State of the Art for Rare Diseases – Activities in EU Member States and Other European Countries

Italy Report

Contents

Co-funded by the Health Programme of the European Union

Definition of a Rare Disease

Italy has adopted the European Commission definition of a rare disease as a disorder with a prevalence lower than 5 cases in 10,000 inhabitants (as stated in Regulation no. 141/2000/CE of the European Parliament and Council of 16 Dec. 1990 concerning Orphan Medicinal Products). The National Health Plan (NHP) 2013-2016 officially espouses this European Commission definition of a rare disease

However, in Italy there are further considerations involved in the 'definition' of a rare disease, relating to the national rare disease decree (Ministerial decree n.279/2001) which contains an official annex listing 546 rare diseases or groups of diseases. The list of rare diseases attached to this law determines which patients are entitled to benefits and access to care. The list contains 331 single diseases or groups of disorders divided into 14 nosological categories. Considering the diseases included in all the groups and the disease sub-types, nearly 3000 conditions are listed, although some diseases, or groups of diseases, are not currently included in the list (e.g rare cancers, which are recorded in the regional cancer registry). These conditions, which are the conditions monitored by the rare disease registry, represent 58% of all rare diseases included within the Orphanet database. The list of rare diseases is going to be updated and a new, more comprehensive, list is anticipated. The new list should provide representation for more groups of rare diseases (increasing from 45 to 111) in agreement with the logic of a new hierarchical multidimensional classification inspired by the Orphanet classification.

Status Quo of any National Plan or Strategy for Rare Diseases

Italy has adopted a National Plan for Rare Diseases with a time frame of three years, from 2013 to 2016.

Rare Disease Policies in Italy: the background to the National Rare Disease Plan

In Italy, national health plans are issued regularly. They define the priority areas and related actions for the Italian National Health system. As Italy has a decentralised health system, this general framework of national plans serves as a reference for the subsequent definition of detailed *Regional* health plans which identify specific actions to be undertaken at the regional level. Both national and regional health plans have a defined time frame.

From the National Health Plan (NHP) 1998 – 2000 onwards, rare diseases have been identified as a public health priority in Italy. All subsequent NHPs confirmed the attention dedicated to rare diseases and the need to promote integrated actions in this field. Three main actions have been identified:

- To guarantee to all citizens an accurate and early diagnosis
- To disseminate all available scientific knowledge

Co-funded by
the Health Programme
of the European Union

- To support basic and clinical research

The first regulation identifying *specific* measures for rare disease patients was the **Ministerial Decree no.279 issued in 2001:** "Regulation for the creation of a national network for rare diseases and for the exemption from the payment of related healthcare services". The key elements of this regulation -which is still in force – are as follows:

- An **official list of rare diseases** is defined: patients with conditions appearing on this list are entitled to receive special benefits;
- The provision of these benefits follows a diagnosis performed by officially labelled centres
- Regions are in charge of labelling rare disease centres through official acts and setting-up rare disease specific monitoring systems;
- The monitoring systems are implementing the national registry, based at the National Institute of Health (ISS).

An important element of this Regulation is the direct link between the possibility to benefit from an exemption from payment of services and the diagnosis made by a Centre which has been formally recognised as competent in taking care of persons affected by a specific disease or group of diseases. Furthermore, the Decree states that *diagnostic pathways* for patients with a clinical suspicion of one of the rare diseases included in the list annexed to the Decree will only be free of charge if diagnosis is carried out or validated by a rare disease centre of expertise. Thus, the Regulation prompted the creation of a national network for diagnosis and clinical care of rare diseases, which includes Centres officially labelled by Regions.

Specific agreements defining certain fields of application of this Ministerial Decree were issued in 2002 and 2007. They dealt with important issues such as the minimum set of data to be sent by regional registries to the national registry (see below), and also the criteria for the identification of national Centres for low prevalence diseases.

Elaboration, Implementation and Evaluation of the National Plan

A dedicated body existed to oversee the *drafting* of the National Plan – this body is best described as 'partially functioning' and does not include all relevant stakeholders. The drafting process was as follows: a first draft of the *National Plan for Rare Diseases 2013-2016* was drawn-up by a working group officially appointed by the Ministry of Health, composed of representatives of the Ministry of Health and several designated experts, namely Dr D. Taruscio, Professor B. Dallapiccola and Professor P. Facchin; this draft was then made public and a dedicated website platform was created by the Ministry in order to receive comments from patients and patient organisations; the National Plan for Rare Diseases 2013-2016 was further adopted through a formal agreement between the State and the Regions in October 2014 (rep. ATTI 140/2014).

However, this body was not tasked with the implementation or evaluation of the National Plan. In 2015, the Parliament, through the Social Affairs Commission, carried out a survey on the state of the art of care and research activities in the field of rare disease. All the relevant stakeholders were audited and a final document was issued and published on the Italian Parliament website. This document also included some proposals regarding, for example, the simplification of certain regulations governing patients' access to care.

Funding of the National Plan

There is no associated funding for the National Plan (i.e. no dedicated funding scheme was approved at the national level); however, actions outlined in the Plan fall into the essential levels of care financed by the National Health Fund.

In addition to these 'essential levels of care', the Italian Regions -with the exception of those who are restricted economically whilst undergoing a finance-monitoring plan- guarantee additional benefits to rare disease patients using their own financial resources. These benefits include the provision of services and treatments free of charge, following specific prescription and authorisation pathways. In such Regions, it may be estimated that half of what is provided free of charge to rare disease patients is covered by regional funds.

Co-funded by
the Health Programme
of the European Union

Coding of Rare Diseases in the National Health System

The National Rare Disease Plan 2013-2016 does address the important issue of coding rare diseases in the national health information system. Italian health information systems are mostly based on ICD classification. Identified actions in the Plan include the following:

- The harmonization and standardisation of disease coding processes
- The planning and experimental adoption (hopefully) of the Orphanet classification coding system in addition to ICD coding.

It is important to note that the Veneto region, in the north-eastern part of Italy, participates in the Joint Action for Rare Diseases, RD-ACTION, via Workpackage 5 which focuses on "Steering, promoting and maintaining the adoption of orphan-codes in MS".

Organisation of Rare Disease Health and Social Care (Centres of Expertise; ERNs; Integrated Care and Social Support)

Centres of Expertise

In Italy, an official policy for designating rare disease Centres of Expertise has been in place since 2001. Italy has both a national and a regional designation process. **The creation of a national network for the prevention, surveillance, diagnosis and therapy of rare diseases, based upon officially-recognised centres, is one of the cornerstones of Ministerial Decree 279/2001**. In the decentralised Italian healthcare system, Regions are in charge of selecting and officially labelling -through formal acts- the Centres of Expertise dedicated to a single rare disease or groups of rare diseases. So in essence, 'Centres for Rare Disease' are those officially designated by Regional health authorities, which together constitute the national rare disease care network. Since 2001, all Italian regions have progressively identified such centres. Interregional agreements have been established: one involving Piedmont and Valle D'Aosta Region; another between Veneto and the Autonomous Provinces of Trento and Bolzano.

The issue of 'criteria' for designation has evolved over time. According to Ministerial Decree 279/2001, Centres of Expertise must have:

- Documented experience in the diagnosis and treatment of a group of rare diseases
- Suitable supporting structures and complementary services;
- Additional resources (e.g. emergency services and genetic or biochemical diagnostic services, etc.)

The State and Regions Agreements, which followed the MD 279/2001 (and were issued in 2002 and 2007), further established the criteria for the designation of Centres of Expertise for rare diseases. In particular, the 2007 Agreement espoused the following criteria:

A. Documented experience in diagnosis, clinical practice and care;
B. Documented structural and functional facilities;
C. Regional or interregional official labelling process supported by the issuing of formal acts;
D. Adoption of protocols and/or elaboration of healthcare pathways defining the contents of care pathways and organisational procedures for the management of rare disease patients (ensuring a multi-

Co-funded by
the Health Programme
of the European Union

disciplinary approach and integration with territorial services, general practitioners, and paediatricians in order to facilitate care near the patients' place of residence, while also maintaining contact with CEs through telemedicine activities).

Subsequent to these activities, Ministerial Decree of 15.04.2008 identified *national* Centres of Expertise for a group of ultra-rare diseases. With the adoption of the National Plan for Rare Diseases 2013-2016, the situation has evolved further. The Plan explicitly refers to the EUCERD criteria in connection with CE designation (and also considered the outputs of an important project involving all national stakeholders, which focussed on defining CE characteristics: "A Community for RD", coordinated by UNIAMO FIMR onlus).

The RD National Plan 2013-2016 **expanded the definition of Ministerial Decree no.279/2001**, stating that: "the national RD network is made by all the regional structures and services, aggregated in Centres, officially labelled to provide care for RD patients, each one with its specific function and competence; they are all in charge of contributing to carry out prevention and surveillance actions, improving diagnosis and access to treatments, promoting information and education activities focussed on Rare Diseases."

