Rare Diseases Strategy of the Spanish National Health System

HEALTHCARE, 2009
MINISTRY OF HEALTH AND SOCIAL POLICY

Rare Diseases Strategy of the Spanish National Health System

HEALTHCARE 2009
MINISTRY OF HEALTH AND SOCIAL POLICY

MINISTERIO
DE SANIDAD
Y POLÍTICA SOCIAL

Limited Edition for the Launching Conference of the Strategy on Rare Diseases of the National Health System.

Rare Diseases Strategy of the Spanish National Health System

Strategy approved by the Interterritorial Council of the Spanish NHS on 3 June 2009

MINISTERIO
DE SANIDAD
Y POLÍTICA SOCIAL

Plan de Calidad para el Sistema Nacional de Salud

TECHNICAL COMMITTEE

Scientific Coordinator:
Francesc Palau Martínez. **Centre for Biomedical Network Research on Rare Diseases (CIBERER). Carlos III Health Institute (ISCIII) and the Institute of Biomedicine of Valencia (IBV), Spanish Council for Scientific Research (CSIC)**

Spanish Federation for Rare Diseases (FEDER)
Moisés Abascal Alonso
Spanish Union of Scientific Nursing Societies (UESCE)
Patricia Arribas Cobo
Spanish Society of Internal Medicine (SEMI)
Francisco Javier Barbado Hernández
Spanish Association of Human Genetics (AEGH)
Salud Borrego López
Spanish Society of Neurology (SEN)
Carmen Calles Hernández
Spanish Federation for Rare Diseases (FEDER)
Isabel Campos Barquilla
Spanish Association for Neonatal Screening (AECNE)
Ernesto Cortés Castell
Spanish Association for the Study of Inborn Errors of Metabolism (AECOM)
Asunción Fernández Sánchez
Spanish Association of Paediatrics (AEP)
Enrique Galán Gómez
Spanish Society of Family and Community Medicine (SEMFYC)
Miguel García Ribes
Federation of Community Nursing and Primary Care Associations (FAECAP)
Ana González Pisano
Coalition of Citizens with Chronic Diseases
Antonio Liger Valverde
Spanish Society of Clinical Biochemistry and Molecular Pathology (SEQC)
José Luis Marín Soria
Spanish Society of Immunology (SEI)
Nuria Matamoros
Spanish Association of Primary Care Paediatrics (AEPap)
Juan José Morell Bernabé
Spanish Federation of Neuromuscular Diseases (F-ASEM)
Yasmina Pagnon
Spanish Society of Primary Care Physicians (SEMERGEN)
Guillermo Pombo Alles
Spanish Association of Human Genetics (AEGH)
Feliciano J. Ramos Fuentes
Spanish Society of Family and Community Medicine (SEMFYC)
José Vicente Sorlí Guerola
Spanish Federation for Rare Diseases (FEDER)
Rosa Sánchez de Vega
Spanish Federation for Rare Diseases (FEDER)
Jacinto Sánchez Casas
Sociedad Española de Medicina General (SEMG)
Jesús Zumeta Fustero
Spanish Federation of Phenylketonuria and other Inherited Metabolic Disorders
Manuel Varela Vivero

EXPERTS CONSULTED:
Rafael Artuch, Carmen Espinós, Pilar Giraldo, José M.ª Millán, Pablo Lapunzina, Teresa Pàmpols, Margarita Plá, Josep Torrent-Farnell, Joan Lluís Vives-Corrons, Susan Webb and Óscar Zurriaga

INSTITUTIONAL COMMITTEE

Andalusia: Antonio González Meneses
Aragon: Francisco Javier López Pisón/ Antonio Baldellou Vázquez
Asturias (Principality): Mario Margolles Martins
Balearic Islands: Juli Fuster Culebras
Basque Country: Itziar Astigarraga Aguirre
Canary Islands: Milagrosa Santana Hernández
Cantabria: Luis Miguel Ruiz Ceballos
Castile-La Mancha: Luis Escribano Mora
Castile and Leon: Blanca Muñoz García
Catalonia: Maite Aguayo Álvarez
Extremadura: Eva María Molinero San Antonio
Galicia: Carmen Navarro Fernández-Balbuena
Madrid: Juan Carlos Ansede Cascudo
Murcia (Region): Roque Martínez Escandell
Navarre (Foral Community): M.ª José Lasanta Sáez
Rioja (La): José Antonio Oteo Revuelta
Valencia (Community): Antonio Pérez Aytes
Ingesa (Ceuta-Melilla): Sara Cristina Pupato Ferrari, Teresa García Ortiz

MINISTRY OF HEALTH AND SOCIAL POLICY

Directorate General of the Spanish NHS Quality Agency
Pablo Rivero Corte - Director General
Health Planning and Quality Office
Concepción Colomer Revuelta - Deputy Director General
Patricia Soria Núñez - Head of Service
Ángel Abad Bassols - Head of Service
Beatriz Gómez González - Technical and methodological support
Amparo Mayor Frutos - Administrative and logistic support
Health Information Institute
M.ª Santos Ichaso Hernández-Rubio - Assistant Deputy Director
Observatory on Women's Health (OSM) of the Spanish NHS
Rosa M.ª López Rodríguez - Programme Coordinator of the Observatory on Women's Health (OSM)
Directorate General for Public Health and Foreign Health Affairs
Julia González Alonso - Technical Advisor
Directorate General for Professional Regulation, Cohesion of the NHS and High Level Inspectorate
Carmen Pérez Mateos - Technical Advisor
Amparo Montesinos Alonso - Technical Advisor
Directorate General for Pharmacy and Health Products
M.ª Dolores Vaquero García - Deputy Director General for Medicine and Health Product Quality
Directorate General for Advanced Therapies and Transplants
Augusto Silva González, Director General
Spanish Medicines Agency (AEMPS)
Cristina Avendaño Solá - Director General
State Reference Centre for Rare Diseases Patients and their Families (CRE) Institute of Elderly and Social Services (IMSERSO)
Miguel Ángel Ruiz Carabias - Managing Director
Directorate General for the Coordination of Sectoral Policies on Disability, IMSERSO. Sub-Directorate General for Management and Planning
Mercedes Jaraba Sánchez - Area Coordinator

MINISTRY OF SCIENCE AND INNOVATION

Rare Diseases Research Institute (IIER). Carlos III Health Institute (ISCIII) - Manuel Posada de la Paz
Centre for Biomedical Network Research on Rare Diseases (CIBERER), Carlos III Health Institute (ISCIII) - Virginia Corrochano James

Contents

Prologue

This Rare Diseases Strategy is set within the framework of the Quality Plan of the Spanish National Health System (NHS) which includes, amongst its other objectives, improving care for people with rare diseases and their families.

Although their prevalence is low, rare diseases (RD) can be life-threatening or debilitating in the long term, which is why they are a priority in the health policy of the Ministry of Health and Social Policy.

The high level of complexity and low prevalence of these diseases calls for a global approach, involving well-coordinated actions at national, regional and local level, as well as combined efforts to promote the research, diagnosis, treatment and dissemination of knowledge and resources regarding these diseases. Likewise, because of the high social burden of rare diseases, the social care required by sufferers of these pathologies is a fundamental part of this Strategy.

Through this initiative the Spanish Government aims to formulate a feasible and adequate response to the needs of people affected by RD, and the combined efforts of all those involved was fundamental to the achievement of that objective. The Spanish NHS Rare Diseases Strategy represents a consensus between the Ministry of Health and Social Policy, the Ministry of Science and Innovation, Spain's Autonomous Communities, patient organisations, scientific societies and experts.

This Strategy sets out 7 lines of action, including the prevention and early detection of rare diseases, healthcare and integrated health and social care, the promotion of research, training and information for professionals and people affected by rare diseases and their families.

A rigorous approach to any rare disease calls for a set of actions that establish evidence-based, agreed criteria regarding the guidelines to be followed in any one of the strategy lines set out herein, in order to enhance

the effectiveness and quality of the treatment of these pathologies in all the health services of the Spanish health system.

This document sets out a series of objectives and recommendations that will contribute to an improvement in the quality and outcomes of the services and healthcare provided in the field of RD. Moreover, they are based on available information and scientific evidence, on clinical excellence and equity, and they propose realistic action in keeping with the available resources and the areas of competence of the Autonomous Communities.

This initiative provides professionals and patients with a very useful tool for the improvement of the health and quality of life of people with RD.

In addition to the Strategy, the Spanish Government has various other tools to guarantee and promote care, prevention and research in this field. One such tool is the Royal Decree on Reference Centres, Services and Units (Centros, Servicios y Unidades de Referencia, CSUR), which prioritises the definition of the criteria, accreditation and designation of CSUR on RD. Noteworthy in terms of research is the work carried out by the Centre for Biomedical Network Research on Rare Diseases (Centro de Investigación Biomédica en Red en Enfermedades Raras, CIBERER), which is involved in collaborative network research projects at a national and international level, or the substantial funding allocated to the research and development of orphan medicinal products.

Since the approval of the Spanish NHS Rare Diseases Strategy, Spain has become one of the pioneering Member States to have a national Strategy and, as such, has moved ahead of the deadlines established in the recently approved *Council Recommendation on action in the field of rare diseases,* a recommendation that is fully in line with the approach of the Ministry of Health and Social Policy.

Lastly, I would like to express my gratitude to all the people who participated in the elaboration of this document, and especially to Dr Francesc Palau, the Strategy's Scientific Coordinator. Without his

dedication and efforts it would not have been possible to create a tool which, undoubtedly, will contribute to improving the quality of the care received both by people affected by rare diseases and by their families.

Trinidad Jiménez García-Herrera
Minister of Health and Social Policy

Introduction

The term «rare diseases» was introduced in the 1970s when several authors drew attention, especially in the field of hereditary metabolic diseases, to the fact that rare diseases share certain common problems despite being very diverse. Rare diseases are a health and social interest problem. Despite their low prevalence —with great variations in frequency— the minority nature of these diseases is associated with certain relevant aspects in the lives of the people who suffer from them and in the natural history of the process, like the fact that in most cases they are serious, chronic disorders that can appear at an early age as well as in adulthood. This means that the people who suffer from these diseases have certain common characteristics which make us think of them as a social group.

The European Union defines rare diseases as those with a prevalence of less than 5 per 10,000 inhabitants. According to that definition, the equivalent of 6-8% of Europe's population, or an estimated 29 million people in the EU-27 and 3 million in Spain, are affected.

Over the last few years social awareness about the problems of people affected by these disorders has increased, largely thanks to their own actions and the actions of associations and organisations for patients and their families. Some of the issues to which patients and their representatives have drawn attention are the difficulty of obtaining an early diagnosis, the lack of multidisciplinary care, the scarcity of information and of support at the time of diagnosis.

The reality that the term «rare diseases» is intended to cover calls for a broad and effective definition for 21st Century medicine and healthcare, which considers the different ways in which people suffering from a disease of this type are affected. The definition should therefore take into account the fact that rare diseases are a broad and varied group of disorders that share certain characteristics, i.e. they all affect a limited number of people, are chronic and incapacitating, present a high morbidity and mortality rate, and therapeutic resources for them are, in general, limited.

However, there are many common diseases that are also chronic and incapacitating, have a high morbidity and mortality rate, and do not always have a therapeutic armoury that is effective for the majority of patients. What, then, differentiates rare diseases from common chronic and incapacitating diseases? How can we establish measures that take into account the problems faced by affected persons and that guide the responses that must be provided by the Spanish NHS and in which,

among other things, quality and equity in relation to the disease and the fact of falling ill are valued? Various elements that could help group together into a single framework the aspects that characterise rare diseases, as well as the actions that health authorities could take, are set out below for consideration. Those elements are:

1. Public health. The concept «rare diseases» elevates a group of pathologies, considered either individually or categorised in pathological groups (e.g., Fanconi anaemia versus congenital anaemias), to the category of a public health problem. Scleroderma or Charcot-Marie-Tooth disease, with a prevalence at the high end of the definition of rare diseases, that is to say, 4.2 and 2.8 per 10,000 inhabitants, respectively, are not per se considered to be a public health problem affecting a large population group. However, the fact that some 3,000,000 people are affected by shared health problems —and, of course, by many others that are not shared— in a population like that of Spain taken as a whole, does become an issue that calls for a healthcare and scientific approach from the perspective of public health. This is known as the paradox of rarity. The extent of RD among the population must be known, reliable data on the epidemiology of these diseases must be available and there must be registers of those diseases to inform us about the population burden they entail when taken as a whole and individually.

2. Natural history: diversity and heterogeneity. Diversity is an intrinsic characteristic in a group of disorders as broad as that of RD. The nature of the pathological processes varies from diseases that affect a single organ system to multisystem diseases. So, in the case of retinitis pigmentosa and the group of retinal dystrophies, for instance, the target organ is the eye and patients suffer from a sensory disorder, or in the case of muscular dystrophies the skeletal muscle is the affected structure and causes locomotor problems. On the other hand, in the case of metabolic diseases like Gaucher disease, for instance, the disorder affects different organs like the hematopoietic system, the nervous system and the bones. Likewise, systemic diseases like lupus erythematosus or scleroderma involve several organs. The heterogeneity of these diseases becomes apparent in the different profiles of their natural history, which conditions the clinical and preventive action taken by health services. Those profiles refer to the causes of the disease (aetiology), the age of onset and the temporal development of the disease (chronobiology), the clinical expression (semiology and physiopathology) and the degree of severity (seriousness and prognosis). Obviously the natural history profiles are very diverse and vary from one disease to the next, from one

patient to the next. In the case of Mendelian diseases the profiles may even vary within a same family.

3. Comprehensive and multidisciplinary care. A rare disease tends to be chronic and debilitating. In many cases people who suffer from this type of disease require care that goes beyond the specific clinical care offered to them by a specialised service. That care must be considered in a context of global management, involving paediatrics or family medicine in Primary Care, the medical specialty or specialties that understand the specific clinical problems, nursing and physiotherapy, social services and psychological support. For many patients, and especially patients with several affected organs or systems, that comprehensive care requires the reconciliation of multiple perspectives, involving the participation of different areas of expertise through a single coordination framework.

4. Integrated health and social care. Many rare diseases involve a high degree of dependence and entail a heavy social, health and economic burden. Although that is not something specific to rare diseases, there are certain aspects that are specific to these diseases which, to a certain degree, set them apart. To a large extent that has to do with the fact that the first symptoms of many of these diseases occur in childhood or adolescence, meaning that the family and social burden is, practically, lifelong. The invalidity or physical or psychological disability appears early on in the person's biography, which means that his or her life history is affected from a very early stage. Consequently, patients with RD have specific healthcare, social, educational and occupational needs over a long period of time, which require constant, ongoing provision of planned, long-term action.

5. Genetic heritage. It is estimated that 80% of rare diseases are genetic, mainly monogenetic, and follow the Mendelian laws of inheritance. That means that the underlying root cause is a gene mutation in autosomal dominant cases, mitochondrial and X chromosome-linked, and two mutations in autosomal recessive cases. Therefore, a natural characteristic of these diseases is that patients show the clinical expression of deleterious mutations that are shared by the whole population. That is especially obvious in the case of recessive mutations. People who are heterozygous carriers of a single recessive mutation tend to be healthy and unaware of their status as carriers, unless they have an affected child with a partner who is also a carrier of a mutation in the same gene. And yet, such recessive mutations are not characteristic to

them, but rather are shared with a subset of the population. The gene load of these diseases is shared by all the individuals of a specific population. The knowledge that we are acquiring about these diseases, including the knowledge on genetics, mutations, genetic variability and the relationships between the genotype and the phenotype, make it technically possible for us to consider the study of the genetic epidemiology of these diseases in specific populations.

6. Risk of recurrence of a genetic disease in families. A natural characteristic of monogenetic diseases is the family recurrence risk, which varies according to the type of inheritance but which is always high, ranging between 25-50% for each gestation. In some cases, like that of congenital malformations or defects that have a non-Mendelian genetic component, that recurrence risk is smaller and, although in many cases difficult to establish, existing empirical data shows that while being less high than the Mendelian risk it is still greater than that of the general population. The genetic cause and the recurrence risk require patients and families to have access to genetic diagnosis and genetic counselling services.

7. Geographical dispersion. The distribution of affected persons and their families across a broad geography is an intrinsic phenomenon of rare diseases. The random distribution means that there could be cases anywhere, whether in an urban or rural environment, without them being concentrated in any specific area. The only exception to that rule occurs in circumstances in which the isolation of a population has led to a bottleneck and founder effect for the mutations that cause a disease, with the consequential increase in the rate of carriers in that population. That geographical dispersion makes it difficult to implement specific actions aimed at these diseases, especially in rural environments.

8. Treatment opportunities and therapy development. In general, therapeutic options for RD are scarce and not very effective. The development of new therapies and drugs for these diseases requires efforts to be made to render the research and development of drugs for rare diseases more appealing. That is the aim of policies on orphan medicinal products, which are understood to be a medicinal product —medicine, genetic therapy, cell therapy— specifically intended for the treatment of rare diseases. The development of orphan medicinal products entails certain aspects and complications that need to be stressed, with the main challenge being that of obtaining sufficient evidence regarding the effectiveness and safety of these medicines or

therapies in people suffering from a rare disease. Various problems can be detected with regard to clinical trials: the availability and interest of clinical researchers, funding and, above all, the recruitment of patients with a correct diagnosis and in the necessary numbers.

The need to tackle the aforementioned aspects in the field of rare diseases and to provide affected persons with quality care justify the creation of this Spanish NHS Rare Diseases Strategy, which is promoted by the Ministry of Health and Social Policy, through its Quality Agency.

This document sets out the seven strategy lines that are considered to be priorities: i) information on rare diseases and available resources; ii) prevention and early detection; iii) healthcare; iv) therapies; v) integrated health and social care; vi) research, and vii) training. For each of those strategy lines and in their subsections the known background has been provided and general objectives have been established which, subsequently, have been developed into specific objectives and recommendations. Finally, the document sets out the procedure for the monitoring and evaluation of the Strategy in time, with guidelines for its planning, dissemination and monitoring, as well as the indicators to use when evaluating the implementation of the objectives established herein.

The document was drawn up by a Drafting Committee, established in February 2008 and made up of representatives of scientific societies and patient organisations, and an Institutional Committee made up of the Health or Healthcare Departments of the Autonomous Communities, the representatives of which joined the Committee in June 2008. The seven strategy lines were approached through different working groups, each with their own coordinator, and with the support of a Technical Office located in the Centre for Biomedical Network Research on Rare Diseases (CIBERER). The work of the different groups was active, involving information exchanges, meetings and extensive debates, thereby making sure that the document was of maximum scientific rigour and that it responded to the needs of patients with clear and realistic proposals from the perspective of effective and efficient healthcare.

The initiative taken by the Quality Agency of the Ministry of Health and Social Policy to promote a Strategy on rare diseases with the participation of all the stakeholders, patients, health professionals and government health departments concerned, must redound to the benefit of affected persons and their families, and of citizens in general, and must lead to an improvement of the Spanish health system. This document is intended as a starting point to help the Spanish NHS take action regarding the healthcare requirements and the health and social needs

of patients with rare diseases. Moreover, it should serve as a guide for the Autonomous Communities in the monitoring of the level of implementation, development, coordination and innovation of preventive, diagnostic, treatment, research and training activities in the field of rare diseases.

We are convinced that the Strategy is going to be an effective tool that will mark a turning point in the care of people affected by rare diseases. It will help make health professionals look at the problems faced by the sufferers of these diseases through different eyes, offering them a new perspective on what rare diseases are, on the needs of affected persons and on what they can do to provide them with comprehensive and multidisciplinary care. Health authorities will have a guide for the development of their health plans and actions in a context of care integrated into the health system. The responses of professionals and authorities to the challenges considered in the Strategy must make patients feel that the system has provided for them, and that a long-requested, specific solution to their problems and needs is available for each disease individually and for rare diseases collectively.

I would like to express my gratitude to everyone who participated in the creation of this Strategy —patients, experts and representatives of the Autonomous Communities— and who will continue to do so by monitoring it over the next few years. Their work and dedication made it possible for us to reach this point, which is not an end but rather a beginning. I would also like to thank the Ministry of Health and Social Policy, through the Directorate General of the Quality Agency, for having given me the opportunity to participate in this project and for the trust they placed in me. It has been, and continues to be, an honour and an extraordinary experience which I sincerely hope will help improve the lives of the people suffering from these pathologies which we have agreed to call rare diseases, many of which start in childhood and, by nature, are uncommon.

FRANCESC PALAU
Coordinator of the Spanish NHS Rare Diseases Strategy

Technical Note

This document is made up of four parts:

General aspects, which covers the general situation of rare diseases in Spain and the justification for this Strategy.

Development of the strategy lines, which were approved by the Interterritorial Council of the Spanish NHS on 3 June 2009, sets out the objectives and recommendations for action that have been proposed for each strategy line, as agreed by the Technical Committee and the Institutional Committee.

Monitoring and evaluation, which sets out the process that makes it possible to monitor the proposed actions.

Appendixes, which includes the bibliography and the list of acronyms and abbreviations used in this document.

1. General aspects

1.1. Justification

According to the definition by the European Union (EU), rare, minority, orphan or uncommon diseases are life-threatening or chronically debilitating diseases with a prevalence of less than 5 cases per 10,000 inhabitants. That definition was adopted by the «Community Action Programme on Rare Diseases (1999-2003)» and is also used by the European Medicines Agency (EMEA) for the declaration of orphan medicinal products, as well as by the large majority of Member States.

It is difficult to determine the exact number of Rare Diseases (RD), but it is estimated that it could range somewhere between 6,000 and 8,000, although only about 100 of those diseases have a prevalence near the threshold at which a disease is considered to be rare (*Orphanet*). Although individually these diseases are uncommon, together they form a substantial group, since they affect between 5-7% of the population of developed countries, which in the case of Spain translates into 3 million affected persons.

Despite being a very heterogeneous group of clinical entities, rare diseases have certain common characteristics:

- In general, they are hereditary diseases that commonly begin in childhood.
- They are of a chronic nature, in many cases progressive, involving high morbidity and mortality and a high degree of disability.
- Their aetiology, diagnosis and prognosis are very complex.
- They need to be treated and monitored in a multidisciplinary manner.

Therefore, the «EU Public Health Programme» identified Rare Diseases as a main priority for action. Accordingly, the «Community Action Programme on Rare Diseases» was adopted for the period between 1 January 1999 and 31 December 2003. The objective of that programme was to contribute, together with other Community measures, to guarantying a high level of health protection in relation to uncommon diseases. As a first EU effort in this area, specific attention was given to improving knowledge and facilitating access to information about these diseases.

Uncommon diseases are now one of the priorities of the «Second Programme of Community Action in the Field of Health (2008-2013)». The two main lines of action under the work plan of the Directorate General for Health and Consumer Protection (DG SANCO) of the European Commission are: the exchange of information via existing European information networks on rare diseases; and the development of strategies and mechanisms for information sharing and coordination on a Community level in order to promote the continuity of work and collaboration on a transnational scale.

Moreover, with regard to rare diseases projects, the DG SANCO prioritises generalist networks, which centralise information on as many rare diseases as possible, and not just on a specific group or a single disease, in order to improve information, monitoring and surveillance.

On 11 November 2008 the European Commission adopted the *Commission Communication COMM(2008) 679 final to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Rare Diseases: Europe's challenges* and the *Proposal for a Council Recommendation on a European Action in the field of Rare Diseases*, which set out a global Community strategy to support Member States in the tasks of diagnosing, treating and caring for the 36 million EU citizens suffering from this type of disease. In view of the limited number of affected patients and the fragmentation of expertise across the entire European Union, rare diseases are a prime example of an area in which an intervention at European level is necessary and beneficial.

The Communication highlights a Community strategy centred around three main lines of action, consisting of: i) improving the recognition and visibility of rare diseases; ii) supporting national plans addressing rare diseases in the Member States, and iii) strengthening EU cooperation and coordination in the field of rare diseases.

European cooperation will help to bring together the limited available resources for rare diseases, which are currently scattered across the different EU countries. European action will facilitate the contact between the patients and professionals of the different Member States, as well as the sharing of knowledge and information and coordination in that field. That objective will be achieved, for example, through the creation of networks of centres of expertise in different countries, and by making use of information and communication technologies (E-Health). The Commission will build on actions that have proved to be successful in the past, like the public health programme on rare diseases, the research and technological development framework programmes, and the specific regulatory framework already in place for the provision of

additional incentives for the development of «orphan» medicinal products to treat these disorders.

In the case of rare diseases, the twenty-seven different national approaches are rendered ineffective and inefficient by the limited number of patients with these diseases.

The added value that the EU can provide must be channelled through different activities: information exchanges, collaborative pluri-disciplinary research, and the development of preventive, diagnostic and therapeutic measures, with the following results:

- reduction of inequities in health in the EU,
- creation of a coherent framework for the identification of rare diseases and the dissemination of information on a European scale,
- improvement of the information, identification and knowledge on rare diseases in order to create a solid base for the diagnosis and care of patients,
- creation of an improved framework for research on rare diseases.

In keeping with those issues, the Commission has put forward a series of objectives, including that of «Supporting policies on rare diseases in the Member States», which encourages the latter to establish strategies organised around different elements, such as the creation of national plans for intersectoral action in the field of rare diseases.

In short, all the abovementioned factors justify the need to approach these pathologies through the National Health System, by developing and implementing the Spanish NHS Rare Diseases Strategy.

Moreover, Article 70 of Spanish General Health Law 14/1986, of 25 April, states that general health coordination shall include the establishment of minimum, common purposes or objectives on the promotion, prevention, protection and care of health, as well as the establishment, in general, of minimum, basic and common criteria for the evaluation of the effectiveness and performance of health programmes, centres and services.

Furthermore, the said Law states that the Spanish State and the Autonomous Communities may establish joint strategies which, when involving all of them, shall be formulated by the Interterritorial Council of the Spanish NHS (Consejo Interterritorial del Sistema Nacional de Salud, CISNS).

The most recent international experience suggests that a good way of approaching these joint actions is by establishing strategies on the most relevant diseases, with the objective of achieving a homogeneous perspective within the National Health System.

Those strategies must establish objectives, actions and recommendations based on scientific evidence and available current best practices in the areas of promotion, prevention, clinical management, rehabilitation and social reintegration, information systems and research. They must be formulated through the active participation of the regional health services of the Autonomous Communities (AC), scientific societies and other social stakeholders, and they must be reviewed periodically.

