

2013 REPORT ON THE STATE OF THE ART OF RARE DISEASE ACTIVITIES IN EUROPE



STATE OF THE ART OF RARE DISEASE ACTIVITIES IN ITALY

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More information on the European Union Committee of Experts on Rare Diseases can be found at www.eucerd.eu.

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ACRONYMS

CAT - Committee for Advanced Therapies at EMA
CHMP - Committee for Medicinal Products for Human Use at EMA
COMP - Committee on Orphan Medicinal Products at EMA
DG - Directorate General
DG Enterprise - European Commission Directorate General Enterprise and Industry
DG Research - European Commission Directorate General Research
DG Sanco - European Commission Directorate General Health and Consumers
EC - European Commission
ECRD - European Conference on Rare Diseases
EEA - European Economic Area
EMA - European Medicines Agency
ERN - European reference network
EU - European Union
EUCERD - European Union Committee of Experts on Rare Diseases
EUROCAT - European surveillance of congenital anomalies
EUROPLAN - European Project for Rare Diseases National Plans Development
EURORDIS - European Organisation for Rare Diseases
FDA - US Food and Drug Administration
HLG - High Level Group for Health Services and Medical Care
HTA - Health Technology Assessment
IRDiRC – International Rare Diseases Research Consortium
JA - Joint Action
MA - Market Authorisation
MoH - Ministry of Health
MS - Member State
NBS - New born screening
NCA - National Competent Authorities
NHS - National Health System
PDCO - Paediatric Committee at EMA
RDTF - EC Rare Disease Task Force
WG - Working Group
WHO - World Health Organization

GENERAL INTRODUCTION

This document was produced by the Scientific Secretariat of the European Union Committee of Experts on Rare Diseases (EUCERD), through the EUCERD Joint Action: Working for Rare Diseases (N° 2011 22 01), which covers a three year period (March 2012 – February 2015).

The present report aims to provide an informative and descriptive overview of rare disease activities at European Union (EU) and Member State (MS) level in the field of rare diseases and orphan medicinal products up to the end of 2012. A range of stakeholders in each Member State/country have been consulted during the elaboration of the report, which has been validated as an accurate representation of activities at national level, to the best of their knowledge, by the Member State/country representatives of the European Union Committee of Experts on Rare Diseases. The reader, however, should bear in mind that the information provided is not exhaustive and is not an official position of the European Commission, its Agencies or national health authorities.

The report is split into six parts:

Part I: Overview of rare disease activities in Europe

Part II: Key developments in the field of rare diseases in 2012

Part III: European Commission activities in the field of rare diseases

Part IV: European Medicines Agency activities and other European activities in the field of rare diseases

Part V: Activities in EU Member States and other European countries in the field of rare diseases

Part VI: Activities at National level in each EU Member State and other European countries in the field of rare diseases

Each part contains the following description of the methodology, sources and validation process of the entire report, and concludes with a selected bibliography and list of persons having contributed to the report.

The present document contains the information from Parts II and V of the report concerning Italy. A list of contributors to the report and selected sources are in annex of this document. For more information about the elaboration and validation procedure for the report, please refer to the general introduction of the main report.

RARE DISEASE ACTIVITIES IN ITALY

Definition of a rare disease

Stakeholders in Italy accept the European Regulation on Orphan Medicinal Products definition of a prevalence of no more than 5 in 10 000 individuals.