The RD National Plan 2013-2016 established national criteria to designate a centre of expertise for rare disease, in agreement with the EUCERD criteria:

- Appropriate capacity to manage rare disease patients for diagnosis, follow-up and care;
- Significant annual volume activity, in consideration of specific RD prevalence;
- Capacity to provide expert advice, to adhere to good practice guidelines and to manage quality controls;
- Demonstration of a multidisciplinary approach;
- High level expertise and experience documented by scientific publications;
- Awards, teaching and training activities;
- Significant contribution to state-of-the-art research;
- Links and collaboration with other CEs realising networks on a national and international level;
- Links and collaboration with patients' organisations
- Periodical monitoring of Centres' activity performed by authorities on the maintenance of the above listed criteria.

199 Centres comply with Italy's National Policy (and thus also comply with the EUCERD criteria, as explained above) equating to 3 per million inhabitants.

❖

European Reference Networks (ERNs)

There is a formal process in place in Italy for the endorsement of Health Care Providers (HCPs)/CEs to participate as members or coordinators of ERNs. Currently two Italian HCPs officially coordinate an ERN:

- ❖ Professor Mosca Marta from Azienda Ospedaliero Universitaria Pisana is coordinating the Rare Connective Tissue and Musculoskeletal disorders (RE-CONNET) network.
- ❖ Dr. Luca Sangiorgi from Rizzoli Orthopedic Institute is coordinating the Rare Bone Disorders (BOND-ERN) network.

In addition, the Azienda Osperdaliera di Padova is closely involved in the coordination of the MetabERN through Prof. Maurizio Scarpa (the official Coordinating HCP is the Helios Dr. Horst Schmidt Kliniken, Germany)

There are a total of 67 Italian HCPs participating as full members of 23 ERNs (all except for GENTURIS), with many of these HCPs participating as full members in numerous ERNs (e.g. the AO di Padova is a member of 18 different ERNs and the Paediatric Hospital Bambino Gesù is a member of 15): for full details see the official list at https://ec.europa.eu/health/ern_en)

Co-funded by
the Health Programme
of the European Union

A specific Commission in charge of evaluating the eligibility of an HCP to participate in an ERN was officially appointed by the Ministry of Health in 2016. The Commission has a 3 year mandate and includes representatives from the Ministry of Health, from Regional Health Authorities, and other designated health experts. The Commission is also tasked with monitoring the endorsed HCPs. The first step of the evaluation process was made by the Regions who then forwarded the approved HCPs to be evaluated by the National Commission. The Commission evaluated the eligibility of HCPs as potential ERN members.

❖

Integration of Rare Diseases into Social Policies and Services

How do Italian Centres of Expertise ensure a holistic approach to care?

In the Italian Rare Disease network described above, the Centres of Expertise designated by the Regions are preferably public hospitals. They are supposed to have documented experience in the diagnosis and care of rare diseases, and must be equipped with appropriate supporting structures and complementary services (i.e. for emergency care, diagnosis, etc.). Social services are present in such hospitals and liaise with territorial social services, when needed. Furthermore, to guarantee a holistic approach to care, CEs are linked to other hospitals involved in a patient's care and territorial services near to the patient's place of residence.

Local health units (ASL) provide by law a special service, known as a "multidimensional assessment unit" (UVMD). Under this service, a multidisciplinary case-conference is performed, which defines the specific healthcare plan (known as a 'PAI') of a patient, taking into account his/her complex social and care needs. General practitioners/family doctors, paediatricians, and hospital clinicians are all typically enrolled in this process and any of them can directly activate it (as can patients/relatives themselves, if they wish). The results of the Care Needs' Assessment determine if the patient requires an integrated home care programme (ADI) or hospitalisation at home. In this way, different socio-health professionals (general practitioners, paediatricians, nurses, therapists etc.) can take care of the patient at home, following the actions jointly defined in the personalised plan. The Care Needs' Assessment can also lead to admission, when needed, into a nursing home or a hospice (for palliative care). The definition of this PAI and the activation of an integrated home-care programme can also take place in hospital before the patient is discharged, in order to ensure the continuity of care from the hospital to the patient's home.

What actions exist to support people living with a rare disease to access social/disability programmes?

Specific actions exist within Italy to enable real access for people living within rare diseases to general social/disability programmes.

For instance, the "Carosello" project, run by the UNIAMO Federation, was created as a guide to the **enforceable rights and right of access to employment for individuals living with a rare disease**. Information was provided on procedures for the recognition of civil disability, blindness, deafness and other handicaps, as well as for targeted employment. This effort was a preliminary step towards the subsequent phase, i.e. the right to contributions, exemptions, concessions, authorizations and services. The principal economic support dedicated to disabled persons was reviewed, together with regulations and services regarding the promotion of work, inclusion of disabled persons, and concessions for disabled workers and/or working family members taking care of them. Dedicated programmes and services have been developed for disabled people, in order to integrate them to the community and provide them with real access. These services are run by the Regions and Municipalities, which are responsible for social care.

Various laws and initiatives define the rights of people with disabilities (resulting from a rare disease or otherwise). Regions and Municipalities fund grants to facilitate access of disabled persons to private or public spaces. Generally speaking, at the local level, a multidisciplinary and multisector approach is adopted, with social services collaborating with other health services to be able to meet the social-health needs of patients: this

Co-funded by
the Health Programme
of the European Union

collaboration is essential to elaborate social-health care plans tailored to the needs of people affected by rare diseases.

- In terms of **education**, there are no special schools in Italy: all children, regardless of their ability/disability, attend the same institutions. Disabled people must be integrated to schools by Law (n.104/92), and are managed by a special dedicated teacher and, if necessary, a healthcare assistant. The integration process is based upon the "individualized education plan (PEI)", defined by a multidisciplinary case-conference which considers the functional assessment of the patient, the child's main difficulties, and the resources required for a personalized educational approach. Hospitals hold special sessions of elementary and middle school education, for children who need to be admitted for a period of time. In terms of higher education, all disabled students have to right to receive special services (e.g. tutors, etc.), economic benefits, and special devices to support them in their University career.
- National legislation (Law n. 68/99) guarantees the rights of disabled people to be integrated to the **employment** sphere; to this end, socio-health services (S.I.L.) are available, dedicated to inclusion of individuals in local health care units (primary care services). These S.I.L are designed to facilitate the "protected" integration of patients to the workplace, (with or without specific supports), based upon their level of functioning. Good, reputable companies are expected to hire disabled people. In the public sector, there are some jobs reserved only for disabled people, which are very competitive. For disabled people who would find 'normal' employment impossible, semi-residential structures (so-called "CEOD") are available, which provide dedicated educational, rehabilitative, socialization and working projects.
- **Social Support/Welfare:** Disabled people (of all ages) and their families receive special benefits depending on the degree of disability (which is assessed and defined in terms of percentage) and severity of their handicap (defined by level of gravity, the highest being "severe handicap").These benefits include fiscal benefits, paid work leave, paid days of leave, exemptions for health expenses, right to prosthesis, social allowance, disability pension, parking permit, etc. In addition, families who care for severely disabled patients in their homes can benefit from a care allowance known as the "assegno di cura". Patients with functional problems (who have been assessed via a multidisciplinary case conference spearheaded by a local healthcare unit, as above) may be granted a home-care assistant to aid them in daily-life activities, which helps people to maintain autonomy and independence for as long as possible. This initiative is known as the *Independent Life* project. Residential or semi-residential respite care services are also available.
- **Essential Levels of Care:** The 'essential levels of care' -i.e. the list of services, devices, medicines etc. guaranteed by the NHS to Italian citizens- will be updated, to foreseeably include increased availability of prosthesis (especially technologically-advanced forms such as eye-tracking devices), and more up-to-date medical devices

What measures exist to support the integration of rare disease specificities into the national system responsible for assessing a person's level of functioning? Centres of Expertise are committed to assessing the functions (motor, cognitive, sensory, etc.) of persons affected by rare diseases. This assessment is conducted before the disability assessment is performed by the national institution (INPS). The Institution is committed to classifying the percentage of those affected by a disability, enabling individuals to receive particular benefits (as described above). There are ongoing local agreements between Regions or health care units with INPS to govern the participation of Centres of Expertise in the disability assessment performed by INPS.

Co-funded by
the Health Programme
of the European Union

Rare Disease Registration

Italy has a national registry for rare diseases, plus Regional-level registries, and disease-specific registries: specific legislation governs their operations (see below).

