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RARE DISEASES ORPHAN DRUGS

Official Newsletter of the Bulgarian Association for Promotion of Education and Science (BAPES)

Dear readers,

FOCUS ON:
RARE DISEASE DAY – EQUITY FOR ALL

The past two months have been extremely eventful for the rare diseases field.

In more general perspective, the most important of them was the fourth consecutive Rare Disease Day. An initiative that has the objective to promote globally the rare diseases problem. Traditionally the Rare Disease Day events in Bulgaria were organized by the National Alliance of People with Rare Diseases with the support of BAPES. This year the "standard" leaflets and balloons were abandoned and it was decided to communicate directly with a professional group, very important for people with rare diseases and their families – the general practitioners. As a result, a series of training seminars on rare diseases were held all over the country. Bulgaria's leading medical professionals joined them as lecturers. Medical students' community also took part actively. We all are really pleased to note once again the strong unity and common position of doctors and patients in Bulgaria for the rare diseases cause.

However, the provision of drug treatment for people with rare diseases stays in a very different situation. The conducted legal and organizational changes from the end of 2010 were seen by the patients as a hope that the problem of access to orphan drugs will be finally resolved and they will no more worry about whether will receive or not treatment next month. The new procedures came into force on 1 March 2011 and they are already working a month and a half.

Although it is a short period for make an objective assessment and having in mind the fact that in every new activity it is likely to have initial malfunctioning in the mechanism, the new organization of the reimbursement have not found yet many supporters and has not shown that the old mistakes are considered and removed.

Coming months will indicate more clearly in what direction the introduced changes are going to.

SECOND NATIIONAL CONFERENCE FOR RARE DISEASES AND ORPHAN DRUGS

The Second National Conference on Rare Diseases and Orphan Drugs will be held on 9-11 September 2011 in Plovdiv, Bulgaria. It will take place at the Congress centre of NOVOTEL – Plovdiv. The forum will include presentations of leading medical experts, workshops and discussions for all rare diseases stakeholders, poster session. The main highlights will include:

- Epidemiological registries for rare diseases
- Best practices and guidelines for prevention, diagnosis, treatment and rehabilitation of rare diseases
- Rare diseases health policy and legislation
- Availability and access to orphan drugs in Bulgaria
- Outcomes of the Bulgarian National plan for rare diseases
- European and international projects in the rare diseases' field

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EUROPEAN AWARENESS OF RARE DISEASES

EUROBAROMETER

In the framework of the Rare Disease Day 2011 (28 February) and on the day of the formal adoption of the Cross Border Healthcare Directive too, the European Commission has released the results of a Eurobarometer Survey on "European Awareness of Rare Diseases".

This is an opinion survey which evaluates the perception of Europeans about rare diseases and how they react upon the national and European policies in the field. It was conducted amongst 26 574 EU citizens in all 27 Member States between 25 November and 17 December 2010.

Confirming the longstanding attitudes, 95% of respondents believe that there should be more European cooperation in this area and that rare disease patients should have the right to access appropriate care in another Member State. Europeans agree that the allocation of specific resources for rare diseases research is justified, as well as for equal healthcare provision and information campaigns for rare diseases.

Particularly for the Bulgarian results, they follow the general European pattern. But there is a very notable difference – the lower level of awareness of rare diseases. Clear evidence of it is that only 8% of the Bulgarian respondents have heard about the "most known" (65%) rare disease by the EU residents – the cystic fibrosis! So, it is very logical the almost unanimous approval of granting resources to improve awareness of rare diseases among health professionals and society as a whole (95% of the Bulgarian participants).

You can download the complete report as well as the results by Member State, in English and in the national language(s), under the sites of DG Health and Consumers or Eurobarometer.

REVIEW ON THE ACCESS TO ORPHAN DRUGS IN BULGARIA

ICRDOD has published an updated and expanded version of its review on the access to orphan drugs in Bulgaria. The report contains 4 sections: orphan drug designation and marketing authorization; pricing, inclusion in the Positive drug list and reimbursement; mechanisms for accelerated access to innovative medicines; conclusions. There are 2 annexes, attached to the review – a list of orphan drugs in EU and Bulgaria, which contains information about the trade name, ATC code, active substance, indication(s), marketing authorization holder and date of marketing authorization for each item (additionally, it is indicated whether the drug is present in the Positive drug list of Bulgaria and if it is reimbursed by public funds), as well as a list of references.