National plan/strategy for rare diseases and related actions

Although there is no specific national plan/strategy for rare diseases in Italy, they have been designated since 1998 as a health care priority in the context of the 3-year national health plans, which are intended by the national government as directions for actions at a national level, whilst the responsibility for actual implementation of measures is attributed to the regional governments. A coordinated and comprehensive framework of actions has been set up by the Ministry of Health Decree 279/2001, which established a national network for prevention, surveillance, diagnosis and treatment of rare diseases, a National Registry of Rare Diseases, a waiver for medical care cost, a diagnostic work-up and therapy for patients with a suspicion or diagnosis of one of the rare diseases included in an identified list. The Ministerial Decree 279/2001 established an inventory (*Livelli Essenziali di Assistenza - LEA*) of rare conditions (284 single rare diseases and 47 groups of diseases), which receive specific cost exemption. These diseases are assessed as being chronic, debilitating and requiring a high cost treatment. The LEA lists services provided by the National Health System (NHS) to citizens representing the “essential” services, granted to all Italian citizens or foreigners legally resident in Italy, and they are currently provided after paying a prescription charge as “co-payment”. In accordance with Decree 279/2001, all LEA services are totally free for citizens affected by a rare disease in the list. A major problem is that only a few hundred of rare diseases and some groups of diseases are included in this inventory, which is not regularly updated, denying cost exemption for diseases not included in the list. The act that updates the LEAs, drawn up by the Ministry of Health, has not yet come into force, because the Ministry of Finance is still assessing its feasibility and LEAs remain as first defined in 2001. When effective, the act will allow progress in quality, appropriateness and efficiency, because it includes not only a new list of 110 additional diseases, but also a list of procedures (for example, laboratory assays for the diagnosis of metabolic diseases). Following repeated requests to the Ministry of Health to add specific rare conditions to the list, stakeholders have joined together and circulated in 2012 a petition demanding that diseases not included under the current scheme should be added. Many of these are conditions identified in the most recent years following advancement of scientific and medical knowledge. While certain Regions of the country have recognised and extended care to some diseases not included under Decree 279/2001, rare disease patients in other Regions remain without exemption for co-payment for diagnostics, treatment and care. The Europe-wide petition was launched to bring attention to this issue. On December 2012, the Minister of Health, prof. Renato Balduzzi, has approved the new list of 110 additional single/group of rare diseases and send it for final endorsement to the Ministry of Economy.

A Committee ensures the interregional coordination for rare diseases between the Ministry of Health, the Istituto Superiore di Sanità (ISS – the National Institute for Health - NIH), and all Italian Regions. This Committee has several aims, which include harmonisation of the regional service networks for rare diseases, implementation of the National Registry for rare diseases and management of the list of rare diseases for which patients can obtain free diagnosis and treatment. Rare diseases’ costs are included in the general national health care budget, but €20 million of the total National Health Fund are assigned to rare diseases (art. 1, par. 34 and 34bis, Law dated 23 December 1996, n. 662 and the Agreement between the Government, Regions and the Provinces of Trento and Bolzano, concerning guidelines for the correct use of bound resources by the special statute Regions and Provinces). Until 2010, dedicated funds were available for the implementation of specific projects aimed at strengthening the regional service networks (€30 million for 2008 and €5 million for the following years).

In 2008 the National Centre for Rare Diseases (CNMR) was established at ISS, with the mission of promoting and developing scientific research and public health actions, as well as providing technical expertise and information on rare diseases and orphan medicinal products, aimed at the prevention, treatment and surveillance of these diseases. The CNMR took over the activities carried out for many years by a specific unit within the ISS to tackle rare diseases¹.

¹ www.iss.it/cnmr

In 2009, following an agreement between the Ministry of Health, the NIH and the Italian Regions, €8 million were allocated to research projects on rare diseases: €5 million from Ministry of Health and Welfare and €3 million from AIFA (the Italian Drug Medicines Agency).

On 11-13 November 2010 the Italian Federation for Rare Diseases (UNIAMO FIMR Onlus), in collaboration with EURORDIS, organised a national conference on rare diseases² in Florence in the context of the EUROPLAN project. All stakeholders showed great interest in the sessions and worked together to draw up a final report, whose results were presented during a final plenary session open to the public. The aim was to develop an integrated, global and long term strategy for rare diseases in Italy, with the active involvement of all stakeholders to share common European guidelines. Several drafts of laws focusing on the incentives for research and access to therapies for rare diseases and the production of orphan medicinal products have been presented to the Italian Parliament over the last few years. Their approval lies outside the direct domain of the Ministry of Health.

In 2011 a working group was established at the Ministry of Health in Rome to thoroughly analyse the issues related to the National Plan for Rare Diseases and to draft the preliminary document. On 23 February 2012, a conference was held at the Chamber of Deputies, and a white paper presented, with the aim of encouraging the government to put in place the rare diseases plan. Between March and April 2012 both Orphanet and UNIAMO organised public consultation on rare diseases with the aim of providing input from stakeholder into the process. The working group of the Ministry of Health preparing the draft of the national plan concluded in June 2012, and the document was sent by the Ministry of Health to AIFA for comments and subsequently again to the Ministry of Health for final assessment. The document was illustrated officially in December 2012 at the Ministry of Health in the presence of 200 stakeholders. The next step is for the document to be commented on by stakeholders. Their comments will be evaluated and implemented into the document by the Ministry of Health and sent for approval by the permanent Conference for relations between State, Regions and the autonomous provinces of Trento and Bolzano.