The guiding principles of the Spanish NHS Rare Diseases Strategy are solidarity, equity and collaboration, with the aim of reducing inequalities and of promoting health and healthy lifestyles, as well as quality in care.

Accordingly, each Autonomous Community shall, to a greater or lesser extent, implement those elements which, it has been agreed, are the most efficient and have the greatest impact, thereby using this document as a reference guide.

This document was developed through the participation, on the one hand, of a Technical Committee, made up of representatives of scientific societies and patient organisations related to rare diseases; and, on the other hand, by an Institutional Committee, made up of representatives of all the Autonomous Communities, as well as representatives of the Ministry of Science and Innovation, and all the Directorates General of the Ministry of Health and Social Policy concerned.

The work of the Drafting Committee of the Spanish NHS Rare Diseases Strategy started in January 2008, and led to the creation of an initial technical document that described the current situation. In the summer of 2008, on the basis of that initial document, the Strategy was redefined and a validated methodology was applied for the prioritisation of objectives, activities and indicators.

Those efforts led to the establishment of 44 objectives (13 general objectives and 31 specific objectives) with their respective recommendations or proposals for action and evaluation indicators.

1.2. Current situation of rare diseases in Spain

The first national initiative taken in relation to rare diseases was the creation of the Toxic Oil Syndrome Research Centre (Centro de Investigación sobre el Síndrome del Aceite Tóxico, CISAT), of the Carlos III Health Institute (Instituto de Salud Carlos III, ISCIII), in 1996, with the mission of coordinating the treatment of, and research on, Toxic Oil

Syndrome. As of the year 2000, the Government progressively became involved in care and research regarding rare diseases, and extended the activities of the CISAT, which by Ministerial Order of 27 December 2001 became the Toxic Oil Syndrome and Rare Diseases Research Centre (Centro de Investigación del Síndrome del Aceite Tóxico y Enfermedades Raras, CISATER). The tasks assigned to the aforementioned centre were those of maintaining and supporting the development of research and of implementing a National Research Programme in that field. The initiatives undertaken by the CISATER led to the creation of the first Spanish-language Rare Diseases Information System (Sistema de Información de ER en español, SIERE), to the inclusion of Rare Diseases on the list of priority areas for research of the ISCIII, to the participation in both national and European Thematic Networks for Collaborative Research in Health (Redes Temáticas de Investigación Cooperativa en Salud, RETICS), and to the creation of a Rare Diseases Ethics Committee.

In Spain, the approval of the European Union's *Action Programme on Rare Diseases* in 1999 and the *Regulation on Orphan Drugs* in 2000 gave new impetus to RD, which were included among the priority areas for research in the calls for proposals of the Health Research Fund (Fondo de Investigación Sanitaria, FIS) of the ISCIII. At the same time, organisations of affected persons, professional societies, general practitioners and researchers were starting to liaise with each other. A total of 12 out of 69 Thematic Networks for Collaborative Research in Health (RETICS) emerged that were related to RD and approved by the FIS. The more general networks among them, namely the Epidemiological Network on Rare Diseases Research (Red de Investigación Epidemiológica en Enfermedades Raras, REpIER), the Research Institute for Genetic Rare Diseases (Instituto de Investigación de Enfermedades Raras de Base Genética, INERGEN) and the Network of Clinical and Molecular Genetics Centres (Red de Centros de Genética Clínica y Molecular, RECGEN), created a system of epidemiological information and genetic diagnosis resources. Also noteworthy is the work carried out by the Network of Hereditary Metabolic Disorders (Red de Enfermedades Metabólicas Hereditarias, REDEMETH) in terms of advances in clinical, biochemical and genetic diagnosis, the study of the molecular bases and etiopathogenesis of metabolic diseases, new therapeutic approaches and epidemiological studies and registers.

In 2003, the CISATER became the Rare Diseases Research Institute (Instituto de Investigación de Enfermedades Raras, IIER). The Institute's objectives are to promote and carry out clinical and basic research, to provide training and support to healthcare providers, and to boost innovation in the care of patients with rare diseases.

In November 2006, the Centre for Biomedical Network Research on Rare Diseases (CIBERER) was created. It is one of the nine public consortiums set up by the Carlos III Health Institute (ISCIII), and is intended to foster and coordinate biochemical research on rare diseases in Spain. The CIBERER was born with the objective of becoming an international reference centre for research into the causes and mechanisms of rare diseases, and of laying the groundwork for the undertaking of translational research to benefit people affected by these disorders. Since its foundation it has brought together 61 research groups spread throughout 9 Autonomous Communities, and has allocated 18 million euros to programmes for human resources, training, equipment and research projects.

Lastly, the most recent initiative taken in Spain with regard to rare diseases was the Position Paper delivered to the Senate in 2006 by a Joint Commission made up of the Health and Consumption Commission and of the Labour and Social Affairs Commission, which spent a year analysing the situation of people with rare diseases. The Position Paper stressed the need for all the initiatives taken by the Autonomous Communities to be coordinated through a national plan that would manage all the resources for the care of patients with RD. The full Senate approved the Position Paper in which the Government was urged to establish the said action plan for rare diseases.

One of the issues referred to in the Position Paper is the Central Government's objective of guaranteeing the coherence, quality and equity of the system. Accordingly, in Spain, Royal Decree 1302/2006, of 10 November, establishing the conditions regarding the procedure for the designation and accreditation of the Reference Centres, Services and Units (CSUR) of the Spanish NHS, defines the characteristics that must be met by pathologies or groups of pathologies that are prevented, diagnosed or treated by means of techniques, technologies or procedures included in the Spanish National Health System's common services portfolio, in CSUR of the Spanish NHS.

Moreover, in the area of social services, the year 2009 also saw the creation of the State Reference Centre for Rare Diseases Patients and their Families (Centro de Referencia Estatal de Atención a Personas con Enfermedades Raras y sus familias, CRE) located in Burgos.

The Reference Centre on RD, which was created by the General State Administration, the Institute of the Elderly and Social Services (Instituto de Mayores y Servicios Sociales, IMSERSO), which is currently attached to the Ministry of Health and Social Policy, was set up as a centre dedicated to the promotion, development and dissemination of knowledge, innovative experiences and methods for the care of people with rare diseases; as a

centre highly specialised in services for the care and support of families and carers; and as a centre for the promotion of personal autonomy and the social participation of people suffering from those diseases.

The objectives of the State Reference Centre for Rare Diseases Patients and their Families (CRE) are to:

1. Promote, on a national level and in connection with other centres on an international level, the development, innovation and optimisation of the resources for people with rare diseases and of the skills of the professionals who work with these groups.
2. Provide support and highly specialised services that serve as an example for the rest of the sector's resources, and provide technical information and assistance to government bodies, institutions, public and private entities, professionals and other people who are interested in the integrated health and social care and the social participation of people with rare diseases and of their families.
3. Give people suffering from rare diseases, as well as their families and carers, access to guidance and support services, care provision training and practice services, intensive rehabilitation services, as well as respite care services for periods of temporary relief.

Initiatives taken by the Autonomous Communities

The situation varies greatly from one Autonomous Community to the next. The Regional Government of Andalusia (Junta de Andalucía) created a genetics plan, the *Plan de Genética de Andalucía 2006-2010,* which, in turn, led to the creation of the *Plan de atención a personas afectadas por ER 2008-2012,* a plan regarding care for people affected by RD. Both plans are currently in force and being developed.

The Regional Government of Extremadura (Junta de Extremadura), which already referred specifically to RD in its health plan, the *Plan de Salud de Extremadura 2005-2008*, is developing a comprehensive rare diseases plan for the period 2009-2014, the *Plan Integral de Enfermedades Raras en Extremadura 2009-2014 (PIER*).

The Health Department of the Autonomous Government of Catalonia (Generalitat de Catalunya) recently approved an Order for the creation of a an Advisory Commission on minority diseases, with the aim of enhancing the implementation of specific health policies aimed at these pathologies, some of which are already included in Catalonia's different existing master plans (on integrated health and social care, mental health, oncology, etc.).

The Autonomous Community of the Basque Country (CAPV) has a *Plan de Genética*, or genetics plan, which sets out recommended actions for the CAPV in relation to the portfolio of services regarding genetic counselling, genetic tests, reference laboratories and the allocation of resources.

At the other extreme are the Autonomous Communities that do not refer to rare diseases at all in their health plans or that have not taken any measures that address this category of diseases.

The situation in most of the Autonomous Communities is somewhere in between those extremes.

1.3. Document description. Methodology

Like for the other Strategies approved to date by the Interterritorial Council of the Spanish NHS (CISNS), namely those on Cancer, Ischaemic Heart Disease, Diabetes, Mental Health, Palliative Care, Assistance at Normal Childbirth and Strokes, this Strategy was developed according to the following elements:

a) The choice of the Scientific Coordinator and the creation of the Strategy's Technical Committee.

b) The conclusions of a first meeting with the Technical Committee of the Spanish NHS Rare Diseases Strategy, organised by the Ministry of Health and Consumer Affairs in February 2008.

c) The creation of the Strategy's Institutional Committee.

d) A descriptive analysis of the situation of rare diseases in Spain and internationally with the aim of identifying the background, the way care is organised, the critical issues and the available evidence on best practices.

Two Committees were set up:

Firstly, a **Technical Committee** made up of the following scientific societies and patient organisations:

Scientific societies

Spanish Society of Clinical Biochemistry and Molecular Pathology (SEQC).

Spanish Society of Family and Community Medicine (SEMFYC).

Spanish Society of General Medicine (SEMG).

Spanish Society of Primary Care Physicians (SEMERGEN).
Spanish Association of Paediatrics (AEP).
Spanish Association of Primary Care Paediatrics (AEPap).
Spanish Association of Human Genetics (AEGH).
Spanish Society of Internal Medicine (SEMI).
Spanish Society of Neurology (SEN).
Spanish Society of Obstetrics and Gynaecology (SEGO).
Spanish Society of Immunology (SEI).
Spanish Association for the Study of Inborn Errors of Metabolism (AECOM).
Spanish Association for Neonatal Screening (AECNE).
Federation of Community Nursing and Primary Care Associations (FAECAP).
Spanish Union of Scientific Nursing Societies (UESCE).

Patient organisations

Coalition of Citizens with Chronic Diseases (Coalición de Ciudadanos de Enfermedades Crónicas).
Spanish Federation of Neuromuscular Diseases (F-ASEM).
Spanish Federation for Rare Diseases (FEDER).
Spanish Federation of Phenylketonuria and other Inherited Metabolic Disorders (Federación Española de Fenilcetonuria y OTM).

Secondly, an **Institutional Committee** made up of the representatives appointed by the Health Departments of the Autonomous Communities. One of its main tasks was to assess the suitability and feasibility of the proposed objectives, since they, the Autonomous Communities and their Health Services, will be in charge of actually organising and providing the healthcare.

The coordination of the drafting of the document by both Committees was, at first, carried out by the Centre for Biomedical Network Research on Rare Diseases (CIBERER), after the Ministry of Health and Consumer Affairs entrusted its management to the Carlos III Health Institute (ISCIII).

Moreover, the institutional coordination of the Strategy is the responsibility of the Ministry of Health and Social Policy, and more specifically of the Directorate General of the Spanish NHS Quality Agency, through the Health Planning and Quality Office.

Due to the inherent complexity of rare diseases, all the Directorates General involved in the provision of care for people with those disorders also participated in the development of the Strategy:

— Directorate General for Public Health and Foreign Health Affairs.
— Directorate General for Professional Regulation, Cohesion of the NHS and High Level Inspectorate.
— Directorate General for Pharmacy and Health Products.
— Directorate General for Advanced Therapies and Transplants.
— Spanish Medicines Agency (AEMPS).

Likewise, representatives of the Ministry of Science and Innovation were also part of the aforementioned Institutional Committee.

The two Committees worked together in an interactive manner, through meetings as well as emails and other IT tools.

In a first phase, they identified the **critical issues** of the Spanish NHS with regard to care for people with RD through the development of a descriptive analysis of the situation in Spain, used to identify the objectives of the Strategy.

Next, that analysis was used to determine the **objectives and recommendations**, which were presented to the Interterritorial Council of the Spanish NHS on 3 June 2009.

With the support of experts in health policy evaluations, a set of **indicators** were then determined for the proposed strategy lines. Those **indicators** make it possible to conduct systematic and continuous evaluations, and to monitor and evaluate the Strategy throughout its implementation process by means of an information system that can be applied to the Spanish NHS as a whole, and to all the plans and programmes addressing rare diseases in the Autonomous Communities.

When drafting the document, the gender perspective was taken into account. Its inclusion within the framework of health strategies is established in Organic Law 3/2007, of 22 March, on effective equality between men and women (1).

(1) **Article 27** sets out the Incorporation of the principle of equality in health policies: **1.** Health policies, strategies and programmes shall incorporate, in their formulation, development and evaluation, the different needs of men and women and the measures required to approach them in an adequate manner. **2.** Government bodies guarantee equal rights to health for men and women, through the active incorporation, in the objectives and actions of health policies, of the principle of equal treatment, thereby avoiding that their biological differences or the social stereotypes associated with those differences, lead to discriminations between them. **3.** Government bodies, through their Health Services and the respective competent bodies, shall in all cases develop, in accordance with the principle of equal opportunities, the following actions: **a)** The systematic adoption, in health education actions, of initiatives aimed at enhancing the specific promotion of the good health of women, as well as at preventing their discrimination. **b)** The promotion of scientific research that deals with the differences between men and women in relation to the protection of health, especially with regard to diagnostic and therapeutic accessibility and efforts, in relation to clinical trials as well as care. **c)** The

1.4. Document structure

This document is structured into three parts:

The first part, **General aspects**, includes the justification, the purposes of the Strategy (its mission, principles, the values it inspires), the definition of rare diseases and their situation in Spain. In addition it covers their historical development and epidemiological situation. Finally, it sets out the strategy development methodology.

The second part, **Development of strategy lines**, sets out the objectives and recommendations. The participants of the Strategy decided, by consensus, to establish the following strategy lines:

- Strategy line 1: Information on RD.
- Strategy line 2: Prevention and early detection.
- Strategy line 3: Healthcare.
- Strategy line 4: Therapies.
- Strategy line 5: Integrated heath and social care.
- Strategy line 6: Research.
- Strategy line 7: Training.

The strategy lines are broken down into general and specific objectives, with their respective technical recommendations and monitoring and evaluation indicators.

In short, this document aims, on the basis of available information/ evidence, to establish a set of objectives and recommendations to be achieved which, in a realistic manner and according to the available resources and the areas of competence of the Autonomous Communities, will help improve the quality of interventions and outcomes in the field of rare diseases.

The third part, **Monitoring and Evaluation**, sets out the process that makes it possible to monitor the proposed actions.

consideration, within the protection, promotion and improvement of occupational health, of sexual harassment and gender-based harassment. **d)** The incorporation of the principle of equality in the training of the staff serving health organisations, thereby guaranteeing, in particular, their ability to detect and deal with situations involving gender violence. **e)** The presence of equal numbers of men and women in management positions and in positions with professional responsibilities throughout the entire Spanish National Health System. **f)** The collection and processing, whenever possible disaggregated by gender, of the data contained in the registers, surveys, statistics or other medical or health information systems..

1.5. Definition of general concepts

Objectives (both general and specific) are challenges that need to be met, and which are applicable to the entire population at which they are aimed. They have been established on the basis of the different recommendations of scientific societies, patient organisations and authorised institutional entities. Objectives are achievements, not a process for the development of tools or instruments, which is why it has to be possible to monitor, quantify and updated them.

This first version of the Spanish NHS Rare Diseases Strategy is considered to be a starting point based on the current real situation which, in the future, should lead to more demanding objectives. Moreover, the situation should progress towards more ambitious challenges in order to guarantee a continuous increase in the quality of care.

Recommendations are general actions that must be undertaken, one way or another, according to the different organisational criteria of the different government bodies. They help guarantee the achievement of the objectives and are subject to the changes linked to the evolution and progress of knowledge. Therefore, they must be updatable.

Indicators are measurements of processes or outcomes, that are essential for the evaluation of the effectiveness of the Spanish NHS Rare Diseases Strategy and which, in short, generate clear, consistent and updatable information.

2. Development of the strategy lines

2.1. Information on Rare Diseases

2.1.1. Information on RD and Available Resources

2.1.1.1. Background

From an essentially epidemiological perspective, RD are diseases which as a consequence of their chronic and debilitating nature present a prevalence that is so low that they call for specific and combined efforts, aimed at preventing morbidity, premature mortality or the reduction of the quality of life and socio-economic potential of the people suffering from them.

In this context, rare diseases are a challenge for health systems, since they form a conglomerate in which well-known diseases with treatment options are intermingled with others that are largely unknown and, therefore, difficult to treat.

The generation and dissemination of exact information in a format that is adapted to the needs of professionals, affected persons and their families, is key to the improvement of the diagnosis and care of patients with RD.

Over the last few decades there has been a true explosion of knowledge in the field of RD. However, it is often difficult to access certain aspects of the information regarding a specific rare disease. That leads to the paradox of the ignorance that surrounds many RD, and has been identified as a need not only of patients and their families, but also of professionals and government bodies.

The dissemination of the available information is a complicated task, since the knowledge about RD, whether regarding their diagnosis, treatment, prevention or the resources available to affected persons, is disperse.

Different initiatives on both a national and international scale have been taken to satisfy that need for information and to facilitate access to it. The identification of the needs and the satisfaction of the demands of the stakeholders involved in RD are the objectives which, progressively, have led many other countries to show an interest in RD.

Noteworthy among national initiatives is that of the Rare Diseases Research Institute (IIER) of the ISCIII which, in December 2000,

published the first Spanish-language Rare Diseases Information System (**SIERE**), which can be accessed freely and free of charge, with corroborated information and written in straightforward language.

In 2004, those efforts culminated in the publication of a guide on the practical approach to rare diseases, ***Enfermedades Raras: un enfoque práctico***, which was based on the work developed by the SIERE, and aimed at patients, their families, health professionals and other social stakeholders involved in RD. The guide contains information about some 400 RD, grouped together according to the broad groups of the ICD-9; a description of the diseases that includes its signs and symptoms; a brief overview of the complementary diagnostic techniques, basic preventive aspects, therapeutic options and, where available, genetic options; as well as information about medicines.

Likewise, it includes information about available social resources and disability-related aspects, and contains the available inventory of mutual aid associations and their contact details.

Another initiative which, precisely, takes the associative movement as a starting point, is the Guidance and Information Service (Servicio de Orientación e Información, SIO) on RD, which was created by the Spanish Federation for Rare Diseases (Federación Española de Enfermedades Raras, FEDER) in January 2001. It aims to respond to two of the requirements highlighted by people suffering from RD, their families and health professionals: the lack of information and the isolation suffered by people affected by RD.

The service is directed at people affected by RD and their families, professionals who work in different intervention areas and who need information about these pathologies, as well as the population in general.

The SIO provides basic information on RD (disease definition and main symptomatology), as well as advice on existing resources and specialists. Moreover, it facilitates the establishment of contact and the sharing of experiences between people affected by a same pathology or group of pathologies.

On an international level, and more specifically in Europe, **Orphanet** was established in 1997 in France as a web portal offering information on RD. Originally entirely supported through national funding, since 2000 the DG SANCO has funded the encyclopaedia and the collection of data from European countries.

Orphanet is a database of information on rare diseases and orphan drugs aimed at all publics: patients and their families, health professionals, researchers, industry professionals and policy makers. It aims to contribute to the improvement of the diagnosis, care and treatment of people affected by rare diseases. It also includes

a Professional Encyclopaedia, which is expert-authored and peer-reviewed, a Patient Encyclopaedia and a directory of specialist services. The Directory includes information on specialist medical practices, diagnostic laboratories, research projects and patient organisations.

Its services include the Orphanet encyclopaedia (a comprehensive collection of review articles on rare diseases); the Orphanet directory of services; a disease search by clinical sign; the public database of orphan drugs that provides information about medicinal products with orphan designation and/or marketing authorisation in Europe, USA, Japan or Australia; OrphanXchange (a database of molecules with a potential orphan indication, and of research projects); OrphaNews Europe, which is the monthly electronic newsletter of the European Commission's Rare Diseases Task Force (RDTF); OrphaNews France; and a Register of volunteers (affected persons who wish to participate in future research projects).

Moreover, the functions that will be carried out by the **State Reference Centre for Rare Diseases Patients and their Families** (**CRE**) in Burgos, which will be inaugurated soon, should not be forgotten. It will disseminate information on rare diseases, as well as information on guidance and support services and the integrated health and social resources available for this type of pathologies, to patients, their families, institutions and professionals.

2.1.1.2. General objective

To support strategic action that makes it possible to improve information on RD and the existing resources for their care.

2.1.1.3. Specific objectives and recommendations

Objective 1

To improve the available information on RD as well as the existing resources for their care, in order to respond to the needs of patients, health professionals, researchers and the people in charge of health departments and social services.

Recommendations

- Support information resources that render information more accessible to both professionals as well as affected persons.
- Coordinate, through the Ministry of Health and Social Policy, the existing information and resources concerning RD, at all levels, whether central or autonomous.

— Identify information sources and available resources for RD that make it possible to establish priorities and to identify the shortcomings of those resources.
— Analyse existing information directories and resources, on both a national and international level, in order to evaluate their capacity to provide information, and promote those which are most appropriate.
— Promote tools that help link information on aid to resource maps, leading to intersectoral and inter-ministerial collaboration for the exchange of information in different areas and the adaptation of that information to render it more accessible to the patients and professionals who request it.
— Promote the availability, through a common tool, of all the Autonomous Communities' healthcare or social resources for rare diseases.
— Once they have been designated as such, publish information about the Reference Centres, Services and Units (CSUR) on RD on the website of the Ministry of Health and Social Policy.
— Encourage academic institutions, research centres, scientific societies and patient organisations to work together in order to promote and disseminate knowledge about the directories of available resources for RD.

2.1.2. Health Registers

2.1.2.1. Background

All proposals for the promotion and protection of health, as well as for early diagnosis and other aspects, must be based on sound epidemiological studies that make it possible to outline the health policy best suited to the problem that needs dealing with.

A preliminary report of a recent bibliographical study developed by Orphanet revealed the scarcity of documented information on the epidemiology of rare diseases. Despite contributing heavily to the morbidity and mortality of the population, rare diseases are invisible in health information systems due to the lack of appropriate coding and classification systems.

This highlights the need to estimate the approximate number of affected persons and the prevalence of each disease. Likewise, it emphasises the need to evaluate the natural history of rare diseases with the purpose of adapting healthcare interventions and of improving the processes used to monitor them.

In Spain, the most noteworthy initiative was the creation of REpIER, one of the twelve research networks on RD which were approved within the framework of the Thematic Networks for Collaborative Research in Health (RETICS), created by the Carlos III Health Institute (ISCIII) in 2002. Its main objective was to «develop an epidemiological research programme for rare diseases in Spain, which will enhance the knowledge about their clinical, epidemiological and therapeutic situation, as well as providing more suitable information for the development of guidelines for health and social care interventions».

REpIER, which was made up of sixteen research centres/groups from eleven of the Autonomous Communities and of the Carlos III Health Institute (ISCIII), studied the possibilities offered by the existing databases in their respective Communities, in order to build an epidemiological information system on RD. Moreover, it tried to identify the existing registers and their functions, analysed the strategies for the study of quality of life, and conducted an analysis of treatment costs and health expenses.

Those efforts led to the development of several studies on the prevalence of rare diseases per AC. Despite their unquestionable value as a first approach to the epidemiological study of rare diseases, most of the reports are limited by the information sources used, the Minimum Basic Data Set (MBDS) and the coding system applied.

Another national initiative worthy of mention is that of the Department of Health and Dependence of the Regional Government of Extremadura (Consejería de Sanidad y Dependencia de la Junta de Extremadura), in collaboration with the REpIER node of Extremadura which, since the year 2004, has offered a «Rare Diseases Information System».

Since information about them is fragmented and expertise on them is limited, **health registers** are key tools for the handling of uncommon diseases.

The term health register can be defined as a systematic, anonymised, continuous and efficiently retrievable file of data concerning elements of importance to health, in a given population, so that the registered elements can be related to a base population. Health registers require the collection of relevant and reliable data that can be used to make specific inferences with respect to the target audience for the development of actions regarding the prevention, management or research of rare diseases.

In the case of **patient registers**, patients personally provide their data on a voluntary basis. The purpose of these registers is to develop clinical research and to improve patients' understanding of the diseases affecting them.

A first step regarding patient registers was taken by the Rare Diseases Research Institute (IIER) of the Carlos III Health Institute (ISCIII) in 2005, when it registered the Rare Diseases Register and Sample Bank (Registro de Enfermedades Raras y Banco de Muestras) with the Spanish Data Protection Agency. This register started to streamline its work on the basis of the work developed through the REpIER network.

The main objective of the Rare Diseases Patient Register (Registro de Pacientes de Enfermedades Raras, REGPER: http://registroraras.isciii.es) is to provide information to patients, professionals and institutions.

From a broad perspective, in the article *Los Registros de Enfermedades en la Investigación Epidemiológica de las ER en España*, on disease registers in epidemiological research on RD in Spain, published in 2006 in the magazine *Revista Española de Salud Pública*, a descriptive study was carried out on the basis of the two directories of health registers developed by the Health Technology Evaluation Agency (Agencia Española de Evaluación de Tecnologías Sanitarias, AETS) in 2000 and 2005. Those directories constitute the only existing standard and homogeneous base in Spain, to date, that makes it possible to assess the existence of health registers in the field of rare diseases.

The abovementioned directories classify those registers as «specifically on RD», «not specific but with information on RD» and «no information on RD». The report for 2005 concludes that in Spain there are a total of 19 health information sources, mechanisms and registers «specifically on Rare Diseases» and 58 «not specific but with information on RD».

That list of specific registers could be updated by means of the results obtained in the project by the Health Research Fund (FIS) on rare diseases databases and registers in Spain, *Registros y Bases de Datos Existentes en España sobre las Enfermedades Raras,* in which three of the AC (the Canary Islands, the Community of Valencia and La Rioja) participated and which was completed in 2007. The information on registers was obtained through a systematic review of scientific literature, with the aim of locating and characterising the existing registers and databases on rare diseases in Spain.

Besides the abovementioned registers, many health centres, research groups, and networks of scientific centres or societies keep registers of specific diseases or groups of diseases.