Status quo of the National RD Registry and Regional RD registries

The surveillance of rare diseases was identified as a priority in Italian National Health Plans as early as 2001. Ministerial Decree No 279 (of the 18th May 2001) called for the creation of a **National Rare Disease Registry,** based at the National Institute of Health. **Given the decentralised nature of Italy's healthcare system, this same Decree assigned the Regions the task of setting-up specific registries to monitor rare diseases at the population level. These registries are linked to the National Rare Disease Registry.**

The goal of the regional registries was to support and monitor the national and regional interventions put in place to address rare diseases. According to the agreement of 10th May 2007, between the State and Regions (Rep. Atti CSR n. 103), part of the data collected by the regional/interregional registries is periodically sent to the National Rare Disease Registry hosted by the Istituto Superiore di Sanità (ISS). **Reports on this data are then produced and published at the regional and national level.** The agreement identified a minimum number of variables, i.e. a minimum dataset, which must be collected at the regional level and thus constitutes the basis of the National Registry.

Besides this minimum dataset, the Regions can collect *additional* data, according to the priorities set by regional health authorities. Therefore, regional/interregional registries can differ in terms of their organisation, methods of collecting data and purpose of data collection, all of which are determined by the regional/provincial authorities; for instance, some have largely epidemiological purposes, supporting regional planning, whilst others were designated to support healthcare activities and to coordinate care provided to people living with rare diseases.

Interregional agreements and collaborations between the Regions have resulted in the creation of two 'interregional rare areas' which now share policies and information systems to support the registries. One such interregional area exists between the Piedmont Region and Valle d'Aosta, encompassing almost 4.5 million inhabitants. The second exists between the Veneto Region, the Autonomous Provinces of Trento and Bolzano, Emilia-Romagna, Liguria, Apulia, Campania, Umbria and Sardinia, and has almost 24 million inhabitants.

Main Regulations and laws governing registry operations:

1. Italian Ministry of Health: Ministerial Decree 18th May 2001 No 279. *Regolamento di istituzione della rete nazionale delle malattie rare e di esenzione dalla partecipazione al costo delle relative prestazioni sanitarie, ai sensi dell'articolo 5, comma 1, lettera b), del decreto legislativo 29 aprile 1998, n. 124, Volume 160*. Gazzetta Ufficiale; 2001:180. [http://www.trovanorme.salute.gov.it/norme/dettaglioAtto?id=17169]. Article 3 of this Decree established the National Registry, which is functionally linked to regional and interregional registries of rare diseases (as above).

2. Agreement between State and Regions 11 July 2002 (Rep. Atti CSR n. 1485) "*Agreement between the State, the Regions and the Autonomous Province of Trento and Bolzano regarding the selection criteria for the identification and revision of interregional RD Centres*". This agreement established the creation of an interregional group with clear aims, including "the identification of tools and procedures aimed at guaranteeing, in collaboration with the National Institute of Health, the epidemiologic surveillance of RD and the monitoring of care activities carried out for RD patients" [http://www.iss.it/binary/cnmr4/cont/STATOREGIONI2002.1205943700.pdf]

Co-funded by the Health Programme of the European Union

3. Agreement between State and Regions 10 May 2007 (Rep. Atti CSR n. 103) "*Agreement between the State, the Regions and the Autonomous Province of Trento and Bolzano regarding the identification of regional/interregional coordinating Centres, Centres of expertise for ultra-RD and the creation/implementation of regional/interregional RD registries*" [http://www.iss.it/binary/cnmr4/cont/STATOREGIONI2007.1205943700.pdf]

4. A National Decree on surveillance systems and registries is in an advanced stage of approval.

5. The majority of the Regions have included their regional RD registries in regional laws governing the functioning of registries established for public health purposes.

Status quo of the rare disease-specific registries

In addition to the National and Regional registries, other registries and databases collect data on specific rare diseases or groups of rare diseases. These registries differ in terms of coverage, governance, tools used for data collection, funding methods, and age of the collection (i.e. when it was established). Although these resources are very valuable, the rationalisation and integration of the data collected is very challenging. The sustainability of the registries is also a major concern, as most were funded for a fixed time in the context of a financed project, but subsequently experienced a lack of human and technical resources. For this reason, in order to avoid duplication of efforts and generate positive economies of scale, several projects have sought to create "nested" disease-specific registries *within* population-based/regional registries. For instance, the National Institute of Health, through the National Centre for Rare Diseases (CNMR), coordinated the EPIRARE project, one output of which was a definition of the needs of EU registries and rare disease databases. In performing this activity, a survey on existing registries was carried out, the details of which are available on the EPIRARE website (www.epirare.eu). The National RD Centre hosts the database on Paroxysmal Nocturnal Haemoglobinuria and Cystic Fibrosis.

The Orphanet database represents a valuable and frequently-updated source of information on the individual RD registries based in Italy: almost 70 registries were operational in Italy in 2015.

Funding of Rare Disease Registries

- The National Rare Disease Registry is funded by the National Health System
- The Regional rare disease registries received funds from the NHS through dedicated projects, and are now funded by the Regions
- Disease-specific registries can be funded through the NHS, namely through research projects, or may be funded by Regions, industry, non-profit organisations or patient associations

Number of patients registered

The Ministerial Decree n.279/2001 established the mandatory monitoring of a defined list of rare diseases, which cumulatively included more than 2,000 rare disease entities. According to data collected by the National Rare Disease Registry, in December 2014 **almost 195,000 patients were affected by one of these 2000 focal diseases**. This of course constitutes the *minimum* number of those afflicted with a rare disease in Italy, as it does not include patients with rare diseases not monitored by rare disease registries, nor patients with rare tumours. Plans are in place to update the list of monitored rare diseases, and the revised list will include most of the known rare diseases which were not covered under the 2001 list; nevertheless, rare tumours will not be included in this updating process.

Co-funded by
the Health Programme
of the European Union

Coding systems utilised

11 Regional registries out of 19 in Italy use Orpha-Codes (i.e. use the Orphanet nomenclature) to codify rare disease monitored entities. 8 of these 11 registries (all sharing a common information system managed by the Veneto Region) supplement the Orpha-Code with ICD (versions ICD9-CM and ICD-10) and OMIM. (None of the established regional registries use SNOMED-CT.) This information is not collected at the national level. No information is available at present regarding usage of Orpha-Codes in the disease-specific registries.

How the registry data is used

The purpose of registry data varies, depending on the *type* of registry. As stipulated by Decree 2001 no. 279, the data collected by the National Registry is used for planning purposes on the National level. However, as above, data from the Regional registries is used for various different purposes, in accordance with the complexity of the systems put in place for data collection and the level of detail of the information recorded. In several Italian Regions, data is directly linked to the provision of care and services to patients, including the following activities:

- Health services planning (e.g. establishing the number of Centres of Expertise required for a certain number of rare disease patients, the most appropriate geographical distribution of CEs, the relative necessity of a paediatric or adult focus, etc.)
- Evaluation and monitoring of the activities of the Centres of Expertise;
- Evaluation of the function of the rare disease care network as whole (e.g. its 'attraction and escape' rates)
- Monitoring patient outcomes, in terms of morbidity and survival (enabled through linkage with other data sources, e.g. health discharge records, death certificates etc.)

In some Regions, the registries are supported by an information system which is used by clinicians when prescribing/providing treatments. In such cases, data can also be used to monitor the use of drugs and medical devices, to estimate the impact of RD on the regional health expenditure (including an estimation of the resources needed to provide treatments free of charge for patients), to monitor adverse drug reactions, etc.

Data from the regional and national registries has recently been used by the Italian Commission tasked with selecting Centres of Expertise to participate as members of European Reference Networks: a ranking of candidate Centres, based on the number of patients 'followed' per rare disease grouping, formed the basis of the endorsement process, and was demonstrable through robust registry data (as opposed to self-declaration).

Genetic Testing

In view of its importance for many people with rare diseases, genetic testing is an integral part of the 'essential levels of assistance' (LEA) provided by the Italian NHS. Genetic testing is granted free of charge through the Regional systems, in compliance with the criteria of effectiveness, quality and appropriateness, as well as in agreement with the ethical principles of equity and universality of access. The NHS ensures quality of service delivery and issues performance standards.

During the period 1987-2011, genetic testing activities in Italy were monitored by the Italian Societies of Medical and Human Genetics. Based on the last survey, there were 372 genetic laboratories, performing more than 684, 000 tests per year. Genetic testing was available for more than 900 disease-causing genes (BMC Health Serv Res 2016 Mar 17; 16:96. doi: 10.1186/s12913-016-1340-7).

Although there are no up-to-date formal data, it is likely that in 2015 molecular testing was available for no less than half of all the genes associated with Mendelian phenotypes. **Whilst there is currently no *official* national**

Co-funded by
the Health Programme
of the European Union

list or registry of the reference laboratories providing specific genetic tests, the Orphanet-Italy team has been actively involved in collecting and updating information on genetic testing activities since 2001: according to the latest Orphanet data, at the beginning of 2017 Italian laboratories cumulatively provided genetic testing for **1361 diseases and 1355 genes** (excluding panels of genes).

