

# Rare Diseases in Europe: from a Wide to a Local Perspective

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**ABSTRACT:** The European Union defines rare diseases (RDs) as life-threatening or chronically debilitating conditions whose prevalence is less than 5 per 10,000. Moreover, for many RDs, including those of genetic origin, combined efforts are required to reduce morbidity or perinatal and early mortality, and address the considerable decline in an individual's quality of life and socioeconomic potential. Their specificities, i.e., a limited number of patients and scarcity of relevant knowledge and expertise, make RDs a unique condition which requires wide cooperation at a supranational level. Many steps were therefore taken to develop a network of European Reference Centers and to improve RDs coding and classification. In Italy, the RDs issue was addressed in 2001 with the development of a national network and a national registry coordinated by the National Center for RDs of the Italian National Institute of Health. Registries are an important resource for the development of appropriate public health policies and research on specific RDs. Research on RDs is essential for the development of novel therapeutic approaches and requires the involvement of scientific societies and patient organizations. Nevertheless, the management of patients with a chronic RD requires a qualified care network. The network for RDs of Piedmont and the Aosta Valley (northwest Italy) represents an example of health care organization based on the availability of advanced therapies close to the patient's home.

*IMAJ* 2016; 18: 359–363

**KEY WORDS:** rare diseases (RD), registries, European Reference Network (ERN), local health care network, scientific societies

**R**are diseases (RDs), including those of genetic origin, are defined by the European Union (EU) as life-threatening or chronically debilitating conditions whose prevalence is so low (less than 5 per 10,000) that special combined efforts are needed to prevent significant morbidity or perinatal and early mortality and address the considerable reduction in an individual's quality of life or socioeconomic potential. This definition first appeared in EU legislation on 16 December 1999 regarding orphan medicinal products (OMPs) [European Commission (EC) regulation # 141/2000]. The attention to rare diseases was later extended

to public health (European Commission Communication: “RDs: Europe's challenges” of 11 November 2008, and European Council Recommendation: “An action in the field of RDs” of 9 June 2009) [1]. Thousands of distinct RDs exist today: more than 8000 diseases or groups of diseases affecting between 6% and 8% of the European people are described in the Orphanet database. In other words, between 27 and 36 million persons in the European Union are affected by a rare disease [2].

The specificities of RDs, i.e., a limited number of patients and the scarcity of relevant knowledge and expertise, make RDs a unique condition that requires wide cooperation at the European level. There is probably no other area of health care where collaboration between 27 different national approaches is as efficient and effective. This coordination at the EU level involves the following steps:

- making RDs more visible by developing proper identification and coding since many RDs currently go unrecognized
- encouraging EU member states to develop national RD plans in their health policies to ensure equal access to prevention, diagnosis, treatment and rehabilitation
- providing European support and cooperation, such as ensuring that common policy guidelines are developed and shared throughout Europe in specific areas including research, centers of expertise, access to information, orphan medicines, and screening.

## RARE DISEASES CLASSIFICATION

The EU should cooperate closely with the World Health Organization (WHO) in revising the existing International Classification of Diseases (ICD) to ensure better codification and classification of RDs. All RDs should be adequately coded and traceable in all health information systems, thus contributing to their correct recognition in national health care and reimbursement systems. The WHO has established various Topic Advisory Groups (TAGs) to serve as planning and advisory bodies in the update and revision process for specific areas. A TAG for RDs was established in April 2007, so RDs should now be traceable in mortality and morbidity information systems. The collection of necessary information to develop a first draft of the classification of RDs has been assigned to Orphanet. Orphanet has developed a strictly clinical in-house classifica-

tion to meet the needs of clinicians, and serves as a basis for building the ICD-11 proposals of revision.

In the meantime, the European Commission supports the Orphanet approach to improving the quality and traceability of RDs in health information systems by using “Orphacodes” on a voluntary basis at a national level. The Orphacode refers to the Orphanet classification of diseases and is a stable and evidence-based nomenclature based on published expert classifications and peer-reviewed papers [3].