After reviewing the situation it can be concluded that there are currently different types of health registers in Spain that can be used to monitor RD, although with certain complications. Those complications

originate, on the one hand, from the typology and characteristics of these pathologies, especially with regard to exhaustiveness, due to:

— the dispersion of cases, not only from a geographical perspective, but also according to the ownership of the medical care centres, some of which are public, others private,
— the difficulty, in many cases, of reaching a diagnosis.

On the other hand, those complications arise from the fact that RD registers cannot be considered as registers of Diseases of Compulsory Declaration (Enfermedades de Declaración Obligatoria, EDO), since they do not meet all the necessary requirements to be considered as such; in other words, they are not transmittable diseases that require the adoption of control measures when faced with a community alert.

The epidemiological surveillance of RD is a basic tool for knowledge and, therefore, can contribute to solving one of the main problems in the field of RD. It must be guided by the following objectives:

— Know the incidence, spatial distribution, temporal evolution and other characteristics that lead to enhanced knowledge about the disease.
— Enable studies on availability, effectiveness, efficiency and access to health services.
— Recognise available and necessary resources.
— Act as a support tool for planning and decision-making.

Patients, professionals and institutions seem to agree on the need and importance of developing integrated information systems on RD.

In short, the achievement of those goals calls for combined efforts, at national and European level, for the development of information systems on rare diseases as key instruments for the organisation of the surveillance of these pathologies.

That system involves the systematic collection and ordered filing, according to a predefined system, of data, so that they can be used as a base to produce information relevant to the understanding of RD and to decision-making about them.

2.1.2.2. General objective

To support strategic action that helps improve knowledge about the epidemiology of rare diseases, for the purpose of planning suitable health policies.

2.1.2.3. Specific objectives and recommendations

Objective 1

To analyse existing RD registers, both at national and autonomous community level, and to promote, through the Ministry of Health and Social Policy, the coordination and compatibility of those registers, as well as research on them.

Recommendations

- Define basic common quality criteria for RD registers.
- Promote, through the Ministry of Health and Social Policy, the coordination of the RD registers of the different Autonomous Communities.
- Support the development of patient registers that can be used in the field of research and information on RD.
- Reinforce the availability and accessibility of registers by supporting their computerisation and enhancing the knowledge about them, thereby fostering their dissemination and implementation.
- Promote the establishment of processes to monitor and evaluate the registers and to assess the possibility of creating a generic register in the light of Spanish and European initiatives taken in this regard.
- Collect, in the registers, epidemiological data desegregated by age and gender, allowing analyses from a gender-perspective.

2.1.3. Coding and Classification of RD

2.1.3.1. Background

From an epidemiological point of view, what we know as rare diseases are mostly «invisible» in health information programmes due to the lack of appropriate systems for their coding and classification.

It is obvious that an early diagnosis is essential for the delivery of appropriate care to people affected by rare diseases, but only an effective classification method makes it possible to know the true epidemiology of these pathologies, to design the care structures needed to meet the healthcare demand they produce and to evaluate the effectiveness and efficiency of the social resources available to them.

Therefore, it is essential to work on the development of a common classification, thereby making use of the work that has already been

undertaken in this regard. Moreover, the classification must be in line with the system currently being developed by the Rare Diseases Task Force-Working Group (RDTF-WG).

For more than a decade, many different types of national and international organisations have been working on the diagnosis and treatment of rare diseases. They all unanimously recommend the creation of a «universal classification system». Yet the organisations that have designed their own classification have done so from a specific perspective (geographical, medical, social, etc.) from which they analyse these problems, which is why more or less substantial differences are found between them.

Supranational entities like the WHO and especially the Rare Disease Task Force Working Group (RDTF-WG) on Coding and Classification are in the process of developing a classification of these diseases for universal use.

Any method used to classify these pathologies must overcome an important hurdle which, until now, has delayed the adoption of a definitive rare diseases classification, and which is fundamentally caused by:

- The difficulty of deciding whether a specific disease should, or should not, be classified as a rare disease, because the criteria used are not always universally accepted.
- The medical terminology used is very varied, which makes the list of nosological entities and their respective synonyms very diverse and introduces an element of confusion in any classification system.
- Some of these diseases have a multifactorial aetiology and many of them affect different organs and systems, which can make it difficult to place them in a specific group of diseases.
- The rhythm of identification of new diseases and new groups of diseases is so high in certain fields (i.e., inborn errors of metabolism, tumours, etc.) that new entities are continuously being added to the alphabetic lists of rare diseases in search of the position that corresponds to them.
- The difficulty of the final diagnosis of certain rare diseases and their grouping into families of diseases.

In practice, all the classification systems currently in use correspond to one of the following types:

1. Alphabetically ordered nominal list of rare diseases

This system is the base of the classifications currently used by Orphanet, by the Dutch group (CINEAS), by REpIER (includes codes ICD-9 and ICD-10), and by the Health on the Net Foundation (HON).

The advantage of this system is that it can be completed with the international codes (ICD, OMIM, etc.) used for epidemiological surveillance based on the Minimum Basic Data Set (MBDS) at Hospital Discharge. Moreover, this system allows for the inclusion, in an individual manner, of all known diseases and of any new diseases identified in the future.

Its main drawback is that a list of more than 5,600 diseases, or 5,682 registered in the Orphanet database (2), some of which are extraordinarily rare, is not efficient from an epidemiological point of view, and does not allow for the organisation of individual management systems for each and every one of those diseases. To overcome that difficulty every group usually works with a small group of entities, but since the latter are selected according to different criteria in each case (local prevalence, socio-cultural implications, severity, etc.) the resulting rare diseases lists differ in number and composition, ranging from 300 to 1,500 diseases.

2. Classification «according to levels» of rare diseases, using the WHO's International Classification of Diseases (ICD)

In this type of coding, the first level is nosological (i.e., Endocrine Disorders «E00-E90»), the second level defines the different disease groups (i.e., Disorders of aromatic amino-acid metabolism «E70») and the third level defines the specific diseases.

This classification is currently being used as a basic working tool, with specific variations for each country, by the Community of Andalusia, the working group of the Registro Nazionale Malattie Rare, the German working group (DIMDI) and the Rare Diseases Research Institute (IIER) of the Carlos III Health Institute (ISCIII). The information made available to date suggests that the RDTF-WG is also working according to this methodology.

It is a universally applied system for the epidemiological surveillance of morbidity, mortality and disability. Its first step is very sensitive, making it possible to detect and classify any pathology. In Spain its codes are used in the Minimum Basic Data Set at Hospital Discharge,

(2) Updated on 27 April 2009.

which means it is easy to assimilate and, obviously, it allows for the inclusion of any new disease into any of the groups.

Its most noticeable drawback is the fact that certain rare diseases, presently clearly identified, are coded neither in the ICD-9 nor in the ICD-10, and the definition of new groups of diseases would appear to be necessary in order to include some of those diseases in the ICD-11.

The definition of objectives calls for prior thought about the purpose of the classification of rare diseases:

- If the objective is to know, for statistical purposes, the prevalence of each of the individual entities classified as rare diseases, a complete list must be available. Each of them could be provided with an information alert that identifies it when entering the hospital discharge or primary care reports. However, it is obvious that the scarce frequency of some rare diseases would lead to rather undemonstrative data.
- If the objective is to identify the prevalence of RD so that the medical care of patients with this pathology can be coordinated at national level, thereby making maximum use of all existing resources and developing any necessary ones, a classification according to «levels» is required. That classification would first identify groups of pathologies, and would then identify the diseases of that group requiring care.

At present that could be the most reasonable option and, therefore, the system for the classification and coding of rare diseases must meet the following requirements:

- It must be accepted and used by all the Autonomous Communities.
- It must be compatible with, and in all cases easily adaptable to, the future International Coding and Classification of Rare Diseases. Likewise, it must be consistent with the current International Classification of Functioning, Disability and Health (ICF).
- The coding system must be incorporated in the Minimum Basic Data Set at Hospital Discharge or in the future Electronic Medical Record format.
- It must, as a minimum, allow for the detection of rare diseases on a nosological level and on a group level.
- It must allow the entry, for its subsequent classification and coding, of any new entities that are identified in the future.

— The chosen epidemiological information system must directly contribute to the improvement of the healthcare provided to patients.
— The classification and coding used must make it possible for health authorities to quantify the demand for care at a national and autonomous community level, with the aim of ensuring that all people with RD receive due healthcare, thereby facilitating coordination between the different existing medical centres in every Community and promoting and establishing any others necessary for the treatment of pathologies which, because of their nature, require specific Reference Centres, Services and Units (CSUR).

2.1.3.2. General objective

To work on the development of a rare diseases classification and coding system with the aim of coordinating the health policies relating to the comprehensive care of patients with these pathologies at national level. The system must be easily transferrable to the future international classification system for these pathologies. Moreover, maximum use should be made of all existing resources and any necessary resources must be developed.

2.1.3.3. Specific objectives and recommendations

Objective 1

To support and participate in the coding and classification working groups working in this field at international level, such as the Rare Disease Task Force Working Group (RDTF-WG) of the Health and Consumer Protection Directorate-General (DG SANCO), the World Health Organization, etc.

Recommendations

— Establish coordination mechanisms with the European and international groups that are currently leading the development of this task, so as to incorporate the new modifications of the ICD-10 currently in force. Those mechanisms must be designed on the basis of the current Rare Diseases Task Force, its respective working groups and Spain's representatives in those groups. In the future, the collaboration will have to be approached through the EU Advisory Committee that will replace the aforementioned Task Force, in accordance with the provisions of the Commission Communication approved in November 2008.
— Study the viability of working in parallel with international organisations in relation to the codification system (ICD-9)

currently used in hospitals for the collection of data at hospital discharge, at all times taking into account the evolution of the future coding systems (ICD-10 and ICD-11).
— Create a working group, within the framework of the Strategy, to study the existing RD classification proposals.
— Promote and enhance the upkeep of the classification and coding of RD according to the advances made on an international level.

2.2. Prevention and early detection

2.2.1. Prevention

2.2.1.1. Background

Although there are very few rare diseases for which primary prevention is possible, certain environmental factors are believed to cause uncommon congenital malformations (teratogenic malformations) and certain childhood cancers. In order to prevent RD it is important to target the period prior to conception, as well as the pregnancy, through public health measures aimed at promoting healthy life styles and avoiding the consumption of harmful substances, and especially of alcohol, during pregnancy.

Obstetricians' epidemiological knowledge and understanding of the associated risk factors is fundamental to the primary prevention of birth defects. The implementation of primary prevention strategies responds to the advances in scientific knowledge regarding risk factors.

2.2.1.2. General objective

To carry out primary prevention interventions in the case of rare diseases for which, in view of their aetiology, they could be beneficial.

2.2.1.3. Specific objectives and recommendations

Objective 1

To adopt measures that reduce the incidence of those RD that could potentially benefit from primary prevention programmes.

Recommendations

— Promote the dissemination of information regarding the teratogenic potential of certain chemical substances, medicines, cosmetic products and environmental factors.

— Reinforce existing programmes for the prevention of endocrine-metabolic disorders in newborns.
— Advise women, prior to conception and during the first months of pregnancy, on the management of chronic diseases like diabetes or epilepsy and the prevention of other risks.
— Continue to promote interventions aimed at the prevention of congenital anomalies. For example, folic acid supplementation prior to conception reduces the risk of spina bifida and other birth defects.
— Participate in the debates being held on this topic on an EU-scale, with the aim of determining which rare diseases can benefit from the primary prevention measures.
— Raise awareness among women about the importance of a preconception medical visit.

2.2.2. Early Detection

2.2.2.1. Background

In general, one of the main difficulties faced by people affected by rare diseases is that of obtaining a correct and timely diagnosis.

The consequences of a delayed diagnosis can be tragic, depriving patients of timely therapeutic interventions (when available), leading to the consequential clinical deterioration, physical and at times intellectual and psychological sequelae which could have been avoided or lessened through an early diagnosis. In the case of genetic diseases, the absence of a diagnosis means that parents are unaware of the risk of having more affected children, and deprives the patient and his or her family of access to genetic counselling.

The first step towards increasing access to early diagnoses consists of the reinforcement of a series of actions ranging from an increase in early detection programmes, which must be corroborated with available scientific knowledge, to the promotion of research applied to the diagnosis, and the guarantee of equitable access for all affected persons to the diagnostic tests required in each case.

Moreover, the *Programa del Niño Sano*, or healthy child programme, which was launched in Spain over twenty years ago and is today a very consolidated, fully integrated programme that is well accepted by families and professionals alike, is one of the main Primary Care services provided to children in all the AC. The *Programa de Salud Infantil*, or child health programme, consists of a series of activities for the prevention and early detection of diseases, and for the promotion of good

health. Its effectiveness has been widely acknowledged. Primary Care for children is facing a changing scenery following the decrease, or near eradication, of infections that can be prevented through vaccinations, although they persist and sometimes other infectious diseases re-emerge or new ones emerge. Conditions arising in the perinatal period, as well as chronic and degenerative diseases, are gaining importance, and an increase can be seen in disabilities in children who have survived serious diseases (including RD).

In the year 2007 the Public Health Commission of the Interterritorial Council of the Spanish NHS (CISNS) carried out a study on the situation of newborn screening programmes in Spain, the *Informe sobre la situación de los programas de cribado neonatal en España*. The aim of the study was to strengthen and promote the early identification and treatment of affected persons, thereby avoiding neurological damage and reducing morbidity, mortality and possible disabilities associated with certain diseases through timely interventions. Accordingly, the new recommendations of child health programmes stress the importance of the early detection of diseases and at-risk groups, as well as the supervision of the growth and overall development of the child, which enables the identification by paediatricians and other health professionals of warning signs and of the early detection of developmental disorders, which can be part of the symptoms associated with several RD.

A. Genetic counselling

Although according to estimates by the European Organisation for Rare Diseases (Eurordis), 80% of these diseases are of genetic origin, less than 50% of patients receive genetic counselling. Spanish Law 14/2007 on Biomedical Research, which considers genetic testing in research and care, stipulates that when carrying out a genetic analysis for health purposes «the interested party must be guaranteed appropriate genetic counselling».

Since the early 1970s genetic counselling in Spain has been provided by specific hospital services, although in the case of hereditary metabolic diseases that task was usually carried out by the actual paediatrician or the diagnostic laboratory. These services offer cytogenetic, molecular genetic and biochemical genetic tests (in the case of hereditary metabolic diseases) as well as genetic counselling.

The laboratory services are provided by health professionals: medical staff, highly qualified non-medical staff, nursing staff and laboratory technicians; and the genetic counselling services usually by highly qualified staff. The basic training of these health professionals varies, and they may well come from different specialties.

B. Genetic diagnosis

The term genetic diagnosis refers to the clinical process used to determine the presence of a genetic or hereditary disease or the risk of suffering from one, by carrying out genetic analyses or tests.

In many cases a genetic diagnosis requires a correct clinical evaluation of the patient. That evaluation must ultimately be carried out by a doctor with experience in clinical genetics and dysmorphology.

In Spain, genetic diagnostics and counselling are disciplines which, initially, were associated with activities in hospital environments. In the Spanish NHS those activities are currently carried out by different professionals who have been trained and who have acquired experience in these areas (3).

As regards patients' access to genetic testing and counselling, in Spain «referral of patients for genetic testing is nearly exclusive of hospitals and specialised care, without any established standard protocol. It can be performed for clinical reasons or as part of a research protocol», according to the conclusions of a study carried out by the Institute for Prospective Technological Studies (IPTS).

At this point, it is important to distinguish between genetic diagnosis and genetic testing. The term «genetic diagnosis» is used to indicate a clinical intervention process defined in the context of the relationship of the healthcare staff with the patients and their families. The term «genetic testing», on the other hand, is used to refer to the techniques and instruments used to analyse the genome and genes (chromosomes, genes, mutations) or the genetic products (proteins, enzymatic activities).

A clarification of what is meant by genetic analyses (genetic testing), as well as by each of the types of genetic diagnosis, is provided below:

B.1. Genetic testing

Most rare diseases are genetic disorders, which is why genetic analyses are an essential part of the genetic diagnosis and counselling. They have to be contextualised within the patient's clinical situation. Spanish Law 14/2007 on Biomedical Research defines «genetic testing» as the «procedure to detect the presence or absence of, or change in, one or more segments of genetic material, including indirect tests for the detection of a gene

(3) Royal Decree 1277/2003, of 10 October, establishing the general conditions concerning the authorisation of health centres, services and establishments, in Appendix II defines the health services that make up the healthcare offered by health centres, among which it includes the Genetic service (U.78) as the «healthcare unit which, under the supervision of an adequately trained doctor, performs genetic tests and issues the corresponding reports for diagnostic purposes.»

product or other specific metabolite that is primarily indicative of a specific genetic change».

It is estimated that tests are currently available for more than 1000 genetic diseases. Nevertheless, their clinical use has been limited for several reasons. At times there are no external quality assessment services and at others insufficient data is available for their interpretation and validation. But the protocols and guidelines of best practices applicable to each case must always be taken into account, as must the legislative framework in which the genetic testing must be performed, whether for research or in the health system (Spanish Law 14/2007 on Biomedical Research). The project *Towards Quality Assurance and Harmonisation of Genetic Testing Services in the EU,* which was undertaken by the Institute for Prospective Technological Studies (IPTS), set the objective of identifying and evaluating the technical requirements and the means needed to guarantee the quality of genetic diagnostic services in the European Union. While performing the study it became evident, among other issues, that there was a lack of up-to-date information about who was performing the genetic diagnoses, and that there is no quality assurance with regard to the genetic diagnoses. All those issues highlighted the need to adopt a common strategy to govern the activities of genetic diagnosis centres in Europe.

The importance of the EUROGENTEST project should also be stressed, as a network of excellence set up under the Sixth Framework Programme for the development of the necessary infrastructure, tools, resources, guidelines and procedures that should structure, harmonise and improve the quality of services for genetic, molecular, cytogenetic, biochemical and clinical analyses in the European Union.

B.2. Clinical genetic diagnosis

This is understood as the process in which genetic testing is used to confirm or exclude a diagnosis of a suspected genetic disease based on the anamnesis, physical examinations, laboratory tests and complementary tests.

B.3. Prenatal diagnosis

A prenatal diagnosis (PND) is defined as the set of ultrasound, cytogenetic, biochemical and molecular techniques that are performed with the aim of detecting foetal congenital anomalies and hereditary diseases. The PND is offered to at-risk couples and pregnant women with the relevant clinical indications. In the absence of a personal or family history of chromosomal anomalies or hereditary diseases, the population of women with a high risk of having a child with a chromosomal

alteration is selected on the basis of three criteria: the mother's age, the biochemical screening tests and the foetal ultrasound. In the event of a maternal age of 35 or over, of altered biochemical results or of the presence of abnormal ultrasound markers, a cytogenetic analysis is offered, usually using cells from the amniocentesis, although sometimes also from the chorionic villus.

B.4. Preimplantation genetic diagnosis

Today, assisted reproduction techniques offer at-risk couples new resources to have healthy children, like gamete donation (eggs and sperm), preimplantation embryo sex selection in the case of X chromosome-linked diseases and the so-called preimplantation genetic diagnosis (PGD).

A preimplantation genetic diagnosis (PGD) is applied to embryos obtained through in vitro fertilisation techniques before being transferred to the uterus, enabling the selective implantation of unaffected embryos in couples with a high risk of a serious genetic disease and with the appropriate medical indications.

The multitude of centres performing PGD and the absence of a regulation on the use of the technique are a cause for concern.

Therefore, the European Commission commissioned one of its centres, the Institute for Prospective Technological Studies (IPTS), to investigate those issues (report published by the European Commission JRC-IPTS in January 2007: *Preimplantation Genetic Diagnosis in Europe*). The study involved a survey aimed at European centres performing PGD, identified the tests offered and the service provided in terms of genetic counselling. It was concluded that the said service is not offered in a consistent manner. The study also highlighted the problems surrounding quality control and the need to improve the accreditation procedures, as well as the monitoring and follow-up of PGD interventions.

B.5. Presymptomatic and predictive diagnosis

This diagnosis is used in the case of asymptomatic individuals at risk of developing a hereditary disease. In Spain, several initiatives have been taken in this regard. Its importance in preventive medicine was stressed in Andalusia's *Plan de Genética de Andalucía*, or genetics plan, and many studies have been conducted to evaluate its effectiveness in pathologies like Huntington's disease (*Programa de Diagnóstico Presintomático*, or the presymptomatic diagnosis programme, of the La Fe University Hospital in Valencia), neurofibromatosis, Alzheimer's disease (Hospital Clinic of Barcelona), ataxias, and certain kidney diseases or familial adenomatous polyposis.

B.6. Newborn screening programmes

Newborn Screening Programmes (NSP), which are deemed to be essential in the context of Public Health, are aimed at the «presymptomatic identification of certain genetic, metabolic or infectious statuses through the use of tests that can be applied to the entire population of newborns», with as objective the «early identification and treatment of affected persons, so that morbidity, mortality and the possible disabilities associated with those diseases are reduced through a timely medical intervention».

A number of diseases are included in the different NSP, among which there is general consensus with regard to hyperphenylalaninemias and congenital hypothyroidism.

A study carried out in 2004 by the Commission on Inborn Errors of Metabolism (Comisión de Errores Congénitos del Metabolismo) of the Spanish Society of Clinical Biochemistry and Molecular Pathology (SEQC), highlights the inequality of the services offered in the different AC.

The abovementioned inequality was still present in 2007, as was confirmed by the *Informe sobre la situación de los programas de cribado neonatal en Españ*a, a report on newborn screening programmes in Spain undertaken by the Ministry of Health and Consumer Affairs, in collaboration with the Autonomous Communities.

Since the implementation of the first newborn screening programme in Spain 30 years ago, the number of diseases included in the programmes has been increasing. Different Autonomous Communities, presently including Galicia and Murcia, have been pioneers in expanding the aforementioned screening. Extremadura too is currently evaluating the said expansion through its groups of experts and advisory councils.

Changes to the newborn screening programmes must be based on up-to-date knowledge and scientific evidence. Therefore, it is recommended to perform the newborn screening tests for those diseases that pose a serious threat to the newborn's health, and to make sure that their natural histories are properly understood and that appropriate and effective treatments are available, so that the overall intervention provides substantial benefits to the affected persons. In this context, before making decisions about the incorporation of a disease into a newborn screening programme, it is important that a consensus is reached by all those involved: screening professionals, paediatricians, epidemiologists, scientific societies, associations of parents of affected children, etc. Lastly, the agreement must be submitted to an Ethics Committee that will assess the ethical and social implications entailed.

2.2.2.2. General objective

To provide people affected by a RD with easier and faster access to specialist services, with the objective of improving the diagnosis and early detection of those diseases.

2.2.2.3. Specific objectives and recommendations

Objective 1

To improve early diagnoses, including prenatal diagnoses, by reinforcing the role of Primary Care (PC) in the diagnosis of a suspected RD, and by facilitating access and streamlining referral processes to clinical services with experience in the care of patients with this type of disease.

Recommendations

- Improve training in clinical warning signs and symptoms for RD in the following areas: family medicine, paediatrics, obstetrics, midwifery and Primary Care nursing, in order to avoid delays in the referral of affected persons to whomever can make the diagnosis.
- Promote the creation of directories of services with experience in RD and of the RD that they work with, in order to facilitate referrals from Primary Care.
- Foster the development of clinical services with experience in the different groups of RD, or the coordination with other existing services, with the aim of counteracting the current lack of services in certain geographical areas.
- Propose, through the Commission for Benefits, Assurance and Funding (Comisión de Prestaciones, Aseguramiento y Financiación) of the Interterritorial Council of the Spanish NHS (CISNS), the study of the definition of the portfolio of common genetics services for the Spanish NHS.

Objective 2

To improve care in the case of pathologies diagnosed during the prenatal period.

Recommendations

- Use the referral pathways for pregnant women with a foetal RD risk (foetal malformation, suspected hereditary metabolic disease or genetically-based disease) to hospitals with prenatal diagnosis units (in the case of certain malformations also foetal therapy), neonatal intensive care units, paediatric surgery units, metabolic disease units and other highly specialised services for the care of at-risk newborns.

— Homogenise the offer of Prenatal Diagnosis Units by providing them with the appropriate material means and staff.
— Consolidate the prenatal screening for congenital defects programmes (triple screening, ultrasound for the detection of dysmorphology, etc.) throughout the whole of Spain.
— Foster the creation of Perinatal Pathology Committees, made up of specialists from all the departments involved in foetal-newborn care (obstetrics, reproductive medicine, neonatology, genetics, paediatric surgery, paediatric cardiology, paediatric pathology, metabolic diseases units and others).
— Establish protocols for the taking of biological samples for subsequent biochemical and genetic studies in cases of suspected RD in deceased foetuses or newborns.
— Promote training in prenatal diagnosis (foetal ultrasound diagnosis and techniques with foetal access: amniocentesis, chorionic biopsy, cordocentesis) and foetal therapy in Obstetrics and Gynaecology residency programmes.
— Reinforce pathological studies of foetuses in cases of foetal deaths and voluntary interruption of pregnancy (VIP) due to the third circumstance set out under the Spanish Abortion Law (foetal malformation or serious injury for the foetus).
— Create protocols to establish whether the prenatal diagnoses of affected foetuses that encourage VIPs are always confirmed.
— Promote training in foetal pathology as part of Pathology residency programmes.
— Reinforce training, in Paediatrics residency programmes and, especially, in Neonatology departments, in the diagnosis and management of the different groups of RD and of birth defects in general.

Objective 3

To improve newborn screening programmes for RD, taking into account the available scientific evidence, equity criteria, the cost-effectiveness of the tests and ethical aspects, in keeping with the *Informe sobre la situación de los programas de Cribado en España*, a report on the situation of newborn screening programmes in Spain drafted by the Public Health Commission of the Interterritorial Council of the Spanish NHS (CISNS).