You can read the review at the Registries & Statistics section.

TRANSPARENCY MEASURES IN THE REGULATION OF PRICING AND REIMBURSEMENT OF MEDICINES

The European Commission has launched a public consultation in view of modernising rules on the transparency of Member States' decisions regarding the pricing and reimbursement of medicines. The consultation invites all interested parties to share their views on the review of Council Directive 89/105/EEC, often referred to as the 'transparency directive'. Although the prices of medicines and reimbursement are decided at national level, the Transparency Directive is aimed at facilitating the free movement of medicines in the EU. The consultation will help the Commission determine how to best update the existing rules to reduce pharmaceutical prices, guarantee transparent national procedures and facilitate a broader and timely access to medicines.

The consultation can be found the EC website.

PRESS-CONFERENCE OF PATIENT ASSOCIATIONS

On 20 April 2011 Association Cystic Fibrosis, Association of patients with acromegaly "Hope for Life", DEBRA Bulgaria, Bulgarian anti-thalassemic organization and Association of patients with ankylosing spondylitis will hold a press conference at Festival and Congress Centre in Varna. Patients will present their perspective on the current changes in the drugs provision for rare diseases, which is already organized by the National Health Insurance Fund. Patient associations believe that the new rules do not reflect the chronic nature of rare diseases and represent real risk for patients to remain untreated for a long time.

FIRST COMMENTS ON THE CHANGES IN THE PROVISION OF DRUGS FOR RARE DISEASES

Doctors and patients about how should and how should not be organized rare diseases treatment in Bulgaria

Major reforms in the provision of drugs for rare diseases have been undertaken in Bulgaria since the end of 2010. Through changes in three fundamental ordinances this activity was transferred from the Ministry of Health (MoH) to the National Health Insurance Fund (NHIF). The idea was to ensure better access of patients to these drugs, since NHIF does not hold tenders and just pays the lowest market price of the drug, while MoH is required to conduct tenders upon the Public Procurement Act. It was the challenging procurement procedure that had often put MoH into position, where it was unable to buy and provide life-saving medications on time.

A month after the launch of the new mechanisms, we decided to look for the first impressions and reactions of the most concerned stakeholders – doctors and patients. We have chosen the rare disease thalassemia major for several reasons. There is medicinal therapy for it, which has become focus of these changes. It is one of very few rare diseases, for which there is precise and updated information in Bulgaria thanks to the already 2-years working National registry of patients with thalassemia major. Not at last place, Bulgarian thalassemia patients have their own structures, which are among the most active and well organized patient associations here.

We have invited the following persons to answer the same questions:

Dragomir Slavev and Ivan Ivanov (chair and member of the governing body respectively of the Thalassemics' Oraganization in Bulgaria, TOB)

Assoc. Prof. Valeria Kaleva, MD, head of Clinic of pediatric hematology and oncology at "St. Marina" University Hospital, Varna; chair of the National thalassemia workgroup to the Bulgarian Scientific Society for Clinical and Transfusion Hematology

Dr. Denka Stoyanova, MD, Thalassemia sector, Clinic of hematology at the Specialized Pediatric Oncohematological Hospital, Sofia; member of the National thalassemia workgroup to the Bulgarian Scientific Society for Clinical and Transfusion Hematology

By this moment (April 2011) how do you assess the initiative for reimbursement of rare diseases treatment by NHIF, instead of MoH?

TOB: It is an experiment which creates confrontations between patients, doctors and institutions. The change is not implemented in practice yet. It will be a fact when patients receive their medicaments through the pharmacies, working with NHIF. The procedure itself, we could define it as "complicated and clumsy".

VK: The reimbursement of rare diseases treatment by NHIF has advantages only when treatment and follow-up of these patients is done in specialized centres.

DS: In my view, things were set down as best as possible last year. We were receiving drugs in the hospital on a regular basis, there were no therapy interruptions. Now, it is perhaps less comfortable for patients who have to visit monthly their GP, who has no perspective in their therapy, and also to deal with NHIF procedures every 6 month. That will definitely irritate some of the patients. But on the other side, it is really an outpatient treatment and it is reasonable to be organized by NHIF.

Do you think that this model will further stabilize the rare diseases' drugs provision or it is just the next experiment?

