EMBERI ERŐFORRÁSOK MINISZTÉRIUMA

NATIONAL PLAN FOR RARE DISEASES

healthcare policy strategy for rare diseases until 2020

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MAGYARY PROGRAM

MAGYARORSZÁG MEGÚJUL

A projekt az Európai Unió támogatásával, az Európai Szociális Alap társfinanszírozásával valósul meg.

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Introduction

The category of rare diseases includes low-prevalence diseases with severe risk to life or involving permanent loss of function, or rare combinations of prevalent diseases. In the Member States of the European Union any medical condition with a prevalence of less than 5 per 10,000 people is considered rare. The limited occurrence of certain diseases, however, does not mean that the number of people affected by these types of diseases is low. It is estimated that in the European Union currently 5% of the population, that is 20–30 million people, are suffering from one or other of approximately 6000 rare diseases. There are numerous patients with even rarer diseases, which affect not more than one person in 100,000. Most of these diseases are induced by genetic disorders, but harmful external effects sustained in the foetal stage or later may also contribute to their onset, particularly if there is genetic predisposition. These include certain tumours, immune disorders, congenital development disorders and infectious diseases as well. The signs of some rare diseases can already be observed at birth or in childhood, but 50% develop only in adulthood, in a life-threatening form, or leading to permanent disability, serious deterioration in the quality of life, early death or significantly shorter life expectancy.

There is an extreme diversity of rare diseases, and their number is constantly rising. The reason for this is not that new diseases are developing. The answer lies in the use of advanced biotechnological appliances enabling the identification of health conditions with dissimilar features, which were previously classified under single generic terms. Various genetic differences can be shown between patients previously treated with the clinical diagnosis of locomotor or mental disorder, and with more precise methods the number of these differences is also growing. Health conditions with different features dissociated from single medical terms are rare, but their separation is highly important, since their processes differ, options for their treatment vary and their genetic transmission may also be divergent. The situation is made even more complicated by the fact that a symptom induced by a rare disease associated with frequent and complex health conditions may conceal the real source of the problem and lead to a false diagnosis.

Features of rare diseases

- generally chronic, progressive, degenerative and life-threatening;
- deterioration in the quality of life, limitation or complete loss of the autonomy of the individual;
- often accompanied by strong pains;
- place a serious burden on affected families;
- their treatment is often not solved;
- the number of currently known rare diseases is at least 6000;
- one third of rare diseases affect children;
- 30% of the affected do not live to the age of 5;
- 80% of these diseases are genetically induced, while the rest are infective, immune or degenerative diseases, external damage or rare (familial) tumours.

The aim of the recommendations and suggestions set out in the National Plan for Rare Diseases is to support research efforts focusing on the consolidation of currently available services into a unified system, the development of conditions allowing high-quality care, an improvement in the availability of care and the development of new procedures of diagnostics and medical treatment.

In most cases there is no effective cure, but proper treatment can lead to an improvement in the quality of life and life expectancy. The medical care of rare diseases requires services structured on the basis of specific principles. With a view to achieving this, Member States shall develop a harmonised action plan for rare diseases by 2013 pursuant to the Recommendation of the European Council (Commission Decision of 30 November 2009 establishing a European Union Committee of Experts on Rare Diseases; 2009/872/EC). In the past, many well-organised services functioned in Hungary, which provided adequate care for patients with certain rare diseases. However, there is no complex strategy at hand to meet the medical and social requirements of patients with rare diseases, which would ensure the efficient use of resources in this field.

1. Foundation of the strategy: assessment of the current situation

1.1. Epidemiology

The significance of rare diseases (RDs) for national health is not well known. The available epidemiological data related to them are scarce, and the effectiveness of RD control measures is also in need of more insight. Unfortunately, this lack of knowledge hinders the development of optimal improvement programmes, since the RD policy should also be based on the monitoring of health status using reliable indicators.

The currently available data on mortality, morbidity, care organisation and quality of life give us a good estimate of the overall significance of RDs. Except for a handful of RDs, the development of data collection methods effectively supporting the foundation of detailed programmes remains an unfulfilled promise. There is a need for improvements in the effectiveness of care and in the method of assessment for the burden of diseases occurring on the level of national health.

1.2. Prevalence of rare diseases

The most comprehensive register of RDs, Orphanet (code system and knowledge base developed by EU DG SANCO) reported 5954 diseases in its database. (www.orpha.net) With this amount of diseases even the most elementary epidemiological data are difficult to define. Altogether we have reliable prevalence data for 662 RDs. These include relatively frequent RDs, which show a consolidated prevalence of 4.85%, which equals to 485,000 Hungarian and 23 million European patients.

Only the prevalence at birth is known for an additional 39 RDs. Moreover, 1345 RDs can only be described based on the number of registered patients, and for most of these only a few cases were reported. (Prevalence of rare diseases: Bibliographic data. Orphanet Report Series, 2011/1)

In summary, by adding the number of cases of very rare diseases to the 4.85% prevalence of diseases with known frequency of occurrence, the number of patients suffering from rare diseases in Hungary is estimated at 500,000.

Rare diseases	Estimated number of cases in Hungary
Down's syndrome	5000
Scleroderma	4200
Primary congenital hypothyroidism	3750
Pigmentary retinopathy	3020
Amyloid degeneration	3000
Fragile X syndrome	2800
Myelodysplastic syndrome	2280
Marfan syndrome	2000
Myasthenia gravis	2000
Williams syndrome	1330
Cystic fibrosis	1260
Tuberous sclerosis	880
Huntington's disease	700
Galactosemia	660
Amyotrophic lateral sclerosis	520
Epidermolysis bullosa dystrophica	500
Rett's syndrome	415
Smith–Lemli–Opitz syndrome	330
Von Hippel–Lindau disease	190
Fabry's disease	175
Cystinosis	50
Scheie's syndrome	20
Alpers' syndrome	2.5
Progeria	0.5

Number of cases of rare diseases in Hungary based on the prevalence estimated by Orphanet.

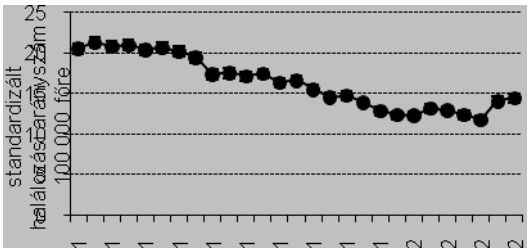
1.3. Death caused by rare diseases

A survey of death caused by rare diseases in Hungary was conducted using the country-wide database of causes of death between 1980 and 2006 developed by the Central Statistical Office of Hungary. Out of the cause-of-death diagnoses ICD-9 and ICD-10 only causes which met the definition applied by the Spanish REpIER (Red des Investigación en Epidemiología de las Enfermadades Raras) were included in the analysis. A total of 44775 cases classified into 47 disease groups were identified from the cause-of-death diagnoses from 27 years.

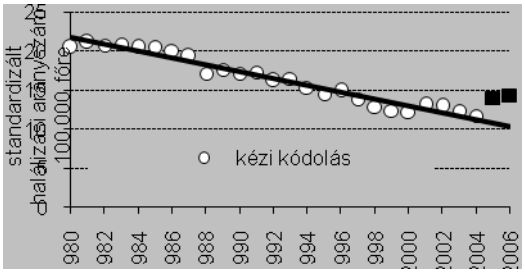
As a result of the continuous decrease of mortality observed in the 80s and 90s, the number of standardised deaths caused by RDs dropped from 208 million to 142 million in the assessed period. The ICD shift in 1996 did not lead to any change in the number of registered deaths associated to RDs. However, the automatic coding for the cause of death in 2005 raised significantly (by 30%) the number of registered deaths.

Deaths associated to RDs have shifted to a later age in the studied period. The number of deaths at infancy has decreased from the initial 615/million (28.3% of deaths caused by rare diseases occurred under age 1 in 1980) to 147/million (between 2005 and 2006, 9% of deaths caused by RDs occurred under age 1). The average age of death has risen from 37.3 to 57.7 in this period. The potential loss of years related to 66,120 RDs observed in the 80s had dropped to 21,900 by 2006.

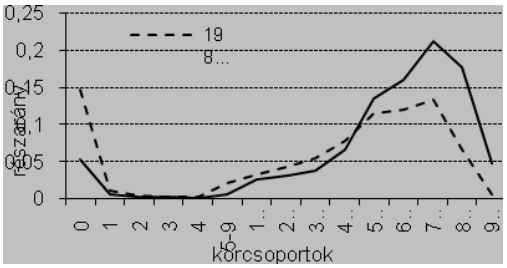
As a result of a longer lifetime due to the improvement taking place in care, RD as a social phenomenon has changed, which the systems of social care, education and labour have to react to.



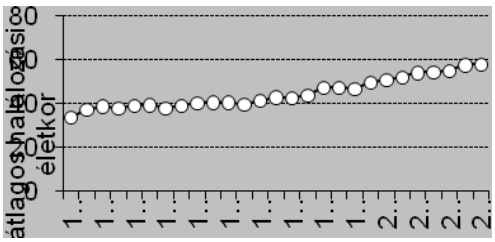
The mortality rate of rare diseases in Hungary projected to 100,000 people standardised to the European population between 1980 and 2006.



The effect of automatic cause of death coding on the registered mortality rate of rare diseases standardised to the European population.



The proportion of deaths caused by rare diseases broken down into age groups between 1980–1984 and 2005–2006 in Hungary.



The change of average lifetime in connection with deaths caused by rare diseases between 1980 and 2006 in Hungary.

1.4. Patient pathways on the basis of performance reports

In principle, keeping track of RD patient pathways is possible in Hungarian IT systems in cases where the RD has a separate ICD code. Currently, ICD10 contains 250 RD-specific codes.

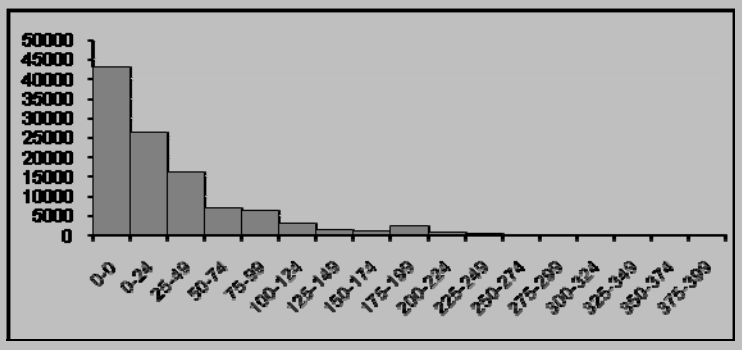
The World Health Organisation is presently working on the reform of international categorisation of diseases. The release of ICD11 is expected in 2015. This coding system will include over 2500 RD-specific codes, and it will also be possible to apply the supplementary code for rare diseases alongside every ICD11 disease group code. This change will have beneficial effects on detecting issues of care related to RDs. Until then we have to limit ourselves to the indicator assessment of already registered RDs.

The features of care of RD-indicator disease groups with codes E70-90, G10-13, G70-73, Q00-99 and for patients under 18 with code C00-D48 ICD10 were assessed using the database developed during the performance reporting of outpatient and inpatient specialist care conducted by the National Institute for Quality and Organisational Development in Healthcare and Medicines (GYEMSZI) between 2004 and 2006.

The registered prevalence for many of the indicator RDs was low compared to the international prevalence values (e.g. Tuberous sclerosis, Marfan syndrome, von Recklinghausen's disease). These diseases can only be examined with limited reliability within the system of performance reports. As regards other diseases, even epidemiological features could be studied adequately with this methodological approach, since the registered prevalence of diseases was within the range determined in the literature (e.g. Epidermolysis bullosa dystrophica, Cystic fibrosis, myasthenia gravis, Down's syndrome, children's brain tumours, childhood lymphoid leukaemia).

	number of institutes
Tuberous sclerosis	4
Epidermolysis bullosa	7
Marfan syndrome	10
von Recklinghausen's disease	11
brain tumour under the age of 18	1
Myasthenia gravis	3
Down's syndrome	4
Cystic fibrosis	2
lymphoid leukaemia under the age of 18	3
indicator rare diseases altogether	20

Number of major institutes in Hungary covering 50% of the care episodes of indicator rare diseases.



Number of episodes in the function of the distance between the institutes providing care for indicator rare

50% of indicator RDs received treatment in 25 specialist institutes in Hungary, to which 80% of patients did not have to travel more than 50 km. The scope of interventions carried out in the institutes, the frequency of treatment and the resources per patients showed significant variation. The life expectancy of those living farther from the centres was worse than those living closer to them. (Patients with myasthenia gravis lived 6 years, while patients with cystic fibrosis lived 19 years less, if they were living farther than 100 km from the institute proving care.)

RD care in Hungary is centrally concentrated, but the quality requirements specified for centres were not met even when there was a policy for RD care in Hungary. Evidently, the development of the accreditation system is needed, which would be partially monitored through the system of performance reports.

1.5. Level of satisfaction among patients regarding care

The regular assessment of experiences of patients with rare diseases is an important driver of improving care, since all care providers set the primary aim of increasing patient satisfaction beyond improving the objective performance indicators.

The EurordisCare2 survey launched by Eurordis strived to describe the conditions of delayed diagnostics and the way towards the right diagnosis in European countries. The survey

conducted in Hungary covered 5 indicator diseases (cystic fibrosis, tuberous sclerosis, Williams syndrome, pigmentary retinopathy, Duchenne muscular dystrophy). 252 patients participated in this local survey (with a response rate of 47.7%).

50% of patients had to wait for 490 days (min: 155, max: 1825), while 75% of patients had to wait for 1795 days (406–6205) to receive the correct diagnosis. (European reference range, EUR: 45–5040 and 450–10080 respectively) 79.7% of responders did not have a diagnosis in the first 3 month of their lives. 62 of them (30.8%) had a false first diagnosis (EUR: 41%). 19.9% of patients (40 people) felt that finding the right diagnosis placed an exceptionally large burden on them (EUR: 10%), and 34.8% of patients (70 people) had to travel outside the region of their residence (EUR: 26%). 27.4% of the participants of the survey (69 people) regarded the circumstances under which they were given notice of the diagnosis as acceptable (EUR: 35%).

The survey shows that in terms of the pathway towards diagnosis, Hungarian rare diseases have problems different from European ones, but their situation is similar overall. (They have to wait longer for diagnosis, but are less likely to receive a false first diagnosis; the pathway towards diagnosis places a heavier financial burden on them, but they are less commonly faced with unacceptable ways of communicating diagnoses.) Accordingly, the diagnosis of RDs needs improvement, and well-organised patient pathways need to be created both in Hungary and in Europe.

A survey coordinated by Eurordis collected data on the accessibility to health care (EurordisCare3). The objective of the survey was to give voice to the opinion of patients, thereby facilitating the development of the healthcare system engaged in the treatment of rare diseases. 408 patients took part in the the survey covering Hungary (cystic fibrosis, epidermolysis bullosa, myasthenia gravis, Prader–Willi syndrome, tuberous sclerosis, Willams syndrome).

The highest level of education in the family of Hungarian patients was 8% basic, 48% intermediate and 43% higher. 44% of patients/parents were working actively, 4% were unemployed, 2% have never worked, 44% were retired, 6% were students. 21% of patients/parents had to give up their job or profession and 14% of them had to move to another place due to their medical condition.

In the course of two years an average of 4.2 specialist doctors were contacted, 3.3 types of examinations were performed on them, they participated in 1.9 care programmes and 55% of these patients were hospitalised (on 3.2 occasions and for a total duration of 24.5 days on average). 21% of them experienced some kind of refusal while receiving medical treatment. 19% of patients would have been in need of the assistance of a social worker, most of them (67%) gained access to this service with difficulty or could not gain access to it at all.