Recommendations

— Develop specific health policies for RD, coordinated by the Public Health Commission of the Interterritorial Council of the Spanish NHS (CISNS), following the recommendations established by the

latter, thereby guaranteeing an appropriate approach to early detection (newborn screening in asymptomatic newborns), confirmatory studies that lead to the diagnosis of the disease and its long-term treatment and follow-up in the respective specialist units.
— Apply Evidence-Based Medicine (EBM) tools to evaluate any universal diagnostic screening tests that are added to existing tests, with the aim of obtaining data to support the decision-making of health strategy planners.
— Create mechanisms to streamline the inclusion in newborn screening programmes of RD that exert a positive genetic pressure on a specific population (immigration effect).
— Reinforce the cooperation between the newborn screening programmes of the different AC and establish health policies that are common to all of them, so that the specific actions are part of a minimum common strategy on rare diseases.
— Define protocols for the key steps of the medical intervention: detection, (biochemical and/or genetic) confirmatory diagnosis, treatment and monitoring to allow the equitable evaluation of the programmes of the different AC.
— Develop awareness-raising campaigns on newborn screening aimed at the community of professionals working in Primary Care, public opinion, health policy-makers and social services.
— Encourage, through the Public Health Commission of the Interterritorial Council of the Spanish NHS (CISNS), the tackling of aspects like information sharing, the definition of criteria for the incorporation of new diseases, the homogenisation of the priority aspects of the programmes and the review of the situation of sample storage, among other issues.

Objective 4

To improve access to clinical diagnoses and laboratory tests, as well as support for the implementation and validation of new techniques and tests.

Recommendations

— Homogenise the specialised clinical and laboratory tests offered in all the AC.
— Foster multidisciplinary research among professionals from different areas (hospitals, university, research centres, etc.) involved in the field of the diagnosis, management and study of the molecular, metabolic and cellular bases of RD.
— Strengthen the coordination between the clinical genetics services and units (biochemistry, molecular and cytogenetics) of

the Spanish NHS by creating directories of the laboratories of all the areas covered by the Spanish NHS.

— Promote the certification/accreditation of genetics services or units that use specialised techniques for the diagnosis of RD, with the aim of assuring the quality of those techniques. Likewise, those services and units should be encouraged to participate in internal and external quality programmes, at national and international level, that assure the quality of the tests.
— Develop protocols for diagnostic interventions in the event of a suspected rare disease, and disseminate those protocols in the health sector, with the aim of facilitating the rational and effective use of the biochemical and/or genetic tests that contribute to the timely and reliable diagnosis of the disease.

Objective 5

To improve access to multidisciplinary genetic counselling.

Recommendations

— Encourage the Health Departments of the different AC to improve Genetic Services, offering services with their own, differentiated identities within the hospitals of their area of competence, whenever considered to be necessary.
— Inform both Primary Care (PC) and Secondary Care (SC) doctors about the different services that will be offered by the Reference Centres, Services and Units (CSUR) on RD once they have been designated; likewise, inform any Genetics Services (cytogenetics, molecular genetics, biochemical genetics) in their area.
— Improve access to predictive, presymptomatic, preimplantation and carrier diagnoses by channelling affected persons and their family members to genetic counselling services, thereby assuring a good patient pathway.

2.3. Healthcare

2.3.1. Background

The starting point of the pathways of patients with RD is, without a doubt, Primary Care. Therefore, the coordination between Primary Care and Secondary Care is especially important in the case of these pathologies, and must involve a combination of multiple approaches and multidisciplinary care.

In order to provide quality care to patients with RD, Health professionals in Primary Care centres require tools. Firstly, specific training in RD is fundamental for the appropriate early detection, care and follow-up of people affected by RD, since it enhances the quality of life of patients and their families by avoiding visits to multiple specialists and unnecessary diagnostic tests.

Moreover, PC professionals should be provided with IT resources that allow them to provide information to patients with RD. In other words, they must have access to information about both healthcare and social resources, as well as any existing RD patient organisations.

In addition to the necessary specific training in RD and the knowledge about the IT resources available to health professionals, another fundamental aspect is the coordination between Primary and Secondary Care, which will redound to the benefit of the care provided to patients and the improvement of their quality of life (i.e. the reduction of the time of referral of the patient to the specialist who is able to diagnose him or her).

In short, the objective is, on the one hand, to strengthen the coordination between the different levels of healthcare (PC/SC), as well as the coordination between healthcare and medico-social care and with the Reference Centres, Services and Units (CSUR), once they have been designated as such; and, on the other hand, to guarantee the delivery of quality care to persons affected by RD and to their families.

Moreover, and in keeping with the aforementioned *Council Recommendation on a European action in the field of rare diseases*, which is currently being discussed, the healthcare-related aspects concerning the Reference Centres, Services and Units (CSUR) on RD are set out below.

The European Union does not have a common definition of what a Centre of Reference is.

The following three situations can be found in the different Member States:

— Countries with a specific policy on rare diseases and that have established centres of reference within the framework of that policy.
— Countries that have centres of reference but not necessarily on rare diseases.
— Countries without official centres of reference but with centres that act as such.

Five European countries have officially adopted the concept of Centre of Reference for Rare Diseases: Bulgaria, Sweden, Denmark, France and Italy. In Spain, Royal Decree 1302/2006 of 10 November, which establishes

the conditions regarding the procedure for the designation and accreditation of the Reference Centres, Services and Units (CSUR) of the Spanish NHS, refers to rare diseases by defining what type of care should be provided by the CSUR in this case. Other countries have health centres that are considered as centres of reference on areas relevant to rare diseases, but they have been established without a specific RD policy.

The type and number of centres per country differs substantially from one country to another, and is not proportionate to the size of the population. Whereas the United Kingdom, Belgium, Spain and France follow a national strategy, the other countries have a more regional approach.

There are two main models:

— Centres of Reference that group together many and very diverse pathologies (Denmark).
— Centres that are highly specialised in one or a few pathologies (Italy, the United Kingdom, France). The centre of reference is defined for categories of diseases that require specific multi-disciplinary care and that share common characteristics.

Moreover, the criteria used in each country differ when it comes to designating centres of reference. Some countries stress the fact that the centre engages in important research activities (France), while others (Sweden) expect centres to be centred on clinical, diagnostic and therapeutic care.

In Spain, the role of CSUR of the Spanish NHS is to provide care, although as a designation criterion all the CSUR are requested to participate in research projects and publications related to the pathologies or procedures which they have been appointed to treat or establish.

Moreover, with regard to rare diseases, Royal Decree 1302/2006 states that the mission of the CSUR may not imply the ongoing care of the patient in the CSUR, but rather that it could act as a support for diagnostic confirmation, the definition of therapeutic strategies and follow-up strategies and as an adviser for the clinical units that usually treat those patients.

With the aim of homogenising the concept and the functions of centres of reference, the Directorate General for Health, DG-SANCO, through the Rare Diseases Task Force (RDTF) Working Group, issued a proposal regarding the technical-scientific aspects to use as criteria for the selection of Centres of Reference. It considers the following aspects:

— Appropriate capacities for the diagnosis, follow-up and treatment of patients with proven good outcomes.

— Volume of activity (which must be significantly larger than anticipated from the prevalence of the diseases and the catchment area of the centre). The catchment area is the loco-regional area normally served by the hosting hospital for non-rare diseases or national coverage.
— Capacity to provide expert advice on diagnostics and care.
— Capacity to produce and adhere to best practice guidelines and to implement quality control and outcome measures.
— Demonstration of a multidisciplinary strategy.
— High level of expertise and experience documented through publications, financial aid, research projects, grants, honorific positions, teaching and training initiatives.
— Strong contribution to research.
— Close relationship and collaboration with other expert centres at national and international level and the capacity to network.
— Collaboration with patient organisations.

With the aim of achieving the established goals, the DG-SANCO Working Group recommended that all Member States adopt the same definition of RD based on prevalence; that ad hoc committees be created for the designation of centres; and that the Member States contribute to the establishment of a list of expert centres, thereby facilitating access to the Centres of Reference and to any existing reference networks. Moreover, it proposed that funding be guaranteed in the following areas: mapping of existing expert centres; networking of centres; development of case management systems (telemedicine, online diagnosis, etc.); designation of the centres and dissemination of information; as well as periodic evaluations and accreditations at European level according to agreed minimum criteria. Other proposed principles that should be taken into account are those of favouring the networking of centres and of prioritising the travel of the expertise (professionals, samples or information) over patients travelling.

In view of the importance of collaborating with the other EU countries in the field of rare diseases, the proposal must be aimed at the adoption of the measures agreed by the Rare Diseases Task Force, with the goal of homogenising criteria and actions that will lead to more fluent cooperation.

In Spain, Royal Decree 1302/2006 of 10 November, which establishes the conditions regarding the procedure for the designation and accreditation of the Reference Centres, Services and Units (CSUR) of the Spanish NHS, refers to rare diseases by defining the characteristics that must be met by pathologies or groups of pathologies that are prevented,

diagnosed or treated by means of techniques, technologies or procedures included in the Spanish National Health System's common services portfolio, in CSUR of the Spanish NHS:

a) Diseases that for their adequate care require preventive, diagnostic and therapeutic techniques, technologies and procedures of a *high level of expertise* requiring experience in their use, which can only be acquired and maintained through certain volumes of activity.

b) Diseases that require *high technology* for their prevention, diagnosis or treatment and for which, in view of their cost-effectiveness and the available resources, the concentration of a minimum number of cases is required.

c) *Rare diseases* which, because of their low prevalence, require a concentration of cases for their adequate care, which does not imply the ongoing care of the patient in the reference centre, service or unit, but rather that the latter can act as a support for diagnostic confirmation, the definition of therapeutic strategies and follow-up strategies and as an adviser for the clinical units that usually treat those patients.

Likewise, the Royal Decree defines what is understood by Reference Centre, Service or Unit of the Spanish NHS:

— *Reference Centre*: a health centre that mainly provides care related to specific pathologies or groups of pathologies which fulfil one or several of the characteristics set out in the Royal Decree.

— *Reference Service or Unit*: a service or unit of a health centre or service that performs a technique, technology or procedure, or that provides care related to specific pathologies or groups of pathologies which fulfil one or several of the characteristics set out in the Royal Decree, although in addition this service or unit treats other pathologies for which it would not be considered a reference service or unit.

Royal Decree 1302/2006 establishes the conditions regarding the procedure for the designation and accreditation of CSUR of the Spanish NHS, the objective of which is to guarantee equitable access and safe, efficient, quality care for people with pathologies which, because of their characteristics, need care of a high level of expertise, requiring the concentration of the cases needing treatment in a limited number of centres.

The entire procedure for the designation of CSUR is formulated through the CSUR Designation Committee of the Spanish NHS, which was created in the aforementioned Royal Decree and which reports and submits proposals to the Interterritorial Council. The tasks of the Designation Committee are: to study the needs and propose the

pathologies or the diagnostic or therapeutic techniques, technologies and procedures for which a CSUR needs to be designated; to propose the procedure for the designation and accreditation of a CSUR and to report on it; to assess the designation applications received and make designation proposals to the Interterritorial Council; to study and propose the renewal/revocation of the designation of CSUR; and to establish the procedure for the referral of users.

The Designation Committee is presided over by the Directorate General for Professional Regulation, Cohesion of the NHS and High Level Inspectorate and is made up of a representative from each of the AC, the National Institute for Health Management (Instituto Nacional de Gestión Sanitaria), the Cohesion Fund and Economic Analysis Sub-directorate General (Subdirección General de Análisis Económico y Fondo de Cohesión), the Carlos III Health Institute (ISCIII), the Spanish NHS Quality Agency and the National Transplant Organisation (Organización Nacional de Trasplantes). The Committee may, whenever it deems appropriate, invite any experts on each of the subjects to its deliberations or promote the creation of working groups in the situations and under the circumstances that it deems appropriate.

In its inaugural session the Committee, which was created on 28 November 2006, approved a work programme to tackle the issues entrusted to it under Royal Decree 1302/2006. Since it is very difficult to deal with all specialist areas simultaneously, it was agreed to prioritise their approach. Each of the different areas is being developed by groups of experts appointed by the Autonomous Communities, scientific societies and the actual Ministry of Health and Social Policy. Those groups of experts in each specialist area are working around two objectives: drawing up a justified proposal of the pathologies or of the diagnostic or therapeutic techniques, technologies or procedures for which a CSUR should be designated in the Spanish NHS; and drawing up a proposal of the criteria that must be fulfilled in order for a centre, service or unit to be designated as a CSUR, according to the type of activity for which they are going to be designated.

Once the work of each group of experts has been completed it will be presented to the Designation Committee for approval and, where appropriate, submitted to the Interterritorial Council for approval.

Once the criteria has been agreed a period of CSUR application is opened, and the respective Autonomous Communities can present their proposals through the Designation Committee.

Once they have been admitted for processing, the applications are sent to the Spanish NHS Quality Agency for the start of the audit and accreditation process. After the respective accreditation reports have been

received, the said Committee studies them together with the other information on each file and submits its proposals for designation, or non-designation, to the Interterritorial Council.

The Ministry of Health and Social Policy, at the suggestion of the Designation Committee and with the prior consent of the Interterritorial Council, decides on the designation of the CSUR for a maximum period of 5 years. Before that period has terminated the designation will have to be renewed, provided that, after a re-evaluation by the Spanish NHS Quality Agency, all the criteria that led to the designation continue to be fulfilled. From a financial point of view, the Healthcare Cohesion Fund (Fondo de Cohesión Sanitaria) will fund healthcare referrals between the different Autonomous Communities to CSUR of the Spanish NHS.

Moreover, the evaluation of the different models followed in each Member State as well as the results of the Eurordiscare survey, which reflected the perception and level of satisfaction of the users and professionals involved, make a good starting point for the elaboration of a proposal that is adapted to the specific case of the Spanish NHS.

So, in the case of Spain the proposal must be based on the guidelines laid down in Royal Decree 1302/2006, and the adoption of a CSUR model in which the diseases are grouped according to pathology types or groups should be considered. The French classification model could be used as an example for the Spanish model, making any necessary modifications.

The CSUR will operate as centres specialised in comprehensive care and as centres that provide information and training to professionals (in person or via networks) regarding the pathologies for which they are centres of reference. Accordingly, their mission is to:

- Act as a support for diagnostic confirmation, the definition of therapeutic strategies and follow-up strategies and as advisers for the clinical units that usually treat those patients.
- Define and disseminate protocols for care.
- Coordinate research and participate in epidemiological surveillance.
- Participate in information and training programmes for health professionals, patients and their families.
- Coordinate the networks of healthcare and medico-social care providers.

2.3.2. General objective

To provide ongoing, comprehensive care that is coordinated between the different levels of the healthcare system, with the aim of delivering comprehensive and quality assistance to patients with RD.

2.3.3. Specific objectives and recommendations

Objective 1

To improve the healthcare provided to people with RD, making sure that it is comprehensive, ongoing and coordinated between the different levels of the healthcare system.

Recommendations

- Define intervention plans approved by consensus with patients and their families, and in collaboration with Primary and Secondary Care services, and that cover clinical aspects as well as those regarding family and social integration.
- Foster coordination between all the professionals involved in the care of patients with RD, at both the Primary and Secondary Care levels, in the respective Autonomous Communities.
- Guarantee continuity in the care of patients with RD who have survived beyond childhood.
- Identify the training and research needs of the professionals who treat patients with RD, both in Primary as well as Secondary Care services.
- Encourage centres providing care to patients with RD to participate in national and international research projects.
- Periodically evaluate the satisfaction of users and professionals with the service received from centres providing care to patients with RD.
- Promote collaboration with RD patient organisations and scientific societies (regarding training, information exchanges, joint activities, etc.).
- Take appropriate measures to avoid gender bias in care for patients with RD.
- Promote coordination and information sharing between related units providing care to patients with RD.
- Foster national and European collaboration at all levels, taking into account the European dimension and the need to collaborate with centres of reference in other countries.
- Elaborate guides and/or protocols on Care for patients with RD, with the objective of homogenising the interventions of the different health professionals from both PC and SC, based on available scientific evidence and providing specific information for affected persons, their families, carers and teachers.

Those guides should include the following contents:

- Genetic aspects.
- Anticipatory guide.
- Preventive aspects.
- Diagnostic interventions. Suspicion and confirmation.
- Therapeutic interventions.
- Early intervention needs.
- Care pathways. Treatment, rehabilitation and follow-up.
- Health aspects for school and occupational adaptation.
- Available resources and list of CSUR.
- Existing patient organisations.
- Health and social aspects of the disease, links and bibliography

Objective 2

To propose to the CSUR Designation Committee of the Spanish NHS that it study the possibility of establishing Reference Centres, Services and Units (CSUR) within the Spanish NHS for the care of patients with RD.

Recommendations

— Encourage patient organisations and experts on RD to participate in submitting proposals to the CSUR Designation Committee regarding the pathologies or groups of pathologies that they have identified as priorities and for the care of which they considered a CSUR should be designated.
— Improve RD classification and coding procedures.
— Create inventories of the available resources for the care of patients with RD (clinical genetics units, referral pathways, early intervention, rehabilitation, mental health, among others).
— Propose a list of groups of RD according to pathologies as well as a list of priority RD subgroups in each of the groups to be handled through CSUR.
— Identify the groups of rare diseases that receive the poorest care (the most neglected) and for which CSUR should be promoted.
— Keep the list of CSUR of the Spanish NHS on the websites of the Ministry of Health and Social Policy and of the Health Departments, and foster its dissemination among patient organisations and health professionals.
— Promote the participation of Spanish CSUR in European reference networks (with as prior condition that they have been designated as a network of reference for the respective pathology, technique or procedure in Spain).

2.4. Therapies

2.4.1. Orphan Medicinal Products, Adjuvants and Health Products

2.4.1.1. Background

Within the framework of the EU, the term «Orphan Medicinal Product» applies to products intended for the diagnosis, prevention or treatment of a life-threatening or seriously debilitating and chronic condition, affecting no more than 5/10,000 inhabitants. Moreover, it refers to medicinal products whose marketing in the Community, without incentives, is unlikely to generate sufficient returns to justify the necessary investments, and which bring significant benefits to those affected by the condition in question.

Situation in the EU

In the European Union, an Orphan Medicinal Product Policy was established through the approval of Regulation (EC) No. 141/2000 in December 1999, with the objective of implementing a communitarian procedure for the designation of orphan medicinal products. In addition, an incentive system was created to stimulate investments by pharmaceutical companies, approving measures to incentivise the research, development and marketing of those medicinal products, especially through the granting of a ten-year market exclusivity, aid in the development of clinical trial protocols, the waiver of fees and the granting of subsidies, among others. The said Regulation regulates the criteria and the procedure for the designation of a drug as an orphan medicinal product and sets up the Committee for Orphan Medicinal Products (COMP) within the European Medicines Agency (EMEA).

In 2005, the COMP issued an evaluation report on the first five years of the orphan medicinal product legislation in the European Union, producing the following data: between April 2000 and April 2005, 458 applications for orphan designation were submitted, of which 260 were designated and 22 received a marketing authorisation. The report concluded that orphan designation had stimulated research into rare diseases across the European Union, increased the level of scientific and public awareness of rare diseases and promoted the creation of expert networks on some 350 rare diseases. The application of the Regulation also fostered the dialogue and collaboration with patient organisations and implied the development of liaison with medicinal agencies in other non-

Community countries like the US and Japan, with the World Health Organization and with NGOs dedicated to rare diseases.

Although the evaluation was positive, the Commission issued recommendations with the aim of improving and strengthening certain aspects, namely: reinforcing orphan medicinal product research through the 7th Framework Programme; encouraging the adoption of national measures to support the development and/or access to orphan medicinal products; and exploring the coordination of measures that enhance transparency between Member States to speed up and ensure the availability and equitable access to medication.

The countries that have taken measures to facilitate access to orphan medicinal products are Belgium, Hungary and the Netherlands, through the creation of Orphan Medicinal Product Committees. France has created a system of temporary authorisations in combination with a funding system, Ireland has a Platform of Patients, Academics and Industry and Poland hosts the National Forum on the treatment of Orphan Diseases.

Although the new legislative focus on orphan medicinal products means that they are becoming increasingly accessible, access to them remains insufficient.

On 27 April 2000 the European Commission adopted Regulation EC No. 847/2000, laying down the criteria for orphan designation. The designation of a drug as an orphan medicinal product is based on the criteria established in Regulation (EC) No. 141/2000, and its subsequent evaluation will be made according to criteria regarding the safety, quality and effectiveness required for the authorisation to place a medicinal product on the market.

Situación en España

In Spain, Spanish Law 29/2006, of 26 July, on Guarantees and the Rational Use of Medicinal and Health Products, refers to orphan medicinal products in Article 2, Supply and Dispensing Guarantees: «In order to guarantee the supply of medicines, the Government may adopt special measures regarding their manufacture, importation, distribution and dispensing. In the cases of "orphan medicinal products", in keeping with the provisions of Regulation (EC) No. 141/2000, and of drugs "of no commercial interest", the Government may adopt, besides the aforementioned measures, additional measures relating to the economic and fiscal regime of those drugs».

Over the last five years, 36 orphan medicinal products were marketed in Spain, which equates to 87% of those authorised by the European Commission. The laboratory has not applied for the authorisation to market the remaining orphan drugs in Spain.

In Spain, once the European Commission has authorised the marketing of a drug, the maximum industrial price and the conditions for the financing of the drug are established. Thanks to the efforts made by the Ministry of Health and Social Policy since the last term of office, the time it takes to complete the procedures regarding orphan medicinal products in Spain has been halved.

Among the orphan medicinal products marketed to date in Spain, those relating to oncology and endocrinology/metabolism stand out. The latter include the treatment of inborn metabolic disorders, rare diseases of genetic origin for which no treatment was available until now, which is why these drugs are a genuine therapeutic innovation.

Regulation (EC) No. 141/2000 of 16 December 1999, laid down a Community procedure for the designation of orphan medicinal products and for the provision of incentives for the research, development and marketing of those drugs.

Likewise, the use of drugs that are not authorised in Spain and that are classified as drugs for «compassionate use» (4), is referred to in Article 24, Guarantees regarding the availability of medicinal products in specific situations and special authorisations, of aforementioned Spanish Law 29/2006: «The prescription and application of unauthorised medicinal products to patients who are not included in a clinical trial, with the objective of satisfying, through a compassionate use, the special treatment needs of the clinical situations of specific patients, shall be governed according to the regulations, thereby fully complying with the provisions of the current laws on patient autonomy and clinical documentation and information-related rights and obligations.»

The possibility of a «foreign medicines» application is also considered in the event of the nonexistence in Spain of a marketed drug with the same composition, pharmaceutical form or dosage and the nonexistence in Spain of an appropriate, authorised alternative for that specific indication (Spanish Law 29/2006, Article 24.4).

(4) It may happen that a patient needs to receive a medicinal product that is not authorised or marketed in Spain, although it is in other countries. Although this occurs very rarely, a mechanism is in place to resolve this situation, known as «foreign medicines", requiring a prior application justified by a medical report and sent to the Spanish Medicines Agency (AEMPS). Although the drugs should only and exclusively be used according to the indications approved on their data sheets (for which they were authorised in conditions of quality, safety and effectiveness) and according to their conditions for use, in certain exceptional cases, a prescription may be issued in an unauthorised clinical situation and, for that purpose, there is a procedure called «compassionate use of medicinal products« (which also requires an application justified by a medical report to be sent to the AEMPS for the said use to be authorised).

At the current date of November 2008, a Draft Royal Decree regulates the availability of drugs in special situations and lays down the conditions for compassionate use, access to foreign medicines and use in conditions other than those authorised. In addition, it aims to facilitate access, harmonise models and procedures for application and enable the telematic management of applications. That Royal Decree «is adopted in development of articles 24.3 and 24.4 and the First final provision of Spanish Law 29/2006 and, for the purposes foreseen in Article 149.1.16 of the Spanish Constitution, has the status of legislation on pharmaceutical products.»

Concerning national initiatives taken to foster clinical research independently from the pharmaceutical industry, in February 2007 the Ministry of Health and Consumer Affairs organised a Grant Programme through the Carlos III Health Institute (ISCIII) and in collaboration which the Directorate General of Pharmacy and Health Products. The Programme was intended to promote the research and development of orphan medicinal products for the paediatric population, and identified orphan drugs and medicines of high health interest and «no commercial interest» as priority areas for research, among others. Since nearly 600 projects (22 in the field of rare diseases) were submitted to the call for proposals, the Ministry decided to continue the initiative by earmarking funds for 2008 within the framework of Strategic Action for Health Research (Acción Estratégica en Salud, AES) under the *Plan Nacional de I+D+i 2008-2011*, Spain's national R&D&I plan for the period 2008-2011.

Noteworthy among the efforts made by the Autonomous Communities are those of the regional governments of Andalusia and Extremadura. In the case of Andalusia, the *Plan de Atención a Personas Afectadas por ER 2008*-2012, a plan for the care of people affected by rare diseases, fixes specific goals concerning orphan medicinal products. The Regional Government of Extremadura approved the Order of 13 February 2006 which created and regulates the Committee for the Compassionate Use of Medicinal Products in Extremadura, and issued Decree 68/2006 which regulates the right to free pharmaceutical products for chronically ill children and disabled persons.

Since their launch on the Spanish pharmaceutical market in the year 2000, a growing number of orphan drugs have progressively been introduced, with a total of 36 new active principles on the market, which equates to 15% of the total new principles over the period 2000-2007. Over the last year, 11 new orphan medicinal products were approved, accounting for 30% of the total new active principles.

Adjuvants and health products

This group includes different types of therapeutic products as well as technical aids which are essential for the monitoring and treatment of the inherent complications of this type of disease (i.e., skin protection creams, lotions, dressings, etc.).

2.4.1.2. General objectives

To foster the research and development of orphan medicinal products to treat people affected by rare diseases, guaranteeing equitable access to those drugs throughout the whole of Spain, in keeping with current legislation.

To promote and reinforce procedures that facilitate equitable access throughout Spain to the health products and adjuvants indicated for the treatment of RD.

2.4.1.3. Specific objectives and recommendations

Objective 1

To guarantee timely and appropriate access to the orphan medicinal products required to treat rare diseases throughout Spain.

Recommendations

- Promote solidarity-based financial collaboration mechanisms between the Autonomous Communities, coordinated through the Interterritorial Council, to improve the provision and equitable access to orphan medicinal products in the Spanish NHS.
- Encourage the improvement of the current administrative procedure for access to treatments with «compassionate use» medicines and/or «foreign medicines», reducing the time between the application for, and the receipt of, treatment.
- Improve equitable access to orphan medicinal products and medicines under research, thereby facilitating access to innovative treatments.
- Avoid inequities in terms of the availability of orphan medicinal products in the different health centres and services.
- Optimise the time it takes to fix the prices of orphan medicinal products that have obtained a marketing authorisation.
- Request the Spanish Medicines Agency (Agencia Española de Medicamentos y Productos Sanitarios, AEMPS) to consider, prior to suspending or revoking a marketing authorisation for a

medicinal and/or pharmaceutical product, the option of adding to the current considerations and studies of the impact of that withdrawal, the possibility of consulting the relevant patient organisations and/or existing units of reference.