TOB: Any new thing has its potential threats and opportunities. Whether the model will be successful depends on its realization, including all the stakeholders too. According to us, to be successful it must be as simplified as possible, but right now it is not.

VK: The model, which is used now, is not the most appropriate when talking about expensive medication and rare diseases patients' treatment. The optimal way has been probated in many countries and it includes organizing specialized centres for rare diseases.

DS: If there is no delay with the protocols and no changes in the dosage regime by the NHIF commissions, I hope that the situation will stabilize. But I am afraid if the therapy will be stopped or moved to lower dosages when the resources come to an end eventually. I am also worried if there would be financial possibilities to include new patients to orphan drugs therapies and to increase the medication dosage if necessary.

Have your experience and position been taken into account especially when elaborating the requirements for chelation therapy for beta thalassemia patients?

TOB: Partly.

VK: The requirements for chelation therapy were prepared after consultations with the National thalassemia workgroup.

DS: The requirements were elaborated exclusively after our position and experience.

How have the new procedures for provision of rare diseases medication started? Were there more serious problems?

TOB: There are still places where these procedures are just beginning and there is a delay. The procedure itself requires much more efforts from the patient for preparing the necessary documentation and to submit it to NHIF.

VK: The chelators are supplied for all patients till the end of March by the hospital pharmacies. The problems with medication provision from external pharmacies will be from now on.

DS: Until now, I have no returned protocols. A part of them has been already validated. I am not sure if the next 6 months will pass easily when the financial expenses are calculated. I hope to be wrong.

In your point of view, what could be possibly changed in order to organize more properly the rare diseases treatment?

TOB: Rare diseases should be subject of treatment by specialized institutions.

VK: The creation of university centers for treatment and follow-up of patients with rare diseases is the most effective solution to this issue.

DS: I think these patients would have better treatment if it is concentrated in 2-3 centres throughout the country. These centres should be responsible for overall treatment and follow-up of rare diseases patients. It will be better if they are common for common for children and adults. By this way the stress from the transition will be removed and the medical professionals' efforts will be united.

Bulgaria is at the last places in EU on the provision of access to orphan drugs. What is your explanation?

TOB: Rare diseases are a field of healthcare which was practically unknown until recently. There is a shortage of medical specialists who are acquainted with the details of this problem, as well as a lack of specialized structures for treatment and prevention. And it is only a part of the components, needed for an overall policy in rare diseases' field. On the access to orphan drugs, in Bulgaria no one works on that question and it remains unsolved.

VK: There are no problems with thalassemia patients in this particular aspect. At the moment there are no limitations in medication provision and the treatment of all patients is conducted upon the present-day therapeutic standards criteria.

DS: Bulgaria is with a very low standard. I also think that the funding is not appropriately distributed in order to improve the access to orphan drugs. However, in recent years a lot of progress was made and I hope this trend to continue under the new reform.

EDITORIAL COMMENT

The resemblance in the answers is impressing. Good or bad, the new reimbursement model is a fact. Whether it would smoothly work, it depends on the actions and attitudes of all the stakeholders. It is ascertained insufficient awareness among patients of the requirements of the new reimbursement procedure. When such a serious organizational change is undertaken and having in mind the specifics of rare diseases where any therapy delay could be fatal, it is inadmissible not to conduct more effective information campaign nationwide. Besides the lack of enough coverage of the topic on the national media, the sporadic publications were having rather contradictory and confusing character.

There are doubts about the possibilities for increasing the drug dose, as well as for allocation of resources for newly diagnosed patients. There were definitely such problems under the old system, where after the tenders and the distribution of drugs, doctors were often forced to treat at suboptimal doses and the newly diagnosed patients had to wait until the next tender.

At the end of the interview, the lack of expert and reference centre for rare diseases in Bulgaria is once again stressed. Similar structures already exist in some form (based on the assessment of patients and on reputation), but it does not allows them neither to deploy even a small part of their potential nor to meet the needs of all. It is clear the necessity of special policy in this area – the creation of specialized centres of expertise at the university hospitals where patients with rare diseases could be diagnosed, followed up and treated by a multidisciplinary team of specialists. This is distinctly underlined in the Recommendation for actions of the EU Council of 9 June 2009, where it is called for concrete measures on this matter. Last but not least, it is required to ensure sustainable funding of these centres for their development and inclusion in larger European networks. We believe that there are in Bulgaria enough highly qualified medical professionals in terms of diagnosis, treatment and rehabilitation of rare diseases. For more than two years, Bulgaria has an acting National Plan for Rare Diseases, which, however, because of severely reduced funding and inefficient in our opinion allocation of resources, does not meet the expectations of patients with rare diseases.