According to the vast majority of patients, CEs that were the most appropriate for the treatment of rare diseases were those with a multidisciplinary scope (>95%), those monitoring the entire lifetime of the patient (97%), providing non-medical care (>95%), coordinating research programmes (96%), monitoring the needs/condition of patients (94%), and those responsible for specialist training (98%). Based on the opinion of patients, the development of coordination between professions and sectors as well as the organisation of CEs would substantially improve the standard of care.

In a comparison with the European average values, the Hungarian data do not show significant differences in terms of the frequency of use of the healthcare system and the frequency of refusals within health care. However, Hungarian patients receive social assistance more rarely and are more likely to be unsatisfied with the services.

	EurordisCare3	Hungary	HUN/EC3
use of medical care during the last 2 years (cases)	**9.4**	**9.2**	**0.98**
use of non-medical care during the last 2 years (cases)	**2.4**	**1.9**	**0.81**
experienced refusal in the course of medical care (%)	**17.8%**	**15.1%**	**0.85**
- refusal owing to the complexity of the medical condition (%)	14.7%	12.6%	0.86
- refusal owing to the physical appearance of the medical condition (%)	1.8%	1.3%	0.69
- refusal owing to the behaviour of the patient (%)	1.9%	1.1%	0.60
- refusal owing to difficulties of communication (%)	2.6%	1.9%	0.72
number of patients requiring social care (%)	**29.0%**	**21.0%**	**0.72**
- access to social care was impossible (%)	4.8%	7.5%	1.58
- access to social care was difficult (%)	27.4%	34.2%	1.25
- access to social care was easy (%)	67.8%	58.2%	0.86
the professional career was compromised as a patient (%)	**29.0%**	**30.1%**	**1.04**
the professional career was compromised as a family member (%)	**29.9%**	**24.8%**	**0.83**
forced to change residence (%)	**17.8%**	**25.1%**	**1.41**
- to an apartment/house offering more suitable circumstances (%)	10.8%	18.3%	1.70
- to institutional care (%)	2.3%	3.0%	1.33
- closer to a specialist (%)	2.5%	1.2%	0.47
- closer to relatives (%)	2.9%	3.7%	1.27

Characteristics of accessibility to health and social care in Europe and Hungary

1.6. Situation of registers of rare diseases and professional databases

Hungary has officially joined the international tender initiated in the framework of the European Public Health programme (2008–2013) to standardise the care of rare diseases (Joint Action Orphanet Europe). In the database the conditions contributing to the care of patients with rare diseases and the research into rare diseases will be registered on a transnational level. Orphanet made a quality-assured information portal for the general public on rare diseases and orphan drugs. The aim of Orphanet is to contribute to the diagnostics of rare diseases and the improvement of the treatment and care of patients with rare diseases by developing a common knowledge base at the level of the EU.

National Register of Congenital Disorders:

Under the management of the National Institute of Health Development the National Supervisory Office of Rare Diseases and Congenital Disorders has operated the National

Register of Congenital Disorders (VRONY) since 1970. The register gathers medical and personal data on foetuses, neonates and infants affected by prenatal diagnostics in the foetal age and congenital malformation recognised and reported between the date of birth and age 1. The collected data are cleansed, archived, processed and analysed in statistical and epidemiological aspects, and then the results are published.

The objective of the register is to accurately measure the prevalence of certain registered disorders, define their frequency and detect any accumulation of disorders. Awareness of the number of affected people in need of care supports decision-makers in planning medical and social care. External causes of the development of congenital development disorders are examined and their genetic background is revealed by operating the Pathogenic Monitor in the framework of case control examinations (in case of the accumulation of cases) or scientific cooperation. Furthermore, base data are provided for measuring the effectiveness of prenatal screenings as well as their national and regional analysis. A contribution is also made to prevention by processing the data of preventable disorders.

. Disorders to be reported to VRONY:

Based on revision 10 of the International Classification of Diseases (ICD), main group 17 includes the groups of congenital disorders, deformities and chromosomal abnormalities (Q00-Q99). In order to improve the quality of data the new version of the ICD10 coding system published by EUROCAT on 23 July 2008, Chapter XVII (Q00-Q99) (version 23 June 2008), was introduced. The application of this version is accepted in almost all EU Member States, since it enables a more accurate registration of diagnoses. The modified coding system is the extended version of the coding system generally used in Hungary, which allows for a more detailed subdivision by introducing a 4-numeral extension for subgroups of certain disorders, especially for syndromes and rare diseases.

The public health significance of congenital development disorders is justified by the vast number of affected people and the severity of their condition.

Main features of congenital disorders:

- Prevalence: 5–6%.
- In Hungary these are among the ten main causes of death.
- These disorders are the second most dominant cause of infant death (responsible for nearly one fourth of prenatal mortality and half of the deaths of mature infants at birth).
- These disorders imply a condition of deficiency, where a complete recovery is seldom possible, hence the optimal solution is prevention.
- Pregnancies of mothers bearing a defective foetus frequently end in miscarriage, premature birth or stillbirth.
- The delayed development and adaptation difficulties of infants are common phenomena with foetuses surviving selection.

The database of the Budapest Neuromuscular Centre:

At the Department of Molecular Genetics and Diagnostics of the National Institute of Environmental Health, only patients with genetic diagnosis satisfying the international requirements are registered in the national and international database. The Department keeps the DNA sample of 5042 patients and relatives in its biobank. The genetic deviation of 199 DMD/BMD and 319 SMA patients were identified from the clinically suggested cases, thereby confirming the diagnosis. The international database of TREAT-NMD currently contains 106 Duchenne and 81 SMA (Spinal Muscular Atrophy) patients.

Data in the database:

- Obligatory data: molecular genetic data, diagnosis, motor functions, drug therapy (in case of DMD disease: steroid therapy, cardiovascular medicine), artificial nourishment, scoliosis, participation in clinical tests; age, data update, region.
- Recommended data: clinical data (cardiac echography, breathing functions; in case of DMD disease: cardiomyopathy), muscular biopsy, registration in other databases, family case history.
- Data collection: The patients are contacted based on the patient data available after the genetic diagnosis is established. Inclusion in the database is voluntary, and requires the completion of a statement of consent. Method: contacting via mail, online possibilities (downloadable datasheets, communication through email.)

Register of the Hungarian Cystic Fibrosis Association (OCFE)

The Association has operated a patient register since 2005. The Association provides reliable and authentic data to the European Cystic Fibrosis Society (ECFS) on an annual basis.

In 2011, 592 patients were processed, of which 43% were under the age of 18. The data were provided by 13 centres for children and 3 centres for adults. In 2011 a total of 3 deaths were registered. The number of newly diagnosed cases exceeded the figures of mortality to a high degree. Hence the total number of patients is constantly rising. At the same time the average age and number of patients living to adulthood is also rising. It is observable that the disease, previously primary affecting children, has become a disease widely affecting adults as well. This implies a difference in care, so centres for adults were also established.

The average age of patients, 16.9 years, is somewhere in the middle of the range indicated by statistics of European countries. In the upcoming 5 years 25-17 children will reach adulthood. This figure also signals the change occurring in the number of patients found in existing centres. The respiratory insufficiency developing in young adulthood requires lung transplantation. Therefore, the knowledge of the number of adult patients is a good indicator for the future.

In 2009 the ECFS assessed the data of nearly 18,000 patients, and Hungary provided information regarding 90% of the 555 patients in care. For the year 2012 the questionnaire developed by the ECFS will be filled out, which enables wider clinical survey and assessment.

1.7. Current situation of newborn screenings

Definition of screening examinations:

Systematic application of the examination method for those who, based on the symptoms of their disease, would not fall within the scope of medical care (or only too late, after the onset of symptoms and the occurrence of irreversible damage), and for whom further examinations or therapy would be beneficial.

- In Hungary the newborn screening of congenital metabolic diseases is compulsory. The legal representative of the minor is responsible for the participation of the minor person in the obligatory screening examinations (Article 81 (3) of Act CLIV of 1997).
- The newborn screening panel currently in effect was set out in a Decree of the Minister of Health (2007/44 (IX.29.)).

In Hungary the newborn screening of congenital metabolic diseases was commenced in 1968 by the screening of phenylketonuria in Csongrád, Békés and Jász-Nagykun-Szolnok counties, with the organisation of the Paediatric Clinic of the Semmelweis University of Medical Sciences as a screening centre. A few years later, in 1975, screening examinations grew into a country-wide programme supplemented with galactosaemia and the foundation of the Budai Children's Hospital as a second screening centre. Later, two additional diseases, hypothyroidism (1985) and biotinidase deficiency (1989) were included in the newborn screening panel. There was significant change in 2007: by the application of the tandem mass spectrometry method the extended screening examination with an additional 22 diseases was introduced to the newborn screening panel (see Annex 4). In the same year the national screening centre in Budapest moved to Paediatric Clinic No. 1 of Semmelweis University. With regard to territory and population, Hungary belongs to these two centres in a 50-50% proportion (Paediatric Clinic No. 1 of Semmelweis University, University of Szeged).

1.8. SWOT analysis of the situation of rare diseases

Strengths:	**Weaknesses:**
Relatively small number of experts participating. Significant improvement in efficiency could be achieved by organisational development projects with a low demand for financial resources. At some universities, centres for rare diseases have already been established, while networks have been created at others. Recognised members of international scientific organisations are leading numerous university health centres. There are excellent biobanks for rare diseases. The receptiveness of professionals (clinicians, researchers, pharmaceutical factories) to technological innovations. Higher education is open to change (diagnostics, therapy and care of rare diseases were integrate into curricula). Existing legal regulations (biobank, genetic diagnostics). The patient organisations engaged in this area are well-organised and active.	For many diseases there is no centre-type care due to low capacities. The introduction of new technologies is difficult. Shortcomings in the development of unified Hungarian patient registers. Insufficient inter-sectoral cooperation (between the industry, universities, health care institutions, international organisations). Low R&D resources. The funding entity is hard to adapt to new principles of care organisation. Uneven qualification of health care professionals and doctors. Lack of knowledge on the part of laymen regarding the optimal use of the care system. The quality management of laboratories is not solved.
Opportunities:	**Threats:**
The Semmelweis Plan supports the development model of centre-type care of rare diseases and the involvement of Hungarian centres in European networks. Currently the development of a standardised electronic system of health care is under way at paediatric clinics. These may become parts of the Hungarian clinical best practice by adapting international protocols. Participation of the Hungarian intellectual capital in international projects. The representatives of certain sectors (industry, universities, health care institutions, international organisations) are open to strengthening cooperation. The efficiency of care can be improved by the modification of the funding system (by the accommodation of telemedicine, genetic diagnostics and special therapy of rare diseases). European and Hungarian projects are open to the involvement of Hungarian working groups.	The interests of operators of the field are different (clinician-funding entity, diagnostics laboratory and funding entity). The state often cannot take part in developments due to the absence of a comprehensive strategy. There are no developments owing to the slow change in the structure of financing and subsidising. Resistance of doctors/patients against innovations. The social support of patients is insufficient. The insufficiency of social care, the financial burden placed on those receiving care. Doctors working in basic and special care cannot keep pace with technological

Continuous development of the education of doctors and patients, and the introduction of modern tools of telecommunication.	developments.

2. International relevance and EU obligations

The "Together for Health: A Strategic Approach for the EU 2008–2013", published in the white book of 23 October 2007 of the Commission for the development of the health care strategy of the EU, sets the area of rare diseases as a action priority. The tasks are demonstrated herein by highlighting some of the chapters from the Recommendation:

2.1. COUNCIL RECOMMENDATION of 8 June 2009 on an action in the field of rare diseases:

"The Council of the European Union (...) hereby recommends that Member States: Plans and strategies in the field of rare diseases

Establish and implement plans or strategies for rare diseases at the appropriate level or explore appropriate measures for rare diseases in other public health strategies, in order to aim to ensure that patients with rare diseases have access to high-quality care, including diagnostics, treatments, habilitation for those living with the disease and, if possible, effective orphan drugs, and in particular:

a) elaborate and adopt a plan or strategy as soon as possible, preferably by the end of 2013 at the latest, aimed at guiding and structuring relevant actions in the field of rare diseases within the framework of their health and social systems;"

Adequate definition, codification and inventorying of rare diseases

(Member States) Aim to ensure that rare diseases are adequately coded and traceable in all health information systems, encouraging an adequate recognition of the disease in the national healthcare and reimbursement systems based on the ICD while respecting national procedures. Contribute actively to the development of the EU easily accessible and dynamic inventory of rare diseases based on the Orphanet network and other existing networks as referred to in the Commission Communication on rare diseases.

Research on rare diseases

Identify ongoing research and research resources in the national and Community frameworks in order to establish the state of the art, assess the research landscape in the area of rare diseases, and improve the coordination of Community, national and regional programmes for rare diseases research.

Include in their plans or strategies provisions aimed at fostering research in the field of rare diseases.

Centres of expertise and European reference networks for rare diseases

Identify appropriate centres of expertise throughout their national territory by the end of 2013, and consider supporting their creation.

Encourage centres of expertise to be based on a multidisciplinary approach to care when addressing rare diseases.

Gathering the expertise on rare diseases at European level

adequate education and training for all health professionals to make them aware of the existence of these diseases and of resources available for their care;

the development of medical training in fields relevant to the diagnosis and management of rare diseases, such as genetics, immunology, neurology, oncology orpaediatrics;

the sharing of Member States' assessment reports on the therapeutic or clinical added value of orphan drugs at Community level where the relevant knowledge andexpertise is gathered, in order to minimise delays in access to orphan drugs for rare disease patients.

2.2. DIRECTIVE 2011/24/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 9 March 2011 on the application of patients' rights in cross-border healthcare

Article 12

European reference networks

(1) The Commission shall support Member States in the development of European reference networks between healthcare providers and centres of expertise in the Member States, in particular in the area of rare diseases. The networks shall be based on voluntary participation by its members, which shall participate and contribute to the networks' activities in accordance with the legislation of the Member State where the members are established and shall at all times be open to new healthcare providers which might wish to join them, provided that such healthcare providers fulfil all the required conditions and criteria referred to in paragraph 4.

(2) European reference networks shall have at least three of the following objectives:

a) to help realise the potential of European cooperation regarding highly specialised healthcare for patients and for healthcare systems by exploiting innovations in medical science and health technologies;

Article 13

Rare diseases

The Commission shall support Member States in cooperating in the development of diagnosis and treatment capacity in particular by aiming to:

a) make health professionals aware of the tools available to them at Union level to assist them in the correct diagnosis of rare diseases, in particular the Orphanet database, and the European reference networks;

b) make patients, health professionals and those bodies responsible for the funding of healthcare aware of the possibilities offered by Regulation (EC) No 883/2004 for referral of patients with rare diseases to other Member States even for diagnosis and treatments which are not available in the Member State of affiliation.

Increasing the role of bodies of patient representation

Member States shall support the activities of representative bodies of patients in the areas of information, capacity and support to patients in extremely isolated cases.

3. Future prospects

Mission Statement of the National Plan for Rare Diseases

It is the natural need and expectation of patients with rare diseases to receive medical and social care equal to that provided to patients suffering from more frequent medical conditions. It is the legitimate demand of family members living with them and their relatives. The health care administration sets the aim of providing the highest quality of life possible for patients with rare diseases

The following shall be implemented:

- Coordination and management of professional, scientific and public health tasks related to rare diseases,
- Providing financial resources from the healthcare chapter of the budget,
- Establishing centres and local centres for rare diseases,
- Establishing the missing regulatory conditions,
- Maintaining international relations and the exchange of information,
- Coordination of cooperation at all levels of the Hungarian healthcare system,
- Providing social care of the highest quality possible,
- Cooperation with healthcare and social authorities, non-governmental organisations and the media,
- Extensive cooperation with patient organisations.