— Foster the use and dissemination of orphan medicinal products and medicines under research, as well as of effectiveness data and possible side effects of the treatments, with the aim of improving the knowledge of professionals and persons affected by RD.
— Promote the participation in projects for the creation of telematic tools with information on medicines that facilitate improved access to quality information and the availability of better evidence on drugs for the treatment of rare diseases.
— Promote and encourage laboratories that market orphan medicinal products to provide pharmacoepidemiological data as soon as their products have been placed on the market.
— Assess, in an individual manner, the possibility of including in the category of prescription-based or reduced contribution dispensing, those prescription drugs required for the treatment of rare diseases and of their complications, since those used in hospitals are entirely free of charge.
— Encourage the Spanish Medicines Agency (AEMPS) to promote the necessary mechanisms to establish a suitable system for the monitoring and evaluation of the proposals for new rare diseases treatments.
— Assess and encourage, through the Spanish Medicines Agency (AEMPS), evaluation studies on the safety of orphan medicinal products within the current Pharmacovigilance system.
— Foster information exchanges between the different European evaluation agencies and those of the Spanish NHS on Added Therapeutic Value (ATV), consolidating the scientific evidence on the effectiveness of orphan medicinal products, with the aim of improving the administrative procedures.
— Encourage the study and review of national R&D&I incentives for the development of orphan medicinal products and analyse the supporting national policies.
— Promote the carrying out of needs analyses regarding health products, materials for dressings and medical devices used in the treatment of RD, as well as of other products not classified as medicines (i.e., sunscreens, cosmetic products, etc.) that are required for the treatment of rare diseases, so that the quality of equitable access to those products throughout Spain is improved.

Objective 2

To promote the research on, and development of, orphan medicinal products.

Recommendations

— Strengthen the coordination of mechanisms that boost the development of orphan medicinal products by the pharmaceutical and biotechnology companies that complement the grants and measures adopted in the European Union.
— Promote sectorial agreements regarding orphan medicinal products.
— Make sure orphan medicinal products and rare diseases continue to be considered as priority areas for research in national R&D&I plans.
— Adapt the performance of clinical trials to the characteristics of rare diseases (reduced number of patients, geographical dispersion of those patients).
— Favour the harmonisation of the requirements of the different Member States in terms of the performance of clinical trials with the aim of facilitating trials of a transnational nature.
— Foster support for databases of clinical trials and collaborate with existing international initiatives in this area.

Objective 3

To facilitate and speed up the transfer of the results of the research, surveillance and monitoring of the marketing of new medicines.

Recommendations

— Foster translational research, reducing obstacles for the start of clinical trials with new compounds.
— Draw together measures that favour the prompt transfer of laboratory findings to clinical medicine.
— Foster a national policy for the development of orphan medicinal products that lays down strategies to reduce the time it takes for experimental drugs to reach the people who need them, especially in the case of molecules which are already marketed for other diseases.
— Reinforce the effectiveness of the Support Unit for Non-Commercial Clinical Trials (Unidad de Apoyo para Ensayos Clínicos No Comerciales), with the aim of facilitating the work of clinical researchers.

— Promote the creation of programmes for the evaluation, monitoring and funding of highly complex pharmacological treatments.

Objective 4

To analyse the need for health products, adjuvants, materials for dressings and other medical devices required for the treatment of RD, thereby searching for alternatives that guarantee equitable access to them.

Recommendations

— Promote, within the framework of the RD Strategy, the study and analysis of the need for health products, materials for dressings and other products (sunscreens, cosmetics (5), etc.) required for the treatment of RD, thereby studying any necessary amendments of the current legislation to guarantee equitable access to those products to all people affected by this type of disease.

2.4.2. Advanced Therapies

2.4.2.1. Background

Scientific evidence shows that Cell Therapy and Regenerative Medicine are a way of providing therapeutic solutions in pathological situations that currently lack treatments, or of improving existing treatments.

An advanced-therapy medicinal product is understood to mean any of the following (in accordance with Regulation (EC) No. 1394/2007):

— Gene therapy medicinal product
— Somatic cell therapy medicinal product
— Tissue engineered product, meaning a product that «contains or consists of engineered cells or tissues, and is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue».

(5) Cosmetic product: any substance or preparation indented for placing in contact with the various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with teeth and mucous membranes of the oral cavity, with the view exclusively or principally to cleaning them, perfuming them, changing their appearance and/or correcting body odours and/or protecting them or keeping them in good condition (Royal Decree 209/2005).

Products based on human cells or tissue offer quality treatments to many patients suffering from life-threatening or chronically debilitating diseases.

Clinical trials are currently being conducted in the field of gene and cell therapy for the treatment of genetic diseases, neoplasms and neurodegenerative diseases. The use of gene therapy in certain rare diseases, like the primary immunodeficiencies, has yielded promising preliminary results. Nevertheless, at the present time no advanced-therapy medicinal products have been authorised in our field.

«The Ministry of Health and Social Policy understands and acknowledges that research with human stem cells, from adults and embryos, is a priority. Since it involves an area in which society is particularly sensitive, it is essential to combine support for research with an exquisite control of the ethical limits for carrying out this research». With the aim of harmonising strategic stem cell research interests and its ethical and legal implications, the ISCIII created the Sub-directorate General for Research in Cell Therapy and Regenerative Medicine (Subdirección General de Investigación en Terapia Celular y Medicina Regenerativa), with the following priorities:

— Monitor and control stem cell research projects.
— Create and coordinate the National Bank of Cell Lines (Banco Nacional de Líneas Celulares, BNLC).

More recently, in October 2007, the Council of Ministers approved the *Plan de Terapias Avanzadas*, or advanced therapy plan, which aims to locate therapeutic alternatives for 12 pathologies which currently do not have a therapeutic protocol. Those pathologies include amyotrophic lateral sclerosis (ALS), multiple sclerosis and the muscular dystrophies. The Ministry of Health will, in addition, allow the use of experimental therapies in patients suffering from one of those diseases and with a very short life expectancy.

Following the launch of the *Plan de Terapias Avanzadas*, the Regional Government of the Balearics and the Ministry of Heath and Consumer Affairs signed an agreement in early 2008, with the aim of promoting research on pulmonary repair and regeneration mechanisms and on advanced stem cell therapies in the field of regenerative medicine.

Another similar initiative was the elaboration of the *Plan Andaluz de Terapias Avanzadas*, or Andalusia's advanced therapy plan, which is intended to promote the undertaking of clinical trials that make it possible to translate the results of basic research in the field of adult stem cells into treatments for diseases which are still lacking curative treatments.

In Spain, the main cell therapy research groups are associated through the Cell Therapy Network (Red de Terapia Celular, TERCEL), which was created in 2002 under the project for thematic networks for collaborative research, funded by the Carlos III Health Institute (ISCIII). The Network, which is still in force, consists of 26 nodes with as their common denominator cell therapy research directed at various pathologies. Many of those groups include several working subgroups from different AC.

Concerning the legal aspects, Directive 2001/83/EC and Regulation (EC) No. 1394/2007 lay down which Advanced Therapies are medicinal products and which are not, and among those that are medicinal products, which need to be authorised through a Community procedure and which don't. In all cases, clinical trials with advanced-therapy medicinal products must be conducted according to the provisions of Directive 2001/20/EC, which was transposed into Spanish Law 29/2006 by RD 223/2004. In compliance with the said Royal Decree, over the last few years the Spanish Medicines Agency (AEMPS) has evaluated more than 70 applications for clinical trials with advanced therapies.

The marketing authorisations for the respective advance therapy medicinal products are managed by the Commission through a centralised procedure for the entire European Union. The European Medicines Agency (EMEA) is the scientific-technical body that evaluates this type of products on the basis of a report issued by a Technical Committee specialised in this type of therapies, the Committee for Advanced Therapies (CAT), according to reports prepared by the authorities of three Member States. The Spanish Medicines Agency (AEMPS) acted as a relevant authority in three of the four procedures that have been presented to date.

Spain has also established a system for promotion and coordination in the field of human embryonic tissue and cell research. Noteworthy is the regulation of the National Bank of Cell Lines, attached to the Carlos III Health Institute (ISCIII). Likewise, there is a Human Tissue and Cell Use and Donation Guarantees Commission (Comisión de Garantías para la Donación y Utilización de Células y Tejidos Humanos), which is a deliberative body, attached to the Carlos III Health Institute (ISCIII). Its tasks are to advise and guide research and experiments with samples of a human embryonic nature, and to contribute to the upkeep and dissemination of scientific and technical expertise on this subject.

Legislative framework

— In the European Union, the elaboration of cell and tissue therapy products is regulated by Directives 2001/83/EC (transposed into Spanish RD 1345/2007), and certain aspects by 2004/23/EC,

2006/17/EC and 2006/86/EC, transposed into Spanish legislation by RD 1301/2006.

— Regulation (EC) No. 1394/2007 of the European Parliament and of the Council, on advanced-therapy medicinal products, lays down the rules concerning the authorisation, supervision and pharmacovigilance of advanced-therapy medicinal products prepared industrially or manufactured by a method involving an industrial process, and intended to be placed on the market in Member States. RD 1344/2007 lays down the criteria for the notification of adverse effects. Products resulting from tissue engineering legally sold on 30 December 2008 shall comply with the Regulation, at the latest, on 30 December 2012. The remaining advanced-therapy medicinal products shall do so, at the latest, on 30 December 2011.
— The requirements regarding medical devices set out in Directive 93/42/EEC apply to medical devices used in combined advanced-therapy medicinal products. Active implantable medical devices used in combined advanced-therapy medicinal products should, in turn, comply with the conditions set out in Directive 90/385/EEC.
— In the European Union, the donation, procurement and control of human tissues and cells that are part of certain medicinal products are governed by Directives that were transposed into Spanish legislation by Royal Decree 1301/2006. That same decree establishes the standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, and approves the coordinating and operating standards for their use in humans.
— The procedure for the authorisation, registration and dispensing conditions of industrially manufactured medicinal products for human use are governed by RD 1345/2007 of 11 October.
— Clinical studies with advanced-therapy medicinal products are regulated by Spanish Law 29/2006 of 26 July, issued by RD 223/2004 of 6 February.
— The use of human embryonic cells is subject to stricter regulations, and differs slightly from one EU country to the next. Spanish legislation authorises research with human embryonic stem cells obtained from surplus or supernumerary embryos from in vitro fertilization procedures. Europe has a European Human Embryonic Stem Cell Registry in which ten EU countries, including Spain, participate. Its main goal is to provide information on all the embryonic stem cell lines available to the scientific community.

For a cell therapy to be considered for clinical use, it must have proven to be satisfactory in terms of quality, effectiveness and safety. The validation of a cell therapy for clinical use must be proven through preclinical and clinical models with their respective development stages. Some of them, however, may fall within the definition of advanced therapies, and could therefore reduce and/or avoid some of the development stages that classically apply to medicinal products.

In certain cases, «they are therapeutic products developed "a la carte", for a specific patient, often of autologous origin or directed from a specific, compatible donor». Nevertheless, the quality of all those medicinal products, even of those whose manufacturing process follows production dynamics that are far removed from pharmaceutical industrial manufacturing, is guaranteed by the application of Good Manufacturing Practices (GMP) in their development process. This includes advanced-therapy medicinal products at the clinical research stage, with the Spanish Medicines Agency (AEMPS) having carried out the inspection in 8 centres throughout Spain.

2.4.2.2. General objective

To promote safe access for people affected by rare diseases to advanced therapies by incentivising the research, development and authorisation of these products within an appropriate legislative framework.

2.4.2.3. Specific objectives and recommendations

Objective 1

To promote public and private research on advanced therapies, as well as the clinical application of those therapies to rare diseases.

Recommendations

- Allocate funds for public research on advanced therapies intended for people affected by rare diseases.
- Foster basic and university research on preclinical development by increasing the level of funding for research in the field of advanced therapies applied to rare diseases.
- Foster links and collaboration with recently created, European high production platforms, and encourage the use of European shared molecular libraries.
- Develop transversal action in the field of regenerative medicine, nanobiotechnology, bioengineering and health technology and innovative molecules.
- Adapt the legislation on advanced therapies in relation to informed consent for the use of biological material in research.

— Establish legal frameworks for research with stem cells, at all times respecting the rights laid down in the Oviedo Agreement or in the Charter of Fundamental Rights.
— Foster the development of the *Plan Nacional de Terapias Avanzadas*, or the Spanish national advanced therapy plan, and enhance its development and implementation, with regard to all rare diseases, starting with those that are most seriously debilitating.
— Improve the dissemination of information regarding the different advanced therapy methods and their available applications to the patient organisations and professional groups concerned.
— Establish measures and protocols for actions regarding clinical trials, taking into account the low prevalence of RD.
— Increase collaboration at European level by creating and funding a public-private forum on RD that favours the development of multicentre projects with the necessary experience and funding.
— Study the possible designation of advanced therapy products as orphan medicinal products so that they can enjoy the same fiscal incentives and market exclusivity periods.
— Incorporate advanced therapies into the diagnostic and treatment protocols of centres of reference, where appropriate, once they have been designated as such.
— Foster the creation of multidisciplinary committees of experts for the elaboration of regulations for the use, monitoring and appropriate surveillance of advanced-therapy medicinal products.
— Promote the creation of advanced therapy hospital units that stimulate their development, ensure their quality and provide ongoing advice and training in this field.

2.4.3. Rehabilitation

2.4.3.1. Background

Beyond the pharmacological aspects, the treatment of many RD requires early intervention, rehabilitation and speech therapy services, which the health system must continue to develop.

In view of the lack of alternative and effective pharmacological treatments, early intervention and rehabilitation allow people with RD to optimise their capacities by preventing complications and improving personal and social abilities.

Motor rehabilitation and speech therapy translate into functional and neurological improvements, which lead to greater autonomy for patients and, therefore, to increased quality of life. Statistics show that 68% of

patients receiving a rehabilitating treatment improve their physical and coordination capacities, like the start of the visual displacement, upper limb coordination, etc., and therefore their quality of life.

Like for other therapies, the principles underlying rehabilitation must be based on the best available scientific evidence regarding the restoration or improvement of the patient's quality of life and the cost-effectiveness of the rehabilitation.

These problems are stressed by Spanish Law 13/1982, on the Social Integration of Disabled Persons (LISMI), as well as Spanish Law 51/2003 of 2 December, on Equal Opportunities, Non-discrimination and Universal Accessibility for Disabled People (LIONDAU) and Spanish Law 39/2006 on the Promotion of Personal Autonomy and Care for Dependent Persons. Since certain rare diseases are seriously debilitating and/or generate a high degree of dependence, people affected by these diseases fall within the scope of these laws which establish the principles of independent life, normalisation and the mainstreaming of policies that address disability issues.

Rehabilitation is covered in Royal Decree 1030/2006, of 15 September, establishing the portfolio of common services of the Spanish NHS and the procedure for its upkeep (6). Nevertheless, within the Spanish NHS, physiotherapy is mainly directed at the acutely ill and to a

(6) Appendix II includes, within the portfolio of common primary care services: «5. Basic rehabilitation. Comprising educational, preventive and rehabilitation activities that are usually provided in the scope of primary care, on an outpatient basis and on medical prescription, and in keeping with the programmes of each health service, including home care if considered necessary due to clinical circumstances or limited accessibility. It includes:

5.1. Prevention of the development or the progression of musculoskeletal disorders.
5.2. Physiotherapeutic treatments for symptom control and functional improvement in chronic musculoskeletal conditions.
5.3. Recovery of mild acute musculoskeletal conditions.
5.4. Physiotherapeutic treatments for neurological disorders.
5.5. Respiratory physiotherapy.
5.6. Health guidance/training for patients or carers, where appropriate.»

In addition, Appendix III of the said Royal Decree includes, within the portfolio of common secondary care services:

«8. Rehabilitation for patients with recoverable functional deficits. Comprising the diagnostic, evaluation, preventive and treatment procedures in patients with functional deficits, aimed at facilitating, maintaining or restoring the largest possible degree of functional abilities and independence for the patient, with the aim of reintegrating patients into their usual environments. It includes rehabilitation in the case of disorders of the musculoskeletal system, the nervous system, the cardiovascular system and the respiratory system, through physiotherapy, occupational therapy, speech therapy that is directly related to a pathological condition being treated in the Spanish NHS and self-help devices (prosthetic and orthotic devices, regulated in Appendix VI of the portfolio of common prosthetic and orthotic services).»

much lesser extent at the chronically ill, who tend to be discharged after a brief rehabilitation period.

However, that is not the case in all the Autonomous Communities. In the Autonomous Community of Castile-La Mancha, the Department of Health agreed to provide people suffering from ataxia with intensive rehabilitation in the National Centre for Paraplegics (Centro Nacional de Parapléjicos) and/or access to health centres equipped with a rehabilitation room and physiotherapists all year round.

The Autonomous Government of Catalonia developed the *Plan Director Sociosanitario*, a master plan for integrated health and social care for people with neurological diseases possibly involving disabilities. The Plan includes rehabilitation in specific installations like day hospital or integrated health and social care centres for more intensive rehabilitation.

Another specific example of the development of integrated health and social care in different areas is the *Plan Integral de Atención Sociosanitaria al Deterioro Cognitivo en Extremadura* (PIDEX), Extremadura's comprehensive integrated health and social care plan for cognitive deterioration, which deals with the needs of people with degenerative dementias, acquired brain damage and developmental deficit syndromes, and considers cognitive stimulation, the provision of social services and psycho-social support to carers and relatives.

2.4.3.2. General objective

To facilitate continuous access to early intervention, rehabilitation and speech therapy services for people affected by a RD, with the aim of maintaining and improving the personal autonomy, as well as the quality of life, of rare disease patients.

2.4.3.3. Specific objectives and recommendations

Objective 1

To reinforce ongoing, comprehensive rehabilitation (physical, sensorial and cognitive) for people affected by a RD, with the aim of optimising, preserving and/or assuring their residual capacities.

Recommendations

- Make sure the principles underlying rehabilitation are based on the best available scientific evidence as regards the restoration or improvement of the patient's quality of life and the cost-effectiveness of the rehabilitation.
- Promote access for children with RD to early intervention services, near their homes, as well as the continuity of care in

rehabilitation or functional restoration services in the specific developmental areas required (physical therapy, speech therapy, psychomotility, etc.).
- Make sure that the rehabilitation for people affected by RD included in the portfolio of common services of the Spanish NHS is provided continuously.
- Promote the work of palliative home care teams, who meet the needs of people affected by a RD during the advanced stages of the disease.
- Promote speech therapy treatments in the case of RD involving speech impairment.
- Develop guides on sensory, cognitive and physical rehabilitation and comprehensive treatments adapted to the specificities of rare diseases.

2.5. Integrated health and social care

2.5.1. Background

Most rare diseases are complex and chronic entities involving substantial morbidity and a high degree of disability and/or dependence, and requiring long-term care and multidisciplinary interventions. Likewise, they substantially reduce the quality of life of affected persons and their families, not only in terms of strictly health-related aspects, but also in psychic and social areas, affecting family and financial needs, the inclusion in school or work environments, etc.

Moreover, the nature of rare diseases entails a series of further circumstances that aggravate the conditions of life of sufferers and their families. The lack of information and training in these diseases leads to a series of problems for sufferers and cause patients and their families to find themselves in a socially isolated situation which, in order to be remedied, needs to be studied in depth.

As with other chronic or debilitating diseases, the needs of people with rare diseases can only be met through comprehensive care delivered through a variety of services. It must involve different care systems and health providers, and easier access to health, social and other services (educational, occupational, pharmacy dispensing, etc.). Spanish Law 16/2003 on Cohesion and Quality of the NHS requires the coordination of various sectors with the aim of guaranteeing the availability of a comprehensive and ongoing care system to improve the level of health and the quality of life of affected persons and their relatives or carers.

From an intersectoral perspective, integrated health and social care can act as the basic backbone of the necessary combination of health, social and non-professional assistance, in order to guarantee the continuity and coherence of the multiple types of care required by people with rare diseases and by their families.

Integrated health and social care, as set out in Article 14 of Spanish Law 16/2003, on Cohesion and Quality of the NHS, consists of the different types of care available to people with a disease, usually of a chronic nature, and to people with a disability who because of their special characteristics may benefit from the simultaneous and synergic action of health and social services to increase their autonomy, lessen their limitations or suffering and facilitate their social reintegration.

Integrated health and social care will be provided at the care levels determined by each Autonomous Community and in all cases shall include:

a. Long-term healthcare.
b. Healthcare during convalescence.
c. Rehabilitation of patients with recoverable functional deficits.

In the area of social services, Spanish Law 39/2006 on the Promotion of Personal Autonomy and Care for Dependent Persons, leaves it up to the Autonomous Communities to «establish the procedures for the coordination of health and social care services, involving the creation, wherever necessary, of any coordination bodies required to guarantee effective care».

In a broad sense, the social services field is the door that gives access to the many existing resources and requires the classification of people with rare diseases as «people with a disability» or as «people in a situation of dependence». That is the case, more specifically, for access to the financial services and benefits of social services, to non-contributory social security, employment promotion and tax relief.

Currently, both disabilities as well as situations of dependence are assessed by specialised bodies of the Autonomous Communities. However, there are decrees for both which unify the assessment procedures and scales for these situations at state level.

Over the last thirty years the attention paid to the different needs of people with disabilities has led to the creation, from a human rights-based perspective, of a complex system of equalisation of opportunities. That system mainly consists of «positive action» measures (favourable treatment and additional support) and, to a lesser extent, of measures against discrimination, whether direct or indirect, which obstruct or hinder the participation of people with disabilities in equitable conditions and under equal opportunities.

This set of measures is based on a series of laws of a basic nature and intersectoral scope, in addition to which there are sectoral regulations applicable at autonomous community or state level (7).

The Public System for the Equalisation of Opportunities for Persons with Disabilities (Sistema Público de Equiparación de Oportunidades para las Personas con Discapacidad) covers different types of measures, which are managed by the departments (at state, autonomous community or local level) responsible for those areas. Below is a summary of the measures included in that system:

Cash benefits. The main financial aid available to people with disabilities or their families are: social security benefits (disability pension, dependent child benefit and income support), social assistance benefits (financial dependence benefits, individual benefits for care, rehabilitation and self-help devices, subsidies and service agreements with NGOs) and tax relief (income tax, tax on inheritance and donations, VAT, tax on mechanically powered vehicles, etc.).

Social Services. In addition to the financial aid for social assistance, the Social Services System has general primary care resources (information, guidance, referral, etc.) and specialist services for people with disabilities (home-help, telehomecare, day care centres and vocational training schools, professional rehabilitation services and residential care centres).

The System for Autonomy and Dependence Care (Sistema para la Autonomía y Atención de la Dependencia, SAAD) was recently created within the framework of Social Services. That system guarantees, by law, access for dependent persons to the portfolio of services and cash benefits laid down by Spanish Law 39/2006 on the Promotion of Personal Autonomy and Care for Dependent Persons.

Moreover, there are currently action plans in this field which promote policies for people with disabilities and which, therefore, are in many cases useful for people with rare diseases. Examples are the *Council of Europe Action Plan*; the *Plan Nacional de Accesibilidad*, or Spain's national accessibility plan; the *Plan de Acción para las Mujeres con Discapacidad*, which is an action plan for women with disabilities; and the *Acuerdo sobre criterios comunes y condiciones mínimas de los Planes de Atención Integral a Menores de tres años*, which is an agreement on the common criteria and

(7) The general Spanish laws on which the comprehensive policies for disabled persons are based, are: Law 13/1982, on the Social Integration of Disabled Persons (LISMI), Law 51/2003, on Equal Opportunities, Non-discrimination and Universal Accessibility for Disabled People (LIONDAU) and Law 39/2006, on the Promotion of Personal Autonomy and Care for Dependent Persons.

minimum conditions of plans for the comprehensive care of children under the age of three, which still needs to be approved by the Territorial Council of the SAAD.

Labour market integration. Spanish labour legislation provides specific regulations as well as special measures included in general regulations for the promotion and support of the integration into the labour market of working people with disabilities (8).

The driving force behind the policies promoting the employment of working people with disabilities is contained in the *Estrategia Global de Acción para el Empleo de Personas con Discapacidad 2008-2012*, Spain's global action strategy for the employment of people with disabilities. The Strategy is aimed at increasing the activity and occupation rates, as well as the integration into the labour market, of working-age people with disabilities. Likewise, it is aimed at improving the quality of employment and enhancing working conditions for people with disabilities, thereby actively seeking to prevent discrimination.

Informal support. A network of resources that should be taken into consideration when discussing integrated health and social care, is Informal Support. In this context, informal support is understood as the care provided by NGOs for disabled persons, by caregiving families and by voluntary services. NGOs play a very important role in the disability sector, as representatives as well as service providers, above all in the areas regarding information-guidance, education, employment and care for the most severely disabled people. Caregiving families are today a fundamental source of support in the care of people with disabilities; they are an invaluable resource which, in turn, requires its own support. Moreover, the voluntary sector is very present in recreational and care programmes for these patients, and the subsidiary support they provide deserves to be acknowledged.

At present Spain does not have a uniform model neither for the provision nor for the coordination of health services and social services, although for many years now work has been undertaken towards the creation of such a model. The debate regarding the need to coordinate the

(8) Training and professional rehabilitation services (social guarantee courses, employment workshops, work preparation centres, etc.), labour intermediation services (professional guidance, personal and social-oriented services, placement and support services, etc.), sheltered employment centres (vocational training schools, selective employment, sheltered workshops, etc.), sheltered employment-ordinary employment transition programmes (employment enclaves, supported employment, etc.) and measures to promote ordinary employment (employment in companies, public employment and self-employment).

different service provision systems has led to initiatives such as the Spanish NHS Analysis and Evaluation Commission (Comisión de Análisis y Evaluación del SNS); the *Acuerdo Marco Interministerial*, or inter-ministerial framework agreement, of the Ministry of Health and the Ministry of Social Affairs; and the *Congreso de los Diputados de consolidación y modernización del Sistema Nacional de Salud*, which is the agreement of the Congress of Deputies for the consolidation and modernisation of the Spanish NHS.

The coordination between the Primary Care (PC) service of the Spanish NHS and Social Services currently tends to be carried out by the social work services of public health centres. Several of the AC have set up bodies for the management of integrated health and social care, in charge of coordinating the interventions of the Health Services and the Social Services. In general, the responsibilities are divided between the Health Departments and the Social Services Departments, with independent health networks and social networks.