We would like to thank Dragomir Slavev and Ivan Ivanov of TOB, as well as Prof. Valeria Kaleva and Dr. Denka Stoyanova for their cooperation and assistance in preparing this article.

RARE BUT EQUAL

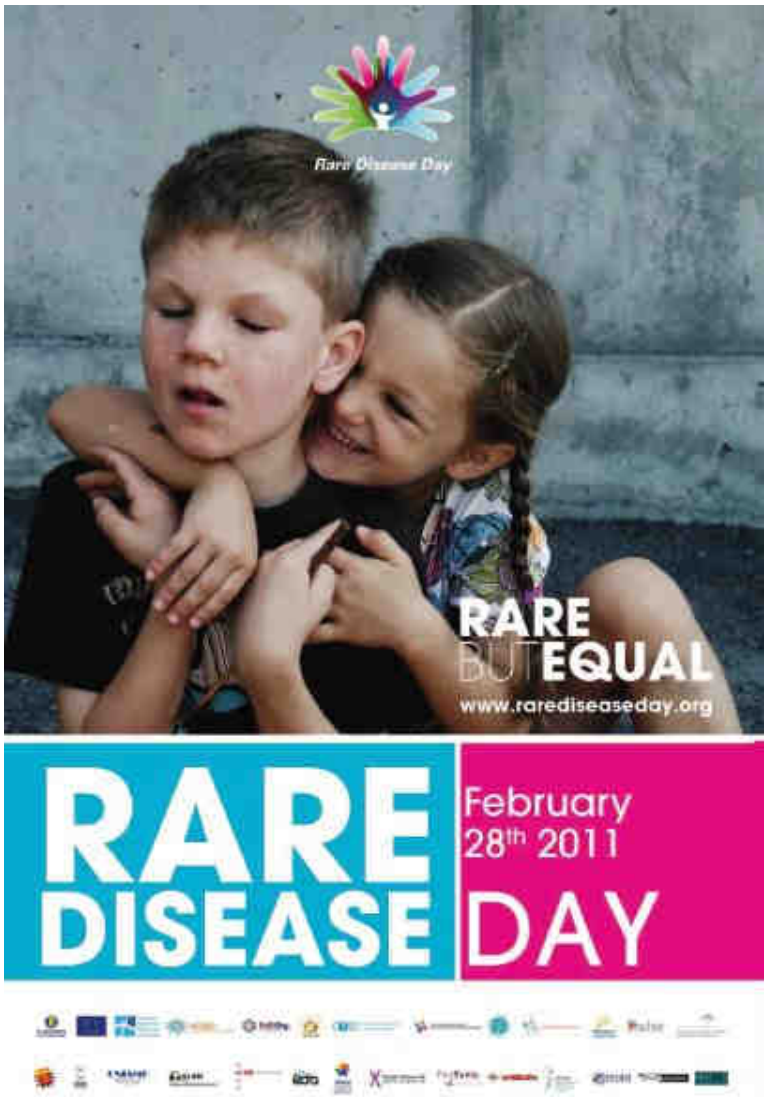
Rare Disease Day for fourth year in a row in Bulgaria and all over the world

Rare Disease Day is a special day. It was firstly organized on 29 February 2008 by EURORDIS together with national alliances of patients with rare diseases in several European countries. This date is loaded with eloquent symbolism. It is intended to manifest the need to raise awareness of rare diseases among society, to conduct research, to develop methodologies for rapid and definitive diagnosis, to implement successful therapies and to have access to them. In brief – to preserve the hope of people with rare diseases and their families that one day they will feel complete and happy persons.

Each consecutive year the number of participating countries in celebrating Rare Disease Day is growing and 54 countries from across the globe took part in 2011. It is a strong proof of the globally increasing awareness of this problem. Even more happily, this is a purely patient initiative and a clear sign of the greater commitment of patients with rare diseases to take their destiny in their own hands and to participate actively in the process of rare diseases decision making.