Cooperation on a national scale is necessary with the contribution of the best professionals to discover, diagnose, provide treatment and care, and organise the rehabilitation of patients suffering from rare diseases. The aim is to provide the care that the patient needs within the shortest time possible.

The following shall be implemented:

- Establishing multidisciplinary cooperation,
- Improvement of inclusion into the international care system,
- Establishing working patient pathways,
- Harmonising policies and customised medical treatment,
- Participation in graduate and postgraduate programmes,
- Participation in Hungarian and international research projects,
- Professional PR activity towards all levels of the healthcare system,
- Organising congresses and conferences.

For patients with rare diseases, constant communication and the possibility of sharing their difficulties and speaking about their doubts can provide a feeling of security. It is an important objective to ensure that patients with the same diseases can form communities and are given all relevant information.

The following shall be implemented:

- Establishment of as broad a unity as possible among all affected patient groups,
- Continuous consultation between patient groups and professional organisations,
- Active inclusion of affected persons in decision making,
- Operating a communication network accessible to everyone.

All interested parties of the National Plan for Rare Diseases are committed to implementing the above objectives and tasks by giving the best of their knowledge.

4. Specific objectives, strategic priorities

4.1. Primary aim:

In accordance with the principle of equal treatment and solidarity, improvement in the diagnostics and treatment of rare diseases with a multidisciplinary approach, improvement of access to high-quality medical care and therapeutic options by creating rationalised patient pathways as well as supporting related education and research by exploiting the potential in the European cooperation.

4.2. Further objectives:

Improvement in the diagnostics of rare diseases for early detection of diseases:

- Centres of diagnostics and their network shall be established, and quality management shall be provided to the system created,
- Adequate personal and material conditions shall be made available,
- The patients and/or their family members shall be given proper information.

Creation and operation of multidisciplinary CEs for high-quality patient care:

- Developing the system of conditions for the establishment and operation of CEs,
- The CEs shall have a well-defined competence and scope of responsibility,
  Development and operation of registers, organisation of patient pathways for adequate data provision,
- The objectives and infrastructural background of the register shall be defined.

Improvement of education and training for high-quality patient care:

- Education and training related to rare diseases shall be improved,
- The aims and levels of courses shall be defined,
- Education materials shall be developed and curricula shall be extended.

Improvement of newborn screenings for establishing early diagnoses:

- The conditions of screening shall be improved,
- New screenings shall be introduced.

Improvement of access to medicine and medical appliances:

- Developing a pricing strategy and procedural order of adaptation,
- Conducting targeted studies of health economics.

Support of research efforts in the field of rare diseases:

- Examination of the quality of life and satisfaction of patients and their access to social care,
- Examination of the background, prevention techniques and epidemiological characteristics of rare diseases,
- Support of clinical studies revealing the background of rare diseases and their treatment options,
- Collaboration and coordination in Hungary and at an international scale.

Development of social care and access to its services:

- The accessibility of the social care system and the range of services to patients with rare diseases shall be improved,
- The quality and accessibility of currently available services shall be improved,
- An institution representing and providing complex social care to patients with rare diseases shall be established.

5. Policy measures to achieve the objectives

5.1. Introduction of measures for the development of the diagnostics of rare diseases

5.1.1. Organising genetic diagnostics into centres

5.1.2. Developing a quality management system for the units created (levels 1, 2 and 3)

5.1.3. Training a suitable team of specialists to perform tasks necessary for operating the units

5.1.4. Providing a level of instrumentation that meets the levels of progressiveness

5.1.5. Giving information to affected patients and their family members on diagnostic results in accordance with international guidelines, and providing the ethical and legal framework of giving information

5.2. Designation of CEs with accreditation

5.2.1. Setting the objectives of CEs related to rare diseases

5.2.2. Defining the competence of CEs related to rare diseases

5.2.3. Defining the scope of responsibilities of CEs related to rare diseases

5.2.4. Ensuring compliance with EU requirements

5.3. Providing conditions necessary to establish the Register of Rare Diseases

5.3.1. Defining requirements related to quality management and validity

5.3.2. Defining the operation and privacy policy as well as establishing the legal background of the register

5.3.3. Defining data collection and data provision

5.4. Improvement and facilitation of education and training related to rare diseases

5.4.1. Extending the knowledge of the participants of graduate and postgraduate students of medicine, increasing the number of programmes

5.4.2. Ensuring the training of patients and their relatives, development of training programmes, and providing other opportunities for education

5.5. Providing the conditions necessary to introduce new newborn screening examinations

5.5.1. Defining the objectives of CF screening and providing the appliances necessary to perform the screening

5.5.2. Defining the improvement in the quality of life that can be achieved by newborn CF screening

5.5.3. Providing adequate care with DMD newborn CK screening and family planning options.

5.6. Improvement of the supply of medicine and medical appliances for rare diseases

5.6.1. Developing an evidence-based pricing strategy

5.6.2. Developing specific procedural rules for the adaptation of orphan drugs

5.6.3. Subsidising expensive medicine, supplemented by the support of studies in the field of health economics

5.7 Inviting tenders aimed at promoting the social, epidemiological and clinical research of rare diseases

5.7.1. Launching research projects through tendering to measure the dimensions of patient care and patient satisfaction

5.7.2. Implementing epidemiological studies examining the background and prevention of rare diseases

5.7.3. Developing protocols supporting the process of giving information on diagnoses

5.7.4. Developing the epidemiological use of data assets created within the system of health care

5.7.5. Supporting clinical examinations contributing to the therapy of rare diseases

5.7.6. Promoting and supporting cooperation between institutions and teams performing research into rare diseases

5.7.7. Participation in clinical research

5.8 Defining the tools and interventions necessary for the improvement of social care

5.8.1. Defining the development objectives of social and rehabilitation services

5.8.2. Education, training and improvement of employment of patients with rare diseases

5.8.3. Establishing the National Institute of Rare Diseases tasked with providing information, habilitation, development and services

5.8.4. Measures necessary for cooperation with patient organisations

5.8.5. Organising information campaigns

5.8.6. Organising training and education programmes

6. Interventions

6.1. Improvement of the diagnostics of rare diseases

The key to a comprehensive strategy for rare diseases is the detection of diseases, which can be followed by all other activities. It is a generally accepted view that 80% of rare diseases are genetically induced, hence it is obvious that the implementation of the national plan for the improvement of the diagnostics and treatment of rare diseases depends on the system of diagnostic services. As a consequence of the rapid development of genetics seen in the last two decades, the European Commission has, in several recent documents, drawn the attention of Member States to the need for a state-controlled and state-managed genetic services network, which shows overlap with the main programme points of the complex care of rare diseases (specialised network organised into centres, continuous scientific research, support of education, establishment of a structure aligned to the tasks).

In the current situation the small number of genetics consultants, genetics experts, the hours available and qualified laboratory workers can be observed as compared to the number and capacities of laboratories capable of performing genetic tests.

Currently, there are no registered genetics centres. Institutes/work groups were established based on individual initiatives and personal interest and ambition, where the professional conditions evolved to perform genetic research and provide adequate care to patients belonging to that region and those coming from outside. Patient pathways usually follow the regional division, but they are often ad hoc. Consequence: an unacceptably high number of genetic tests are performing without genetic consultation that would meet European standards or any professional indication, for the most part absolutely unnecessarily.

6.1.1. Interventions

Organising genetic diagnostics into centres

Since there is a genetic component to all diseases, and the genetic background of more and more diseases is being demonstrated, the number of patients referred to examination with the suspicion of otherwise rare medical conditions is increasing. The special nature, complexity, the demand of appliances and financial resources of diagnostic examinations and the strict ethical and legal requirements raise the need for providing all genetic care in a centralised form.

The infrastructural background of the system of genetic care and the satisfaction of the need for specialised professionals of the system of care should be designed on three levels:

- appointing national centres, so called CEs (see below) (care of level 3–4);
- genetic service locations on a county level (level 2) on the lower level of progressiveness (consultants, laboratories occasionally linked to them);
- specialised genetic ambulatory clinics providing basic care (level 1, in the vicinity of patients' homes) with low-competence genetics consultants;

Developing a quality management system for the units created (levels 1, 2 and 3)

- The result of the genetic test is valid for the entire life of a patients, hence the operation of units performing genetic tests requires a quality control of higher level guarantees than generally expected in medical care.

Training the suitable team of specialists to perform tasks necessary for operating the units

- The adequate level of diagnostics of genetically induced rare diseases requires highly qualified specialised professionals and methodology;

Providing a level of instrumentation that meets the levels of progressiveness

- The examination of the individual could imply the exploration of risks affecting family members or blood relatives, and has a transgenerational impact.

Giving information to affected patients and their family members on diagnostic results in accordance with international guidelines, and providing the ethical and legal framework of giving information

- Giving information of the diagnosis (either positive or negative) requires discretion and suitable circumstances, since this is followed by actions (care, further examinations, risks to children, etc.) influencing the entire lifetime of the individual;
- The service requires strict ethical standards and legal regulation regarding the indication of the examination and the assessment of results (see Act XXI of 2008 on Genetics);

Since the need for genetic examinations is present in all areas of patient care, it is reasonable for centres to assume a *multidisciplinary* approach. In Hungary these conditions are met by the clinics of universities running medical programmes (see also *CEs*).

6.1.2. Expected outcome

The care structure gathering experienced professionals and special instruments into centres shortens the time needed to obtain accurate diagnoses. The centralised and multidisciplinary care of genetic diseases showing symptoms typically affecting more than one organ systems decreases the rate of false diagnoses. Consolidating care into a network has a beneficial effect on the utilisation of advantages lying in the collaboration between Hungarian and foreign medicine, while harmonisation based on progressiveness decreases overlap.

6.1.3. Indicators measuring implementation

Indicator	Description of the indicator	Type of indicator
Number of available diagnostic genetic tests	The accessibility of genetic tests carried out by units applying high-level quality control.	output
Establishment of a specialised diagnostics centre	Reduction in the number of false diagnoses in order to shorten the time necessary to obtain correct diagnoses.	process
Introduction of a system monitoring the length of time until diagnosis	Development of a system registering the time of delay in diagnostics.	process

6.2. Establishment of the system of CEs

The development of the system of conditions for establishing and operating the centres of excellence is an important component of the policy programme. A multidisciplinary approach in terms of patient care and an improvement in education and research activities for high-quality patient care are fundamental expectations. In accordance with the standardised system of professional and quality criteria of the EU, the care of rare diseases shall primarily take place at specialised institutes already operating in universities of medical science, however, numerous service providers operating as separate units offering special care can also be found in the country.

6.2.1. Interventions

The aim of CEs related to rare diseases:

- The CEs provide treatment and care to patients living in the defined care area and suffering from rare diseases. These centres deal with diseases and medical conditions which require special care due to diagnostics, prevention of complications and the uniqueness of the treatment itself.
- The network of CEs in the country covers all needs of patients with rare diseases, even if it cannot provide all-round service with uniform expertise in the case of certain rare diseases.
- The CEs collect or coordinate the multidisciplinary capabilities and skills available within the specialised system of healthcare (including the capabilities of healthcare professionals and social services), which are required to satisfy the needs of patients with rare diseases in terms of medical treatment, rehabilitation and palliative care.

The competence of CEs related to rare diseases:

- The CEs shall contribute to the development of patient pathways starting from basic medical care. The aim of planned care is to allow for the establishment of diagnosis for all patients with rare diseases within the shortest time possible so that they may have access to necessary care and assistance, may improve their state of health and quality of life, thereby decreasing their difficulties and that of their family members as well as easing the burden placed on society.
- The CEs shall maintain a connection with specialised laboratories and other institutes providing special services. They shall keep a record of officially appointed CEs and this record is also made available to everyone through the Orphanet portal.
- The CEs shall contribute to the development and promotion of policies related to the treatment of patients with rare diseases.
- The CEs shall organise theoretical and practical training for professionals working with patients with rare diseases.
- The CEs shall ensure accessible information in cooperation with patient organisations and Orphanet in accordance with the special needs of patients and their family members, as well as medical and social professionals.

- The CEs shall support the better understanding of diseases and research into diagnostics, care and treatment, including clinical assessment of the long-term effects of new treatment methods.
- The CEs shall maintain contact with other national and European CEs.
- The CEs shall cooperate with patient organisations and operate a helpdesk in order to improve information provided to patients with rare diseases.

Other tasks of CEs related to rare diseases:

- The continuous patient care encompassing the entire lifetime of the patient shall be organised and coordinated, from childhood to adulthood.
- A patient register developed in accordance with European recommendations shall be operated, on the basis of which the centres shall take part in the maintenance of the national patient register.
- The centres shall operate a quality management system into which the requirements of both Hungarian and international standards shall be integrated.
- Indicators suitable for measuring the quality of patient care shall be developed and using the measured indicators the centres shall participate in national surveys by providing data.
- The centres shall be in possession of the personal and material conditions necessary for participation in clinical studies.
- The centres shall be capable for performing clinical and public health research as well as the relevant data collection as necessary.
- There shall be a well-developed thematics for the remote education programmes organised by these centres, which shall be provided through accredited training centres.

Ensuring compliance with EU requirements

- Pursuant to the Recommendation "Quality Criteria for Centres of Expertise (CEs) for Rare Diseases in Member States" (www.eucerd.eu) of the European Union Committee of Experts on Rare Diseases (EUCERD), the appointment of CEs is the responsibility of the competent ministry.
- The CEs shall be granted adequate support (capacity, human resources), which ensures continuous compliance with quality requirements and high-quality patient care.
- The definition of accreditation criteria adapted to the domestic system of care shall be developed in accordance with EU Recommendations. The objective of compiling and testing the compliance criteria for declaring an institute a CE of rare diseases: ensuring compliance with international quality requirements expected from CEs in Hungary providing care to patients with rare diseases, and training of the professionals performing assessments.
- The monitoring of continuous compliance with criteria shall be performed through independent audits, which are carried out in an organised form by a qualified and appointed organisation with the participation of specially trained professionals (auditors).

6.2.2. Expected outcome

The establishment of Centres of Expertise is expected to harmonise patient pathways, reduce the time necessary for obtaining diagnosis, improve the quality of life of patients with rare diseases, improve the chances of patients with rare diseases in Hungary and channel the sites providing care to patients with rare diseases into ORPHANET. An earlier diagnosis prevents the performance of unnecessary examinations, and the early treatment of symptoms can, in many cases, prevent permanent damage to health. Severe diseases can be prevented by the help of prenatal diagnostics.

6.2.3. Indicators measuring implementation

Indicator	Description of the indicator	Type of indicator
The number of accredited CEs covering the entire country and operating in alignment to actual needs	Establishment of accredited CEs appointed in accordance with the EUCERD recommendation laying down the quality criteria of CEs and in alignment to the area of the country.	output
Participation of Hungarian CEs in the European Reference Network	Development of telemedicine, establishment of consultation and ensuring the possibility of sending diagnostic materials to examination.	output
Proportion of patients with rare diseases appearing at CEs compared to the number of registered patients with rare diseases	How many of the monitored patients appear at CEs compared to the total number of registered patients.	output
Helpdesks for patients with rare diseases	Accessibility to helpdesks for providing information to patients, providing social, psychological and information solutions in accordance with the needs of patients with rare diseases.	process

6.3. Development of patient registers specialised in patients with rare diseases

Currently IT systems support the local objectives of patient care of various sites providing care, but they are not compatible and not communicating with each other, and are applied for the management of the medical care of patients with rare diseases.
In these systems mostly structured (but aligned to various objectives) and unstructured data masses is available, which makes data exchange between work groups, or creation of national registers and achievement of the research aims impossible. Moreover, these systems are less suitable for cooperation with international registers.