The coordination between the healthcare and social care mechanisms is a problem that traditionally becomes apparent when analysing the way in which integrated health and social care services are organised.

The *Libro Blanco de Atención a las Personas en situación de Dependencia* (2004), or white paper on care for dependent persons, from which the description of the general situation of the coordination of integrated health and social care was taken, sets out a series of proposals that, mainly, were those elaborated in 2001 by the Mixed Commission in charge of drafting a document, *Bases para un modelo de atención sociosanitaria,* regarding the foundations of an integrated health and social care model.

In this context, in view of the nature of its functions and its current privileged membership of the Ministry of Health and Social Policy, the State Reference Centre for Rare Diseases Patients and their Families (CRE) in Burgos is in charge of promoting the coordination between health and social care services. Moreover, it should act as a driving force behind the cooperation between the different services and units with responsibilities in the fulfilment of the needs of people with rare diseases and of their families, and also between the public sector and the associative movement.

Its main role consists of bridging the gap between the Spanish NHS and the Social Services System, and of integrating into a single strategy the assistance foreseen by the system for the equalisation of opportunities for people with disabilities. To achieve that mission it will use its functions in the areas of the management of information and publications, the training of specialists, as well as the promotion of actions in the field of innovation, development and technical aid services.

2.5.2. General objective

To improve integrated health and social care through the availability of a comprehensive and continuous care system for people affected by rare diseases.

2.5.3. Specific objectives and recommendations

Objective 1

To promote the coordination between the different bodies and institutions involved in the provision of comprehensive care for people affected by rare diseases.

Recommendations

- Encourage cooperation and co-responsibility between all those involved in the provision of comprehensive care for patients with RD.
- Promote the appropriate planning and management of existing health resources and social resources for people with rare diseases and their families, thereby guaranteeing the availability of a comprehensive and continuous care system.
- Enhance the development of frameworks of services and responsibilities regarding people with RD, to be coordinated in the field of integrated health and social care of each AC.
- Foster the creation of an Interdepartmental Coordination Commission between the Departments of Health, Social Services and Education. The Commission will incorporate RD policies and guide the development of the RD Plans of the Autonomous Communities, making sure that they are consistent and coordinated with the National RD Strategy.
- Promote the collaboration between the Spanish National Health System's Reference Centres, Services and Units (CSUR) on RD, once they have been designated as such, and the State Reference Centre of the Social Services System (Centro de Referencia Estatal del Sistema de Servicios Sociales), for Rare Diseases Patients and their Families (CRE) in Burgos.
- Promote, through the System for Autonomy and Dependence Care (SAAD), the establishment of a general framework that determines the involvement and role of the Spanish Law on the Promotion of Personal Autonomy and Care for Dependent Persons with regard to people with RD.

— Encourage the design, implementation and evaluation of coordination models between health services and social services that help guarantee the continuity of care for patients with RD.
— In the event of service agreements and/or purchases, establish criteria for their quality and evaluation, similar to the criteria that have to be met by the organisational structures for the care of patients with RD in each specific Autonomous Community.
— Develop complex care protocols and models that specify the care and referral processes, as well as the health services and social services.
— Strengthen, in both the health system as well as the social system, the concept of a «case manager» to supervise the monitoring, application and continuity of the measures.

Objective 2

To collaborate with and inform, through the health sector and in as far as possible, all stakeholders of social services about the socio-economic, occupational, educational and technical needs, both of people affected by RD as well as of their carers, to make sure that those needs are adequately met.

Recommendations

— Provide advice about the rights of affected persons and of their carers, as well as those of their families.
— Provide advice on information points or centres that provide information about state benefits, the resources of specific associations or organisations and the health services in patients' Autonomous Communities, which may help improve their quality of life.
— Inform the affected person and his or her family about the administrative processes involved in obtaining the health and social assistance required for the adequate care of the affected person.
— Provide information about the location of employment guidance and advice services, as well as the services that assess and advise people with disabilities.
— Encourage the occupational reintegration and continuity of the family member caring for the patient.
— Collaborate, through health services, in the drafting of occupational reports and guides aimed at the adaptation of workstations to disabilities.
— Together with the education sector, promote access to hospital classrooms for schoolchildren with RD and to other school

support measures which facilitate the intellectual development of affected children.
— Make sure that the adequate healthcare is guaranteed in any respective education centres that requests it.
— Participate in the drafting and dissemination of educational guides for teaching staff, explaining what type of care is required by children and adolescents in specific situations (i.e., in the event of a crisis, etc.), and setting out certain guidelines that facilitate their educational integration.
— Collaborate with the education sector on basic health information that should be considered when working with children affected by RD.

Objective 3

To promote adequate access to mental health services for people affected by RD and their families.

Recommendations

— Offer psychological care, support and guidance throughout the process of the disease as well as at the time of diagnosis and during genetic counselling.
— Foster and promote resources that improve the quality of life of people affected by RD and that help the people close to them (home assistance services, hospital at home services, day centres or short-stay centres, etc.).
— Reinforce and develop tools for training in the provision of care, emotional support and the promotion of self-help for people caring for patients with RD.
— Raise awareness among health professionals and provide them with instruments for the detection, assessment, follow-up and appropriate referral of patients with RD.

Objective 4

To promote, through integrated health and social care, the adoption of measures to improve the quality of life of people affected by RD and of their families.

Recommendations

— Encourage, at the level of the AC and local government bodies, the adaptation of internal regulations and procedures to promote the integration of people with RD.

— Facilitate social integration through leisure and recreational activities adapted according to disabilities, age and gender.
— Encourage physical activity and sport by promoting measures for the adaptation of sports centres.
— Promote respite care structures and centres for the temporary relief of the carers of people with RD (residential centres, supervised apartments, temporary admissions so the family can rest).
— Promote, through the State Reference Centre for Rare Diseases Patients and their Families (CRE) in Burgos, cooperation in the development of the measures set out in this Strategy, as well as the measures arising from the implementation of the System for Autonomy and Dependence Care (SAAD).

Objective 5

To foster awareness-raising campaigns about rare diseases directed at health professionals and citizens in general, thereby increasing the visibility and recognition of those diseases.

Recommendations

— Promote the organisation of conferences/symposiums on RD to raise awareness among health professionals and citizens in general.
— Encourage awareness-raising campaigns and health education through talks, leaflets, posters and any other means of communication that can be used to reach the general public through the Ministry of Health and Social Policy, the Departments of Health and Social Issues, scientific and professional societies, as well as through any other interested entities.
— Support the organisation of the World Rare Disease Day (28 February or 29 February in the case of a leap year).
— Collaborate with scientific and professional societies so that they disseminate information regarding RD through their publications.

Objective 6

To reinforce support for charitable organisations and volunteer work.

Recommendations

— Acknowledge the importance of non-professional support, and of patient organisations and volunteers as social and health stakeholders.

— Promote the creation of charitable organisations, and encourage and support their participation and collaboration in the development of activities and programmes.
— Encourage the participation of voluntary organisations in integrated health and social care programmes and activities for people with rare diseases and their families.
— Help organisations for ill people to overcome the social and health barriers arising as a result of the scarce number of patients with each disease as well as the geographical dispersion that hampers their work.
— Foster health sector activities developed by patient organisations at different levels: exchange of information and best practices, awareness-raising campaigns, education, training and research.
— Participate in awareness-raising and dissemination activities that enhance awareness, inform the public and support involvement in charitable organisations.
— Work with the State Reference Centre for Rare Diseases Patients and their Families (CRE) in Burgos on the development of the Programme for the support of families, carers and NGOs on information and guidance, training in the provision of care and respite care services.

Objective 7

To support and promote the abovementioned agreement on common criteria, recommendations and minimum conditions for the comprehensive care of children under the age of three, once it has been approved by the Territorial Council of the System for Autonomy and Dependence Care (SAAD).

Recommendations

— Guarantee early intervention as a subjective right of children under the age of three with a RD in a situation of dependence or at risk of dependence.
— Raise awareness and understanding among society in general so that the inclusion from a very young age of people with RD in a situation of dependence or at risk of dependence becomes a reality.
— Facilitate access to information about resources and services regarding early intervention for children under the age of three in every AC, about child development, developmental anomalies and children with RD in a situation of dependence or at risk of dependence.

— Improve the prevention of risk factors and the early detection of children aged 0-3 years with RD, both of a congenital as well as of an acquired nature, which may affect the normal development of those children.
— Guarantee the immediate referral, as soon as a RD has been detected, to early intervention that enhances the patient's capacity to develop and enjoy wellbeing, that allows his or her integration into the family, school and social environments, and that allows him or her to enjoy personal autonomy in as normal a way possible.
— Guarantee underage patients and their families and tutors access to social intervention.
— Establish the coordination between professionals of the different systems and services involved in the early intervention of children under the age of three with RD in a situation of dependence or at risk of dependence, by facilitation the sharing of information that guarantees the said intervention.
— Facilitate the provision of technical support and advice among professionals of the different systems involved, in order to be able to guarantee the fulfilment of the portfolio of services of each system.

2.6. Investigación

2.6.1. Background

Broadly speaking, the EU policy on the funding of research on rare diseases is characterised by its limited scope compared to the massive investments made in other more common disorders, as well as by the lack of a general strategy and coordination.

In September 2007, the main points of the *Plan Nacional de I+D+I*, or Spain's national R&D&I plan, were presented. According to the expectations of the Ministry of Education and Science, the General State Administration (the Central Government and the Autonomous Communities) will increase its investments at a rhythm of 16% per year, starting in 2008, and until reaching a total expenditure of 2.2% of the GDP in 2011, in line with the EU's current investment. That estimate includes the business sector, which will fund 55% of the total investment.

In Spain, the first initiative taken towards the promotion of research on rare diseases is set out in Royal Decree 375/2001, which approved the Statute of the Carlos III Health Institute (ISCIII). Likewise, Article 21 of the aforementioned Royal Decree determined that the research, scientific,

technical and teaching activities entrusted to the ISCIII would be carried out through centres or institutes with an organic level that is inferior to that of the Sub-directorate General.

The Order of 27 December 2001 created several centres within the Carlos III Health Institute (ISCIII), including the Toxic Oil Syndrome and Rare Diseases Research Centre (CISATER).

From then onwards the need to strengthen action in the field of rare diseases, as well as the need for additional efforts in terms of research and information within the technical-care framework, was highlighted. Units of reference need to be identified, and a system of coordination needs to be put in place with the health services of the Autonomous Communities in order to guarantee the availability of adequate healthcare.

In this regard, the Rare Diseases Research Institute (IIER) was created in 2003 as part of the ISCIII. The IIER's goal is to promote and carry out basic and clinical research, to provide training and support to health professionals and to innovate healthcare for rare diseases.

Another important initiative taken by the Ministry of Health and Consumer Affairs regarding rare diseases was the creation of the Thematic Networks for Collaborative Research in Health (RETICS), in which research groups and centres from the entire Spanish NHS participate.

The twelve specific networks on RD were created according to the health-related priorities set out in the *Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica 2000-2003*, Spain's national plan for scientific research, development and technological innovation over the period 2000-2003. They were financed by the Carlos III Health Institute (ISCIII), through the Research Fund foreseen under the Agreement signed with the Spanish Ministry of Health and Consumer Affairs and Farmaindustria (employers' association of Spanish pharmaceutical companies), after passing a selection process, on the basis of publicity, objectivity and competition. It had an initial budget of 20 million euros for three years.

The purpose of those networks was to enhance the use of human and technical resources in order to guarantee the prompt transfer of research to the hospital and biopharmaceutical sectors. However, in contrast to the quality of its research groups and centres, Spain does still not have a well-established platform on which to build a sound, national system for the storage, cataloguing and supply of samples. Likewise, Spain has still not developed a population registration system for rare diseases, and is far behind other countries in terms of clinical and translational initiatives like the development of new therapeutic approaches and diagnostic methods.

The Centre for Biomedical Network Research on Rare Diseases (CIBERER) was created in November 2006. It is one of the nine public

consortiums set up by the Carlos III Health Institute (ISCIII), and is intended to foster and coordinate research on rare diseases in Spain. Its origins lie in the Research Networks of centres and groups of the ISCIII with subjects related to rare diseases. In this case, the investment earmarked for research equalled 12 million euros over 2 years (similar to RETICS, which was granted € 20 m over 3 years). The CIBERER offers a comprehensive and dynamic approach to research in the field of RD.

Over the last few years the calls for research projects of the Health Research Fund (FIS) and those of Strategic Action for Health Research (Acción Estratégica en Salud, AES) for the years 2008 and 2009, have specifically identified RD as an area for promotion. In fact, the AES, in the aforementioned national R&D&I plan for 2008-2011, refers to rare diseases as a «Línea de Investigación Prioritaria», or a priority area for research. Moreover, rare diseases are included in the «Línea de actuaciones complementarias de refuerzo», which concerns complementary reinforcement actions in areas such as basic research, clinical trials or the development of orphan medicinal products.

Other initiatives regarding research into orphan medicinal products include those of Farmaindustria's technological platform for innovative medicine (Plataforma Tecnológica de Medicamentos Innovadores) and the European Innovative Medicine Initiative (IMI).

At European level, the Fifth Framework Programme (5FP) was aimed at promoting cooperation, collaboration and better knowledge in the field of rare diseases. Accordingly, it financed a total of 47 research projects through an overall budget of 64 million euros. Later, the goal of the Sixth Framework Programme (6FP) was to continue to strengthen the development of technical and scientific knowledge, which translated into two thematic priorities: to translate genome data into practical applications for the improvement of human health, and to support the formulation and implementation of Community policies.

Spain participated in 31 European 5FP and 6FP projects, even though the projects were only occasionally led by a Spanish group.

The ERA-Net project, which addresses rare diseases and is funded by the EC under the 6FP, fosters joint and transnational activities. The project includes E-Rare, a network consisting of public bodies, ministries and research management organisations from nine Member States, responsible for the development and management of national or regional research programmes on rare diseases. It is expected to lay the foundations for continued and sustainable cooperation between partners of the Member States, thereby overcoming the fragmentation of research on rare diseases and promoting interdisciplinary approaches. Spain participated in six of the projects financed through the most recent E-Rare call for proposals.

The goal of the current Framework Programme (7FP) is to continue to promote transnational cooperation by emphasising translational research, the development and validation of new therapies, the promotion of health and primary prevention, as well as the adoption of national policies and the drafting of comprehensive plans for the care of affected persons. More specifically, research efforts will focus on the natural evolution and physiopathology of diseases and on the development of preventive strategies and diagnostic and therapeutic means.

2.6.2. General objective

To promote the transfer of RD research findings to the clinical practice, diagnosis and development of new therapeutic alternatives.

2.6.3. Specific objectives and recommendations

Objective 1

To support initiatives for epidemiological, clinical, basic and translational research on rare diseases.

Recommendations

— Promote future national R&D&I plans in the field of RD within the framework of Strategic Action for Health Research (AES). The following actions may contribute to the achievement of that goal:
  • Increase the efficiency of the available resources by promoting their shared use within the Spanish NHS.
  • Promote the raising of new public and private funds, as well as systems for the allocation of public funding to research.
— Maintain an adequate human capital by promoting the development of research among health workers and increasing the critical research mass. The following actions may contribute to the achievement of that goal:
  • Continue to support and develop, both at state and autonomous community level, the programmes included under the Strategic Action for Health Research (AES).
  • Boost the development of research, clinical-experimental or advanced diagnosis support units.
  • Support the development of the Associated Consortiums for Biomedical Research Networks (Consorcios Asociados de

Investigación Biomédica en Red, CAIBER) and the accreditation of the Health Research Institutes.

— Maintain adequate structural support. The following actions may contribute to the achievement of that goal:
  • Reinforce the development of the CIBERER in close collaboration with the Spanish NHS.
  • Analyse the viability and usefulness of creating mixed research centres between public health institutes with a transnational approach, as well as of systems for the shared use of infrastructures and the development of service platforms and research support units (biobanks, animal houses and others).
  • Foster scientific cooperation between public institutions (hospitals, universities, the CSIC and other pubic research organisations), technological centres and companies.

Objective 2

To promote the prioritisation of research projects on RD and favour national and international joint project proposals.

Recommendations

— Promote the maintenance of rare diseases as a priority area for research under the aforementioned national R&D&I plan.
— Foster institutional support for the development of new technologies, like biotechnology and nanotechnology, and their incorporation into the biomedical sector.
— Promote the aforementioned «complementary reinforcement actions» for clinical research with medicines, within the Subprogramme of non-commercial clinical research with medicines for human use of the national R&D&I plan.
— Support, under the CAIBER sub-programme, the following specific areas: advanced therapies in regenerative medicine, human genetics, rare diseases and orphan medicinal products.
— Foster gender equality in relation to the participation in research studies and clinical trials, thereby avoiding gender bias.
— With regard to the **areas of research on RD that need strengthening**, the priorities of the EU's Seventh Framework Programme should be taken into account:
  • Descriptive and analytical epidemiology in relation to the natural history of the disease and of the clinical nosology: development of multidisciplinary networks, development of tools needed to create shared databases and registers and cohort studies.

- Characterisation of hereditary mechanisms, the genes involved and metabolic and cell bases of rare diseases.
- Pathophysiology: development of infrastructures for the functional use and analysis of transgenic animals; support for the analysis of data obtained via transcriptomics and proteomics; identification of biological markers and metabolic profiles to be used for diagnostic purposes and the evaluation of disease progression; development of cell models and development of animal models different than mice.
- Development of diagnostic tests: support for projects with the industry for the joint development of diagnostic methods, and support for projects aimed at the evaluation of new diagnostic methods.
- Therapeutic research: determine new therapeutic targets, as a base for pharmacological therapies and for the development of gene and cell therapy.
- Quality of life studies.
- Studies on health services and social services that allow for the evaluation of the adequacy and efficiency of assistance and care processes.

Objective 3

To maintain and improve the structures and tools needed for the development of research on rare diseases.

Recommendations

— Encourage the networks of centres and/or groups of excellence in research on RD to work in a coordinated manner.
— Reinforce and sustain the actions carried out by any well-established structures conducting research in relation to RD.
— Promote a committed research policy, especially in relation to clinical trials in specific populations (paediatrics), diagnostics and the treatment of RD.
— Stimulate participation in research activities on RD funded by the European Union, providing support through the European Project Office (EPO).
— Foster translational research on RD, thereby taking into account some of the following measures:
  - Promote the training of mixed research groups through specific calls (clinical research groups in hospitals and basic research groups in universities).
  - Translate the findings of clinical research into clinical practice.

- Promote the incorporation of healthcare professionals into research areas for the development of specific projects.
- Incentivise the development of spin-offs by scientific institutions on projects with a translational approach.
- Promote the implementation of knowledge management tools.

2.7. Training

2.7.1. Background

The lack of specific training in the field of rare diseases and the large number of them, together with the pressure on Primary/Secondary Care services, further complicates an already difficult situation.

As mentioned in other parts of this document, professionals require a series of skills and knowledge when approaching rare diseases. In addition to undergraduate and postgraduate training, it is fundamental that all professionals involved in the provision of care for patients with RD receive ongoing training.

The importance of the coverage of RD as part of the training process of both Primary Care as well as Secondary Care health professionals must be stressed. However, that importance is perhaps greatest in Primary Care, since as mentioned throughout this document, for patients with rare diseases PC is the point of access to their pathway through the healthcare system. The training must be aimed at professionals of multidisciplinary teams (nursing, general medicine, paediatrics, etc.) that treat adults, children and adolescents alike.

The current shortcomings of undergraduate and postgraduate teaching plans and the scarcity of ongoing training initiatives in the field of rare diseases call for training to be intensified and awareness to be raised about the problems surrounding RD.

In undergraduate training, the problem lies in the fact that knowledge about the disease takes precedence over knowledge about the patient. So, although there are exceptions, the absence of Primary Care in universities is behind the lack of a broad, humanist vision that integrates other professionals (medicine, nursing, physiotherapy, speech therapy, psychology, social work, etc.) and that characterises Primary Care.

Specialist training processes (postgraduate training) enhance students' knowledge of diseases, including rare diseases, and the skills required to handle them. However, it presents the same shortcomings as undergraduate training, since here too the disease takes precedence over the patient.

The teaching programme for general medical practitioners recently underwent a significant reform in order to adapt the training of resident general practitioners to the new needs highlighted by Primary Care professionals and patients. Despite the growing importance attributed to rare diseases in Spain's health system in recent years, the aforementioned reform does not include anything on rare diseases.

Finally, ongoing training is often conditioned by the providers of that training, who prioritise according to the criterion of the prevalence of diseases.

In order to tackle this situation, certain proposals were set out during the Position Paper delivered to the Senate (February 2007) by the Joint Commission that was entrusted with the responsibility of analysing the special situation of patients with rare diseases. It defined 10 strategic axes regarding the approach to adopt when addressing RD, which included the training of health professionals in order to enhance their ability to identify rare diseases.

The objectives set out in the Position Paper presented to the Senate were: to update the knowledge on rare diseases among health professionals; to locate resources and information; and to adapt the initial and ongoing training of professionals. The creation of a medical specialty in genetics as well as the inclusion of human genetics as a core subject in faculties of medicine, were deemed to be of fundamental importance. Moreover, the paper highlighted the «importance of training with the aim not of creating specialists in rare diseases, which is difficult in the case of infrequent processes, but rather of providing professionals with the mental discipline required to handle the situations to which rare diseases give rise».

Likewise, government bodies should promote the progressive introduction of such training into teaching programmes at undergraduate, postgraduate and ongoing training levels, and should foster knowledge and awareness among health professionals.

Several scientific societies, like SEMFyC, SEMERGEN, SEMI or SEN, have recently created working groups dedicated to raising awareness and increasing training in RD among health workers. The activities of those groups currently include the organisation and provision of «Trainer of Trainers» courses and of PhDs related to RD; round tables on the problems surrounding RD in the respective national congresses; and the publication of articles on RD in the magazines of the different scientific societies.

2.7.2. General objective

To develop a training strategy that includes specific content on rare diseases in undergraduate, postgraduate and ongoing training, and that considers measures aimed at raising the awareness of, and the interest in, problems surrounding RD.

2.7.3. Specific objectives and recommendations

Objective 1

To stress the problems surrounding rare diseases in the undergraduate training of health science degrees, with the aim of increasing the knowledge and awareness of those diseases and of related problems.

Recommendations

- Approach the University Coordination Council about the curricular inclusion of the body of knowledge on RD, involving the adaptation of the initial training in health science study programmes and awareness-raising about RD among undergraduate students.
- Organise practical workshops on the different clinical subjects that teach undergraduate students the skills required to suspect rare diseases, deal with patients and their surroundings and provide them with everything necessary to ease the disease burden (pharmacological and non-pharmacological treatments, rehabilitation, health and social support, etc.)
- Promote the inclusion of a section dedicated to rare diseases in training programmes.

Objective 2

To promote a more in-depth study of the notion and handling of RD in postgraduate training programmes, thereby prioritising knowledge about the patient over knowledge about the disease.

Recommendations

- Analyse the viability and suitability of the possible training models for specialists in genetics.
- Include monographic courses on RD and genetic counselling in MA and PhD programmes, in keeping with the Bologna Declaration.

— Propose an MA on RD within the training options of the Spanish National Health School (Escuela Nacional de Sanidad) of the ISCIII.
— Approach the Spanish National Council of Medical Specialties about increasing the knowledge on RD within the different areas of specialisation.
— Foster, under the Teaching Programmes of healthcare centres (mainly hospitals and health centres), activities like the organisation of bibliographic sessions, clinical sessions and specific seminars on RD.
— Maintain and promote the programmes proposed under the abovementioned national R&D&I plan.
— Offer health professionals optional and complementary university training centred on awareness-raising and the acquisition of skills required when caring for people affected by RD.
— Promote the drafting of consensus documents on rare diseases.

Objective 3

To foster ongoing training initiatives related to RD in Primary Care and Secondary Care, taking into account the population, institutional and individual needs and, in as far as possible, including the recommendations set out below in strategic ongoing training plans.

Recommendations

— Create ongoing training modules aimed at the comprehensive care of people affected by RD.
— Promote the rotation of professionals in medicine, psychology, nursing etc. in the CSUR on RD, once they have been designated as such.
— Foster, in as far as possible, contact between patients with RD and students during the latter's training period.
— Encourage health professionals and associations of people affected by RD to collaborate and cooperate in training activities.
— Propose rotation periods for resident general medical practitioners and residents of other specialties (paediatrics, internal medicine, etc.) in genetic counselling services, with the aim of training them in preconception genetic counselling, prenatal diagnosis, teratology, the clinical follow-up of patients with genetic diseases or diagnostic tests, among other issues.
— Propose that a section on RD, or in which RD are considered, be included in the different evaluation mechanisms of resident doctors (resident log-book, portfolio, annual report, etc.).

— Propose to scientific societies that they create a «Rare Diseases Section» or similar, according to the conclusions of the Senate Position Paper.
— Promote the offer of ongoing training programmes on RD at state and autonomous community level.
— Promote joint meetings centred on RD between Primary Care professionals, Secondary Care professionals and experts from the CSUR, once they have been created, with the aim of fostering the communication between those groups, of sharing standards, harmonised procedures and best practice guidelines, among others.

Objective 4

To promote, through the Spanish NHS as well as through Social Services, the training of family members of people with RD, primary carers, volunteers as well as patient organisations.

Recommendations

— Include training programmes and activities for non-professional support under the *Plan Anual de Formación Especializada en Servicios Sociales*, which is IMSERSO's annual plan for specialist training in social services, and in the Training Programme of the State Reference Centre (CRE) in Burgos.
— Develop a programme for families caring for patients with RD to meet each other.
— Promote the creation within the CRE in Burgos of a training school for carers and provide them with practical training in the assistance and care of people with RD.
— Provide the sector's NGOs with information and advice regarding care for people with RD.
— Provide advice to organisations of patients with RD and their families about technological aids and accessibility measures through the Spanish National Centre for personal Autonomy and Technical Aids (Centro Estatal de Autonomía Personal y Ayudas Técnicas, CEAPAT) of IMSERSO.

3. Strategy monitoring and evaluation process

3.1. Planning of the dissemination, implementation and monitoring process

Once the Rare Diseases Strategy has been approved by the Interterritorial Council of the Spanish NHS (CISNS), its Technical Secretariat will be located in the Health Planning and Quality Office of the Directorate General of the Spanish NHS Quality Agency. The aforementioned Secretariat will operate as a coordination structure.