#### EUROPEAN REFERENCE NETWORKS (ERNS)

The 2011/24/EU directive on the application of patients’ rights in cross-border health care clarifies patients’ rights to access safe and good quality treatment across EU borders and to be reimbursed for it [4]. The directive will provide a firm basis for increased cooperation between national health authorities. Some provisions address the issue of RDs. Article 12 foresees enhanced cooperation among member states through the development of the European Reference Network (ERN). The same article also states that the EC must decide, through legal means, the criteria and conditions that the ERNs and the health care providers must fulfill [5]. The aim of the directive is not to create new centers, but to identify already established centers of expertise and encourage the voluntary participation of health care providers in the future ERNs. The model envisaged by the EC includes ERNs dedicated to specific group of RDs (e.g., immunological diseases, renal diseases, etc.). Each ERN will be formed by a core of major centers, with coordination functions, and by associated centers. These Centers would have to fulfill the criteria provided in the EC

Delegated Act and would serve as a hub between national health care providers and ERNs. National centers in the ERNs will be voluntary members, designated by national authorities according to national criteria, and committed to the general goals and rules of the network. These centers can be either associated or collaborative. Associated centers’ primary field of work is health care provision; they have expertise in the conditions/diseases of the ERN, and they provide and coordinate highly specialized health care as well as follow-up. Collaborative centers have expertise in knowledge dissemination, and their primary goal is to build and disseminate knowledge and competence.

#### REGISTRIES AS TOOLS TO STUDY RDS

One of the main obstacles to clinical research and the resultant treatment advancements in RDs is the difficulty in conducting clinical trials. Clinical trials on RDs have to deal not only with the geographic spread of patients but also with the high heterogeneity within the same disease. The approval process of orphan drugs by regulatory agencies may also have to address limitations inherent to small populations. Joppi et al. [6] observed that randomized clinical trials were conducted for only 38 of 63 orphan

drugs that received market authorization by the European Medical Agency (EMA) between 2000 and 2010. Placebos were used as comparators for nearly half the 63 licensed drugs. One-third of the OMPs were tested in trials involving fewer than 100 patients, and more than half in trials with 100–200 cases. The clinical trials lasted less than one year for 42.9% of the approved OMPs. These data confirm that studies on RDs are vulnerable to bias, and in some cases a trial of sufficient power to provide a definite answer is virtually impossible.

Therefore, the implementation of RD registries seems to be a promising approach to better understand the natural course of diseases, to distinguish which patient subgroups are at risk for poor outcome, and to identify new targets for treatment [7,8]. Patient-specific data are most often collected in the form of registries linked with biorepositories to achieve meaningful patient numbers and establish long-term outcome.

Several studies have demonstrated the usefulness of registries. Buscarini and co-authors [9] analyzed 16 years of surveillance data from an Italian tertiary hereditary hemorrhagic telangiectasia (HHT) referral center involving 502 individuals. The study showed that substantial morbidity and mortality are associated with liver vascular malformations and urged for more intensive clinical management and surveillance for patients in this subgroup [9].

The international registry of recurrent and familial hemolytic uremic syndrome (HUS), established in 1996, collected more than 800 cases of atypical HUS from Italian and other centers worldwide. Participant centers shared biological material and provided a huge amount of clinical data. Extensive biochemical and genetic screening was performed and showed that clinical phenotype, response to treatment, and long-term outcome with and without kidney transplantation are predicted by specific gene abnormalities [10]. With regard to Alport syndrome, data from the European registry indicated that early treatment with angiotensin-converting enzyme inhibitors prevents the onset and progression of chronic kidney disease [11].

Evidence showing that RD registries may be useful for predicting individual survival probabilities, directing therapy and designing ad hoc studies, is progressively increasing. Registries can be used as a source of historical controls and for assessing comparative effectiveness; however, it must be noted that purely observational findings may not be internally valid owing to the absence of randomization. The current priority is to gather relevant information about patients through the use of registries on selected RDs as a means to implement clinical research and treatment.

Moreover, registries adopting the so-called basket approach could be useful in the field of ultra-rare and undiagnosed diseases. The “basket approach” has been developed in oncology to both identify tumors with different histology but common

### The correct coding of RDs is essential to monitor and develop adequate support for health policy within a European framework

molecular markers [12], and predict their response to targeted therapies [13]. A similar approach could be adopted to seek a common molecular pathway within rare and undiagnosed diseases with different phenotypes. To allow this, we need to record phenotypic data of patients with the information provided by analysis of the genome and exome. The Undiagnosed Diseases Network International (UDNI) reflects precisely this goal [14].