Aspects of development
In order to avoid the above problems, the registers of patients with rare diseases shall operate on the basis of the system of conditions set out in the National Plan of Rare Diseases. The operation of existing registers shall be renewed in accordance with the aspects specified in the National Plan of Rare Diseases.
As a guiding principle, all possible data sources shall be utilised in these registers, and the most intensive use of electronic databases shall be promoted; and CEs shall have a register, and, if possible, CEs shall cooperate in the registration of patients not treated by them.
Clear objectives shall be defined for every register, and the entire data collection and processing system shall be developed with a view to achieving these aims. The data of the register shall be utilised for research and public health objectives, and to this end, the registers shall support:

- Regional, national or European policy development,
- Clinical and epidemiological research,
- Monitoring of the quality of care.

A practice of inventory planning shall be developed that enables the connection of data from the register with data from other registers in order to obtain a sample large enough to fulfil the tasks of research, monitoring or policy development and to make registers suitable for international cooperation and enable the use of their data for a large enough sample of clinical and public health research. To this end:

- The international coding system (ICD11, OMIM and Orpha codes) shall be applied for the registration of diseases.
- An obligatory data set shall be adopted, which shall be obligatorily collected for all rare diseases.
- In connection with this, data especially recommended for rare diseases are needed, with particular regard to the clinical care of the patient.
- The registers shall adopt and apply minimal data requirements specifically defined for individual diseases.

- In case of several registers operating in several countries a unified system shall be applied to the identification of patients, which enables the linking of data on patients registered in several places.
- The development and application of a patient identifier to be used on a European level shall be promoted in pseudonymised registers.
- Data management must be done in compliance with the effective international ethical regulations and with the regulations of Hungary and the European Union.

The registers shall operate in accordance with the guidelines related to them. The affected patients, specialised policy-makers, researchers and clinicians (possibly industrial partners) shall collaborate in the operating practice (the system of data collection, the methodology of maintaining the register). The affected parties shall develop the framework of cooperation in the form of a body working in accordance with a regulated system.

The informed consent of patients shall be developed with a view to all tasks of the register. Patients who have already registered shall make a renewed statement regarding the use of their data in the register redesigned on the basis of the National Plan for Rare Diseases.

The registers shall make up the system which forms the basis of giving information to patients and professional partners regarding the way they operate.

Rules of procedure shall be established in the registers that will enable the all-round modification of the operating rules for the development of the system of tasks of the register and the achievement of new objectives (e.g. monitoring the effectiveness of a new therapeutic procedure).

The registers shall operate in a sustainable manner. Rules of financing shall be developed for the maintenance of these registers. PPP programmes can only be applied in financing the register if the agreement of cooperation is for the long term, if it serves the maintenance of the register and if it produces results which could not be obtained otherwise.

6.3.1. Interventions

The aim of the Information System of the Register for Rare Diseases is to create an unified IT system that will:

- contain the data related to patients with rare diseases in Hungary and to their care as a **register**, and makes these data available in a structured manner to users appointed by the regulator and in the possession of necessary permission;
- provide data and information through an adequate connection interface to the "**Katéter & Mónika**" application;
- provide data and information through an adequate connection interface to the financing entity;
- the **decision support system facilitating routine patient care**, which provides the necessary information (e.g. genetic data) to health care professionals, and serves as a bridge between the professionals involved in the care of patients (CEs of levels 1–4);
- the **research tool** with data content and functionality that enables the definition of research issues and their solution;
- its data and information content facilitates the **training of professionals**;

- as a **domain model** it provides a framework for the development and operation of CEs/network, patient pathways and care protocols;
- with its data and information content it provides **assistance to decision makers** for the improvement of the medical care of patients with rare diseases.
- with its data and information content it facilitates the quick organisation of clinical trials.

Definition of IT infrastructure requirements

Requirements related to quality management and validity

As opposed to the unified system, the principal requirement is continuous accessibility, version tracking, access to updates and the provision of maintenance options, which assumes a service provided through an online interface with adequate hardware infrastructure. The deployment of the hardware infrastructure is conceivable in an adequately centralised environment (server centre) with continuous electronic and internet access (fast and redundant internet connections). The issue of data protection and data security shall be handled as a priority due to the nature of the stored data.

The definition of data protection

The server centres shall ensure the physical protection of servers (e.g. multi-scale cooling system, protection against the intrusion of unauthorised persons), and the application of a redundant hardware architecture is of high importance (redundant servers with redundant parts). The regular backup of the data content is important (the entire database shall be stored encrypted at a remote and independent site, e.g. at a server farm). The logical data protection includes the management of authorisations, which covers ("the principle of minimal access": everyone only has access to the data specifically needed for their work), the tracking of versions, the encryption of sensitive data, the storing of the hash print of passwords and providing safe access through the https:// protocol.

Definition of the operation of the register

The register shall be able to keep track of patients and patient pathways. The use of existing codes for rare diseases in the current modified ICD10 coding system is essential to maintain a register of diseases. The system shall be capable of automatically switching to the ICD11 expected to be released in 2015 and containing a significantly higher number of rare disease codes.

In addition to ICD codes, the register shall contain the current coding system of the Orphanet database.

Besides taking into consideration the Hungarian and EU ethical regulators, in the unified system users with adequate authorisation shall be given

- access to the data of clinical and genetic tests, which would exclusively be a research function and not a clinical diagnostic function in case of numerous non-rare diseases.
- the integration of screening, data requesting and data mining functions shall be promoted in order to support the achievement of future research objectives. In addition to these clinical and other data, this shall be feasible for genetic data as well.
- Patient tracking shall be made available, by inputting the codes of interventions (OENO), so that information is available which enables the possibility of providing patient care of

adequate quality, which will form the basis of future modifications and corrections of applied treatment protocols.

- Establishing the legal background

When the detailed functionalities of the IT system are determined, the relevant legal and ethical rules and guidelines shall be taken into consideration.

Perhaps the most important of the above is compliance with the current national data protection laws. In the course of developing the system, the up-to-date data protection and data security solutions expected in the field shall be applied. The genetic samples and data as well as all procedures, activities and the submission of genetic samples and data shall be stored in the system for the duration laid down in the applicable law. The version tracking, management of authorisations, verification of the existence of statements of consent (informed), the option of cancelling the consent (data destruction) and the integration of other functions specified by the decision maker shall be ensured.

Determining data collection and data provision

The introduction of an adequate and unified coding system serves as a basis for the survey of rare diseases in the country, since in this case the organisation of the broadest reporting possible is particularly important due to the small number of cases. For all of this, the following is necessary:

- Organisation and publication of a professional recommendation on the types, ways of development, licensing, and maintenance of registers for rare diseases, which shall contain information on a standardised use of the ICD, the process of the ethical licensing of register development and the manner of connecting to the international register.
- The annual assessment of the developments of the ICD-OENO system in Hungary and in other countries and the situation of Hungarian and foreign registers for rare diseases by the Committee of Experts of Rare Diseases. The Committee shall give a proposal towards the Ministry regarding the actions to be taken and shall inform parental organisations.
- The use of recommended ORPHA codes shall be integrated into current electronic data collection in Hungary. The ICD-OENO system is the basis of funding; by harmonising this and modifying the HBCS system, the appropriate financial background shall be ensured for testing and giving treatment.
- The list of national patient registers shall be drawn up and the rules of regular maintenance of the list shall be set.

6.3.2. Expected effects:

- Effects on patients: adequate data collection facilitates the survey of demand for care, thereby patients can be provided sites offering care in a sufficient quantity and of an adequate professional quality, hence the overall quality, pace and availability of care will improve.
- The improvement of communication between professionals will facilitate centralised or individual diagnostic testing, consultation with colleagues and the provision of multidisciplinary treatment.
- Accurate statistics are the basis of developing future strategies or measuring the results of changes implemented.

- Valid data on the features of testing and treating rare diseases and their costs provided to the financing system are vital for planning the system of care.
- The knowledge of content stored in biobanks, biological samples and data related to certain rare diseases may be highly significant for users of the register.
- Supporting patient recruitment for clinical trials using the reliable data of the register.

6.3.3. Indicators measuring implementation

Indicator	Description of the indicator	Type of indicator
The number of national registers of rare diseases	Databases registering rare diseases on a national scale	process
Proportion of special patient registers	Number of patient registers specialising in rare diseases enabling individual and systematic data collection	process
Status of processing data from patient registers	Processing and analysing data of the patient register	output
Number of epidemiological research programmes integrated into the patient database	Creating epidemiological indicators through processing data from patient registers	output
Coding used by the system of health care - introduction of a new ICD code	Application of a standardised and internationally recognised ICD coding	process
Development and participation in the comprehensive national information system	Collecting and processing relevant information; policy tool and epidemiological basis for research; information for laymen	process
Participation in the European information network	Exchange of information on an international scale in order to eliminate the lack of information related to rare diseases. Collecting, organising and sharing best practices between the members of the network	process

6.4. Graduate and postgraduate education related to rare diseases

The aim of the courses

- Provide professionals of sufficient number and adequate quantification for establishing early diagnosis and providing appropriate therapy
- Increase recognition and the quality of non medical care by familiarising wider society with information about the individual and social problems caused by rare diseases.

In determining the proportions of education, genetics shall be given priority, without putting other less frequent causes into the background, hence losing the essence of the fight against rare diseases, since one fourth of diseases are of genetic origin. In addition to the above, the booming development of genomics in recent years shall be kept in mind, as well as its appearance in many areas of medicine.

In Hungary, universities of medical science in cooperation with institutes involved in the education of medical professionals and other institutes and patient organisations, or occasionally social and industrial supporters, provide an adequate background for this, which is shown in the following examples. In this chapter, forms of education implemented so far, currently in progress and available are detailed.

6.4.1. Interventions

Description of programmes (graduate medical training):

- Colloquium on rare diseases in the third and fifth years (DE OEC), seminar, fifth year (SZTE)
- Mandatory selectable graduate course on rare diseases, coordinated by the faculty of rare diseases: For students in the third and sixth years, 5x2 lessons, with an expected attendance of 100-200, since 2001, continuously (in English, DEOEC)
- Introductory course on human genetics for strengthening knowledge in genetics and facilitating the understanding of rare diseases genetically induced in 80%, year 2 (PTE)
- Emphasising rare diseases in genomics course with a similar aim, year 3-6 (SE)
- "Rare clinical cases, diagnostic challenges" course held by a senior student (in English, DEOEC 2011, 2012) with an attendance of 80 students
- Announcing thesis topics related to rare diseases (DEOEC, PTE, SE, SZTE)

Description of courses (postgraduate courses):

- The topic of "rare diseases" at the one-week further-education for internal specialists (Days of Internal Medicine in Debrecen) (3 hours, in 2012 for the 10th time)
- Further-education to family doctors (e.g. Károly Méhes Further-Education in Genetics, PTE) (DEOEC, PTE, SE, SZAE)
- "Rare diseases" as a PhD topic (DEOEC, PTE, SE, SZAE)
- Rare Diseases PhD course (DE OEC)
- Medical practice at the Faculty of Rare Diseases of DEOEC prior to the specialised examination in internal medicine and family doctor (1-3 weeks) in order to develop the diagnostic skills and approach (DEOEC)

- National specialised and further-education conferences on rare diseases, 3 times so far (DEOEC)
- Conference on rare diseases and customised medical care (DEOEC, SE)
- Foundation of the Clinical Genetics and Rare Diseases Working Group of the Academic Board of Debrecen (2011)
- Inviting renowned professionals and organisations, holding presentations and further-education sessions (regular, several examples can be given from all universities)
- Education of patients and their relatives

Organising summer camps for patients with haemophilia and other rare forms of blood diseases and their close relatives sponsored by the industry, which provide lifestyle counselling with the involvement of medical professionals (for several years, continuously). The International Day of Rare Diseases was also a good opportunity for giving specialised advice and an exchange of experiences.

Other options of education

There are initiatives in other institutes of higher and intermediate education: the twin class movement of primary and secondary schools educating physically and/or mentally impaired children, organising joint programmes (e.g. Debrecen, Svetits Institute – Gusztáv Bárczi Faculty of Special Education; for many years, regularly).

In order to achieve the above objectives, it is extremely important to harmonise and accredit further-education, graduate and postgraduate education institutes and to ensure uniform standards, which requires the appointment of an education coordinator.

Regular data collection and provision is recommended for the annual reporting of the education coordinator of the National Plan. This requires the organisation of the performance of administrative tasks, that is, ensuring continuous data provision, feedback and updates by the National Centre for Rare Diseases.

In the following chapter a detailed account of measures to be taken in individual areas of expertise is given. The Centre for Rare Diseases provides assistance to the national accreditation of existing presentation sessions and forms of education and makes the further-education programme available in all regions.

The education coordinator holds together and assesses the curricula related to higher education, and in cooperation with the University Centre of Rare Diseases unifies the graduate education materials of the Rare Diseases course, while respecting the autonomies of universities and taking local characteristics into consideration. Beyond the principles in postgraduate and PhD programmes, the local characteristics and focused areas can remain unchanged.

The minimal curriculum of Rare Diseases courses shall be developed by 31 December 2013.

The implementation of the proposed programme requires the following cooperation:

- OEFI is the infrastructural and professional base of the programme,
- the Coordination Centres of Rare Diseases functioning at universities of medical science,
- patient organisations within NORD (National Organisation for Rare Disorders),
- participation of other secular and denominational organisations with a similar aim in the programme

Development of education programmes (graduate education programmes)

- Introduction of rare diseases into the mandatory curriculum of all institutes (of higher and intermediate education) training medical and health care professionals (e.g. an annual 2 lessons in the two years preceding final examinations).
- Launching an elective credit course in the area of rare diseases at all universities of medical science.
- A colloquium/seminar (2 lessons) on the special problems of patients with rare diseases is desirable in non-medical teacher's schools and colleges, which is aimed at raising awareness of rare diseases and give guidance to future teachers regarding how to obtain relevant information.
- Announcing thesis topics related to rare diseases.
- Organising a rare diseases section for scientific student conferences.
- Improving the organisation of guest tutors between universities extending it to institutes of education with a Hungarian mother-tongue in the Carpathian basin.

Development of education programmes (postgraduate education programmes)

- Introduction of the topic of rare diseases in curricula of all universities of medical science, preparatory and maintenance courses for final examinations of internal medicine or general practice.
- Introduction of rare diseases as a PhD course or topic at all universities of medical science.
- Medical practice prior to the specialised examination in internal medicine and general practice (1-3 weeks) in order to develop the diagnostic skills and approach in the area of rare diseases.
- Organising remote further-education programmes for family doctors through case studies.
- The organisation of a national professional and further-education conference on rare diseases would be reasonable on an annual basis, rotated between the four universities.
- Establishing further work groups for rare diseases in the local academic boards is recommended.
- Obtaining the basic qualifying examination (after 4 years in the course) on clinical genetics is recommended.
- Establishing the conditions of the clinical license examination is recommended.
- Forming the molecular genetic diagnostics into basic qualifying examinations with a four-year long programme is recommended.
- Launching a Genetic Councillor (MSc) programme at Faculties of Medicine is recommended (PTE).

Programmes for the education of patients and their relatives

- On the International Day of Rare Diseases, so called "ask-the-expert" round tables shall be organised focusing on individual diseases, involving 3-4 professionals, affected patients and their relatives.
- The foundation of the "Civil Academy" with the topic of rare diseases with the extensive involvement of patient organisations is recommended.