Several important national documents deal with the topic of genetic testing (and govern its use):

- "Bioethical guidelines for genetic testing" (National Committee for Bioethics, 1999; http://bioetica.governo.it/media/171763/p41_1999_genetic-testing_en.pdf);
- "Guidelines for genetic testing" (National Committee for Biosecurity and Biotechnologies (1999; http://presidenza.governo.it/biotecnologie/documenti/linee_guida_test_genetici.pdf);
- "Guidelines for Medical Genetic Activities" (Agreement between State and Regions on July 15, 2004; Official Gazette n. 224 September 23, 23, 2004; http://95.110.157.84/gazzettaufficiale.biz/atti/2004/20040224/sommario.htm);
- "Commission for genetics in the National Health System" (Ministry of Labour, Health and Social Policies, 2007; www.salute.gov,it/imgs/c_17_pubblicazioni_908_allegati.pdf).

In December 23, 2013, Italy implemented Directive 2011/24/EU (often called the 'Cross-border Healthcare Directive' and installed an official 'National Contact Point' at the Ministry of Health, which provides patients with information to facilitate their access to cross-border healthcare in the European Union (www.salute.gov.it/cureUE). Genetic testing (i.e. citizens seeking genetic testing outside of Italy) did not play a major part in the 500 actions managed by this contact point during its first year of activity. This is likely due to the relatively wide availability of genetic testing in Italy, coupled with the tendency of physicians who manage RD patients requiring tests not available in-country to make direct contact with pertinent foreign laboratories.

Neonatal Screening

Since 1992, newborn screening has been mandatory across the whole of Italy for cystic fibrosis, congenital hypothyroidism, and phenylketonuria (Law. 104/1992, Decree n. 548/1993). **Thanks to the increasing availability of tandem-mass spectrometry, over the years the Regions have begun to offer screening for additional diseases**, through specific research projects or/and regional regulations. **14 of the 21 Regions guarantee -through their own resources- expanded newborn screening for a number of inherited metabolic disorders, ranging from 25 to 58**. In the same way, certain Regions (including Emilia-Romagna, Lazio, Tuscany, Campania and Veneto) approved specific laws in order to guarantee screening in terms of hearing and vision for all newborns. These developments resulted in notable regional differences in neonatal screening policies, since expanded screening is considered an extra-LEA (essential levels of care) service for citizens, which is not financed by the NHS. Thus, the cost of screening for diseases beyond those mandated by law 104/1992 had to be borne entirely by the Regions.

In August 2016, the situation changed substantially. To enable the early diagnosis of inherited metabolic diseases in *all* newborns, the Italian Parliament –following two years of debate- issued Law no. 998 "Dispositions for neonatal diagnostic tests required for the prevention and treatment of inherited metabolic diseases". This Law grants an expanded neonatal screening programme for all Italian Regions. At the same time, a Ministerial Decree on expanded newborn screening was concluding its legislative path: this Ministerial Decree will identify a common list of disorders (a panel of 38 inherited metabolic diseases was proposed) to be included in the screening programme, and describes the functions and roles of the nodes constituting the expanded screening system. Furthermore, the Decree underlines the necessity to consider expanded newborn screening as a *programme*, to be accompanied by defined care pathways for patients affected by the screened diseases.

Co-funded by
the Health Programme
of the European Union

Clinical Practice Guidelines (CPGs)

Italy has a national policy for *developing* CPGs; for *adopting* CPGs; and for *Implementing* CPGs.

Regulatory agreements exist between the Government and the Regions concerning the implementation of "diagnosis, treatment and health care pathways" (known-as "PDTA") for particular disease areas, such as neuromuscular disorders, amyotrophic lateral sclerosis (ALS, which has dedicated national funding) and congenital haemorrhagic disorders.

These Guidelines deal with the entire patient pathway, moving from a description of the multidisciplinary approach required at diagnosis, through the definition of a healthcare plan, including treatments, medicines, rehabilitation, prosthesis, etc. (for example, for ALS patients the pathway encompasses assessment, prescription, supply, follow-up of eye tracking devices, etc.)

In addition, the Government and the Regions have reached an agreement on remote counselling to empower regional networks for people with rare diseases: this agreement deals with the clinical consultation of a patient affected by a rare disease when conducted between different Centres of Expertise, or between a hospital and a Centre of Expertise, even if geographically very far apart.

At the national level - the National Guidelines System (NGS) is entitled to issue national guidelines, and has a special section dedicated to rare diseases. Guidelines have been published via this RD section for conditions including congenital aniridia, epidermolysis bullosa, and alternating hemiplegia.

At the regional level - many Regions are active in defining PDTAs for rare diseases/group of rare diseases. Their aim is to identify the best care processes to address specific health needs, according to up-to-date guidance, and adapt them to the local context. Hundreds of PDTAs on specific rare diseases have been issued. Through these PDTAs, some Regions are willing to grant services, medicines (e.g. off-label medicines, not marketed in Italy), implants, and aids which lie outside the essential levels of care (and thus are termed '**non-LEA'**) to persons with rare diseases, if deemed necessary for the integrated healthcare plan of the patient. Such requests must be authorized by a regional technical group or a local group from the health unit.

Training and Education

In Italy, different levels of education and training for physicians and other healthcare professionals have been developed, including the following:

- 'Basic' training and education, under the competence of the Ministry of University and Scientific Research (MIUR);
- Postgraduate training and education, under the competence of the MIUR, the Ministry of Health (for postgraduate schools in the Medical area), and Regions (the Regions are also responsible for the education and training of General Practitioners);
- Continuing medical education (CME, or ECM in Italian), which is mandatory, has both national and regional levels of organisation. CME programmes for GPs, paediatricians, and other physicians working in Regional services are a regional competence, and are arranged in collaboration with the professionals' organisations. The contents of these education and training activities are decided both at national and at regional levels, and are organised around certain priority areas.

Rare Diseases in the education of Physicians

In all medical faculty courses, and in other courses dedicated to health professionals, training on rare diseases is focussed around the peculiarities and specificities of these conditions. The university courses of the 'Conference of the Presidents of Medicine and Surgery' are being revised, and the 'core curriculum' of the

Co-funded by
the Health Programme
of the European Union

medical doctors' training is being updated in-line with emerging needs in healthcare. This process led to a proposal to include rare diseases in the core curriculum for medical doctors.

Examples of existing educational activities addressing rare diseases at university level include the following:

- The high-level Masters degree on Rare Diseases, biannually promoted by the University of Turin;
- A PhD course at Padua University School of Medicine, dealing with rare diseases and health planning.

Rare Diseases in Professional Training

Professional training for healthcare staff, most notably in the form of CME, is organised at the national, regional and local levels. A wide range of organisations are involved in this training, including the Ministry of Health, the National Institute of Health, the Regions, professional associations, scientific societies, and professional federations and bodies. **Since January 2014, 61 CME courses on rare diseases have been organised** (based on data from the Agenas database on CME), excluding courses which focus on a single rare disease. Most of these courses are residential. Regions, through their Coordinating Centres, periodically organise courses for professionals of the rare disease care networks, notably clinicians working in Centres of Expertise, health professionals working in primary care, and pharmacists.

Education and Training activities promoted by Patient Associations

Many educational and training activities -addressed to both professionals and patients- **are promoted by patients' associations: a prime example is the "Known to assist" project organised by UNIAMO** (http://www.uniamo.org/) in collaboration with several stakeholders. This project, dedicated to GPs and Paediatricians, was launched in 2010 and was supported by Farmindustria. A range of different actors - including scientific societies and federations, GPs, paediatricians and geneticists (FIMG, FIMP, SIP, SIMG, SIMGePeD, SIGU)- collaborated in planning these training activities. The training sessions included several key topics:

- How to identify/diagnose suspected rare diseases
- The quality of care for people with rare diseases
- How to manage the transition from paediatric care to adulthood.

These courses have been organised in most Italian Regions and have been attended by more than 500 GPs/Paediatricians and 150 additional healthcare professionals.