The evaluation and monitoring process of the Spanish NHS Rare Diseases Strategy will start with the creation of the Monitoring and Evaluation Committee (MEC) of the Strategy. The MEC will consist of the members of the Institutional Committee and the Technical Committee, who will establish the design of the system to evaluate and monitor the degree of progress of the Strategy, as well as the work schedule for the process.

The Technical Committee shall be in charge of updating the content of the document of the Strategy according to available scientific evidence. The representatives of the Autonomous Communities (Institutional Committee) will establish the methodology for the collection of the information and data that must be provided in the Strategy's monitoring and evaluation report.

The MEC shall meet at least twice every year. The content of the Strategy will be reviewed, updated and evaluated two years after its approval, and every four years thereafter.

The measures set out to promote the implementation of the Strategy are, a priori, the following:

3.1.1. Dissemination and communication of the Strategy

- Editing, publication and dissemination of the documents of the Spanish NHS Rare Diseases Strategy, as well as Situation Analysis. Availability of the documents in electronic format.
- Organisation of a conference to present the Spanish NHS Rare Diseases Strategy after its approval by the Interterritorial Council

of the Spanish NHS (CISNS), with the participation of all those involved.

— Presentation of the Strategy at national and international conferences.

— Participation of the Strategy in national and international projects and initiatives.

3.1.2. Implementation of the Spanish NHS RD Strategy through

— Transfer of funds to the AC to finance projects related to the implementation of Health Strategies, and in particular of the Rare Diseases Strategy. In other words, funding for activities such as: the design/implementation of disease management projects and the management of RD processes (continuity of care between the different healthcare levels); public communication campaigns on risk factors (prevention and early detection) and the content of the Strategy; specific interventions that address RD, training projects, development of information systems and registers, actions between the different Autonomous Communities, etc.

— Collaboration and coordination with the State Reference Centre for Rare Diseases Patients and their Families (CRE) in Burgos.

3.1.3. Monitoring of the RD Strategy

— Organisation of a technical conference one year after the Strategy has been approved by the Interterritorial Council of the Spanish NHS (CISNS).

— Definition of «Best Practices for Rare Diseases», and compilation and assessment of those best practices for their subsequent dissemination and inclusion in the Strategy review.

— Study of the classification proposals for existing RD.

— Drafting of a proposal for the listing of groups of RD according to pathologies, as well as a list of priority subgroups of RD in each of the groups to be dealt with by the CSUR.

— Drafting of situation reports regarding the following issues:

  • European Council Recommendation on action in the field of Rare Diseases.

- Implementation of RD Plans and/or Programmes in the AC.
- Progress of the process for the designation of CSUR on RD.
- Research activities related with RD:
  - Calls for Strategic Action for Health Research (AES) in connection with RD through the FIS and ETES.
  - Activities of any well-established centres and structures conducting research in relation to RD (CIBERER, IIER, RETICS, etc.).
- Monitoring of training activities on RD.

3.2. Evaluation methodology

The evaluation of a national health strategy consists of determining the merit or value of that strategy, for the purpose of identifying its possible areas for improvement. Moreover, and in so far as it concerns an analytical study of a retrospective and reflexive nature, it must be planned in advance.

The first step of the planning of the evaluation will be to determine the questions according to which it will be assessed in the future.

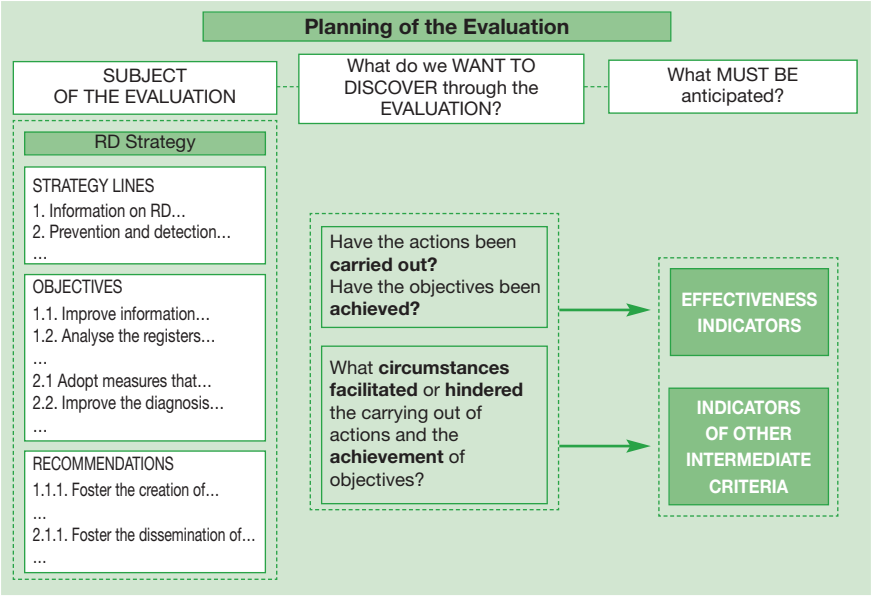
3.2.1. Planning of the evaluation

The first step is to identify the relevant «information needs» required for the evaluation to be a process aimed at improvement: «what do we want to discover through the evaluation?»

The second step is to draft those needs as the «evaluation questions» which, in the future, will have to be answered in order to reach specific conclusions.

Next, in the light of those questions, the third step is to identify «what information will need to be generated and recorded (indicators)» throughout the implementation period, in order to answer them.

The logic that emerges from the planning of the evaluation of the Strategy is shown below:



Evaluation criteria

The evaluation questions that will be considered are related to two criteria:

a) *Effectiveness*: questions (and indicators) related to the attainment of the objectives and the implementation of the recommendations set out in the Strategy.

Contribution: the formulation of questions and indicators will be aimed at: a) the «search» for the most explanatory indicators of every strategy line, and b) the «search» for common and «significant» aspects for the Autonomous Communities or for the Spanish NHS if proposed.

b) *Other intermediate criteria*: the formulation of questions (and indicators) related to the circumstances that facilitated or hindered the implementation of the recommendations set out in the Strategy.

Contribution: the formulation of questions and indicators is related to the «theory of change» of the Strategy (9), and the «search» for the distinctive circumstances related to the relevance of the proposals (suitability, significance and validity) on which to base territorial cohesion.

(9) The Theory of change refers to an evaluation method that has become established as a strategy for the evaluation of complex social programmes (Coote, 2004; Barnes, 2003). The method suggests the representation of how «certain activities» will promote the attainment of «certain objectives» and, on the basis of that representation, the facilitation of thought about the circumstances required for that to actually happen.

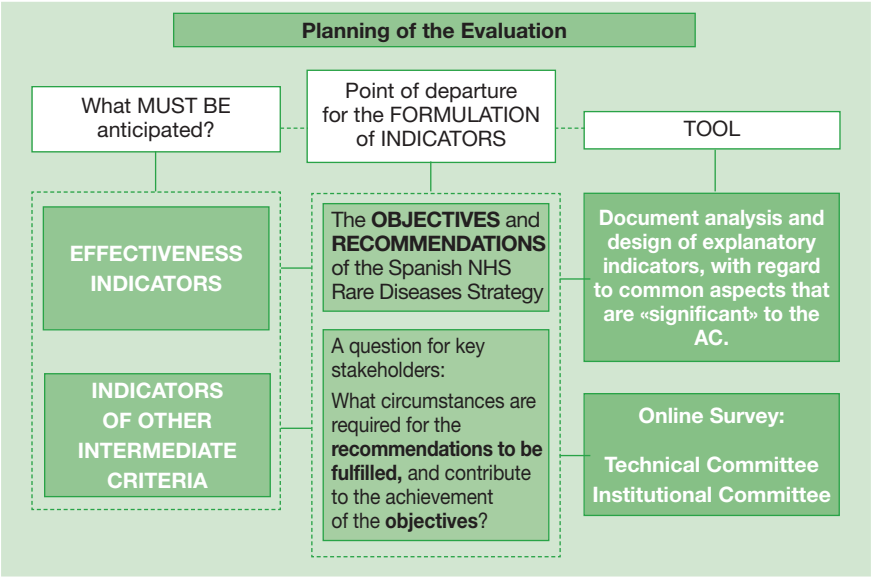
Sources and tools

The following sources and tools are used to formulate the evaluation questions:

Effectiveness: these questions are formulated according to the objectives and the recommendations set out in the Strategy. The fulfilment of the standards proposed on the basis of the indicators show us whether «we are, or are not, heading in the right direction».

Other intermediary criteria: these questions are formulated on the basis of the responses to an online survey, filled out by the Technical Committee and the Institutional Committee, aimed at the anticipation of the different circumstances that may facilitate or hinder the fulfilment of the objectives and recommendations.

The process for the formulation of indicators is shown below:



3.2.2. Effectiveness questions and indicators

The questions and indicators regarding the fulfilment of the recommendations and the achievement of the objectives proposed in the Strategy are set out below.

The selection of indicators linked to effectiveness was made, at all times, by trying to find a balance between simplicity and relevance. With that goal in mind, the text of the Strategy was thoroughly analysed, and different criteria were considered for the establishment of indicators, with clear metrics for their formulation.

DIMENSION SL1. INFORMATION ON RARE DISEASES			
Evaluation questions	**Indicators**		**Sources**
Effectiveness	**Indicator**	**Response options**	
Have the MSPS (10) and the AC coordinated efforts to create a minimum common set of information and resources?	Existence and type of coordination action between government bodies to improve the quality of information on RD and existing resources for their care	YES/NO Types of action: – Organisational meetings to analyse the situation – Inventorying and classification of existing directories, resources and tools that provide information on RD	MSPS/AC/ Scientific and professional societies/ Patient organisations/ ISCIII
Have basic, common criteria been defined for the quality, usefulness, efficiency and compatibility of registers?	Existence and type of coordinated action for work on the compatibility of existing registers	YES/NO Types of action: – Creation of working group to analyse the situation – Inventorying and classification of existing registers	MSPS/AC/ Scientific and professional societies/ Patient organisations/ ISCIII
	Existence of a definition of basic, common criteria for the quality, usefulness, efficiency and compatibility of registers	YES/NO – Definition of basic, common criteria – Analysis of existing registers with regard to those criteria	MSPS/AC/ Scientific and professional societies/ Patient organisations/ ISCIII
Are age and gender variables treated in a disaggregated manner in the Registers?	Existence of registers of epidemiological data disaggregated by age and gender	No. of registers that record pidemiological data disaggregated by age and ender/ No. of existing registers	MSPS/AC/ Scientific and professional societies/ Patient organisations/ ISCIII
Has a working group been created, within the framework of the Strategy, for the coding and classification of RD?	Existence of a working group for the coding and classification of RD	YES/NO	MSPS/AC/ Scientific and professional societies/ Patient organisations/ ISCIII

(10) MSPS = Ministry of Health and Social Policy.
AC = Autonomous Communities.
ISCIII = Carlos III Health Institute (Ministry of Science and Innovation).

DIMENSION SL1. INFORMATION ON RARE DISEASES *(Continuation)*			
Evaluation questions	**Indicators**		**Sources**
Effectiveness	**Indicator**	**Response options**	
Is Spain participating in coding and classification working groups active in this field at international level?	Spanish participation in, or support of, international RD coding and classification working groups	– Total number of groups in which Spain is participating – Type of participation (technical/institutional) – Institution that supports the international group in which Spain is participating	MSPS/AC/ Scientific and professional societies/ Patient organisations/ ISCIII

DIMENSION SL2. PREVENTION AND EARLY DETECTION			
Evaluation questions	**Indicators**		**Sources**
Effectiveness	**Indicator**	**Response options**	
Has action been taken to raise awareness among professionals and the target population about the need to attend preconception visits?	Action taken to raise awareness	No. and types of awareness-raising action taken	MSPS/AC
Have awareness-raising and training activities been provided to Primary Care professionals in order to strengthen their role in the diagnosis of a suspected RD?	– Awareness-raising activities carried out – Training in clinical warning signs and symptoms – Primary prevention programmes implemented	No. and type	AC
Has an analysis, inventory or map been made of the existing laboratories that carry out tests for the early detection of RD?	Existence of a draft directory or map of laboratories that carry out tests for the early detection of RD	YES/NO Draft directory or map of laboratories and the tests they carry out	MSPS/AC
Are the services and tests that they carry out for the diagnosis and early detection of RD known?	Inventory of multidisciplinary genetic counselling (MGC) services and tests	No. and type	AC

DIMENSIÓN L2. PREVENCIÓN Y DETECCIÓN PECOZ *(Continuation)*			
Evaluation questions	**Indicators**		**Sources**
Effectiveness	**Indicator**	**Response options**	
Are the services and tests that they carry out for the diagnosis and early detection of RD known?	Inventory of preimplantation genetic diagnosis (PGD) services and tests	No. and types	AC
	Inventory of prenatal services and tests	No. and types	AC
	Inventory of diagnostic tests for newborn screening	No. and types	AC

DIMENSION SL3. HEALTHCARE			
Evaluation questions	**Indicators**		**Sources**
Effectiveness	**Indicator**	**Response options**	
Has the coordination between PC, SC and related units treating RD improved?	Coordination action undertaken	No. and types of action undertaken	MSPS/AC/Patient organisations
Has an agreement been reached about the criteria for the grouping of RD for their consideration in the proposal for the creation of CSUR?	Existence of a list of groups of RD prioritised according to pathologies, to be covered by CSUR	YES/NO A list of groups of pathologies per CSUR is being drafted	MSPS/AC/ Scientific and professional societies/ Patient organisations/ ISCIII

DIMENSION SL4. THERAPIES			
Evaluation questions	**Indicators**		**Sources**
Effectiveness	**Indicator**	**Response options**	
Has access to orphan medicinal products improved?	No. of orphan medicinal products: – applied for – authorised – being marketed	No. Time lapse between phases	MSPS

DIMENSION SL4. THERAPIES *(Continuation)*			
Evaluation questions	**Indicators**		**Sources**
Effectiveness	**Indicator**	**Response options**	
Has access to treatments on a compassionate use basis or with foreign medicines improved?	No. of treatments on a compassionate use basis or with foreign medicines: – applied for – authorised	No. Time lapse between phases	MSPS/AC
Has access to authorised advanced therapies improved?	Number of authorised advanced therapies	No. Denomination and characteristics	MSPS/AC
Have the needs for health products, adjuvants, materials for dressings and medical devices required for the treatment of RD been analysed?	Existence of an analysis of the needs for health products, adjuvants, materials for dressings and medical devices required for the treatment of RD	YES/NO Being drafted	MSPS/AC/ Scientific and professional societies/ Patient organisations/ ISCIII
Are the early intervention, rehabilitation and speech therapy services for RD known?	Inventory of the early intervention, rehabilitation and speech therapy services for patients with RD	No. and types of services	MSPS/AC

DIMENSION SL5. INTEGRATED HEALTH AND SOCIAL CARE			
Evaluation questions	**Indicators**		**Sources**
Effectiveness	**Indicator**	**Response options**	
Have efforts been made to promote the design, implementation and evaluation of models for the coordination between health services and social services that promote the continuity of care?	Register of coordination action	YES/NO No., types of action and coordination models	MSPS/AC
Are the social and educational resources for people with RD known?	Inventory of social and educational resources for people with RD	No. and type of services offered	MSPS/AC/ Patient organisations

DIMENSION SL5. INTEGRATED HEALTH AND SOCIAL CARE *(Continuation)*			
Evaluation questions	**Indicators**		**Sources**
Effectiveness	**Indicator**	**Response options**	
Are the services and actions for the psychological support of people with RD known?	Inventory of services and actions provided for the psychological support of people with RD and the bodies/entities providing them	No. and type of services and actions per body	MSPS/AC/ Patient organisations
Has social integration been facilitated through leisure activities that take account of disability, gender and social class?	Activities for community integration	No. and types of activities	MSPS/AC/ Patient organisations
Have activities been promoted to raise awareness about RD among professionals and citizens?	Awareness-raising activities and type	No. and types of activities	MSPS/AC/ Scientific and professional societies/ Patient organisations
Has action been taken to promote charitable organisations and volunteer work?	Action to promote charitable organisations and volunteer work	No. and type of action	MSPS/AC/ Patient organisations
Are the number of organisations or associations, their profiles and activities known?	Inventory of organisations/ associations/ federations, profile and activities	No. and type of organisation/ associations/ federations, profile and activities	MSPS/AC/ Patient organisations

DIMENSION SL6. RESEARCH			
Evaluation questions	**Indicators**		**Sources**
Effectiveness	**Indicator**	**Response options**	
Are the centres and groups that carry out epidemiological, clinical, basic and translational research on RD known?	Inventory of centres and groups carrying our research on RD	No. and type	MSPS/AC/ Patient organisations/ ISCIII
Have efforts been made to maintain RD as a priority research area in the national R&D&I plan?	No. of RD research projects No. of joint projects: – of a national scope – of an international scope	No. and research areas	MSPS/AC/ ISCIII

DIMENSION SL7: TRAINING			
Evaluation questions	**Indicators**		**Sources**
Effectiveness	**Indicator**	**Response options**	
Has action been taken to propose the inclusion of training in RD in: – undergraduate training – postgraduate training – ongoing training?	Action taken in each field: – undergraduate training – postgraduate training – ongoing training	In each field: – No. and type – Institution or body promoting the action	MSPS/AC/ Scientific and professional societies/ ISCIII
Has action been taken to train patients with RD, their families and volunteers?	Action taken	No. and type Institution or body promoting the action	MSPS/ AC/ Scientific and professional societies/ Patient organisations/ ISCIII

4. Appendixes

4.1. Bibliography

General aspects

Commission of the European Communities. Communication from the Commission to the European parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Rare Diseases: Europe's challenges. Brussels: Commission of the European Communities; 2008. {SEC(2008)2713}{SEC(2008)2712}. Available from: http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf

Commission of the European Communities. Proposal for a Council Recommendation on a European action in the field of rare diseases. Brussels: Commission of the European Communities; 11.11.2008. COM(2008) 726 final. SEC(2008)2713}{SEC(2008)2712}. Available from: http://ec.europa.eu/health/ph_threats/non_com/docs/rare_rec_en.pdf

European Commission. DG Health and Consumer Protection Programme of Community action in the field of public health (2003-2008). Available from: http://ec.europa.eu/health/ph_programme/programme_en.htm

Health Programme 2008-2013. Available from: http://ec.europa.eu/health/ph_programme/pgm2008_2013_en.htm

French Ministry of Health and Social Protection. French National Plan for Rare Diseases 2005-2008. Ensuring equity in the access to diagnosis, treatment and provision of care. Available from: http://www.eurordis.org/IMG/pdf/EN_french_rare_disease_plan.pdf

Izquierdo Martínez M, Avellaneda Fernández A. Enfermedades raras: un enfoque práctico. Madrid: Instituto de Investigación de Enfermedades Raras (IIER), Instituto de Salud Carlos III (ISCIII). Ministerio de Sanidad y Consumo; 2004. Available from: http://iier.isciii.es/er/pdf/er_libro.pdf

Palau F. Enfermedades raras, un paradigma emergente en la medicina del siglo XXI. Med Clin [Barc] 2009 (doi: 10.1016/j.medcli.2009.06.038).

Position Paper by the Joint Commission: Ponencia de estudio encargada de analizar la especial situación de los pacientes con enfermedades raras y, especialmente, las medidas sanitarias, educativas y sociales que contribuyan a un adecuado tratamiento de los enfermos y de sus condiciones de vida, approved by the Joint Commission of the Health and Consumer Protection Commission and the Social Affairs and Labour Commission in its meeting on 18 December 2006. Boletín Oficial de las Cortes Generales. Senado, n.º 659 (23 February 2007). Available from: http://senaix15.senado.es/legis8/publicaciones/html/maestro/index_I0659.html

Sánchez-Valverde F, García Fuentes M. Rare diseases: medicine's challenge in the XXI Century [in Spanish]. An Sist Sanit Navar. 2008; 31(16 Supl 2): 5-8. Available from: http://www.cfnavarra.es/salud/anales/textos/Vol31/sup2/PDF/00c_Presentacion%20suplemento%2031.2_baja.pdf

Spanish Ministry of Health and Consumer Affairs. Estrategia en Cáncer del Sistema Nacional de Salud. Madrid: Agencia de Calidad del SNS. Ministerio de Sanidad y Consumo; 2006. Available from: http://www.msc.es/organizacion/sns/planCalidadSNS/pdf/excelencia/cancer-cardiopatia/CANCER/opsc_est1.pdf.pdf

Velasco Arias S. Recomendaciones para la práctica del enfoque de género en programas de salud. Madrid: Observatorio de Salud de la Mujer (OSM). Ministerio de Sanidad y Consumo; 2008. Available from:
http://www.msc.es/organizacion/sns/planCalidadSNS/pdf/equidad/recomendVelasco2008.pdf

Information about RD and available resources. Health registers

Botella Rocamora P, Zurriaga Lloréns O, Posada de la Paz M, Martínez Beneito MA, Bel Prieto E, Robustillo Rodela A et al (REpIER). National-Provincial Atlas of Rare Diseases 1999-2003. REpIER editores; 2006. Available from:
http://ec.europa.eu/health/ph_threats/non_com/Atlas_Nacional_Provincial_ER_LD2_prot.pdf

Commission of the European Communities. Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Rare Diseases: Europe's challenges. Brussels: Commission of the European Communities; 2008. {SEC(2008)2713}{SEC(2008)2712}. Available from:
http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf

EU working group on rare diseases, the Rare Disease Task Force (RDTF). Available from: http://www.rdtf.org/testor/cgi-bin/OTmain.php

Orphanet. Prevalence of rare diseases: bibliographic data. Listed in alphabetical order of diseases. Orphanet Report Series. Rare Diseases collection. Orphanet; 2008. Available from:
http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases.pdf

Posada M, Martín-Arribas C, Ramírez A, Villaverde A, Abaitua I. Rare diseases. Concept, epidemiology and state of the question in Spain [in Spanish]. An Sist Sanit Navar. 2008; 31(16 Supl 2): 9-20. Available from:
http://www.cfnavarra.es/salud/anales/textos/Vol31/sup2/PDF/01_Enfermedades%20raras%20concepto_baja.pdf

Serrano Aguilar P, Perestelo Pérez L, García Blasco MJ, Ramalle Gómara E, Pérez Ramos J. Registros y bases de datos existentes en España sobre las enfermedades raras (n.º exp. 05/90228). Funded by Fondo de Investigaciones Sanitarias (FIS), Evaluación de Tecnologías Sanitarias (AETS), Instituto de Salud Carlos III (ISCIII).

Zurriaga Lloréns O, Botella Rocamora P. Distribución de las enfermedades raras en España. JANO Med Humanid. 2008; (1679): 25.

Zurriaga Lloréns O, Martínez García C, Arizo Luque V, Sánchez Pérez MJ, Ramos Aceitero JM, García Blasco MJ et al. Disease Registries in the Epidemiological Researching of Rare Diseases in Spain [in Spanish]. Rev Esp Salud Pública. 2006; 80(3):249-257. Available from:
http://scielo.isciii.es/pdf/resp/v80n3/06original.pdf

Classification and coding

European Commission. Health and Consumer Protection Directorate-General. Public Consultation. Rare Diseases: Europe's challenges. Luxembourg: European Commission; 2008. L-2920. Available from: http://ec.europa.eu/health/ph_threats/non_com/docs/raredis_comm_draft.pdf

Pavillon G, Boileau J, Renaud G, Lefèvre H, Jougal E. Bridge coding studies ICD9-ICD10 and effects on French mortality dada. In: WHO Family of International Classifications Network Meeting.

Reykjavik, Iceland: WHOFIC/04.080; 24-30 October, 2004. [accessed 13 April 2009]. Available from: http://www.nordclass.uu.se/WHOFIC/reykjavik.htm#Report

Rare Diseases Task Force (RDTF). Minutes of the First Meeting of de RDTF. Coding and Classification Working Group. Luxembourg; RDTF; 11 October 2006.

Rare Diseases Task Force (RDTF). Minutes of the Third Meeting of de RDTF. Luxembourg; RDTF; 20 June 2005.

Regional Government of Andalusia. Plan de atención a personas afectadas por Enfermedades Raras 2008-2012. Junta de Andalucía, Consejería de Salud: 2007. Available from: http://www.juntadeandalucia.es/servicioandaluzdesalud/contenidos/gestioncalidad/PlanAndaluzEnfermedadesRaras2088-2012.pdf

Schieppati A, Henter JI, Daina E, Aperia A. Why rare disease are an important medical and social issue [in Spanish]. Lancet. 2008; 371(9629): 2039-2041.

Spanish Ministry of Health and Consumer Affairs. Las Enfermedades Raras en España. Análisis Descriptivo de la Situación. Report by the Technical Drafting Committee of the Spanish NHS RD Strategy. Dirección General de la Agencia de Calidad del SNS. Ministerio de Sanidad y Consumo: 2008.

World Health Organization. International Statistical Classification of Diseases and Related Health Problems. 10th Revision (ICD-10). Washington, D.C.: WHO; 2007. Available from: http://www.who.int/classifications/apps/icd/icd10online/

World Health Organization (WHO). International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) 5th Edition. WHO; 2006.

WHO. International Classification of Functioning, Disability and Health: ICF. 3rd Edition. WHO-Ministerio de Trabajo y Asuntos Sociales; 2001.

Primary prevention and early detection

Alexander D, van Dyck PC. A vision of the future of newborn screening. Pediatrics 2006;117:5350-5354.

American College of Medical Genetics Newborn Screening Expert Group. Newborn screening: toward a uniform screening panel and system-executive summary. Pediatrics. 2006 May;117(5 Pt 2): S296-307.

Artuch R, Moreno J, Puig RM, Quintana M, Montero R, Ormazábal A et al. Laboratory diagnosis of rare diseases [in Spanish]. An Sist Sanit Navar. 2008; 31(16 Supl 2): 91-103. Available from: http://www.cfnavarra.es/salud/anales/textos/Vol31/sup2/PDF/06_El%20laboratorio%20en%20el%20diagnostico_baja.pdf

Asociación Española de Cribado Neonatal (AECNE). Datos acumulados de Programas de Cribado Neonatal en España. Actualizados Diciembre 2007. In: XIV Reunión de los centros de Cribado neonatal. Real Patronato sobre Discapacidad (RPD). 14 October 2008. Madrid: AECNE; 2008. Available from: http://aecne.es/pdf/datos2007.pdf

Bennett MJ. Follow up testing for metabolic diseases identified by expanded newborn screening using tandem mass spectrometry. National Academy of Clinical Biochemistry and Laboratory Medicine Practice; 2009. Available from: http://www.aacc.org/members/nacb/Pages/default.aspx

Bodamer OA, Hoffmann GF, Lindner M. Expanded newborn screening in Europe 2007. J Inherit Metab Dis. 2007 Aug;30(4):439-444.