- Other programmes of education
- The appearance of organisations for rare diseases related to the topic shall be ensured at professional conferences as well as at public health events with rare syndromes relevant to the topic.
- In intermediate education:
- Holding a lesson on rare diseases in the school year preceding the secondary school final examination is recommended.
- Following theoretical preparation, the personal contact of students with patients and patient groups suffering from a rare disease should be organised. Here, patient organisations play a significant role, therefore institutionalised connections should be strengthened or established between schools and patient organisations existing under the umbrella of the National Organisation for Rare Disorders (NORD). (The current list of member organisations of NORD is contained in Annex 3.)

6.4.2. Expected effects

Experiences and benefits of developing education:

- The extension of knowledge on rare diseases among specialised healthcare providers and future professionals will lead to improvements in the effectiveness of care.
- The time necessary to establish a correct diagnosis will reduce.
- Care will become more rationalised, its quality will improve and the number of variations in care will reduce.
- Centres providing care to patients with rare diseases will better understand each other's specialities.
- The relationship between care providers, the Centre of Rare Diseases and patients will be more personal.

6.4.3. Indicators measuring implementation

Indicator	Description of the indicator	Type of indicator
Number of trainings and courses launched in the topic of rare diseases	Organising graduate and postgraduate as well as laymen education in order to extend knowledge related to rare diseases.	output
Number of participants in graduate and postgraduate courses related to rare diseases	The number of participants in courses on rare diseases.	output
Number of guidelines related to the clinical practice developed and published between 2014 and 2020	Continuous integration of guidelines on clinical practice into the process of patient care.	process

6.5. Improvement of newborn screenings

The aim of newborn screening

- Screen patients before the occurrence of symptoms
- Decrease morbidity and mortality
- Avoiding diagnostic labyrinths
- Family planning
- Cost efficiency
- Mental retardation or even death can be prevented.
- Safeguards children from lifelong dependency.
- Safeguards the family from the frustrating and heartbreaking experience that care of a sick child means.

Between 2010 and 2011 the European Union conducted a survey regarding the practice of newborn screening of the Member States, in which Hungary also participated. The summary of this study, "*Evaluation of population newborn screening practices for rare disorders in Member States of the European Union*", released on 18.10.2011, contains the following main statements:

In most EU Member States there is newborn screening (NBS), which was extended following the introduction of tandem mass spectrometry. Screening panels, organisational structures and legal backgrounds differ. (The current screening panel of Hungary is contained in Annex 2.) After giving a detailed overview of the panels, the legal regulation of the screening, information services to future parents, the examinations confirming diagnosis, the commencement of treatments, and the means of quality assurance and control, the survey comes to the conclusion that the proximal steps of the screening (informing parents, laboratory tests) are better regulated than distal steps (epidemiological assessments through the registers and assessment of the outcome of treatments). The thresholds used to diagnose diseases differ in certain countries and and in certain laboratories in the same country. The further-education of professional groups participating in NBS programmes is inadequately organised, and needs significant development. The systems coordinating (e.g. registers) the collection and exchange of data are important as regards the technical and clinical aspects of newborn screening programmes as well as the assessment of cost-efficiency. NBS programmes shall be considered a complex process spanning from legal regulation to the regular assessment of the outcomes of treatments, and not limiting it to the technical part of NBS laboratories.

Screening shall be integrated into the national network of rare diseases in terms of legal background, financing and effective organisation.

6.5.1. Interventions

Improvement of the conditions of screening

- Establishing the minimum requirements of screening
- Establishing the accreditation conditions of laboratories

- Drawing up a development plan for sustainability in personal and material aspects for 15 years.
- Development of standardised procedural rules for the organisation and management of newborn screening examinations;
- Development of a policy for the treatment and tracking of screened patients
- Development of standardised procedural rules regarding informing parents;
- Making informative materials for parents who are presented with the diagnosis or suspicion of a screened disease;
- Development of standardised procedural rules for the training of professionals participating in the screening;
- Promotion of cooperation between laboratories (in order to improve quality and cost-efficiency);
- Creation of a unified patient register, where screened cases can be monitored;
- Establishing the conditions for the application of Wilson-Jungner criteria, which is primarily performed in the assessment of efficiency of certain elements of the screening panel or during the revision of the panel;

Recommendation for the assessment of introducing new screenings

In the last 1-2 decades, following technological developments and genetic research, a few recommendations have been made for the newborn screening of additional diseases (cystic fibrosis, Duchenne muscular dystrophy, hearing impairment, lysosomal storage disorders, fragile X syndrome, congenital hyperaldosteronism). Currently there is no wide consensus between professionals on the mass application of these. The for and against arguments include the benefits arising from detection at a newborn age (better hopes of treatment, change of lifestyle in an early stage of life) and the difficulties caused by the limitations of the capacity of the system of care (the tight costs and organisation demand of screening programmes, system of conditions for treating detected cases for a lifetime).

Below the issue is demonstrated through two specific diseases, noting however, that any extension of newborn genetic screenings can only be realised after science and options have been duly considered due to the rapid development in methods and the growth of the body of knowledge.

Duchenne muscular dystrophy (DMD)

In patients suffering from Duchenne muscular dystrophy(DMD) the activity of the creatine kinase (CK) enzyme is higher at birth, therefore the dried blood sample enables the measuring of CK activity using a fluorometer. In case of higher CK activity the test is performed again at 4-6 weeks. This is followed by a DNA-based mutation test, which includes the method capable of examining the gene exon deletions or duplications of dystrophine (MLPA) and DNA sequencing for the detection of point mutations. The proof-based newborn DMD screening is two-tiered.

The newborn screening of DMD is difficult to align to traditional screening programmes (newborn screening, NBS), since early detection is only possible in certain cases. The most promising therapeutic option is the so called exon skipping (AON therapy) based on

antisense oligonucleotide, which is only suitable for improving certain detections; currently it is in phase 3 of medical trials. Until the targeted therapies supplementing dystrophine protein become available, the generally accepted recommendation is glucocorticoid therapy, which prolongs the ability to walking and the length of life of the sick child. In accordance with international standards the steroid treatment shall be commenced before the activity of the child with DMD starts to decay. Considering that even in developed countries the clinical and genetic diagnoses are performed at age five, an early diagnosis is invaluable.

Therefore, it is a severe problem that the symptoms of DMD only appear some years after birth, which means that affected children are very often born. Hence, in case of DMD NBS, with the help of successful mutation analysis, in the subsequent pregnancy foetal diagnostics provides the greatest advantages for both families and the healthcare system.

In recent years there have been numerous pilot project in many countries of the world (USA, New Zealand, France, Belgium, etc.). The implementation of such pilot studies would assist decision makers in introducing NBS in the future on a greater scale. Due to the expected incidence (1/3500 male newborn) 20,000 samples would need to be screened to detect 4 new cases. Based on the above facts, the possibilities of introducing newborn DMD screening could be assessed by two-year long pilot tests in two or three counties.

Cystic fibrosis (CF)

CF is known to be the most frequent congenital disorder, with an average prevalence in Europe of 1:3 500 (1:2 250 – 1:10 500). With the classic and severe phenotype, death often occurs in the first ten years.

An early diagnosis improves the prognosis of the disease. The condition of nourishment of patients diagnosed at a newborn age by screening is better, their curve of development is normal/close to normal, their lungs are less damaged and they are less frequently hospitalised. Screening might prevent the cognitive dysfunction typical of children who were diagnosed later. The frequency of life-threatening complications and death decreases at infancy and early childhood.

A diagnosis established prior to the age of 2 improves the prognosis of patients to the greatest extent. Without screening there is generally a 15-month delay from the time when the first clinical symptoms appear until the diagnosis. The average delay in Hungary was 227 days in a survey conducted in 2012. The costs of establishing diagnosis and treatment (less hospitalisation) are reduced by screening.

The disease could be detected in the siblings of the newborn diagnosed with CF, so they could also be provided with special care. Parents would be given genetic counselling for family planning in the future. Consequently, prenatal diagnostics would also become available. As a result of screening programmes, screenings, genetic counselling and prenatal diagnostics, usually a reduced CF prevalence is reported.

In Europe (England, Austria, Czech Republic, France, the Netherlands, Ireland, Poland, Norway, Italy, Spain, Switzerland, Sweden, Slovakia) and in all 50 states of the USA and in Australia national newborn CF screening has been performed for an average of around 10 years (1-40 years).

In Hungary attempts were made to introduce CF screening between 1974 and 1977. CF screening was performed on 26,209 newborns at the Paediatric Clinic of the University of Szeged by measuring the albumin content of meconium, however, the test did not become part of the screening program. Currently, there is no CF screening in Hungary and the genetic confirmation of the diagnosis of patients with the suspicion of CF is also unsatisfactory. The diagnosis can be genetically verified in one-third of patients by DNA mutation tests, which also limits the possibilities of counselling for family planning and prenatal diagnosis.

In the future the reassessment of the introduction of CF screening examinations would be important based on the following facts:

- detection of patients under the age of 2 months,
- timely application of special treatments,
- slowing the progression of the disease,
- reducing the number of hospitalisations and the duration of hospital treatments,
- avoiding early death,
- examination of the siblings of the patients to confirm/exclude the presence of CF and, if necessary, to introduce adequate treatment,
- genetic counselling to parents for positive family planning,
- making prenatal diagnostics possible.
-

Interventions and tools necessary to introduce CF screening:

- Introduction of newborn CF screening examination in the entire country,
- Designating CF centres for performing screening, admitting and treating patients,
- Designating the organisational units of genetic counselling.

6.5.2. Expected outcome

- Permanent and continuous improvement of health of newborns belonging to individual special disease groups.
- Ensuring the optimal operating conditions of screening centres.
- Appropriate response-giving ability for the challenges of future new diseases.
- Harmonised development conforming to the healthcare environment of the country.

6.5.3. Indicators measuring implementation

Indicator	Description of the indicator	Type of indicator
Number of screened patients	Processing the data serving the description of the efficiency of the screening.	process
Number of false positive cases		
Number of accredited laboratories	Number of diagnostic laboratories in the country capable of performing genetic tests.	output

6.6. Improvement of the medicine supply for patients with rare diseases

The inclusion procedures for the so called orphan drugs developed for the treatment of rare diseases are not carried out or only with limitations, therefore the care of patients is performed in a special manner. In Hungary besides general subsidised funding, individual subsidies make it possible to provide support to patients based on their unique needs for unsupported medical products with high cost.

The following can be legally financed from the budget for individual subsidies granted on the grounds of equitability:

- Allopathic medicine without social insurance coverage, nutriments satisfying special needs of nourishment, medical appliances;
- Contribution to the repair costs of supported medical appliances based on equitability;
- Prescription of medicine beyond indication is possible after permission is obtained.

Individual requests submitted to the National Health Insurance Fund can be accepted, among others, based on the opinion of an expert in the field.

In the course of treating rare diseases we come across many issues of health care policy requiring health-economic justification, which can be divided into two main categories: issues of pricing, subsidy policy and accessibility of exceptionally costly therapies and the issues of organisation of providing care for individual rare diseases.

The decisions regarding the pricing and financing of therapeutic options of rare diseases, particularly the so called "orphan drugs" are highly important to policy-makers, legislators, medical professionals, leaders of the industry, researchers and naturally patients and their relatives.

Beyond equitability other aspects are also taken into account in many countries with decisions on financing, for instance the severity of the disease, other available therapeutic options and, in the absence of therapy, the costs incurring from the medical condition. As a consequence, the maximum cost for a unit of outcome can be higher with orphan drugs, to which high social benefit can be assigned.

In Hungary 14 orphan drugs of different strength and quantity were granted social insurance coverage in 2011, bringing the total number of subsidised orphan drugs to 23. Most preparations are 0% (hospital financed) and priority, bound to indication, and included in the 100% (pharmacy distributed) support category.

In 2008 1431 patents and in 2009 1732 patients were provided with orphan drugs within outpatient care. Two orphan drugs were accounted for in inpatient care; for 18 patients in 2008, and 20 patients in 2009. In 2009 289 patients received individual subsidies based on equitability. The medicines for approximately 13 rare diseases are supported within the framework of individual subsidies.

6.6.1. Interventions

Developing an evidence-based pricing strategy:

A transparent and evidence-based pricing approach is needed regarding decisions on the pricing and financing of orphan drugs. The relative effectiveness, cost-efficiency and budgetary effect shall be in the focus of such an approach.

Developing specific procedural orders for the adaptation of orphan drugs:

The current practice is to only make a decision on inclusion if there are savings in the medicine budget, which puts orphan drugs into a particularly difficult situation. Unfortunately, there are no specific procedural rules for the inclusion of orphan drugs, particularly there is no higher threshold for the inclusion of orphan drugs (QALY).

Distribution is often only available through requests for individual subsidies made on the basis of equitability. However, the assessment of requests is a complicated and lengthy process. The proportion of distribution on the basis of individual subsidy is determined in a special procedure in accordance with the capacity of the insured.

As regards price-formation, it is necessary to have a decision based on the joint assessment of the EU and on the reference price, a special inclusion policy regulation on inclusion in the supported category, the development of risk sharing models and the restriction of support only to a clearly definable group of patients. The refusal of support cannot be avoided if there is a lack of information or an exceedingly high budgetary effect.

Decisions on health care policy based on transparent evidence in the case of expensive technologies and care organisation shall be made, which facilitate the more efficient use of limited healthcare resources. Due to the lack of resources on the part of the funding entity the improvement of the allocation efficiency of existing budgets seems to be a feasible option for improving the quality and efficiency of healthcare. The preconditions of improving the allocation efficiency is to conduct medical-economic assessments establishing and facilitating decisions.

Subsidising medicine of high cost:

Based on the opinion of medical-economic experts the assessment of the cost-efficiency of orphan drugs can be adopted into the assessment scheme of original medicines within the normal procedural rules by taking into consideration certain special features. However, in numerous cases the incremental rates of cost-efficiency are quite high, and in such cases the recommendation of the product needs to be justified by the assessment committee with reasons of equitability.

A so called ultra-orphan category can be distinguished, which has a prevalence of less than 1/50,000 representing extremely rare diseases. The assessment of these medicines is problematic in the existing situation, so new rules of decision-making need to be set for them, which could extend to a higher cost-efficiency threshold band.

Our objective is for the subsidisation of medicines currently financed on the basis of individual subsidy to be preceded by medical-economic assessments, since this could make the system of assessment more rational and transparent.

Supporting disease-specific medical-economic assessments:

The group of rare diseases is very heterogeneous, so unified modelling is not possible. At the same time, it is worth selecting a disease symbolising a generalisable problem, which could serve as a model for future assessments as well. Based on these aspects the comprehensive medical-economic assessment of the following areas is recommended:

- Assessment of the patient pathway for complex diseases affecting more than one organ, and therefore requiring complex and multidisciplinary treatment, and the development of a detailed medical-economic model for it.

- Medical-economic modelling of the therapeutic options of an oncological disease that can be treated with highly expensive medicinal technology.
- Medical-economic modelling of a disease requiring highly expensive medical appliances.

Subsidy of medical appliances

- Patients with rare diseases, similarly to other patients, may obtain medical appliances on the list of appliances by prescription through social insurance; and may request support towards the price of the medical appliance not eligible for a price reduction from the social insurance fund, based on individual subsidy. In general the prescription of appliances is bound to special qualification, not to institutions.

6.6.2. Expected outcome

- The principle of subsidiarity is a guide: In the course of the reorganisation of the hospital structure system, it is advisable to pay special attention to the care of patients with rare diseases. In Hungary numerous institutions specialising in the care of rare diseases have operated for several decades, and already meet the main criteria for being designated as Centres of Expertise. By using and rationalising existing structural bases, human and material resources and by meeting the missing requirements, the foundation of CEs can be optimised from a financial aspect.
- Objectification of the added value of (ultra) orphan drugs with exceedingly high cost requirements.
- Reduction of administrative burdens by defining time frames and establishing electronic data provision. Providing the highest quality therapy possible by creating financing protocols along professional guidelines.