Distance learning courses and other residential courses

- Under the scientific direction of Professor Dallapiccola, the Bambino Gesù Children's hospital (a research hospital in Rome), in collaboration with the National Academy of Medicine in Genoa, promoted a distance learning course entitled "Approaching Rare Diseases". This course ran from October 2014 to September 2015, and was aimed at physicians and other healthcare professionals. Provided free of charge, and supported by Farmaindustria, the course consisted of a series of lessons delivered by experts in the field. The President of UNIAMO FIMR Onlus was involved, as a representative of patient associations. 16,062 users registered for the course, with 11,359 completing it (including 10,853 who achieved the medical credits).
- A subsequent course was organised on the topic of "Medical Genetics, following the same methodology and using the same distance-learning platform. This time, a total of 11,236 users registered for the course, 8,050 completed it, and 7,729 achieved the medical credits.
- The National Centre for Rare Diseases and the External Relations Office of the National Institute of Health also promoted a distance-training course (free of charge) for physicians and other healthcare professionals, entitled "Expanded new-born screening for the prevention of congenital metabolic disorders (rare diseases)", which was available from March 2015 to March 2016. The aim of the course was to enable participants to recognise the importance of expanding the newborn screening to include

Co-funded by
the Health Programme
of the European Union

congenital metabolic disorders, as a tool for secondary prevention of rare diseases and to convey robust information to empower all actors involved in NBS, from patients' families to healthcare professionals.
- The National Centre for Rare Diseases has organised additional residential courses concerning rare diseases: a complete list is available on the CNMR website (www.cnmr.iss.it).

The National Rare Disease Plan 2013-2016 explicitly refers to training interventions addressed not only to healthcare professionals but also to patients, carers, family members and volunteers. The key areas of proposed action for professionals included the following:

- **Basic education**: in all medicine courses and other courses for healthcare professionals, knowledge should be provided on specific issues concerning the care of people affected by rare diseases.
- **Specialist Education:** higher education courses (Postgraduate/Masters) should incorporate rare diseases in their specific content
- **Specific training in General Medicine**: should include a focus on rare diseases
- **Continuing Education (CME)**: the topic of rare disease should be part of national and regional CME, and of the training plans of health authorities.

For patients, care givers, family members and volunteers, the National RD Plan proposes "specific training programmes which shall be dedicated to patients and their associations, organised by groups of disorders, care needs, praxes and contents of decision-making processes".

Information Resources of Rare Diseases

Orphanet Activities

Italy has an operational National Orphanet team which is housed within the Ospedale Pediatrico Bambino Gesù (OPBG) in Rome. The team produces documents in the Italian language and since 2002 Italian is one of the main languages of the Orphanet database. The national website entitled Orphanet Italy (http://www.orphanet-italia.it) was launched in 2011, followed by the Orphanet mobile application in 2013. In 2015, 12,230 users visited the national website, 85% of whom were new visitors. Users of the site visited a total of 20,935 pages. Documents included in the Orphanet Report Series have been translated into Italian, including the 'List of Rare Diseases', 'Prevalence of Rare Diseases by alphabetical list', 'List of Orphan Drugs in Europe', 'Prevalence of Rare Diseases by decreasing prevalence of cases' and the 2014 Activity report. Together, these reports have been downloaded 203,203 times.
The national plan has not allocated funding to specifically support the Italian Orphanet team. However since Orphanet-Italia is hosted by OPBG, a research hospital whose activities are funded in part by the National Ministry of Health, these resources also contribute to support a segment of the Orphanet team's activities.

At the end of 2015, the Orphanet-Italia database included information on the following:

- 3,356 diseases (via disease-based texts)
- 4,321 diagnostic tests
- 820 research projects
- 236 clinical trials
- 332 patient associations
- 108 patient/mutations-based registries/biobanks
- 1,028 expert centres
- 40 emergency guidelines

The Italian team has produced leaflets and created an Orphanet-Italia Facebook page (http://www.facebook.com/OrphanetItalia), and a dedicated YouTube channel, to improve the dissemination of the database contents and Orphanet activities. Since December 2011, this team has also been charged with the

Co-funded by
the Health Programme
of the European Union

Italian translation of OrphaNews, which, since 2015, is also available through a mobile application accessible via the Play Store and App Store. Orphanet-Italia collaborates with UNIAMO and Telethon.

National Helplines

The National RD plan 2013-2016 identified 'information' as a key area for action. One of the objectives included in the Plan is "to guarantee the improvement and the support of information dissemination activities performed by institutional sources (either through websites, helplines and regional and national information points). Their use should be promoted among all relevant stakeholders. An active patients' participation in the planning of actions addressing rare disease information needs is recommended".

Italy currently has several helplines dedicated to rare diseases, funded through a mixture of public and private funding. Helplines are available for both patients and professionals (i.e. is open for anyone to use).
These helplines fall into different categories.

1. Helplines managed by institutional bodies

A helpline managed by the National RD Centre, based at the National Institute of Health (ISS) and designated as "Telefono Verde Malattie Rare (TVMR)", was established on the occasion of Rare Diseases Day 2008. It operates via a toll-free number (800.89-69-49) and provides information on rare diseases but also on the prevention of congenital defects. A counselling approach is used.

The RD Regional/Interregional Coordination Centres play an important role providing information and guidance to people living with a rare disease, as many specific regulations and clinical pathways are defined at regional/interregional level. The State-Regions Agreement of 10.05.2007, which established these Centres, specified -amongst other institutional duties- a requirement to provide information on RD to patients, family members and health professionals, also through a direct collaboration with patients' associations. Some Regions, even before this Agreement was in place, were keen to establish dedicated rare disease helplines/information Centres (for example the Lombardy and Veneto Regions established helplines/information centres as early as 2002).

A few Italian Regions (Apulia, Sardinia, Tuscany and Veneto Region) supported a toll-free number to receive rare disease information and established dedicated email addresses providing answers to specific questions. Almost all regions now have dedicated helplines (even if not toll-free) and email addresses.

Two helplines, managed by the National Centre for RD and by the Veneto Region RD Coordinating Centre, are part of the European Network for Rare Disease Helplines (ENRDHLs), which is coordinated by EURORDIS. ENRDHLs was created in the period 2006-2008, as an outcome of the Rapsody Project (the Rare Disease Patient Solidarity Project - http://www.eurordis.org/IMG/pdf/draft-leaflet_rapsody08-1.pdf), carried out by EURORDIS and partners. ENRDHLs consists of 11 helplines in 7 countries (Bulgaria, Croatia, France, Italy, Portugal, Romania and Spain) and 2 helplines which are currently under development (in Belgium and Switzerland). The network has developed common activities; for instance, each year all members participate in a survey known as the "Caller Profile Analysis" which seeks to evaluate the network's activities and utility, and the purpose of creating or expanding services. Helplines which are members of this Network are supposed to fulfil certain criteria, such as ensuring the use of OrphaCodes when recording enquiries on specific rare diseases.

For more information about the network, see Houyez et al. 'A European network of email and telephone helplines providing information and support on rare diseases: results from a 1 month activity survey', *Interact J Med Res*. 2014 May 5;3 (2):e9.doi 10.2196/ijmr.2867.

2. Helplines managed by non-profit organisations

Telethon infoline (http://www.telethon.it/la-ricerca/per-i-pazientiil-servizio-infoline) is an information service available to people seeking information on genetic diseases. The service provides answers to requests received

Co-funded by
the Health Programme
of the European Union

by the Telethon Foundation, supplying useful references for the diagnosis and care of patients, as well as the latest news on current research into genetic disorders.
Several patient associations manage helplines (some have toll-free numbers) and Information Centres, providing users with knowledge and advice on single rare diseases or related rare diseases.

Funding of Helplines in Italy

Institutional helplines are financed through public funding: the NHS funds the TVMR and Regional funds sustain the regional helplines. Other helplines, such as those operated by non-profit organisations, are funded privately, and/or are staffed by volunteers (sometimes partially, sometimes entirely).

Official Information Centres

One of the objectives of the National Plan 2013-2016 was to "ensure empowerment and support for the maximum disclosure of institutional information sources currently available (websites, national, regional and local helplines and information points)". Information on rare disease is therefore imparted by several institutions and actors:

- The Istituto Superiore di Sanità (ISS, i.e. the National Health Institute) manages an official Information Centre for rare diseases.
- Regional/interregional 'Rare Disease Coordinating Centres' manage Information Centres as part of their mandatory activities, providing information on regional pathways and regulations (especially where there is a regional specificity).
- Fondazione Telethon manages an information service on genetic diseases, providing useful references for patients' diagnosis and care and the latest news regarding research into genetic disorders.
- The Orphanet website (www.orpha.net) is an official point of reference for rare disease information, as illustrated by the increasing number of visitors to the website and the growing number of subscribers to 'OrphaNews' and 'OrphaNews Italia" (the Italian version of the newsletter).
- Many RD Centres of Expertise, especially those managing large numbers of patients, have information desks to provide information on hospital facilities and to book health appointments.
- Patient associations also play a key role in providing information: they manage helplines, as above, but also increasingly provide information via the internet. These activities can be both informative (e.g. information is available through www.malatirari.it, promoted by UNIAMO F.I.M.R. Onlus) and interactive (a good example is the RareConnect resource promoted by EURORDIS and NORD www.rareconnect.org/it, which offers a social channel through which people with rare disorders can share experiences).

Institutional official information centres for rare diseases in Italy are supported by public funding, while other systems/resources are typically supported by a mixture of public and private funding, or by private funding alone.