**EUROPEAN SERVICE-ORIENTED PLATFORM FOR RD REGISTRIES**

For a better appraisal of the characteristics, expectations and how the funds that were assigned by the EC and other funders to RD registrations were used, the EC selected the EPIRARE project (European platform for RD registries) to implement a survey addressed to all the RD registries existing in Europe. A questionnaire on the activities and needs of existing RD registries was developed between June and October 2011 and implemented in 2012. Although some responses might suggest skepticism, the vast majority were in favor of an EU portal (73%), and especially of an EU platform (80%). There were fewer favorable opinions (61%) regarding the desirability of new EU legislation on the matter, and some doubt was expressed that new laws might even make registration more difficult and lengthy. Expectations regarding public funding to a central registry were positive for about 50% of respondents. The primary services expected from an EU platform by the registry holders seem to refer mainly to technological tools (IT and networking), specific expert advice (legal advice regarding personal data management, methodological advice for codification and classification, and ethical advice), and resources (model documents, quality control systems, access to useful data). The pattern of responses suggests that the registry holders expect the future EU platform to relieve them of the registry work that is not strictly related to the scientific interest but which is necessary for its success and requires particular competence, ongoing attention and resources. These are typical functions of a service-oriented platform.

Based on the above, the EC proposed a common platform that will enable improving and increasing integrated uses of RD registries. The goal of this future EU RD registration platform (EURDP) is to enable data analysis within and across many RDs and to facilitate clinical trials and other studies. The EURDP will serve RD patients and their advocacy groups seeking help and information. It will also help investigators conducting research, clinicians treating patients, epidemiologists analyzing disease data, and researchers seeking patients for new clinical trials and initiating natural history studies.

**THE ITALIAN MODEL FOR RDS SUPPORT**

Since 1998, RDs have been recognized as a health priority in each of the 3 year Italian national health plans, and in 2014 the Ministry

of Health formalized a national plan/strategy for RDs. In the meanwhile, ministerial decree (M.D.) n. 279/2001 [15] established (i) a national network of selected clinical centers for the prevention, surveillance, diagnosis and treatment of RDs; (ii) a National Registry for RDs (NRRD) managed by the National Institute of Health (Istituto Superiore di Sanità, ISS); and (iii) exemptions apart from the costs of medical care for patients affected by a number of RDs (Annex 1 M.D. n. 279/2001). There are two current shortcomings in the list of RDs included in the Annex: it does not include all RDs and groups of RDs, and it is not regularly updated. Since 2001, the Italian regional governments have established local networks, including centers for the diagnosis and treatment of RD patients, and regional coordinating centers.

**THE NATIONAL REGISTRY OF RARE DISEASES**

The NRRD is supported by public funds, meets the legal and ethical requirements, and is a population-based registry, although regional coverage is still heterogeneous. The general objectives of the NRRD are the planning and evaluation of health care programs (utilization of services, patient mobility) and the epidemiological surveillance of RDs.

The NRRD is structured into three levels. The local level comprises clinical centers identified for each region. Clinical centers collect data about patients and store them in the regional registries. Each regional registry may differ in its organization, objectives, and type of information collected; however, a shared common data set, including socio-demographic and disease data, is transmitted to the NRRD. In 2011, the National Center for Rare Diseases (NCRD), in collaboration with the regional registries, prepared a first report [16].

**The registries related to an individual RD, or which include different RDs, are essential for developing new therapeutic approaches and adequate health policies**

**THE NCRD: WHERE RESEARCH AND PUBLIC HEALTH TRANSLATE INTO ACTION**

The history of the NCRD dates back to the institution of the NRRD in 2001, which was the first nucleus of the Center. The NCRD was formally established within the National Institute of Health (Istituto Superiore di Sanità) in 2008. Its mission is to promote and develop experimental research and public health actions, as well as provide technical expertise and information on RDs and orphan drugs. It is also the national focal point for information and communication on patients suffering from one RD and for their families through collaboration with the national organizations of RD patients.

The NCRD employs a broad range of scientific and technical experts from various fields and maintains a network of national and international collaborations. The NCRD provides expert advice to many Italian, European and international institutions, such as the Italian Ministry of Health and the EC, and collaborates with the regions which are responsible for the provision of health services in the Italian health system.

In order to meet challenges posed by RDs, the NCRD has developed its institutional activities along six main pillars: (i) experimental research, (ii) public health, (iii) projects, (iv) information and communication, (v) training and empowerment, and (vi) networks and collaborations [17–20]. The NCRD has contributed to networks and scientific boards at the national and international level and has implemented many strategic projects on RDs, such as EUROPLAN [21], EPIRARE [22], and RARE-Best practices [23,24]. The NCRD has also implemented the international networking of registries by coordinating the EU-funded EPIRARE ([www.epirare.eu](http://www.epirare.eu)) and leading the Workpackage Registries of the EU-funded RD-Connect project, an integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research (<http://rd-connect.eu/>).