6.6.3. Indicators measuring implementation

Indicator	Description of the indicator	Type of indicator
Proportion of financed medicine for rare diseases	Processing the data related to medicine consumption, assessment of accessibility to financed medicine.	output
Proportion of accessible, but not financed medicine	Proportion of non-financed medicine consumption compared to financed medicine consumption.	
Proportion of used orphan drugs	Use of medicine compared to the number of patients with rare diseases.	output

6.7. Research in the field of rare diseases

In addition to research in medical science, the research projects in the areas of social sciences, epidemiology and medical-economics dealing with rare diseases shall also be given attention and resources.
The introduction of new diagnostics and therapeutic procedures shall be handled as a priority, which are facilitated by the designation of CEs, the development of their system and connecting them into the European network.
Nowadays, many children suffering from rare diseases live to adulthood, for this reason access to continuous and cross-border care shall be ensured in all stages of life.

6.7.1. Interventions

Launching research projects through tendering to measure the dimensions of patient care and patient satisfaction

Scientifically justified evidence is needed for the timely diagnosis, adequate care and treatment of patients, which are often impeded by problems arising from the rarity of the disease. For this reason research projects into rare diseases can be supported by a tendering system different from that of diseases of higher prevalence. The induction of research regarding quality of life, patient satisfaction and medical and social care as well as the support of examinations aimed at measuring the accessibility of care are needed.
Effective research can only be performed by creating a strong internal network in the country and the inclusion of this network in the international network. The development model of care of rare diseases through CEs acting as centres that meet EU requirements related to quality and the participation of Hungarian centres in European networks give a chance to the country to join the growing number of EU7 and EU8 programmes.

Cooperation between institutions and teams performing research into rare diseases

The research of rare diseases is complicated due to the large number of diseases, heterogeneity and low prevalence. Advances can only be achieved in the examination of rare diseases by the multidisciplinary cooperation of individual fields of science at a national and international level.

Epidemiological studies examining the background and prevention of rare diseases

Emphasis shall be put onto the initiation and support of epidemiological studies related to rare diseases, since in some areas the amount of scientific evidence is insufficient. The continuous research of the aetiology and nosology of rare diseases with the help of analytical and epidemiological analyses is essential. The possibilities of preventing rare diseases shall be studied at various levels of prevention. Studies explaining the frequency of application of primary preventive tools and the entirety of the factors impeding the implementation of primary prevention. The potential for introducing new screenings shall be examined within secondary prevention, using scientific results and through health impact assessments.

Developing protocols supporting the process of giving information on diagnoses

There are protocols for informing patients in the case of many diseases, but it is essential to improve them and to formulate additional ones for diseases which currently do not have them. It is important to use the protocols already available. In institutions a person shall be appointed who performs this task sequence, who may request the assistance of an expert (psychologist). After notification has been given orally, written material shall be provided to the patients and/or their families.

The epidemiological use of data assets created within the system of healthcare

Currently, the coding of rare diseases is inadequate (only 250 diseases had a dedicated code in version 10 of the ICD). In version 11 of the ICD the number of codes is expected to grow to 2500. Through the extension of the number of codes the coding practice shall be improved and the potential in the use of ORPHA codes and the scope of information that can be acquired (surplus) by them shall be assessed. With the development of the coding practice the reliability of accessible databases improves, hence their possibility of use extends. Following the assessment of the usability of data, epidemiological features such as incidence, prevalence, mortality and lethality can be defined. Beyond these there is a possibility of calculating the indicator related to numerous types of care.

Clinical examinations contributing to the therapy of rare diseases

It is vital to support clinical studies facilitating the medical treatment of rare diseases, due to the nature of rare diseases. It is important to support studies aiming to explain the development and progression of diseases to make new therapeutic procedures scientifically justified by supplementing existing knowledge. Within clinical studies it is essential to continue the existing physiopathological investigations and initiate new investigations. Using the tools of clinical studies new diagnostic tests, and through gene and cell therapy research new therapeutic methods can be developed and introduced in the context of improving the medical treatment of patients suffering from rare diseases. Furthermore, it is necessary to provide tendering possibilities to finance studies initiated by researchers and to further develop biobanking.

Participation in clinical research

The E-Rare (ERA-Net developed for rare diseases) programme is the network of 16 partners in 12 countries, who are responsible for the development and financing of joint national/regional research projects. The network is financing international research projects into rare diseases and also aims to build up the rare diseases research programme. Our aim is to become a member of the E-Rare 2 network with full accession in order to provide better patient care.

We shall join the IRDIRC (International Rare Disease Research Consortium) founded in April 2011 with the objective of promoting the international cooperation of research into rare diseases. Since then numerous European institutions have joined the initiative of the European Council and the Canadian Institutes of Health Research. In January 2012 a connection was established between E-Rare 2 and IRDIRC. The Hungarian institution is a joint partner in RD-Connect, the global infrastructure project related to rare diseases supported by EU FP7 between 2013-2018. The aim of the project also supported by the

IRDIRC is to link the databases, biobanks and clinical bioinformatic data used in the research of rare diseases in a global central data source.

6.7.2. Expected outcome

Effect on patients: the background of more and more rare diseases is revealed in research, and as a result there are even more date for establishing accurate diagnoses, thus less time and fewer examinations are needed for obtaining a diagnosis.

As a result of research projects, unnecessary interventions can be avoided, and based on the data acquired during research, special therapeutic interventions and medicine could be developed. The results of epidemiological studies can facilitate the determination and monitoring of the quality of care, hence the care of patients with rare diseases can be improved.

Effect on professionals: international relationships can be established and specific diseases can be studied in more detail. The guidelines developed by international experts could help Hungarian professionals in diagnosing and treating patients with rare diseases.

Effect on the financing entity: by becoming financially included in international research tenders Hungarian researchers could have the opportunity to be awarded subsidies of larger amounts.

6.7.3. Indicators measuring implementation

Indicator	Description of the indicator	Type of indicator
Number of national research programmes and/or projects	Implementation of research programmes and projects related to rare diseases.	process
Number of scientific conferences organised on rare diseases.	Publication of the results of research projects related to rare diseases.	output
Number of participations in international research initiatives	Organisation of international projects based on inter-sectoral cooperation.	process
Number of scientific publications related to rare diseases	Releasing publications with an impact factor in the topic of Rare Diseases.	output

6.8. Improvement of access to social care by patients with rare diseases

The complete regulation of the rights of the disabled shall include the regulation of the rights of patients with rare diseases for whom the disease is as severe as a disability. Providing social care inevitably necessitates the definition of the notion of "patient with rare disease" that can be inserted into the existing systems of social care. It is important to make the legal regulation of complex rehabilitation understandable also to patients with rare diseases, and as a result patients with rare diseases can be provided equal opportunities, lead independent lives and enjoy active inclusion in social life. In the course of managing state responsibilities the special needs of patients with rare diseases are recommended to be taken into consideration, while in making decisions affecting patients with rare diseases, the fact that these people are equal members of society and the local community means the conditions shall be ensured with which they can be active members of society.

6.8.1 Interventions

The aim of improving social services:

- Teach the affected person and his/her family how to live with the disease and its consequences after the diagnosis has been given
- Improvement of their quality of life
- Establishing communities with people faced with similar challenges, reduction of their isolation
- Facilitating their inclusion in society
- Creating complex individual development protocols
- Continuous counselling, follow-up and family consultation, case management
- Development of cooperation with scientific centres
- Opportunities shall be ensured to provide occasional recreation of some weeks to relatives of patients in severe condition and requiring constant care. This requires temporary services
- Special training sites are needed to teach the tasks of care, where the entire family may turn either for specific knowledge or for new solutions

Development of rehabilitating care

- The preparation of existing providers of social services is needed as regards the special approach to be taken for patients with rare diseases in terms of development, temporary care and family support;
- In addition to the above the tools of special social services shall be developed and ensured: establishing and extending therapeutic recreational programmes, programmes promoting the integration of patients into everyday life, helpdesk, etc.
- The supporting methodology must be implemented containing programme plans suited to the existing and improvable skills of patients with rare diseases, and demonstrating the regular measuring of development in skills achieved in the course of the rehabilitation process and the necessary modifications of and improvements to the rehabilitation programme;

- Patients with rare diseases shall be provided access to services and care designated in the rehabilitation programme in an organised manner,
- The cooperation with organisations and persons contributing to the rehabilitation process and the monitoring of their rehabilitation activities shall be ensured;
- Access shall be granted to the special medical appliances needed for a given rare disease
- It is essential to monitor the collection of data and information related to the rehabilitation services provided by organisations offering the service, and to the organisations themselves, for the purposes of giving information to disabled people, their family members and helpers.

Education and training of patients with rare diseases

Patients with rare diseases, like disabled people, have the right to participate in early development and care, kindergarten education, school education or preparatory courses depending on their medical state and age, even if the disadvantages arising from their condition make it necessary, but do not qualify the affected people as having disability, in accordance with the provisions of the Act on Public Education. The kindergarten or school providing kindergarten or school education for the patient with a rare disease should be chosen by the parent with the supportive cooperation of the expert and rehabilitation committee.

Improvement of the employment situation of patients with rare diseases

Such patients shall be eligible for integrated or, if this is not available, protected employment with similar opportunities to those afforded to disabled people, if the general condition of the patient justifies this. If the patient cannot be employed in integrated employment, then their right to work shall be ensured by operating special workplaces for them, if possible.

Establishing the National Institute of Rare Diseases, charged with the tasks of providing information, habilitation, development and services

The foundation of a centre would significantly facilitate the implementation of the above tasks. From the aspect of public health the main problem related to rare diseases is the lack of information and the consequent delay in establishing diagnosis as well as possible unsatisfactory care. Besides healthcare, the areas of education, employment and social care could contribute the most to the improvement of the quality of life of these families. Patients suffering from chronic, life-threatening and often debilitating rare diseases require supervision and care on a daily basis. In order to compensate for the disadvantages caused by diseases, the effectiveness of social solidarity and state support shall be increased.

If healthcare provides the earlier correct diagnosis, then early development built on that could form the basis of prevention, development, rehabilitation and social inclusion.

All these would be significantly facilitated by the foundation of the National Institute of Rare Diseases tasked with providing information, habilitation, development and services.

A multidisciplinary care providing centre in possession of new development methods and options based on the Scandinavian model would be gap-filling. In this institution not only early development, but also development without limitations of age could be performed,

which would be a modern solution for patients with rare diseases both in Hungary and in the Carpathian Basin.

With the Norwegian Frambu Centre taken as a role model, the project can be implemented in close cooperation with this centre and the Norwegian ministries. The Frambu Centre, as one of the European examples that work very well, enables the use of already developed know-how. A harmonised centre organised around team work, achieving complex habilitation, preventive and re-educational objectives and supported by the cooperation of non-governmental organisations, would effectively provide help to affected children, adults and their families. The institution would directly serve the patients suffering from rare diseases, whose medical condition is often not detected in time and for whom no adequate development is offered. Its activity could include keeping close relationships with families raising affected children as well as counselling services to them. The primary aim of the centre's activity is the earliest possible detection, curing and rehabilitation of damaged or missing functions with a well-qualified professional team.

6.8.2. Expected outcome

Ensuring the rights and services contained in the proposals for measures could effectively contribute to establishing independent lives for patients often faced with compound disadvantages, support for families raising these children and further-strengthening their mental health. The long-term improvement of the situation of families living with a patient with a rare disease could facilitate the social inclusion of this disadvantaged group.

The habilitation and rehabilitation centres would be an important stage for strengthening social awareness and the dissemination of knowledge. The centre would contribute to the development of sustainable cooperation between nations and to participation in European non-governmental networks.

The development of the social and educational system gives a chance to increase the number of disadvantaged citizens of Hungary and adjacent regions suffering from rare diseases who can improve their quality of life and compensate for their social disadvantages. Accordingly, healthcare is closely connected to encouraging disease prevention and health improvement activities, the improvement of mental hygiene care and the extension of the capabilities of non-governmental organisations engaged in healthcare. At the same time, this also promotes the integration of disadvantaged, often multiple disadvantaged children and adults.

6.8.3. Indicators measuring implementation

Indicator	Description of the indicator	Type of indicator
Programmes supporting the integration of patients with rare diseases into everyday life	Providing and developing social services to patients and their family members. Extension of special knowledge and tools related to social services.	process
Existence of an official register of available social allowances	Providing information to those with social needs regarding available allowances and the method of using them.	process
Establishing the National Institute of Rare Diseases tasked with providing information, habilitation, development and services	Multidisciplinary care providing centre serving the affected individuals, which possesses and transfers various development methods and options.	result
Training of social service providers	Training of employees working in social services regarding the knowledge and development methods related to patients with rare diseases.	result

6.9. Cooperation with non-governmental organisations, patient representation, laymen education

There has been cooperation between healthcare institutions and patient groups of certain rare diseases for many years. Many patient organisations were formed at the initiative of doctors or researchers in healthcare, while others were founded through self-organisation. In the next phase of development the patient organisations developed cooperation with other areas for the purpose of achieving a wider care of patients. The organisations of these patients gathered into an association (NORD) in 2006, which commenced the harmonised representation of interests of patients suffering from a wide-range of rare diseases by setting national common objectives in cooperation with foreign patient organisations and experts, such as the EURORDIS with participation in the international operations of EUCERD.
The achievement of the above objectives of the cooperation with patient organisations requires long-term development and the achievement of other aims.

6.9.1. Interventions

The aim of the cooperation with patient organisations:

- The patient organisations, with their experience, support the work of professionals, provide assistance to patients and their families and promote the development of social tolerance and prevention,
- With the help of patient organisations policy-makers may collect useful information, without spending state resources, on diseases, patients and their circumstances and social situation,
- With targeted preparation the contribution of non-governmental organisations makes it easier to cope with psychological needs and improves social integration,
- Patient organisations have an important role in the creation and operation of development and rehabilitation centres, which are necessary for improving the quality of life of patients with rare diseases, their family members and their caregivers.
- The contribution of non-governmental organisations to the organisation of special social services facilitates the reduction of the lack of education and the appearance of the patient with a rare disease on the labour market.

Development of the cooperation with patient organisations:

- The inclusion of patient organisations in the process of long-term planning affecting patients with rare diseases, the development of a system of regulation to be applied in the course of its implementation, the monitoring of execution and the tasks related to rare diseases (e.g. creation of patient databases) are necessary for the inclusion of patient-side information.
- The organised and systematic inclusion of patient organisations in projects related to rare diseases and the work of various forums affecting patients with rare diseases is needed (e.g. in the Council of Medical Therapy, etc.).
- For the purposes of a long-term and sustainable cooperation the replanning of the legal and economic conditions of cooperation with patient organisations, the

development of a support and tendering system facilitating the permanent operation of patient organisations are needed (e.g. creating and maintaining targeted tenders, ensuring the infrastructure of an incubator office, etc.). The simplification and shortening of the duration of support, tenders and other procedures could provide significant help to solving the maintenance issues of patient organisations without substantially increasing the burden on currently available resources.