Rare Disease Research Activities

Existence of RD research programmes/projects within Italy

Italy has specific research projects for rare diseases, funded from the general budget. As yet there has been no policy decision to allocate a portion of the national research budget specifically to rare disease reasearch, but this is under discussion.
Rare disease research projects are approved/conducted through many channels, including the Ministry of Health, ISS, Regions, Italian Drug Agency (AIFA), Ministry of Education, University Institutes, Telethon, CNR

Co-funded by
the Health Programme
of the European Union

(Research National Council), patient organisations, charities and private groups. For instance, the Italian Drug Agency (AIFA) issued calls to fund independent research on the development of Orphan Medicinal Products. AIFA financed a three-year initiative, launched in 2005, to support clinical research into drugs of interest to the NHS which lacked commercial support - rare disease/OMPs was one of the focal areas for this initiative.
Some calls focus exclusively on rare disease research:

- From 2008 onwards, the Ministry of Health funded research into rare diseases and OMPs via a specific 'rare disease' budget, from within the general health research call.
- In 2009, the Ministry of Welfare issued a specific call to fund research projects on rare diseases.

The Telethon Foundation plays a key role in supporting research on genetic diseases. Between 2011 and 2014, 215 projects on rare disorders were funded, with investment ranging from €26.8 million in 2012 to €39 million in 2014, totalling almost €100 million across the three years. This figure includes both "in-house" research projects and "external" research approved in the budget year.

Foundations and Associations also promote funding campaigns for genetic research or research into specific diseases. In addition, voluntary funds are collected through general taxation.

According to Orphanet, in 2015 there were 820 ongoing research projects on rare diseases in Italy.

There are concrete plans to support future rare disease research in Italy. The National Plan for Rare Diseases 2013-2016 explicitly aims to enhance and support research in the field of rare diseases, and the following actions have been defined:

- Identifying research priorities, with a focus on less-developed areas;
- Improving the traceability of research on rare diseases and the accessibility of results, post-completion;
- Promoting multidisciplinary research;
- Supporting synergies between group of diseases;
- Simplifying procedures;
- Increasing the number of phase I clinical trials;
- Promoting the translation of research results to care;
- Ensuring the continuity of research funding;
- **Promoting research on medical devices, with strong impact on the quality of life of patients.**

The last point indicates an interest in conducting research into the social/socio-economic aspects of rare diseases. All of these actions should be implemented in conjunction with full, informed, and appropriate involvement of patients in research programmes.

1

Italy participates in both E-Rare and IRDiRC. Italian partners in E-Rare3 are as follows:

- Italian Ministry of Health (IT-MOH)
- Istituto Superiore di Sanità (ISS)
- Regione Emilia Romagna (RER-ASSR)

In the years 2014 and 2015, Italian Partners Coordinated 2 E-Rare projects, and were partners in a further 5 projects.

IRDiRC Italian members are as follows:

- Istituto Superiore di Sanità
- Telethon Foundation
- Chiesi Farmaceutici S.p.A

Co-funded by
the Health Programme
of the European Union

National Alliance of Patient Organisations and Patient Representation

Italy has a national alliance of rare disease patient organisations, Uniamo Federazione Italiana Malattie Rare onlus (UNIAMO) since 1999. The alliance has accomplished many things since its inception – recent highlights include the following :

- **June 2014,** Research: Presentation and delivery of the "Tool Kit" as an output of the project 'Determinazione Rara' which started in 2013 as an advanced national training programme for the proactive enrolment of patients in research trials, based on workshops with clinicians, researchers and biobank professionals. This was an innovative National empowerment programme involving Research institutions and infrastructures as well as patient organisations, seeking to build an inclusive team-working and problem-solving approach at the frontiers of advanced research (creating a participatory laboratory modelling good practice in research & biobanking/collecting global data.)
- **July 2014** – the Centres of Expertise Community Project: The common definition of a Centre of Expertise, resulting from the first phase of the project, was used by Regions for the subsequent process of Centre identification. A presentation depicting a **shared model of quality assessment for Centres of Expertise** was developed, with the assistance of all national stakeholders. This model was then tested in 5 CEs for Thalassemia, in different regions, to check sustainability and to assess the clarity of the instruments used and the reliability and sensitivity of the indicators. This 'pilot' also served as an opportunity to refine the model before its implementation on a larger scale.
- **November 2014** – Unmet needs Carosello Project: in collaboration with patient organisations, UNIAMO carried out a critical analysis of the healthcare system for people with rare diseases (funded by AGENAS).
- **May 2015** – Carosello Project: UNIAMO developed and presented the 'Guide to the due rights for people living with Rare Diseases' (funded by the Ministry of Welfare).
- **July 2015** – Presentation at the Chamber of Deputies of MONITORARE, the First *Monitoring Report on the condition of People Living with Rare Diseases*, elaborated by UNIAMO using key data on different issues linked to the relevant chapters of the National Plan for Rare Diseases. The report painted a rich and detailed picture of the framework for rare diseases in Italy, in terms of data, socio-health organisation, training and information, research, assistance, and social responsibility. For the first time, the issues affecting and involving 1,079 patient associations representing 670,000 patients suffering from RD in Italy, were amalgamated and reported in an organic and systematic way.
- **October 2015** – Training: An additional training session was organised, in the Umbria Region, under the PROJECT 'Knowing to assist' (funded by FARMINDUSTRIA, Association of Pharmaceutical companies). The session was aimed at family paediatricians and general practitioners and sought to provide participants with a new 'diagnostic sensitivity' and an understanding of the complex care of patients (child or adult) suffering from a rare disease, and the handover of daily care from paediatric age to adult age.
- **October 2015** – Empowerment: Within the European Biotechnologies Week, UNIAMO organised a 'PlayDecide' event ('PlayDecide' is an exercise in which often-difficult and controversial issues are discussed in a simple and effective manner). This included the exchange of pluralistic and multidisciplinary perspectives around 'hot topics' such as orphan drugs/neonatal screening/stem cells. Each session was delivered in close collaboration with industry, universities, patient organisations, and Institutions. The issues were discussed in a collaborative setting, uniting citizens, patients, caregivers, students, researchers, clinicians, scientific journalists, ELSI experts, Pharmaceutical Industry representatives as well as Institutional representatives.
- **November 2015** – Empowerment concerning Registries: Regist-RARE to Infrastru-RARE Project: UNIAMO F.I.M.R promoted a systematic action to empower patient representatives and support community-building, around the shared practice of utilising registries for research. The goal was to enable innovative governance of global data, highlight the proactive role patient organisations (POs) can play in connection to registries, promote registries linked to biobanking as strategic infrastructures, and articulating a practical participatory roadmap (step-by-step, with POs and Institutions).

Co-funded by
the Health Programme
of the European Union

In 2015 and 2016, UNIAMO continued to participate to Parliamentary hearings regarding regulations for supporting people with severe disabilities but no support from family members - "After us".

Level of official representation and consultation of RD Patients in Italy

At the national level - despite what is stated in the National Plan for RD, **patients are not included in the National Committee** (which is not in fact functioning effectively, it is alleged). Similarly, patients were not included in the Group overseeing the implementation of ERNs in Italy. The only opportunities to gather *all* stakeholders to debate on specific 'hot topics' relating to rare diseases have in fact been created by UNIAMO FIMR, through its projects (examples above).

At the Regional level - the degree of representation and consultation of patients varies from one Region to another. UNIAMO representatives sometimes sit on the Regional Board/Forum or Consultative group, which may involve various POs – these bodies are quite formal but POs seem to have little impact on their decisions and activities. In some Regions, however, POs *are* involved in the development of the care of specific diseases and clinic pathways PDTA.

Rare Disease Day

Since 2008, UNIAMO has worked in collaboration with EURORDIS to promote and coordinate events on Rare Disease day. Events have been organised by the National Institute of Health, Regions, associations and rare disease centres of expertise and over the last few years the number of events has increased. There were over 170 events, conferences, stands, fundraisers, exhibitions, workshops, across Italy in 2015. All of the details on these events can be found on the EURORDIS website: http://www.rarediseaseday.org/country/it/italy.

Since the beginning of 2014, the National Centre for Rare Diseases (CNMR) (http://www.iss.it/cnmr/index.php?lang=1&anno=2016&tipo=56) has organised many events focussed on rare diseases. Among them the International Summer School on Rare Disease, Orphan Drug Registries, and RD-Connect BYOD Workshop to Link Rare Disease Registries. Other events have included:

- The RARE-Bestpractices annual meetings – 20th March 2015, 2014
- The 3rd International EPIRARE workshop on RDs and Orphan Drug Registries (24-25 November 2014)
- The 3rd International Summer School on Rare Disease and Orphan Drug Registries (21-23 September 2015)
- The RD-CONNECT Workshop on Data Linkage and ontologies (22 May 2015).