#### THE ROLE OF SCIENTIFIC SOCIETIES

Scientific societies could play a significant role in RD awareness through teaching and training, and should become more proactive in providing advice to policy makers. Published results about RDs are rarely conclusive, and there are significant areas of uncertainty and debate among involved parties. Expert groups, which include researchers, clinicians, patient support organizations and regulatory agencies working on a rare disease or disease groups, are urgently needed to deal with the rapidly advancing technologies and treatments. This is particularly challenging in cases where there is considerable doubt about the effectiveness and sustainability of treatments. For example, in April 2010, the UK Renal Association approved and published the UK Rare Renal Diseases Strategy and established rare diseases working groups to promote and integrate the development of evidence-based clinical care pathways, empowerment of patients with high quality information, advice to commissioners, audit of outcomes, and collaborative translational research for patient benefit [25]. In Italy, a meeting was held in June 2013 to build an alliance between the National Center for Rare Diseases, scientific societies and patient support organizations. Representatives of 16 Italian scientific societies contributed to the debate and emphasized the common issues, the value of a multidisciplinary approach, and the need for closer contact with institutional representatives and policy makers.

#### THE NORTH-WESTERN ITALY MODEL: THE BEST OF CARE CLOSE TO HOME

Piedmont is a northwestern region in Italy with a population of about 4,500,000. Turin, the central city, and the surrounding metropolitan area are home to about 1,700,000 people. The remaining population lives in smaller towns spread in a region characterized by the presence of numerous mountains

and hills. The Piedmont regional health system is characterized by the limited presence of third-level centers of expertise, mainly located in the Turin metropolitan area, and by an extensive network of small local health facilities. In 2004 the Piedmont region developed a regional network for RDs based on decentralization involving all health professionals operating in the regional public health system. In 2008 the network was expanded to the Aosta Valley, a small neighboring region with a population of 300,000 people [15]. The Piedmont and Aosta valley inter-regional network for RDs developed a model of health care assistance that guarantees the quality of diagnosis in centers with proven expertise and offers appropriate health care to patients as close as possible to home. Moreover, the involvement of virtually all hospitals within the two regions provides the opportunity for professional growth in the field of RDs. From June 2005 to December 2013 more than 20,000 patients affected by RDs were followed within the inter-regional network [15].

A widespread network requires both a coordinating center and a monitoring system to evaluate the appropriateness of diagnoses and therapy. The coordinating center was established in 2004, and since 2005 a regional technical board has supported it. Working groups operating in every public health facility guarantee the coordination of clinical activities for RDs throughout the two regions.

A broad network of hospital pharmacies, to date unique in Italy, ensures the supply of pharmaceutical products, including the ones that are not currently available nationwide, off-label agents, and galenic preparations that are essential to treat specific RDs [26].

Another feature of the network for RDs in Piedmont and the Aosta Valley is the presence of widespread multidisciplinary working groups (consortia). Consortia are dedicated to the most prevalent RDs, or to RDs characterized by specific issues such as the therapeutic cost or the lack of reliable data on the effectiveness and efficacy of treatment. Twenty-two consortia were active at the end of 2014. Clinicians, other health professionals, and representative of patients participate in the consortia, and their primary goal is to develop shared protocols and clinical pathways [27]. Moreover, they also identify, if needed, centers of expertise. A center of expertise must have proven diagnostic and therapeutic experience, as well as the availability of support structures and complementary services. The centers of expertise must help the local health authorities in the care of patients and provide specialized training to the local health professionals. To date, centers of expertise have been established for amyotrophic lateral sclerosis, syringomyelia, and Arnold-Chiari syndrome. Lastly, a significant activity of the consortia is the production of clinical and epidemiological studies on RDs [27-35].

#### The collaboration of scientific societies and patient organizations is needed to deal correctly with RDs



**CONCLUSIONS**

Due to their peculiarities – i.e., small samples of patients, chronicity (invariably), severity (often), and clinicians’ lack of experience – RDs represent a major challenge for health care organization. Cooperation of health care providers, patient associations and scientific societies is needed to correctly address this issue.

Several problems, for instance the evaluation of effectiveness of therapy (that cannot be submitted to conventional randomized controlled trials), can be properly addressed if an accurate estimation of the number of patients is achieved by recruiting cases in registries. A deep knowledge of the natural course of the disease can be achieved as well. Presently, registries represent the main source of information on rare diseases. The regional and national registries mainly collect epidemiologic data for planning public health programs, while disease registries are designed to study clinical presentation and natural history.

The effort to take charge of RD patients requires a national and supranational coordination. The European Community has developed several rules to provide a coherent framework for its members. One of the most relevant issues is the promotion of ERNs dedicated to homogeneous groups of diseases. The ERNs serve to share guidelines for disease diagnosis and treatment, and standardize the use of appropriate approaches to RDs in the entire EC throughout regional networks which favor their widespread distribution.

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