- As a part of acquiring resources, the creation of an incentive system with justified tax benefits or other economic benefits is necessary, promoting the donation activities of economic operators and individuals.
- Organising layman education, development of the knowledge of professionals getting into contact with rare diseases is an important task in the whole area of care of rare diseases. In layman education, patient organisations can play an important role from multiple aspects: e.g. the patient organisations can recruit the participants of trainings, they themselves can take part in them and become an information base of qualified professionals playing a role in the coordination between patients and qualified professionals.
- Establishing the information knowledge base and the technical background making it accessible is essential for cooperation between professionals and patient organisations. The adequate technical background facilitates integration into existing Hungarian and international systems.
- The knowledge of experienced helpers shall be increased by training, where the patients may also participate as experts from the side of experience. Such training and preparation facilitates the solution of problems related to rare diseases (e.g. by training helpdesk workers, representatives of patient rights and patient organisations as well as social workers).
- The inclusion of patient organisations in the development, maintenance and operation of a telephone helpdesk, using the expert staff and tools of patient organisations and, if possible, by providing employment to employees with rare diseases.
- The cooperation of accredited CEs shall be ensured with the organisations of patients with rare diseases through consultation and information services.
- At the foundation of the National Institute of Rare Diseases tasked with providing information, habilitation, development and services, the inclusion of patient organisations is necessary, because they can facilitate the improvement of the quality of life of patients with rare diseases, their family members and caregivers.
- Through the continuous maintenance of cooperation it shall be ensured that patient organisations explore and promote the application of international good practice.

6.9.2. Expected outcome

Effects on patients

The inclusion of practical knowledge of patient organisations facilitates the social applicability of the programme and the establishment of regulation suited to the rightful needs of patients and improving their quality of life.

Effects on other affected parties (experts, policy, financing, etc.)

The effect of the strategy developed in the framework of cooperation in practice reduces the burden placed on society, since direct representation of interests contributes to the effectiveness of treatment, efficient medical care, use of medicine and improvement of patients' skills, thereby alleviating the future costs to society.

The patient representations help the dissemination of social knowledge related to the programme, andcommunication between various social groups.

6.9.3. Indicators measuring implementation

Designation of activities	Indicators	Type of indicator
Permanent and official inclusion of patient organisations in decisions affecting them as well as the development, inspection and assessment of the National Plan	Patient representatives officially participate in all phases of planning, management, controlling and assessment	Process
	Inclusion of patient organisations in the development of research strategies of rare diseases	Process
Support of the activity of patient organisations of rare diseases	Budget for the support of the activity of patient organisations	Result
	The extension of patient organisations' role, the existence of supports for the development of sustainable activities (such as raising awareness, capacity-building and training, exchange of information and good practices, building the network of relationships, training the reaching of extremely isolated patients, etc.)	Result
Helpline for rare diseases	Is the national helpline for rare diseases assisting patients and professionals (or both) available or not? For giving information to patients providing social, psychological and information solutions suited to their needs.1. No; 2. Yes; (If the answer is 'Yes', then is it only for professionals, only for patients or for both; and is it state-funded or other)?	Process

7. Schedule

	Name of intervention	Schedule of intervention								
		2013	2014	2015	2016	2017	2018	2019	2020	Total
1. Measures for the develop-ment of the diagnostics of rare diseases	Organising genetic diagnostics into centres		x	x						
	Development of the quality management system of units created				x	x				
	Training the required specialist professionals			x	x	x				
	Providing a level of instrumentation that meets the levels of progressiveness				x	x				
	Ensuring the ethical and legal background for informing patients		x	x						
2. Designa-tion of accredited CEs	Designation of CEs	x	x							
	Introduction of tasks within their competence		x	x						
	Establishing extensive multidisciplinarity			x						
	Ensuring compliance with EU requirements, accreditation				x	x	x			

3. Developing patient registers	Defining requirements related to quality management and validity		x	x						
	Data protection, establishing the legal background		x	x						
	Establishing data collection and data provision			x	x					
4. Training and education related to rare diseases	Training of participants in graduate and postgraduate programmes		x	x	x	x	x			
	Education of patients and their relatives			x	x	x				
5. Improve-ment of newborn screenings	Defining new screenings, creating new tools		x	x						
	Introduction of screenings			x	x					
6. Improve-ment of medicine and medical appliance supply	Developing an evidence-based pricing strategy		x	x						
	Establishing the inclusion of orphan drugs			x	x					
	Establishing large-value medicine subsidies on the basis of economic analyses				x	x				

7. Development of research efforts in the field of rare diseases	Supporting the international participation of research teams		x	x	x	x	x			
	Supporting clinical research facilitating medical treatment			x	x	x				
	Supporting research for measuring patient care and patient satisfaction		x		x		x		x	
	Supporting research related to communicating diagnoses			x						
8. Development of social care	Setting development objectives		x	x						
	Training and developing professionals working with rare diseases			x	x	x				
	Founding a habilitation development institution					x	x	x		
9. Development of cooperation with patient organisations	Organising informative media campaigns		x	x	x	x	x	x		
	Development of training programmes		x	x	x					

Annexes

1. Annex no.: Experts participating in the compilation of the work material

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2. Annex no.: Indicators

Indicator	Description of the indicator	Type of indicator
Background indicators		
Legal regulations or official national resolutions supporting the creation and development of the National Plan	Ensuring the conditions of creating and developing the National Plan through legal regulations and official resolutions	process
Foundation of the Advisory Committee of Rare Diseases	Founding an advisory committee composed of representatives of various organisations with the inclusion of individuals, patients representatives, the state, doctors, funding entities, universities, etc. affected by the topic	process
Permanent and official patient representation in the development, monitoring and assessment of the National Plan	Ensuring the official participation of patients in all areas of the development of the National Plan, including monitoring and assessment	process
Adaptation of the definition of Rare Diseases of the European Union	Application of the definition of Rare Diseases recognised in the European Union taking into account the small number of patients	process
Diagnostics		
Number of available diagnostic genetic tests	The accessibility of genetic tests carried out by units applying high-level quality control.	output
Establishment of a specialised diagnostics centre	Reduction in the number of false diagnoses in order to shorten the time necessary to obtain correct diagnoses.	process
Introduction of a system monitoring the length of time until diagnosis	Development of a system registering the time of delay in diagnostics.	process

Centres of Expertise		
The number of accredited CEs covering the entire country and operating in alignment with actual needs	Establishment of accredited CEs appointed in accordance with the EUCERD recommendation laying down the quality criteria of CEs and in alignment with the area of the country.	output
Participation of Hungarian CEs in the European Reference Network	Development of telemedicine, establishment of consultation and ensuring the possibility of sending diagnostic materials for examination.	output
Proportion of patients with rare diseases appearing at CEs compared to the number of registered patients with rare diseases	How many of the monitored patients appear at CEs compared to the total number of registered patients.	output
Helpdesks for patients with rare diseases	Accessibility to helpdesks for informing patients, providing social, psychological and information solutions in accordance with the needs of patients with rare diseases.	process
Indicator	**Description of the indicator**	**Type of indicator**
Registers		
The number of national registers of rare diseases	Databases registering rare diseases on a national scale	process
Proportion of special patient registers	Number of patient registers specialising in rare diseases enabling individual and systematic data collection	process
Status of processing data from patient registers	Processing and analysing data of the patient register	output
Number of epidemiological research projects integrated into the patient database	Creating epidemiological indicators through processing data from patient registers	output
Coding used by the system of healthcare - introduction of a new ICD code	Application of a standardised and internationally recognised ICD coding	process

Development and participation in the comprehensive national information system	Collection and processing relevant information; policy tool and epidemiological basis for research; information for laymen	process
Participation in the European information network	Exchange of information on an international scale in order to eliminate the lack of information related to rare diseases. Collecting, organising and sharing best practices between the members of the network	process
Education		
Number of training programmes and courses launched in the topic of rare diseases	Organising graduate and postgraduate as well as laymen education in order to extend knowledge related to rare diseases.	output
Number of participants in graduate and postgraduate courses related to rare diseases	The number of participants in courses on rare diseases.	output
Number of guidelines related to the clinical practice developed and published between 2014 and 2020	Continuous integration of guidelines on clinical practice into the process of patient care.	process
Medicine and appliance supply		
Proportion of financed medicine for rare diseases	Processing the data related to medicine consumption, assessment of accessibility to financed medicine.	output
Proportion of accessible, but not financed medicine	Proportion of non-financed medicine consumption compared to financed medicine consumption.	
Proportion of used orphan drugs	Use of medicine compared to the number of patients with rare diseases.	output

Indicator	Description of the indicator	Type of indicator
Screening		
Number of screened patients	Processing the data serving the description of the efficiency of the screening.	process
Number of false positive cases		
Number of accredited laboratories	Number of diagnostic laboratories in the country capable of performing genetic tests.	output
Research		
Number of national research programmes and/or projects	Implementation of research programmes and projects related to rare diseases.	process
Number of scientific conferences organised on rare diseases.	Publication of the results of research projects related to rare diseases.	output
Number of participations in international research initiatives	Organisation of international projects based on inter-sectoral cooperation.	process
Number of scientific publications related to rare diseases	Releasing publications with an impact factor in the topic of rare diseases.	output
Social services		
Programmes supporting the integration of patients with rare diseases into everyday life	Providing and developing social services to patients and their family members, extending the scope of special social services	process
Existence of an official register of available social allowances	Providing information to those with social needs regarding available allowances and the method of using them.	process

3. Annex no.: Current newborn screening panel

Current screening panel	
Disorders of amino acid metabolism:	***Disorders of fat acid oxidation:***
Phenylketonuria	Short-chain acyl-coenzyme A dehydrogenase deficiency (SCAD)
Keto acid decarboxylase deficiency	Medium-chain acyl-coenzyme A dehydrogenase deficiency (MCAD)
Tyrosinemia, type 1 and 2	Long-chain hydroxy acyl-coenzyme A dehydrogenase deficiency (LCHAD a, b)
Citrullinaemia (argininosuccinic acid deficiency, ASS)	Very long-chain hydroxy acyl-coenzyme A dehydrogenase deficiency (VLCAD)
Arginosuccinate aciduria (arginosuccinate lyase deficiency, ASL)	Multiplex acyl-coenzyme A dehydrogenase deficiency (MADD or GA II)
Homocystinuria	Carnitine Palmitoyl Transferase Deficiency (CPT-I, CPT-II)
Disorders of organic acid metabolism:	Carnitine transporter deficiency (CT)
Beta-ketothiolase deficiency	***Endocrine or other disorders of metabolism:***
Ketoglutaric acidemia, type 1 (GA-I)	Hypothyroidism
Isovaleric acidemia (IVA)	Galactosaemia
Methylmalonic acidemia (MMA)	Biotinidase deficiency
Propionic acidemia (PA)	
3-Hydroxi-3-methylglutaril-coenzyme A lyase deficiency (HMG)	
3-Methylcrotonyl-CoA carboxylase deficiency (MCC)	
Multiplex carboxylase deficiency (MCD)	

4. Annex no.: Member organisations of the NORD

- A CML és GIST Betegek Egyesülete (Association of CML and GIST Patients)
- Cri Du Chat Baráti Társaság (Cri Du Chat Friends' Association)
- Dávid Kisemberek Társasága (Dávid Small Peoples' Association)
- Epidermolysis Bullosa Alapítvány (DebRA Magyarország) (Epidermolysis Bullosa Foundation (DebRA Hungary))
- Igazgyöngy Alapítvány (az Angelman szindrómásokért) (Real Pearl Foundation (for patients of Angelman's syndrome))
- Klub a Prader-Willi Gyermekekért (Club for Children with Prader-Willi syndrome)
- Magyar Ataxiás Betegek Alapítványa (Hungarian Foundation for Ataxia Patients)
- Magyar Hemofília Egyesület (Hungarian Haemophilia Association)
- Magyar Izomdisztrófia Társaság (Hungarian Muscular Dystrophy Association)
- Magyar Mukopoliszaccharidózis Társaság (Hungarian Mucopolysaccharidosis Association)
- Magyar Porphyria Egyesület (Hungarian Porphyria Association)
- Magyar VHL Társaság (Hungarian VHL Association)
- Magyar Williams Szindróma Társaság (Hungarian William Syndrome Association)
- Magyarországi PKU Egyesület (PKU Association of Hungary)
- Martin Bell Alapítvány (Martin Bell Foundation)
- Myasthenia Gravis Önsegítő Betegcsoport (Myasthenia Gravis Self-Help Patients' Group)
- Narkolepszia klub (Narcolepsy Club)
- Neurofibromatózisos Betegek és Segítőik Társasága (Association of Neurofibromatosis Patients and their Carers)
- Országos Cisztás Fibrózis Egyesület (National Cystic Fibrosis Association)
- Primer Immunhiányos Betegek Egyesülete (Association of Primary Immunodeficiency Patients)
- Retina Magyarország Egyesület (Retina Hungary Association)
- Retinoblastoma Társaság (Retinoblastoma Association)
- Magyar Rett Szindróma Közhasznú Alapítvány (Hungarian Rett Syndrome Public Interest Foundation)
- Sclerosis Tuberosa Társaság (Sclerosis Tuberoas Association)
- Siket-Vakok Országos Egyesülete (National Society for the Deaf and Blind)
- Turner Szindróma Klub (Turner Syndrome Club)
- Tüdőér Egylet (Pulmonary Hypertension Community)
- Wolf-Hirschhorn-szindróma klub (Wolf-Hirschhorn Syndrome Club)
- Misko Alapítvány (Misko Foundation)
- Gyógyító Jószándék Alapítvány – Izombeteg Gyermekek Alapítványa (Duchenne betegekért DMD) (Healing Goodwill Foundation - Foundation for Children with Muscular Dystrophy (for DMD patients)
- Smith-Lemli-Opitz Szindrómás Gyermekekért Alapítvány (Foundation for Children with Smith-Lemli-Opitz Syndrome)

- Magyarországi Angio-Ödémás Betegek Egyesülete (Hungarian Association of Angioedema Patients)
- Országos Scleroderma Közhasznú Egyesület (National Scleroderma Public Interest Association)
- Mitokondriális Betegek Baráti Köre (Society of Friends of Mitochondrial Patients)

5. Annex no.: Definitions

Data management
Admission, storing, procession and use (including forwarding and disclosure) of personal data, and the modification and prevention of further use of data independent of the applied procedure

Assessment of data
Assessment of data specified by the healthcare service provider following their collection from suitable sources, during which these data may become information allowing the verification and assessment of the compliance and efficiency of the quality management system for determining where the continuous development of the system is possible - Prior to assessment, data are also called raw data

Accreditation
Official verification that a healthcare service provider or institution is competent to perform an activity (test, certification, audit) in accordance with specified requirements

Audit
Assessment of meeting the applicable standards. The audit of hospital standards covers:

- the assessment of documents submitted by the healthcare service provider regarding performance,
- the assessment of expected monitoring data,
- verbal information on fulfilling the standards enabling the defined performance,
- on-site control of auditors

Internal audit
Revision carried out at intervals planned by the healthcare service provider itself as first party or authorised and qualified persons in accordance with the documented procedure of the organisation, in order to review that the operation of the internal quality management system complies with the planned measures, the requirements of revision and the requirements and objectives set by the organisation; and whether its introduction and maintenance is efficient

Internal auditor
A person with adequate professional and auditorial qualifications in an area independent from the area audited by them (the auditor does not audit their own work or work area) entrusted by the senior management of the healthcare service provider with the performance of the internal quality management system audit in the time and area specified in the internal audit programme, who is capable of conducting the process of the internal audit tasked to them in an objective and unbiased manner

Internal quality management system

The internal quality management system of the medical institution shall

- ensure the continuous development of the quality of services
- understand and perform detailed planning of the processes of the service, including planning to avoid potential mistakes,
- enable timely detection of deficiencies arising in the course of providing service,
- implement and monitor measures taken to rectify shortcomings,
- reveal the causes of deficiencies, reduce any resulting costs and damages,
- ensure compliance with professional and quality management requirements and develop an internal system of requirements

Patient rights

The basic health rights of patients, specifically referring to access to care and services, equality in treatment and quality of care

Programmed direction of the patient by the attending doctor to another specialised doctor and/or to a higher level of progressiveness of another healthcare service provider for the purpose of definitive specialised care and/or specialised treatment

Safety

The degree of reducing the risks of intervention and the risks in the environment of care for patients and others, including the provider of healthcare

Safety of patient care (patient safety)

Safeguarding the physical and mental integrity of patients and their personal effects from risk and harm in the course of providing service

Documentation

A set of documents arranged in accordance with a given requirement, which can both contain prescriptive and/or verifying documents

Prescriptive documents (*prescriptions*) define requirements (e.g. a task, responsibility or competence, aspects of controlling, objectives, guidelines, policies) or regulate a certain activity or process. These may come from an external source (e.g. legal regulations, standards, professional guidelines) or be made internally (e.g. Rules on Organisation and Operation, Data Protection Regulation, Guide to Calibration, Quality Plan)

Prescriptive documents include given procedures (process, activity)

Medical documentation (patient documentation)

A record, register or any other data entry coming to the awareness of a healthcare worker in the course of healthcare service containing medical and personal identification data regardless of its media and form

Note: In the practice of a family doctor the documentation of all patients carry sufficient information to verify and support the preventive, diagnostic or therapeutic activity performed during practice and also document test and therapeutic results. The standardised requirements of form and content of the documentation facilitate the maintenance of the quality of care

Medical data

Any data on the physical, mental and emotional state, pathological addiction, medical condition or circumstances of death of the affected person submitted in person or by other person, or detected, examined, measured, processed or originated by the network of medical care; furthermore, any other data that can be linked or that could influence the foregoing (e.g. behaviour, environment, occupation)

Medical employee

A person with a qualification of doctor, dentist, pharmacist or other higher or other medical education, or without medical qualification in the case of those contributing to providing healthcare.