"Rare but equal" was this year's motto of Rare Disease Day. In this way people with rare diseases have tried once again to draw attention to health system's problems that put them into a disadvantage position in terms of healthcare. Generally, the issue of equal, inclusive access to medical treatment. Rare diseases are undoubtedly a challenge for the medicine and health policy of each country. Nobody can deal with that alone, but each country is obliged to start implementing concrete measures to guarantee the basic human right to health. This is a right of which the majority of people with rare diseases have been practically deprived. Without it, these people and their families are placed in an extremely difficult situation, which eventually take away from them other rights and opportunities as education, employment, integration in society. Left unresolved, this issue will continue causing inequality and discrimination, something unacceptable for the XXI century.

Bulgaria, thanks to the National Alliance of People with Rare Diseases and ICRDOD has participated in the Rare Disease Day celebration and organization since the very beginning of the initiative. This year's related events here went in a different way from the previous editions. The target group to which the message was directed were the general practitioners.



Credit ©Rare Disease Day 2011

This was one of the main recommendations and wishes of patients during the Bulgarian EUROPLAN National Conference for Rare Diseases. Bulgaria has good medical specialists but general practitioners are the gateway to healthcare system. The prompt and adequate access to specialized medical therapy and diagnosis depends largely on their awareness and better understanding of rare diseases problem. Unfortunately, rare diseases are not yet sufficiently covered as a separate unit during the education and training of the general practitioners in the country. Therefore it's no surprise their relatively low level of knowledge on this issue. A survey conducted by ICRDOD in early 2008 among this professional group showed very alarming results. Only 2.5% of over 1000 people who took part had some basic information on the rare diseases' matter.

Organizers from NAPRD in Varna

During the week of Rare Disease Day training seminars were held in the cities of Sofia, Plovdiv, Varna, Stara Zagora and Pleven. Organizing partners were the Medical universities in Plovdiv and Varna, the Medical faculty of the Thracian university in Stara Zagora, the Associations of medical students in Plovdiv and Varna. Bulgaria's leading medical specialists took part in the seminars "How to recognize and treat rare diseases" by presenting basic concepts for the prevention, diagnosis, treatment and rehabilitation of some of the more "common" rare disease in our country.

The high interest in these workshops was more than enough proof for the right choice. New training seminars are already planned for the months of May and June. We hope that during the Second National Conference for Rare Diseases (www.conf2011.raredis.org) the results of this campaign will be given.

The Association of medical students of Varna has actively participated in organizing "Teddy Bears Hospital" on Rare Disease Day.

CARE FOR PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS – ADVANCED PRACTICES OF THE LAST DECADE

Definition and short description

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease, characterized by loss of motor neurons in the spinal cord, brainstem and motor cortex. The cause for ALS is still unknown, but there are many successful ways so far to maintain the condition and quality of life of the patients.

Medicinal treatment

Currently, there are no medications that can lead to a cure, but during numerous double-blind and placebo-controlled trials the best results were given by the drug riluzole regardless of dosing regimen. Hopes for improving the survival by lithium carbonate are not justified, as well as the dietary addition of antioxidants, vitamin E, acetylcysteine, selenium, l-methionine and creatine.

According to various authors, there is a clear evidence of better survival and quality of life of ALS patients when treatment is performed by a multidisciplinary team in specialized medical institutions. It must include neurologist, pulmonologist, physical and rehabilitation medicine specialist, speech therapist, psychologist, nutritionist and social worker. In cases, where it is impossible to form such a team, the telemedicine could be used to make the necessary consultations.

