list of medicines for the treatment of rare diseases with and without orphan designation and with marketing authorization in order to define availability of medicines for rare disease in Republic of Srpska (18,19). Of 158 branded

medicines for the rare diseases treatment but without orphan designation from ORPHANET list, in RS 67 medicines are reimbursed, which accounts for 42%. When it comes to medicines with orphan designation of 98 medicines on ORPHANET list only 7 medicines are reimbursed in RS, or less than 7%. Also, there are no special criteria or recognition of orphan designation when it comes to reimbursement process criteria. Orphan medicines are reimburses with the same reimbursement process as any other medicine (19).

Federation of Bosnia and Herzegovina

Based on regulations in the field of health insurance, all children in the FBiH are guaranteed the right to health insurance. The existing legal framework, in the broader sense, also applies to certain rare diseases. It is important to note that, in addition to the possibility of treating rare diseases from compulsory health insurance in the FBiH (hemophilia, phenylketonuria, cerebral palsy, multiple sclerosis etc.), by adopting the Ordinance on conditions and procedures for the transfer of insured persons to treatment abroad, it is also possible to refer abroad to diagnose and treat certain rare diseases, both children and adults. Pursuant to the aforementioned regulations in the Federation of Bosnia and Herzegovina, funding for screening of all children on phenylketonuria, congenital hypothyroidism and adrenal hyperplasia is funded.

In April 2017, The House of Representatives of the Parliament of the Federation of Bosnia and Herzegovina has adopted an initiative for establishing a fund for treatment abroad of patients from the FB&H who are suffering from rare and other diseases (23). Pursuant to the Health Insurance Act, the Solidarity Fund of the FBiH (Federal Solidarity Fund) was established in 2002 with a aim to achieving equal conditions for compulsory health insurance in all cantons, certain priority health care programs of interest to the Federation, and to provide the most critical forms of health care from certain specialist activities (24). This provides funding for the treatment of the most serious illnesses for all insured persons in the Federation of B&H under the same conditions, regardless of the cantonal affiliation of the patients and the financial strength of cantonal health insurance institutions. The funds of the federal Solidarity Fund are secured from contributions for compulsory health insurance and partly from the funds of the Federation B&H budget through transfer of the Federal Ministry of Health.

Funds from the Solidarity Fund are funded:

- Services of the Solidarity Fund as defined in the Solidarity Fund Service List.
- The Solidarity Fund drugs listed in the Decision on the List of Drugs of the Solidarity Fund.
- Treatments abroad in accordance with the Regulations on Treatment Abroad.

Previous studies on access and availability of orphan drugs in Federation of Bosnia and Herzegovina showed low access comparing to EU countries and even neighboring countries like Serbia and Croatia. Only one drug with orphan designation has been available through public financing by Solidarity fund in Federation of Bosnia and Herzegovina (25). We have compared latest Solidarity fund list of reimbursed medicines published in 2016 with ORPHANET list of medicines for the treatment of rare diseases with and without orphan designation and with marketing authorization in order to define availability of medicines for rare disease in Federation on Bosnia and Herzegovina (26, 18). We have identified only 26 medicines intended for rare disease treatment but without orphan designation in EU reimbursed in Federation of Bosnia and Herzegovina, of which 3 are not reimbursed for orphan disease indication. There is no special process for reimbursement of orphan drugs in Federation of Bosnia and Herzegovina since this therapeutic class is not recognized, so the same reimbursement approval process apply like for all other drugs. Detailed overview of available orphan drugs is given in Table 1.

4. DISCUSSION

Development and adoption of the national plans for rare diseases in both entities in B&H were important initial steps towards improving situation in this field. There is currently official designated center for rare disease only in Republic of Srpska but not in Federation of BiH. Both entities still does not create specific register for rare diseases, so making it impossible to fully collect and evaluate information on rare diseases. Newborns are screened for only two rare disorders phenylketonuria and congenital hypothyroidism. Unfortunately, in our country there is no research incentive for rare diseases. So far, neither any of societies for rare disease in both entities, are not the member of any European or International society in the field of rare diseases. Orphan drugs are authorized through the EMA centralized procedure, but there is also a domestic procedure for marketing authorization in BiH. For the medicines that have already been registered via the centralized procedure, domestic procedure for authorization is expedited, according to the Law on Medicines and Medical Devices (3). Orphan drugs in BiH are reimbursed with the same reimbursement process as any other medicine. In FBiHorphan drug financing is done by federal Solidarity Fund.

Like in both entities of our country, national register for rare diseases in nearby Serbia still does not exist. Law on Healthcare provides for the forming of the official center of reference for rare diseases that have the obligation of diagnosing, treatment and patient counseling. The MoH of Serbia plans to create a register by the end of 2017. Neither policy measures, nor research incentives for rare diseases exist in Serbia. The National Organization for Rare Diseases of Serbia (NORBS) was established in 2010. Since neither Serbia nor Bosnia and Herzegovina are members of EU we still do not have representatives in the European Committee for Orphan Medicinal Products (COMP). National Organization for Rare Diseases of Serbia (NORBS) is a part of the European Organization for Rare Diseases (EURORDIS) that has its representatives in the COMP. Registration procedure of orphan drugs is similar like in our country. In Serbia it is stated that there are no fees for authorization of orphan drugs and that orphan drugs may be conditionally registered until the marketing authorization holder has met all obligations. Orphan drugs in Serbia are reimbursed by Health Insurance Fund, funded through the payment of health insurance contributions. Additionally, a special fund has been created to reimburse medical expenses for rare diseases that are not reimbursed by the Health Insurance

Fund. This Fund is provided by the Health Insurance and by the Games of Chance Act as of 2011 in which it is stated that one part of the budget revenue of the Republic from game winnings taxes will be used for funding the treatment of rare diseases (27).

In Latvia (EU member state), the national plan for rare disease was adopted in 2013 (28). Like in our country,according to the data from 2014 they still do not have a specialized center for rare diseases or a register of patients with rare diseases. Newborns are screened for only two rare disorders, phenylketonuria and congenital hypothyroidism. Some prenatal and postnatal diagnostic tests for rare genetic diseases are financed by the National Health Service including cytogenetic analysis, genetic biochemical analysis and DNA diagnostics. Additionally, diagnostics of the genetic disorders like cystic fibrosis, hereditary haemochromatosis, Wilson's disease, Gilbert's syndrome, alpha-1 antitrypsin deficiency etc. are available within the scientific research projects or in laboratories of scientific institutions. The majority of orphan drugs authorized in the EU are not available in Latvia (only 34), moreover those drugs that are available are often not accessible because they are insufficiently reimbursed by the state, and are too expensive to be covered by patients.

In Bosnia and Herzegovina a majority of orphan drugs authorized in the EU are not available because they are still not registered. It is questionable whether many orphan drugs after registration will be available to patients due to limited funds in the entities health insurance funds. The development and adoption of the national plans for rare diseases are an important step towards improving the situation in the eld of rare diseases. However, there is still a lot to do and further action is required to improve access to in- formation on rare diseases for both health care profession- als and patients (29,30).

5. CONCLUSION

The creation of a specific register for rare diseases will improve monitoring of orphan drug efficacy. Having on mind their relatively recent organization, infrastructure building and cooperation, larger involvement of patient organizations is expected in all issues related with rare diseases. Also, separate evaluation of orphan drugs cost effectiveness and using more appropriate evaluation methods (multi criteria decision analysis for example) would both, help decision makers and benefit the patients, while keeping sustainable financing. Steps toward these goals are needed and expected.

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