In April 2015, the Interregional Board of Regions and the Coordinating Centres for Rare Diseases organised an event entitled *State Assistance for Rare Disease patients in Italy: the Regions' Contribution* (http://.www.regionmalattierare.it). Dr Ana Rath, representing the RD-Joint Action attended the meeting together with the representatives from the Italian Ministry of Health, Regional Health Authorities, Orphanet-Italy, AIFA, Farmindustria, Agenas, UNIAMO and other patient associations, clinicians, working within Centres of Expertise, territorial networks, pharmacists, GPs, paediatricians. Over 200 participants attended the event.

UNIAMO F.I.M.R Onlus together with a steering committee, involving many of the main stakeholders of the rare disease community in Italy, organised the 2nd Europlan Italian conference in Rome on 27th and 28th January 2014. In addition, UNIAMO carried out many education and training events dedicated to rare diseases, including sessions dedicated to the *Know to Assist* project. On July 2015 UNIAMO organised a presentation at the Chamber of Deputies of MONITORARE, the first monitoring report on the condition of persons living with rare diseases (PLWRD) in Italy.

In December 2015, the Ministry of Health organised *The Rare Diseases National Plan: the association's requests.* The open day was intended to promote a dialogue between institutions and associations of patients regarding the implementation of the Rare Diseases National Plan.

Co-funded by
the Health Programme
of the European Union

In summary, the rare disease day events in Italy each year are numerous, organised by the 1079 national associations for rare diseases these events are prepared in order to sensitise the public to the plight of those living with rare diseases and raise funds.

Orphan Medicinal Products

The status quo: The Italian Medicines Agency (AIFA) is the main body in charge of introducing orphan medicinal products (OMPs) into the Italian market.

At the end of 2016, 89 OMPs with European Marketing Authorisation were available within the Italian national territory (this figure includes the orphan drugs for which the 10-year period of exclusivity granted by EMA had ended, and which were therefore removed from the Community register).

Indeed, in recent years the total number of orphan drugs available in Italy has continues to rise: 44 OMPs were available in 2012 and 66 in 2015. A comprehensive study of the status quo was carried out in 2015:

- 66 of the 87 orphan drugs approved for use in the EU were available in Italy at the end of 2015, equalling 76%. This figure of 66 included including 13 products still undergoing negotiations and therefore present in Cnn class (C non-negotiated class – see below)).
- Of the remaining 21 drugs approved in the EU:
    - 13 (15%) were not available within the national territory. Of these, 11 (13%) were still waiting to be catalogued in Cnn and 2 (2%) had not yet entered the negotiation stage as no application for price and reimbursement had been submitted at that time.
    - The remaining 8 drugs (9%) were accessible to patients within the national territory through *alternative* means, in accordance with the national legislation (Law 648 of 1996, Law 326 of 2003, art. 48).

The increase in the number of available orphan drugs has been paralleled by their increased use, as measured by the Defined Daily Dose (DDD) which rose from 7.5 million in 2013 to 10.3 million in 2015. In turn, an increase in expenditure was observed, from €917 million in 2013 to €1,212 million in 2015, accounting for 5.5% of the total drug expenditure.

Availability of information pertaining to OMPs: The data provided above is available to the public and was included in the Rapporto OsMed 2015 report. A list of OMPs with European marketing authorization, and the date of their publication in the Official Gazette (i.e. their marketing in Italy) is also available.

Pricing and Reimbursement of OMPs: The orphan drugs are listed by their different classes, depending on their reimbursement status; for example:

- products labelled as Class A are fully reimbursed by the National Health Service (NHS). These include essential products and products for chronic diseases.
- Class H products are fully reimbursed through the hospitals
- Class C products are not reimbursed and have a low evidence level and/or a low benefit/risk ratio).

Reimbursement is granted for most OMPs following the centralised marketing authorisation procedure. 81% of orphan drugs are fully reimbursed by the NHS: 53% of these are in H-class; 23% are in A-class; and 5% are reimbursed from the list of Law 648/1996. Other class C and Cnn drugs are paid for by patients.

Orphan drugs are distributed by hospitals and community pharmacies, and by local health authorities. The prices of all medicines reimbursed by the NHS, including hospital-only drugs, are set by the Italian Medicines Agency (AIFA). Two interministerial committees are involved in this process - the Pricing and Reimbursement Committee and the Technical-Scientific Commission.

Co-funded by
the Health Programme
of the European Union

Facilitating access to OMPs - Italy has particular measures in place to facilitate access to OMPs for patients. Law 189/2012 states that drugs approved through the centralized European procedure, which have yet to undergo negotiations on reimbursement can nonetheless be made immediately available to patients, by placing them in 'Cnn' or C-non negotiated category.

Pre-authorisation access to Orphan Drugs for patients suffering from a rare disease is guaranteed through various regulations. The centralized authorization procedure, available in standard and conditional modes, is the main route to access; however, while waiting for the authorization of an orphan drug for a rare disease, the patient can access the treatment through alternative procedures. Law 648/1996 refers to drugs for which costs are fully covered by the NHS, and highlights three types of medical products:

- innovative drugs, which have received marketing authorization abroad but not in Italy;
- drugs not yet authorized at European level, which are undergoing clinical trial;
- drugs intended for a therapeutic indication which differs from the original indication for which it was authorised ("off-label" use).

Inclusion in these categories is subject to evaluation by the Scientific Technical Commission of AIFA, following a documented request by patients associations, scientific societies, local health authorities, or universities.

Following Law 79 of 2014, 'off-label' use of a product (i.e. use for an indication other than that for which is was originally authorised) is possible even when therapeutic alternatives exist, according to the parameters of cost and appropriateness.

The number of drugs for rare diseases included in the list defined by Law 648/1996 has increased from 13 in 2012 to 27 in 2015. The list is available on the AIFA website and is periodically updated. Since 2014, AIFA marks in red the OMPs on this list.

Another relevant piece of legislation is Law 326 of 2003, art. 48, which governs the modes of access to OMPs - and to drugs offering a therapeutic benefit but awaiting marketing- for specific and severe disorders through the access to the 5% AIFA fund. For orphan drugs awaiting approval, this basket is funded by marketing authorisation holders, based on annual promotional expenditure (the 5% of that expenditure).

In 2015, this fund amounted to €35.6 million. 50% of the fund is used for the purchase of orphan drugs for rare diseases and drugs not yet authorized, which seem promising in treating severe diseases; the remaining 50% is used for drug research (i.e. comparative trials of drugs to demonstrate their added value, and studies on appropriateness and information).

MD of 8 May 2003 (therapeutic use of a drug undergoing clinical trials) governs the access to drugs still undergoing clinical trials and thus awaiting marketing authorization - so-called "compassionate use". This allows for the prescription (paid by the producer) of drugs not yet authorised, but in advanced clinical experimentation for the same therapeutic indication, for which a favourable evaluation in terms of efficacy and safety is expected. The number of patients with a rare disease benefiting from the supply of orphan drugs under MD of 8 May 2003 has considerably increased from 159 in 2014 to 306 in 2015. - Law 94 of 1998 (former Di Bella law), art. 3 par. 2, as amended by the introduction of Finance Acts of 2007 and 2008, governing the national use of off-label drugs. The off-label drug use, at the expense of NHS, is granted to hospitalised patients, as envisaged by article 3, paragraph 2 of Law Decree 23/1998, following the request of a doctor, based on a named patient, documented evidence, absence of valid therapeutic alternatives. - MD 11/2/1997 allows the import of unauthorised orphan medicinal products on a patient basis. The payer is the Region or the NHS, in the case of hospital or reference centre use.