Cocho de Juan JA, Castiñeiras Ramos DE, Fraga Bermúdez JM. Cribado neonatal de los errores congénitos del metabolismo. In: Sanjurjo P, Baldellou A (editors). Diagnóstico y tratamiento de las enfermedades metabólicas hereditarias. 2ed. Madrid: Ergón; 2006. p. 47-61.

Comité de Estándares de la Sociedad Española de Neonatología. Recomendaciones de mínimos para la asistencia al recién nacido sano. An Esp Pediatr. 2001: 55 (2): 141-145. Available from: http://www.se-neonatal.es/upload/files/Minimos%20RN%20sano.pdf

Corveleyn A, Morris MA, Dequeker E, Sermon K, Lawford Davies J, Antiñolo G et al. Provision and quality assurance of preimplantation genetic diagnosis in Europe. Eur J Hum Genet. 2008;16: 290-299.

Dowling M, Pollitt R. Newborn bloodspot screening in the UK-past present and future. Ann Clin Biochem. 2008 Jan;45(Pt1):11-17.

Dulín-Iñiguez E, Espada M, Eguileor-Gurtubai I. Programas de cribado neonatal. An Pediatr Contin. 2006;4(1):61-65. Available from: http://www.neonatos.org/DOCUMENTOS/Cribado_neonatal.pdf

European Commission. Joint Research Centre and the Institute for Prospective Technological Studies (JRC-IPTS). Genetic Testing Services for Hereditary Diseases in Spain: Results from a Survey. Seville: European Commission JRC-IPTS; 2002. Report EUR 20516EN. Available from: http://www.juntadeandalucia.es/salud/orgdep/AETSA/pdf/Tests_Geneticos_ES_IPTS.pdf

European Commission. Joint Research Centre and the Institute for Prospective Technological Studies (JRC-IPTS). Preimplantation Genetic Diagnosis in Europe. Seville: European Commission JRC-IPTS; 2007. Report EUR 22764EN. Available from: http://ftp.jrc.es/EURdoc/eur22764en.pdf

González-Lamuño D, García Fuentes M. Genetically based diseases [in Spanish]. An Sist Sanit Navar. 2008; 31(16 Supl 2): 105-126. Available from: http://www.cfnavarra.es/salud/anales/textos/Vol31/sup2/PDF/07_Enfermedades%20de%20base%20genetica.pdf

González-Lamuño D, García Fuentes M. Rare diseases in paediatrics [in Spanish]. An Sist Sanit Navar. 2008; 31(16 Supl 2): 21-29. Available from: http://www.cfnavarra.es/salud/anales/textos/Vol31/sup2/PDF/02_Enfermedades%20raras%20pediatria_baja.pdf

Ibarreta D, Bock AK, Klein C, Rodriguez-Cerezo E. Towards Quality Assurance and Harmonisation of Genetic Testing Services in the EU (synthesis report). JRC-IPTS and JRC-IRMM. European Communities; 2003. Report EUR 20977EN. Available from: http://www.iss.it/binary/tege/cont/ESTO_eur20977en.1151682475.pdf

Lorda-Sánchez I, Ramos C, Ayuso C. Consulta Genética y Diagnóstico Genético Prenatal. Pediatr Integral (Madrid). 2006; X(8): 559-568.

Pollitt RJ. International perspectives on newborn screening. J Inherit Metab Dis. 2006; 29:390-396.

Red de Investigación Epidemiológica en Enfermedades Raras (REpIER) y Grupo de Trabajo de la Sociedad Española de Química Clínica. Desigualdades de la oferta de servicios de cribado neonatal en España e implantación de nuevas tecnologías [monograph on Internet]. Instituto de Investigación de Enfermedades Raras (IIER), Instituto de Salud Carlos III (ISCIII); [accessed 14 April 2009]. Available from: http://iier.isciii.es/repier/prv/pdf/r_abs3.pdf

Spanish Ministry of Health and Consumer Affairs. Informe sobre la situación de los programas de cribado neonatal en España. Propuestas de actuación. Madrid: Ministerio de Sanidad y Consumo; October 2006.

Healthcare

Asociación Española de Aniridia (AEA). El Síndrome de Wagr - Guía de familias. Madrid: IMSERSO; 2002.

Asociación Española de Esclerodermia (AEE)/FEDER, Instituto de Salud Carlos III (ISCIII), Esclerodermia - Guía de familias. Madrid: IMSERSO; 2004.

Associació Catalana de las Neurofibromatosis. La Neurofibromatosis - Guía de familias. Madrid: IMSERSO; 2004.

Cánovas Sánchez F, Pardavilla Martínez B. La gestión de la calidad en los Servicios Sociales. Madrid: IMSERSO; 2004.

European Organisation for Rare Diseases (EURORDIS). Position Paper on Centres of Expertise and European Reference Networks for Rare Diseases [monograph on Internet]. Eurordis; 2008 [accessed 14 April 2009]. Available from:
http://www.eurordis.org/IMG/pdf/position-paper-EURORDIS-centres-excellence-networksFeb08.pdf

European Organisation for Rare Diseases (EURORDIS). Position Paper on Specialised Services for people living with Rare Diseases [monograph on Internet]. Eurordis; 2008 [accessed 14 April 2009]. Available from:
http://www.eurordis.org/IMG/pdf/position-paper-EURORDIS-specialised-servicesFeb08.pdf

Fernández Fernández S, Iglesias García MT, Martís Flórez JR. Transición escuela-empleo de las personas con discapacidad. Madrid: IMSERSO; 2004. Available from:
http://www.doredin.mec.es/documentos/01720070000003.pdf

García-Ribes M, Gaite L. El médico de familia ante las enfermedades raras: un nuevo desafío para la coordinación asistencial. Aten Primaria. 2005;36:243.

IMSERSO. I Plan Nacional de Accesibilidad 2004-2012. IMSERSO; 2004.

Instituto de Migraciones y Servicios Sociales (IMSERSO). Plan de acción para las personas con discapacidad (2003-2007). 3.ª ed. Madrid: IMSERSO; 2001

Instituto Nacional de Estadística (INE), Instituto de Migraciones y Servicios Sociales (IMSERSO), Fundación ONCE. Encuesta sobre Discapacidades, Deficiencias y Estado de Salud (EDDS). INE 2001 [accessed 14 April 2009]. Available from:
http://www.ine.es/prodyser/pubweb/disc_inf05/discapa_inf.htm

Luengo Gómez S, Aranda Jaquotot MT, de la Fuente Sánchez M. Enfermedades raras: situación y demandas sociosanitarias. 1.ª ed CUANTER, Investigación Social y de Mercado; 2001.

Royal Decree 1302/2006, of 10 November, establishing the conditions regarding the procedure for the designation and accreditation of the Reference Centres, Services and Units (CSUR) of the Spanish NHS. Boletín Oficial del Estado, n.º 270, (11 November 2006).

Spanish Law 13/1982, of 7 April, on the Social Integration of Disabled Persons (LISMI). Boletín Oficial del Estado, n.º 103 (30 April 1982).

Spanish Law 51/2003, of 2 December, on Equal Opportunities, Non-discrimination and Universal Accessibility for Disabled People (LIONDAU). Boletín Oficial del Estado, n.º 289 (3 December 2003).

Spanish Law 39/2006, of 14 December, on the Promotion of Personal Autonomy and Care for Dependent Persons. Boletín Oficial del Estado, n.º 299, (15 December 2006).

Spanish Ministry for Labour and Social Affairs. Libro Blanco de Atención a las personas en situación de dependencia. Ministerio de Trabajo y Asuntos Sociales; 2004. Available from: http://www.imsersomayores.csic.es/documentos/documentos/libroblancodependencia/mtas-libroblancodependencia-01.pdf

Spanish Ministry of Health and Consumer Affairs. Bases para un modelo de atención socio-sanitaria. Bases para un modelo de atención socio-sanitaria. Pleno del CISNS; 2001.

Spanish Ministry of Labour and Immigration. Estrategia Global de acción para el empleo de personas con discapacidad 2008-2012. Ministerio de Trabajo e Inmigración; 2008. Available from: http://sid.usal.es/idocs/F8/FDO20699/estrategia_empleo.pdf

Therapies

Bel Prieto E, Bonet Clos, Posada de la Paz M. Rare diseases and orphan drugs in Spain. Rare Diseases Therapeutic Research Group (GITER) in the REpIER (Epidemiological Network on Rare Diseases Research) [in Spanish]. Cienc Tecnol Pharm 2005; 15(1): 33-42.

Consejo General de Colegios Farmacéuticos. Nuevos Medicamentos en España 2007. Panor Actual Medicam. 2008;32(310):3-7.

European Medicines Agency (EMEA). Points to consider on the calculations and reporting of prevalence of a condition for orphan designation. London: 2002. COMP/ 436/01. Available from: http://www.emea.eu.int/pdfs/human/comp/043601.pdf

European Organisation for Rare Diseases (EURORDIS). Eurordis contribution to the consultation on the future of the EU single market in pharmaceuticals for human use [monograph on Internet]. Eurordis; 2007 [accessed 14 April 2009]. Available from: http://www.eurordis.org/IMG/pdf/contribution-single-market-pharma-oct07.pdf

European Organisation for Rare Diseases (EURORDIS). EURORDIS survey of orphan drugs: Availability and pricing in EU Member States. October 2002-January 2003. Available from: http://www.eurordis.org/IMG/pdf/omp_availability_europe02-03__20report.pdf

European Organisation for Rare Diseases (EURORDIS). Position Paper on the Centralised procedure for the scientific assessment of the Therapeutic Added Value of Orphan Drugs [monograph on Internet]. Eurordis; 2008 [accessed 14 April 2009]. Available from: http://www.eurordis.org/IMG/pdf/position-paper-EURORDIS-therapeutic-added-value-ODFeb08.pdf

Federación Española de Enfermedades Raras (FEDER). Informe sobre las desigualdades en políticas para Enfermedades Raras (ER) en España. FEDER; 2007. Available from: http://www.correofarmaceutico.com/documentos/291007informedesigualdadespolesp.pdf

Health Department. Plan Director Sociosanitario de Cataluña. Barcelona: Generalitat de Catalunya, Departament de Salut; 2008. Available from: http://www.gencat.cat/salut/depsalut/pdf/sociosan2008.pdf

Legislación Vigente de Medicamentos Huérfanos [website]. Universidad Autónoma de Barcelona (UAB). Instituto de Salud Carlos III (ISCIII). European project: Network of Public Health Institutions on Rare Diseases (NEPHIRD). [accessed 14 April 2009]. Available from: http://www.ub.es/legmh/erigener.htm

Red Epidemiológica de Investigación en Enfermedades Raras (REpIER). Dirección General de Salud Pública y Servicios de Epidemiología y Salud Laboral. Enfermedades Raras en Andalucía. 2.ª Ed. Seville: Consejería de Salud de la Junta de Andalucía; 2006. Available from: http://www.juntadeandalucia.es/salud/contenidos/profesionales/vigilanciaepi/docu_az/er/Archivos/libro_enfermed_raras.pdf

Regional Government of Andalusia. Plan de atención a personas afectadas por Enfermedades Raras 2008-2012. Seville: Junta de Andalucía, Consejería de Salud; 2007. Available from: http://www.juntadeandalucia.es/servicioandaluzdesalud/contenidos/gestioncalidad/PlanAndaluzEnfermedadesRaras2088-2012.pdf

Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. Available from: http://eur-lex.europa.eu/LexUriServ/site/en/oj/2000/l_018/l_01820000122en00010005.pdf

Royal Decree 1030/2006, of 15 September, establishing the portfolio of common services of the Spanish NHS and the procedure for its upkeep. Boletín Oficial del Estado, n.º 222, (16 September 2006).

Royal Decree 1301/2006, of 10 November, establishes the quality and safety regulations for the donation, procurement, evaluation, processing, preservation, storage and distribution of human cells and tissues and approves the coordination and operation regulations for their use in humans. Boletín Oficial del Estado, n.º 270, (11 November 2006).

Spanish Law 16/2003 on Cohesion and Quality in the Spanish NHS. Boletín Oficial del Estado, nº 128, (29 May 2003).

Spanish Ministry of Health and Consumer Affairs. Novedades en la Agencia de Medicamentos y Productos Sanitarios (AEMPS). Noticias y temas de interés del Sistema Nacional de Salud. 2007: 31(1);33. Available from: http://www.msc.es/biblioPublic/publicaciones/docs/vol31_1ProgramasAyudaInvClinicaInd.pdf

The European Association for Bioindustries (EuropaBio). Biotech Fact Sheet: Human Cell and Tissue Based Products. Biotech and Healthcare. Brussels: EuropaBio; 2003. Available from: http://www.europabio.org/documents/tissues-cells.pdf

Integrated health and social care

Aldamiz-Echevarría L, Prieto JA, Couce ML, González Lamuño D. On-line resources in dealing with rare diseases [in Spanish]. An Sist Sanit Navar. 2007;30(2)145-152. Available from: http://www.cfnavarra.es/salud/anales/textos/Vol31/sup2/PDF/09_Recursos%20on%20line%20en%20el%20manejo_baja.pdf

Avellaneda A, Izquierdo M, Torrent-Farnell J, Ramón JR. Rare Diseases: chronic diseases that need a new approach [in Spanish]. An Sist Sanit Navar. 2007;30(2)177-190. Available from: http://scielo.isciii.es/pdf/asisna/v30n2/colaboracion.pdf

Del Barrio JA, Castro A. Infrastructure and resources of social, educational and health support in rare diseases [in Spanish]. An Sist Sanit Navar. 2007;30(2)153-163. Available from: http://www.cfnavarra.es/salud/anales/textos/Vol31/sup2/PDF/10_Infraestructura%20y%20recursos_baja.pdf

European Organisation for Rare Diseases (EURORDIS). The voice of 12,000 patients. Experiences and Expectations of Rare Disease Patients on Diagnosis and Care in Europe. A report based on the EurordisCare2 and EurordisCare3 Surveys. France: Eurordis; 2009. Available from: http://www.eurordis.org/IMG/pdf/voice_12000_patients/EURORDISCARE_FULLBOOKr.pdf

Luengo S, Aranda MT, de la Fuente M. Enfermedades Raras: Situación y demandas sociosanitarias. Ministerio de Trabajo y Asuntos Sociales. Colección estudios e informes. 2001. Serie estudios n.º 5.

Servicio de Pediatría Hospital Universitario «Marqués de Valdecilla». Universidad de Cantabria. Necesidades de los pacientes pediátricos con enfermedades raras y de sus familias en Cantabria. Documentos 69/2005. Real Patronato sobre Discapacidad. Ministerio de Trabajo y Asuntos Sociales. 2005.

Training and Research

Avellaneda A, Izquierdo M, Luengo S, Arenas J, Ramón JR. Necesidades de formación en enfermedades raras para atención primaria. Aten Primaria. 2006; 38: 345-348.

Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER) http://www.ciberer.es

European Commission. Health and Consumer Protection Directorate-General. Public Consultation. Rare Diseases: Europe's challenges. Luxembourg: European Commission; 2008. L-2920. Available from: http://ec.europa.eu/health/ph_threats/non_com/docs/raredis_comm_draft.pdf

European Conference on Rare Diseases (ECRD). Report by the ECRD. Luxembourg, 21 and 22 June 2005. Available from: http://www.eurordis.org/IMG/pdf/EN-ECRDtotal-2.pdf

European Organisation for Rare Diseases (EURORDIS). Position Paper on Research Priorities for Rare Diseases [monograph on Internet]. Eurordis; 2008 [accessed 14 April 2009]. Available from: http://www.eurordis.org/IMG/pdf/position-paper-EURORDIS-research-prioritiesFeb08.pdf

Farmaindustria. Enfermedades raras: raras: la cara más social de la investigación traslacional. Redes Investig Medicam. 2007;(9):19-59. Available from: http://www.medicamentos-innovadores.org/documentos/redes/redes_9.pdf

Instituto de Salud Carlos III (ISCIII). Fundación para la Cooperación y Salud Internacional (FCSAI). FCSAI Reports 2005, 2006 and 2007. Ministerio de Sanidad y Consumo.

Spanish Order SCO/3158/2003, of 7 November, establishing the Rare Diseases Research Institute (IIER). Boletín Oficial del Estado, n.º 273 (8 November 2003).

Websites of interest

Clasification and information systems:

- Epidemiological Network on Rare Diseases Research (REpIER). A thematic network for collaborative research. http://repier.retics.net/repier/home.aspx
- Orphanet. European database with updated information on rare diseases, orphan drugs and patient organisations. http://www.orpha.net/consor/cgi-bin/index.php
- Rare Diseases Research Institute (IIER), with information, documents and news about rare diseases. Spanish-language Rare Diseases Information System (SIERE). http://iier.isciii.es/er

Orphan medicinal products:

- European agency for the evaluation of medicinal products. Information about the procedures for the designation and registration of EU orphan medicinal products. http://www.emea.europa.eu
- Information on the regulations governing orphan medicinal products. The University of Barcelona (UAB) and ISCIII compile and discuss regulations concerning orphan medicinal products, aimed at staff working in R&D and in the pharmaceutical industry, health workers, patients and carers. http://www.ub.es/legmh
- NORD. Orphan drugs. http://www.rarediseases.org/search/noddsearch.html
- Orpha.net. Orphan drugs marketed in Europe. http://www.orpha.net/docs/List_of_orphan_drugs_Europe.pdf
- Spanish Medicines Agency (AEMPS). http://www.agemed.es

Patient organisations:

- European Organisation for Rare Diseases (EURORDIS). http://www.eurordis.org
- National Organization for Rare Disorders (NORD). Federation of associations for people affected by RD in the United States. http://www.rarediseases.org
- Spanish Federation for Rare Diseases (FEDER). http://www.enfermedades-raras.org/es/default.htm

Institutional websites:

- Centre for Biomedical Research on Rare Diseases (CIBERER), Carlos III Health Institute (ISCIII) http://www.ciberer.es
- European agency for the evaluation of medicinal products (EMES). Committee for Orphan Medicinal Products. http://www.emea.eu.int/htms/general/contacts/COMP.html
- European Commission. Directorate General for Health & Consumers (DG SANCO). http://ec.europa.eu/health/ph_threats/non_com/rare_3_en.htm
- IMSERSO. Spanish Ministry of Education, Social Policy and Sport, http://www.seg-social.es/imserso/centros/1_centros.html
- Rare Diseases Research Institute (IIER). Carlos III Health Institute (ISCIII). http://www.isciii.es/htdocs/centros/enfermedadesraras/enfermedadesraras_presentacion.jsp
- Royal Board on Disability (RPD). http://www.rpd.es/
- Spanish Disability Information Service (SID). Spanish Ministry of Education, Social Policy and Sport. http://sid.usal.es/
- Spanish Medicines Agency (AEMPS). http://www.agemed.es/
- Spanish Ministry of Health and Social Policy. http://www.msps.es

4.2. Index of abbreviations and acronyms

AC: Autonomous Communities/Regional Communities.
AES: Strategic Action for Health Research.
AETS: Health Technology Evaluation Agency.
AECNE (Asociación Española de Cribado Neonatal): Spanish Association for Neonatal Screening.
AECOM (Asociación Española de Errores Congénitos del Metabolismo): Spanish Association for the Study of Inborn Errors of Metabolism.
AEGH (Asociación Española de Genética Humana): Spanish Association of Human Genetics.
AEP (Asociación Española de Pediatría): Spanish Association of Paediatrics.
AEPap (Asociación Española de Pediatría de Atención Primaria): Spanish Association of Primary Care Paediatrics.
AT: Advanced Therapies.
ATU: Temporary Authorisation for Use.
ATV: Added Therapeutic Value.
BNLC: National Bank of Cell Lines.
CAIBER: Associated Consortiums for Biomedical Research Networks.
CAT: Committee for Advanced Therapies.
CAPV.: Autonomous Community of the Basque Country.
CEAPAT: Spanish National Centre for personal Autonomy and Technical Aids.
CEAS (Centros de Acción Social): Social Action Centres.
CERMI (Comité Español de Representantes de Minusválidos): Spanish Committee of Representatives of Disabled People.
CIAC (Centro de Investigación sobre Anomalías Congénitas): Research Centre on Congenital Anomalies.
CIBER: Centre for Biomedical Network Research.
CIBERER: Centre for Biomedical Network Research on Rare Diseases.
CISAT: Toxic Oil Syndrome Research Centre.
CISATER: Toxic Oil Syndrome and Rare Diseases Research Centre.
CISNS: Interterritorial Council of the Spanish National Health System.
COMP: Committee for Orphan Medicinal Products.
CRE: State Reference Centre for Rare Diseases Patients and their Families.
CSIC (Centro Superior de Investigaciones Científicas): Spanish Council for Scientific Research.
CSUR: Reference Centres. Services and Units.
DG-SANCO: Directorate General for Health and Consumer Protection.
EAP (Equipos de Atención Primaria): Primary Care teams.
EBM: Evidence-Based Medicine.
EC: European Community.
ECB (Equipos de Coordinación de Base): Base Coordination teams.
ECEMC (Estudio Colaborativo Español de Malformaciones Congénitas): Spanish Collaborative Study of Congenital Malformations.
EDDS (Encuesta sobre Discapacidades, Deficiencia y Estado de Salud): Survey on disabilities, deficiencies and state of health.
EPO: European Project Office.
EMEA: European Medicines Agency.
ENCYT (Estrategia Nacional de Ciencia y Tecnología): National Strategy for Science and Technology.
ENERCA: European Network for Rare and Congenital Anaemias.
ESM (Equipos de Salud Mental): Mental Health teams.
EU: European Union.
FAECAP (Federación de Asociaciones de Enfermería Comunitaria y AP): Federation of Community Nursing and Primary Care Associations.
FDA: U.S.A. Food and Drug Administration.

FEDER: Spanish Federation for Rare Diseases.
FIS: Health Research Fund.
FP: Framework Programme.
GDP: Gross Domestic Product.
GITER (Grupo de Investigación Terapéutica sobre Enfermedades Raras): Rare Diseases Therapeutic Research Group.
IC: Institutional Committee of the Strategy.
ICD: International Classification of Diseases.
ICF: International Classification of Functioning. Disability and Health.
IIER: Rare Diseases Research Institute.
IMSERSO (Instituto de Migraciones y Servicios Sociales): Institute of Migration and Social Services.
INERGEN: Research Institute for Genetic Rare Diseases.
IPTS: Institute for Prospective Technological Studies.
ISCIII: Carlos III Health Institute.
LIONDAU: Spanish Law on Equal Opportunities. Non-discrimination and Universal Accessibility for Disabled People.
LISMI: Spanish Law on the Social Integration of Disabled Persons.
MBDS: Minimum Basic Data Set.
MD: Metabolic Diseases.
MEC: Monitoring and Evaluation Committee of the strategy.
MO: Ministerial Order.
MSC: Spanish Ministry of Health and Consumer Affairs.
MSPS: Spanish Ministry of Health and Social Policy.
NB: Newborn.
NGO: Non-Governmental Organisation.
NHS: National Health System.
NSP: Newborn Screening Programmes.
OD: Orphan drugs.
OMP: Orphan medicinal products.
ONCE (Organización Nacional de Ciegos): Spanish National Organisation for the Blind.
OTM (Otros trastornos del metabolismo): Other metabolic disorders.
OTRI (Oficina de Transferencia de Resultados de Investigación): Research Results Transfer Office.
PC: Primary Care.
PCN (Programas de Cribado Neonatal): Newborn Screening Programmes.
PD: Prenatal Diagnosis.
PDSS (Plan Director Sociosanitario): master plan for integrated health and social care.
PGD: Preimplantation Genetic Diagnosis.
PH: Public Health.
PIER: Extremadura's comprehensive rare diseases plan for the period 2009-2014.
PIDEX: Extremadura's comprehensive integrated health and social care plan for cognitive deterioration.
PRO: Public Research Organisation.
RD: rare diseases.
RD: Royal Decree.
RDTF-WG: Rare Diseases Task Force-Working Group.
RECGEN: Network of Clinical and Molecular Genetics Centres.
REDEMETH: Network of Hereditary Metabolic Diseases.
REGPER (Registro de Pacientes de ER): Register of Patients with RD.
REpIER: Epidemiological Network on Rare Diseases Research.
RETICS: Thematic Networks for Collaborative Research in Health.
SAAD: System for Autonomy and Dependence Care.
SEGO (S.E. de Ginecología y Obstetricia): Spanish Society of Obstetrics and Gynaecology.

SEI (S.E. Inmunología): Spanish Society of Immunology.
SEMERGEN (S.E. Médicos de Atención Primaria): Spanish Society of Primary Care Physicians.
SEMFYC (S.E. Medicina Familiar y Comunitaria): Spanish Society of Family and Community Medicine.
SEMG (S.E. Medicina General): Spanish Society of General Medicine.
SEMI (S.E. Medicina Interna): Spanish Society of Internal Medicine.
SEN (S.E. Neurología): Spanish Neurological Society.
SEQC (S.E. de Bioquímica Clínica y Patología Molecular): Spanish Society of Clinical Biochemistry and Molecular Pathology.
SIERE: Spanish-language Rare Diseases Information System.
SID (Servicio de Información sobre Discapacidad): Spanish disability information service.
SITE (Servicio de Información Telefónica para la Embarazada): telephone information service for pregnant women.
SITTE (Servicio de Información Telefónica sobre Teratógenos en Español): Spanish-language teratology telephone information service.
SME: Small and Medium-Sized Enterprises.
SC: Secondary Care.
TC: Technical Committee of the Strategy.
TERCEL: Cell Therapy Network.
UCG (Unidades de Consejo Genético): Genetic Counselling Units.
UESCE (Unión Española de Sociedades Científicas de Enfermería): Spanish Union of Scientific Nursing Societies.
VIP: Voluntary Interruption of Pregnancy.
WHO: World Health Organization

GOBIERNO
DE ESPAÑA

MINISTERIO
DE SANIDAD
Y POLÍTICA SOCIAL