Clinical manifestations and most effective methods to deal with them

- One of the main difficulties for patients is the coming dysphagia, which leads to dehydration and weight loss. Although accurate signs for it are not formed yet, the percutaneous endoscopic endostomy may be regarded as a reliable way to correct this problem, as well as adding to the diet of nutritional supplements such as carnitine - 5-10 g per day, vitamin E - 5000 mg per day. However, if these supplements are not combined with riluzole, their effect is unknown;
- Respiratory failure is a leading cause of the worsening survival in ALS patients. Non-invasive ventilatory therapy (NVT) is discussed as a factor in improving the quality of life of patients. The main criteria for NVT inclusion are the nocturnal oximetry and bulbar involvement. The weakness of expiratory muscles leads to ineffective coughing, mucus retention in the upper respiratory tract and lung infections. Appropriate methods to assist expectoration are the mechanically-aided inspirium and expirium and high-frequency vibration on the chest wall;
- Sialorrhea – amitriptyline, botulinum toxin type B, injected into the salivary glands, radiotherapy, administered once;
- Pseudobulbar affect – fixed dose combination of dextromethorphan/quinidine;
- Fatigue can sometimes be a side effect of riluzole, so reducing or stopping the medicament for a while can be considered. However, the most significant results come by regular exercises according to the patient's state and capacities;
- Cramps – no drug has proven effect on this symptom so far, although gabapentin, vitamin E and riluzole, as well as levetiracetam, vitamins of group B and calcium channel blockers have been applied;
- Spasticity – the effect of baclofen, dantrolene and tizanidine is still without convincing results, but they are applied in severe cases in combination with specialized kinesitherapy to reduce spasticity;
- Depression – most authors suggest including treatment for depressive syndrome in all ALS patients;
- Anxiety – there are not enough studies on this issue. Different methods of psychology and physical therapy have good prognosis;
- Insomnia – previous studies suggest that there is no specificity in ALS treatment here and schemes valid for insomnia in general can be applied too;
- Cognitive and behavioral disorders – multiple teams are working to improve the condition of ALS patients through specialized methods of psychology and pedagogy;

- Dysarthria and other difficulties in communication – various options to improve speech abilities are discussed. There are devices for voice amplification, augmentative alternative communication, prosthetics, palate lifting and others.

Role of physical rehabilitation

In most patients supportive rehabilitation is a method of improving quality of life and periodic assessment of the condition in order to adequately include or exclude other medicinal and supportive therapeutic tools. Carrying it out in specialized institutions guarantees the quality of care and is a starting point for more detailed follow-up of the effectiveness of different therapies in this pathology. Combining preformed and natural physical factors implies more long-lasting results, but treatment programs must be adapted to the individual needs of each patient. Advanced approaches include the application of electrotherapeutic procedures, thermal and physical therapy, focusing on current deficits. The aim is each subsequent course of therapy to include other factors with complementary effects and to redefine the repeating of them according to the individual tolerance. It is advisable to conduct 4-5 courses in outpatient settings per year and one to be dedicated to climate- and water-treatment in sanatorium conditions.

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To get further information on ALS, as well as on opportunities for medical rehabilitation and patients' training, please contact Medical Centre "RareDis".

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Bulgarian Association for Promotion of Education and Science (BAPES) is a non-profit non-governmental organization registered under under the Bulgarian law on legal persons with non-profit purposes in 2003.

The **main objectives** of the association are:

- to stimulate research;
- to encourage development of technologies and their practical application;
- to support all areas of education and science in medicine.

In 2004 BAPES launched the **Information Centre for Rare Diseases and Orphan Drugs (ICRDOD)** – the first and only Eastern European educational and information service dedicated to patients, medical professionals and associations, interested in rare diseases and orphan drugs.

The main functions of ICRDOD are providing free information on rare diseases, specialized clinics, laboratories in Europe and the world, bringing together leading experts, physicians and patients, creating and maintaining multilingual website for informational and educational purposes (www.raredis.org); organizing workshops and conferences; establishing contacts with scientific and patient organizations from Bulgaria and Europe.

ICRDOD is identified as a major and reliable source of information about rare diseases in Bulgaria on the website of the European Commission (DG SANCO) – http://ec.europa.eu/health/ph_threats/non_com/rare_9_en.htm.

BAPES together with other European partners **has successfully prepared, won and implemented 5 major European projects, funded by the European Executive Agency for Health and Consumers (EAHC)** – ORPHANET (2007-2010), EUROPLAN (2009-2011), RD PORTAL 2 (2010-2011), BURQOL-RD (2010-2013) and EPIRARE (2011-2014) with a total funding of over € 6,000,000. Additionally, **BAPES has won and implemented one own project** (4 EEC RDOD, 2009), which was co-funded by the EAHC.

In 2009, guided by the idea of enlarging and integrating its activities, BAPES started the **Medical Center "RareDis"** - a specialized medical centre for rehabilitation and training of patients with rare diseases and their families. **Multidisciplinary team of specialists is currently preparing intensely modern protocols for medical and social rehabilitation as well as projects for medical research.**

More information about us:

www.raredis.org

Editorial Box

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