Several regulations and provisions has been approved in recent years to encourage the access to orphan drugs and to reduce delays for their availability and actual use, representing also one of the main objectives of PNMR 2013-2016. In particular, to make orphan drugs more rapidly available over the national territory, the Balduzzi Law (189/2012, art.12, par. 3) has allowed pharmaceutical companies to submit an application for price and reimbursement to AIFA, after the CHMP (Committee for Medicinal Products for Human Use) approval, and, therefore, before marketing authorization of the drug by European Commission. In addition, drugs approved by

Co-funded by
the Health Programme
of the European Union

the centralized procedure for which negotiation on reimbursement has not started yet, may be placed in a specific class (Cnn), in order to ensure their immediate availability on the market. Based on Decree Law 69/2013, art. 44 (provisions for the classification of orphan drugs of exceptional therapeutic relevance), AIFA evaluates for classification and reimbursement by NHS, orphan drugs of exceptional therapeutic relevance, for which an application was submitted with the relevant documents. Such submissions are evaluated as priorities and before applications pending on the date of submission of the classification request. In such case, the delay for evaluation is shorten to 100 days (the so-called "fast track for authorization"). If the application is not submitted within 30 days from the release of the marketing authorization of an orphan drug or of exceptional therapeutic relevance, AIFA invites the holder of the marketing authorization to submit the application for classification and reimbursement within the following 30 days. When this period is expired without any submission, a communication is published on the AIFA website and the drug is not included in the dedicated classification "Cnn" (not negotiated C-class). According to the stability plan of 2014, if the maximum of hospital pharmaceutical expenditure is exceeding and relates to the budget of companies holding orphan drugs, the compensation is divided between all companies holding marketing authorizations, except for companies producing orphan drugs. In addition, the same draft law introduced an economic protection mechanism for the holders of marketing authorizations for orphan drugs on a list approved by the AIFA (Decision n° 10 of 27 February 2014), available in the AIFA website. Where the national pharmaceutical expenditure ceiling is exceeding, those authorization holders are excluded from the payback, which is instead distributed among holders of marketing authorizations in proportion to their respective pharmaceutical sales volumes. Two Committees of the AIFA are involved in the pricing and reimbursement procedure of medical products, the Scientific-Technical Committee (CTS) and the Pricing and Reimbursement Committee (CPR). In Italy, the management of Managed Entry Agreements (MEAs) is built on web-based Registries. Conditions, such as registration of the orphan drugs in the AIFA monitoring Registries, are applied to the prescription of several orphan drugs.

The AIFA Monitoring Registries, including data on diagnosis and follow-up of patients treated with orphan medicinal products, collect data for managing reimbursement schemes and informing price re-negotiation. In 2012, they officially became part of the NHS Information Technology system. MEAs and monitoring registries allow the application of different conditional reimbursement schemes for several orphan drugs (value-based pricing): - Cost-sharing (provides a discount on the price of the first courses of therapy for all eligible patients, as identified by the SmPC); - Risk-sharing (compared to the previous one, the discount applies only to non-responders); - Payment by results (extends the terms of the risk-sharing, with full refund from the pharmaceutical company for all "non-responders").

In recent years, the role of the Chemical Pharmaceutical Military Institute in Florence (a production unit of Agenzia Industrie Difesa, supervised by the Ministry of Defence) has become increasingly important. The PNMR 2013-2016 recognized the need to "enhance and support the role of the Chemical Pharmaceutical Military Institute (SCFM) to ensure availability at reduced costs of drugs and other treatments for rare diseases". This Institute produces drugs for rare or uncommon diseases that are not produced by large pharmaceutical companies because they are unprofitable (e.g. D-Penicillamine, Cholestyramine). It also manufactures galenic preparations not produced for single dispensaries, hospitals or regional facilities, because of variability and discontinuity of human and technological resources, and difficulty in finding low quantities of their active substance on the international market.

The Institute is able to solve also emergency situations caused by the sudden non-availability of essential drugs on the market. The role of this Institute as a Pharmaceutical Institute of the State capable of intervening in the case of shortages, was organically provided by a Collaboration Agreement signed with AIFA on 31 March 2012. - OD are catalogued in A, H and C classes, depending on their reimbursement. In the last years, many Regions have provided RD patients with treatments, otherwise not reimbursed, free of charge, using their own resources, while other Regions, bound to strong budgetary limits and measures to contain their health care cost levels and trends, cannot provide extra LEA services to their citizens, including C Class drugs. For those drugs which are not currently reimbursed by the NHS, reimbursement is regionally based within “extra LEA services”, which means further services decided by the individual Regions and covered by their own economic resources (through the approval of therapeutic protocols for disease entity or authorizations ad personam by Local Health Authorities

Co-funded by
the Health Programme
of the European Union

of patients' residence). – The RD Interregional Board has issued a document, approved by the National Health Commission, defining a proposal for the transfer of data regarding orphan drugs prescription from regional registries directly to AIFA, as many information systems set-up at regional level collect this information routinely from clinicians working in Centres of expertise, thus avoiding a work overload to clinicians. - In 2013, the RD Interregional Board produced a document, approved by the National Health Commission, defining common modalities and pathways to access home cared infusion therapies for RD patients.

As already mentioned, AIFA has established an innovative funding scheme (Fondo AIFA 5%). Established under Article 48 of Law 326/2003 and operative since 2005, the Italian pharmaceutical companies are required to donate 5% of their promotional expenditure to an independent research fund. The fund amounted to approximately 32 million Euros in 2012, and approximately 35.6 million Euros in 2015. Half of this allowance is used for the reimbursement of orphan and life-saving drugs awaiting market entry, while the other half is aimed at supporting independent research, drug information programs and pharmaceutical vigilance. This funding program for independent clinical research on drugs is open to researchers working in public and non-profit institutions. One of the research areas of the program is dedicated to orphan medicinal products for rare diseases. At the beginning of 2009, three calls for proposals (2005-2007) had been finalised and 69 studies received funding in the area of rare diseases. Since 2008, however, rare diseases and orphan medicinal product research were not listed among the priority areas. A new call is expected at the end of 2016.

Other Important Activities:

Telemedicine and e-Health Initiatives **–** In 2014 an agreement on the use of Telemedicine was signed between the Italian State and its regions. This was a framework for the development of specific actions in this field. Following the approval of this document, a working group within the interregional RD Board drafted a proposal of an agreement on the teleconsultation activity in the field of RDs. This activity lead to the approval of a subsequent agreement between the State and the Regions on *Teleconsultation supporting RD care Networks,* approved in January 2015.

Since 2002, information systems have been implemented which seek to support the functioning of the RD care networks established at the regional level. Over the years these systems have become more and more complex. They are shared among groups of Regions, covering a wide area of the country. The aim is to support the functioning of the established regional/interregional RD care networks, through recognition of the teleconsultation activity performed by clinicians working within Centres of Expertise as a response to clinical questions regarding diagnostics, therapeutic and patient management issues. This activity is centred on the transfer of information through use of IT tools, rather than the physical movement of patients. The agreement establishes an experimental phase which should address the issues of how to pay for the provision of teleconsultation activities, with a particular focus on cost-effectiveness and cost benefit analysis.

Consortia to support Italian engagement in ERNs – during the preparatory phase preceding the European Commission call for applications for European Reference Networks (ERNs), Italian Regions formulated a proposal regarding Italian Centres' participation within ERNs. The aim of the proposal was to support the participation of Centres which fulfilled the EC criteria and to create a strong relationship between the future ERN structures and the national/regional organisation already established and is committed to the care of Persons Living with Rare Diseases (PLWRD). The main points of the proposal are as follows:

- The Selection of Centres is a transparent process based on agreed, predefined criteria. The number of patients cared for, as documented by data collected from the national and regional registries, is a guiding criteria. Only Centres which have a significant number of patients which fulfils the current established thresholds, depending upon disease epidemiology, are eligible for participation in ERNs
- The establishment of 21 Consortia at a national level, each one dealing with one of the broad groupings of rare diseases around which ERNs are organised. Consortia are composed of centres

Co-funded by
the Health Programme
of the European Union

which have been deemed eligible for participation by the Ministry of Health and Regional representatives and representatives of patient organisations.

A specific charter governs the Consortia's establishment and day to day functioning. Consortia undergo a periodic monitoring process of their activities and are dynamic in their Centre composition, according to the fulfilment of specific criteria. The proposal was jointly submitted by the Presidents of all Regions to the Ministry of Health. The same proposal was submitted to the Ministry of Health by the High Council of Health (Consiglio Superiore di Sanita) and received the support of POs.

According to the proposal the Consortia were granted permission to participate as Italian Centres within ERN applications. Considering the short time frame allotted by the European Commission for ERN coordinators to coordinate, complete and submit their applications only one Italian HCP was granted endorsement; however, the proposal is following its course and all Regions have supported it.

The new essential levels of care – The Ministerial decree 279/2001 established an inventory of rare conditions. This inventory provided details of some 284 single rare diseases and 47 groups of diseases which receive specific cost exemption. The list constitutes the 'essential level of care – Livelli Essenziali di Assistenza – LEA'. The LEA services provided by the National Health System (NHS) to citizens are essential services granted to all Italian citizens or foreigners legally residing within Italy. They are provided after the patient pays a prescription charge, known as a co-payment. In agreement with Decree 279/2001, all LEA services are free to citizen's affects by a rare disease included in the aforementioned list. A major problem is that only a percentage of the total number of rare diseases within Italy are included in the list which ensures access to benefits. The acts that updates the LEAs, drawn up by the Ministry of Health in agreement with the Italian Regions, has not yet come into force but it is in an advanced stage of approval. When available the act will allow further improvement in the areas of quality, appropriateness and efficiency as more diseases and groups of diseases will be addressed, improving greatly upon the 2001 list. However it has been decided that rare tumours will not be included within the update. The act will also add additional data on procedures and prostheses etc. which in earlier years has not been addressed.

Co-funded by
the Health Programme
of the European Union