Medical care

The entirety of healthcare services related to a given medical condition of the patient

Medical costs

The costs incurred by a medical condition or disease can be divided into several categories. There are **direct** medical (e.g. time consumed by specialised staff, costs of medicine, etc.) and non-medical (e.g. costs of travelling to the healthcare institution, informal home care or assistance, etc.), **indirect** medical (e.g. additional medical expenses because of longer lifetime as a result of treatment) and non-medical (e.g. the loss incurred due to decrease in the ability to work, sick-leave, etc.), and so called **intangible** (incorporeal) costs. In case of patients with rare diseases burdens beyond direct medical costs are obviously heavier (e.g. if such a patient is provided home care by a relative, the income lost due to the difficulties of this care-giver, while this activity can unburden institutions providing outpatient care). Therefore, instead of a narrower **financing perspective**, a **social** perspective shall be given priority in the assessment of medical technologies for the care of rare diseases (orphan drugs, orphan appliances, procedures targeting the care of rare diseases , and consequently these, or any other ethical aspects or aspects of equitability, should not be eluded in the course of decision-making on subsidies.

Medical specialised authority

An organisation with the lawful competence of an authority (licensing and supervision), which conducts the licensing procedure for giving entitlement for providing healthcare services based on specific legal requirements, and which issues the operating licence for the healthcare service provider to commence its activity or continue it. This authority is empowered to regularly control the existence of conditions necessary for operation at the healthcare service provider.

healthcare service provider (inpatient and outpatient care, family doctor/practice, district nurse)

Regardless of the form of ownership and the operator, an eligible legal person, an organisation without legal personality and any natural person providing services in their own name may provide any healthcare services based on the operating licence issued by the medical authority

Health technology assessment (HTA)

A multidisciplinary process summarising and synthesising systematically, transparently, and in an undistorted and robust manner medical-biological, clinical, social, economic and ethical-legal information related to the application of a given health technology (medicine, biological preparation, therapeutic or diagnostic appliance, procedure, or supporting, organisational or management system). The primary aim of the HTA: informing decision-makers in order to support them in establishing their opinion regarding the use of a health technology

The features and consequences of the assessed technology could include technical specifications, proofs on safety, effectiveness, efficiency observed in everyday practice, patient report outcomes (PRO), costs and cost-effectiveness as well as social, legal, ethical and policy effects expected as a result of application. Accordingly, the HTA covers a much wider area than the study of medical and economic outcomes of a medical technology.

Steps of the health technology assessment (HTA)

1 description of the health technology, 2 assessment of clinical evidence (clinical outcome assessment), 3 assessment of costs (economic assessment), 4 comparison of healthcare and economic outcomes (assessment of cost-efficiency), 5 ethical considerations.

Based on extensive consensus it is a generally accepted view that 40% affects the medical–professional, while 20% affects the economic, ethical and equitability components, respectively, from the individual elements of the HTA. However, the current Hungarian practice shows that the majority of assessments only involved clinical and economic assessments, while other human aspects were only studied as subordinate elements.

Among the methods to be applied in medical-economic assessments, the application of the financing perspective is obligatory, however, it does not specifically forbid the application of other perspectives (e.g. patient, patient relative, employer, healthcare provider, institutional and sectoral or social perspective including any of the foregoing). However, this circumstance means that in the assessment only so-called direct medical costs can be taken into account.

Levels of care

Activities that can be carried out in certain progressive levels of care and service providers suitable for pursuing the activity and in the possession of adequate personal and material conditions are determined and designated by Special Colleges and Medical Institutions

Result, outcome

The change observed in the current and/or future state of the patient, which is the consequence of medical interventions or preventive medical services

Rate of result
Results achieved in everyday routine environment, which is generally used, depending on the objectives, to provide a percentile assessment of the results obtained in the health condition of patients.

Assessment
A medical service from the aspect of assessing the programme (effectiveness, efficiency, compliance, accessibility) and drawing conclusions relying on results of the assessment

Ethical norms
Manners of behaviour related to communication between the staff of the institution and patients and giving information to patients

Disabled person
A person living with permanent or enduring sensory, communication, physical, mental, psychosocial damage, or the accumulation of them, which limits or impedes actual and equal participation in society due to environmental, social or other substantial obstacles

Continuous improvement of quality
A quality improvement activity where the aim is the development of the entire system, particularly the prevention of quality issues, the identification and perfection of problematic or potentially problematic processes and the introduction of new quality elements

Care
Continuous medical supervision, inspection, treatment, prevention of worsening and reduction of symptoms of a patient with a known chronic medical condition

Efficacy
Effect on the health condition in an ideal (laboratory) environment

Effectiveness
The relation between outcome (service product) and input (resources used for providing the service). Increasing effectiveness means fewer resources with the same outcome or greater outcome with the same amount of resources

Local procedural rules
Description of local procedural practice applied at a healthcare provider and on a given level of care based on professional policies, protocols or, in the absence of these, the practice of the healthcare provider, regarding the treatment of a disease or a condition

Accessibility
The affected patient can use the medical services necessary based on their current health condition regardless of their financial condition and geographical location of their home

Demand
The skill and/or capacity of the patient to look for, use and with certain conditions pay for the healthcare service. Demand depends on social/financial status, school education, cultural environment, etc. The demand for a service is rightful, if the need for it makes it reasonable

Indicator
A relative number indicating the situation and tendency of a process for achieving a performance or outcome as a function of time
A measurable variable (or feature) used to define the degree of satisfying a standard or quality aim
The quantitative indicator of events occurring in the course of care, which can be used to measure, assess and improve quality. The indicator does not necessarily measure quality, but draws attention to areas where the reasons of observed divergences require further detailed assessments

Information
Any data with meaning that are received during patient care or in connection with patient care

Future prospects
The long-term position and role in the changing environment from the aspect of the affected

Unfavourable events
The total of negative effects on the patient, relative or legal representative while the service is provided

Competence
Occupational knowledge and skills. This means the understanding of knowledge, facts and procedures. The capacity is the ability to perform special actions. For example a competent cardiologist knows the physiology and pathology of the heart and how to detect arrhythmia using an electrocardiogram. Behaviour, such as the ability to work in a team, is often seen as a part of competence

Criterion
The measurable expression of the expected or desired quality of a product or service, which expresses how the activity is performed

Mission statement, mission
A written statement in which the aims or a component of that aim of a healthcare provider is published. The creation of a mission statement is typically preceded by the establishment of objectives and tasks

Key processes
Processes determining the efficient and successful operation of an organisation inn the long term or having a direct effect on curative/preventive activities

Key indicators (see also: *Data, Indicators*)
Indicators suitable for predicting the expected development of results of key importance, so called intermediate indicators, which are also capable of continuous tracking

Adequacy
Medical care is considered adequate if, as a result of care, the expected improvement in the health condition exceeds the expected negative consequences (e.g. death, complications of surgery) to an extent that makes application of the intervention reasonable, as opposed to it not being applied or another intervention being applied

Quality
The value judgement of those participating in the preservation, recovery and maintenance of health expressing the degree of the realisation of expected demands. The degree of realisation can be described with the relevant index for each component

Quality management
The part of general management defining and implementing the quality policy

Improvement in quality
The improvement of standards to a higher level and performance of the same on this level. Quality is improved with the logic of quality management: looking for errors, confirmation and correction

Multidisciplinary
Professionals of various qualifications, various areas of specialisation and areas of services

Policy
The rule or opinion specified by the management related to the performance of a given activity valid for the entire healthcare provider organisation. The procedure descriptions, processes and professional protocols on the operation of care-giving units are based on rules and policies. For instance, the healthcare provider's organisational policy can determine the level of competence for the administration of a medicine. The method of implementation is specified in a departmental

procedure description or professional protocol. The guideline following in the structure and operation of the organisation

Progressive care
Care built on a system of healthcare institutions based on the principle of division of labour and progressiveness and defined at all levels of the health condition of patients

Rehabilitation
The harmonised and customised system of all services that enable disabled people to be successively integrated in society. Comprehensive rehabilitation is seen as a process, which harmonises the performance of the disabled person with the expectations of society. Therefore, for successful rehabilitation, the wider community also needs to take active part.
It is organised assistance that is provided by society to people with permanent or enduring medical, physical or mental disabilities in order for them to be included in society using their recovered or remaining skills

Rehabilitation services
Medical or social services or joint assessments of skills and qualifications for the treatment, training, education and re-education of individuals damaged due to a disease or injury. The objective is to enable those in need to reach the highest level of their functional skills

Standard
General but accurate definition of expectations laid down in advance, which aims to describe all functions, activities and operating conditions of the healthcare provider

Standard-based assessment
A process of assessment defining the adequacy of a healthcare provider organisation or care-giver compared to expectations laid down in advance

System of standards
A system of expectations specified by a competent authority (ministry) in advance Standards describe the acceptable level of performance of the healthcare provider organisation or individual as regards local structure, the implementation of a process or achievement of measurable outcomes

Strategy
Management function of the provider for which the provider sets strategic objectives adjusted to the mission and vision. By setting the objectives the provider determines and rethinks the long-term success factors

Strategic plan
A long-term managerial plan for the achievement of a vision, which takes into consideration the support and threats of external environment

Professional supervision
The professional supervision by the healthcare authority over healthcare providers and services

Professional guideline
Series of decision recommendations supported by available scientific evidence and systematically developed, and the definition of various care methods of a disease group with the aim of improving the quality, effectiveness and efficiency of healthcare and assisting the doctor and the patient in selecting the most suitable care

Professional protocol
Organised list of activities related to the process of scientifically-supported preventive, diagnostic, therapeutic, treatment or rehabilitation care of a disease or medical condition in a determined disease group and level of care, which forms the basis of the professional examination and funding of healthcare services and is aimed at ensuring the safety and uniform standard of care

Personal data
Data related to the affected individual, particularly the name, identification number or one or more pieces of physical, physiological, mental, economic, cultural or social information; from such data conclusions can be drawn on the affected person

Needs
Problems originating from the state of health and requiring medical intervention, which can be influenced positively by medical intervention. The need is recognised, if it is known to healthcare, but unrecognised, if the patient would require care, but does not see a doctor or does not want to go to the doctor, or fails to recognise the problem

Certification
A third party audit performed by an external and independent organisation (certifying organisation) at the request of the organisation, where the certifying organisation assesses and declares that the certified organisation complies with the relevant requirements (e.g. ISO 9001:2000, KES),
A voluntary programme in which the healthcare institutions have to meet certain standards

Further-referral

Directing (referring) the patient to another healthcare provider based on the needs of the patient, where their care and treatment continues

Evidence-based medicine

The method of healing activities, where decisions are made using the most recent reliable scientific results, professional experience of many years, and the preferences of patients. A methodology used for a healing activity or in professional decision-making, which enables decisions to be made based on the collection and critical assessment (quality and strength of evidence) of the best scientific evidence (results) available for diagnostic interventions, therapies, care methods and other medical services

6. Annex no.: Target and means matrix

Target and means matrix		In accordance with the principle of equal treatment and solidarity, the improvement of the diagnostics and treatment of rare diseases, improvements of access to therapeutic options by creating rationalised patient pathways, as well as support for related education and research by exploiting the potential in European cooperation.												
		Improvement of the diagnostics of rare diseases			**Establishment of the network of CEs**		**Creation and operation of registers**	**Development of education and training**		**Improvement of newborn screenings**		**Improvement of access to medicine and medical appliances**		**Support for research efforts in the field of rare diseases**	
		The networks of genetic diagnostic centres shall have quality management	Adequate personal and material conditions shall be made available	Adequate information shall be provided to patients and/or their family members	Establishing the operating conditions of CEs	Defining the competences and tasks	Developing the register of rare diseases and patients	There shall be graduate and postgraduate education related to rare diseases	There shall be programmes for the education of patients	The conditions of screening shall be improved	New screenings shall be introduced	There shall be a specific admissions procedure	The level of support shall be optimised	The background, treatment, prevention techniques and epidemiology of rare diseases shall be examined	Hungarian and international participation in clinical studies
Introduction of measures for the development of the diagnostics of rare diseases	Organisation of genetic diagnostic centres	x	x	x						x					
	Development of the quality management system of units created	x													
	Training of necessary staff of experts		x		x			x							
	Providing a level of instrumentation that meets the levels of progressiveness		x		x										
	Patient information, developing the rules for giving information	x							x					x	

Designation of CEs with accreditation	Designation of the tasks of CEs				x	x	x	x	x						x
	Specification of the competences of CEs					x									
	Definition of specific tasks						x				x				
	Harmonisation with EU requirements	x			x		x								
Providing conditions necessary to establish the Register of Rare Diseases	Defining requirements related to quality management and validity				x	x	x								
	Determining the register as well as establishing the legal background of the register						x								
	Determining data collection and data provision	x		x										x	x
Improvement and facilitation of education and training related to rare diseases	Extending the knowledge of graduate and postgraduate students of medicine		x					x	x						x

	Ensuring the training of patients and their relatives, development of programmes, and providing other opportunities of education							x	x						
Providing the conditions necessary to introduce new newborn screening examinations	Defining the objectives of CF screening and providing the appliances necessary to perform the screening				x					x	x				
	Defining the improvement in the quality of life that can be achieved by newborn CF screening			x										x	
Improvement of the supply of medicine and appliances for rare diseases	Developing an evidence-based pricing strategy											x	x		
	Developing specific procedural rules for the adaptation of orphan drugs											x	x		x
	Subsidising expensive medicine and studies in the field of health economics											x	x		x

Inviting tenders aimed at the social, epidemiological and clinical research of rare diseases	Inviting tenders for studies surveying patient care and patient satisfaction			x	x									x	
	Studies on giving information about diagnoses and other epidemiological studies			x										x	
	Studies promoting medical treatment				x					x					x
Development of social care	Setting social development objectives											x	x		
	Educating patients with rare diseases about rare diseases								x						
	Foundation of a special institution											x	x		