On 25 May 2011 the Permanent Conference for relations between State, Regions and Autonomous Provinces of Trento and Bolzano, ratified an agreement, formalising the engagement of health authorities in guaranteeing, through concrete actions, including the global, continuous and homogeneous nationwide management of patients affected by neuromuscular diseases. This goal was achieved via the intensive work carried out by the Ministerial Conference for Neuromuscular Diseases.

The CNMR at ISS coordinated from 2008-2011 the European Project for Rare Diseases National Plans Development (EUROPLAN). The project was co-funded by the EC to promote and implement National Plans or Strategies to tackle rare diseases, to share relevant experiences within countries, linking national efforts with a common strategy at European level. This “double-level” approach ensures that progress is globally coherent and follows common orientations throughout Europe. These activities continue under the EUCERD Joint Action with the main goal of establishing an international and interactive network of stakeholders (mainly policy makers) to speed up the elaboration and the implementation of Rare Diseases National Plans/Strategies, through scientific and technical assistance, workshops and the active participation of patients Groups (EURORDIS and National Alliances). In 2012 a group of key indicators for National Plans on Rare Disease was selected to be considered by the EUCERD with a view to adopting a recommendation in this area.

Centres of expertise

In 2001, the Ministerial Decree 279/2001 foresaw the establishment of a national network for rare diseases (Rete Nazionale delle Malattie Rare), made up of hospitals and referral centres, for around 500 rare diseases, those included in the aforementioned list (LEA). Soon after the delivery of the Ministerial Decree, the Italian Constitution was changed, and health programmes and their organisation were delegated to the Regions. Because of their autonomy, the 20 Regions used different criteria to identify centres for rare diseases and adopted different models to organise their networks. Around 215 centres have been identified.

According to the n. 279/2001 decree, each patient suspected to be affected by a rare disease is addressed to designated hospitals where a free of charge diagnosis can be achieved and, if the disease is confirmed, free treatment is offered by any hospital or outpatient facility within the NHS. Coordination centres have been created at regional level in order to manage the activities of referral centres, to exchange information between them, and to provide expertise and data to the regional rare disease registries.

²http://download.EURORDIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_italy_europlan.pdf

In 2011, UNIAMO F.I.M.R.³ developed the project “A Community for Rare Diseases”, aimed at defining a model to assess the quality of expertise centres for rare diseases in Italy. The project gathered all relevant stakeholders who reached a common definition of a Centre of Expertise.

Registries

The Italian National Registry for Rare Diseases, was established at ISS in 2001 in agreement with article 3 of the Ministerial Decree 279/2001. It is located at Italian CNMR– ISS and it is supported by public funds. The general objectives are epidemiological surveillance of rare diseases and national and regional planning of measures to assist rare disease patients. Specific objectives include the following: i) estimation of incidence and prevalence; ii) temporal and geographical distribution of cases and diseases at national level; iii) diagnostic delay. The legal provisions envisage the Registry as a tool to support scientific research in the clinical, biomedical and epidemiological fields. The National Registry collects the data coming from Regional registries. From 2001 onwards each Italian Region established its own registry for rare diseases. These registries collect epidemiological information provided by accredited Centres for rare diseases (Presidi) and every 6 months they send the agreed common data set to the National Registry. The Regional Registries differ in their internal organisation, aims and collected information. Some of them have mainly epidemiological and public health purposes to support regional planning, while others are aimed at evaluating health services and diagnostic procedures. Agreements have been established between regional administrations in order to create interregional registries. These registries have been established between Piedmont and Valle d'Aosta, and between Veneto and Autonomous Provinces of Trento and Bolzano, Emilia-Romagna, Liguria, Campania and Puglia. Each interregional system has its informatics infrastructure, acting as a network connecting different centres involved in the management of patients with rare diseases.

On November 2011 the CNMR-ISS published the first Report on “National Registry and Regional/Interregional Registries for rare diseases⁴”, describing the surveillance system for rare diseases in Italy. In addition to a background of European initiatives on rare diseases, this Report also provides detailed information of the evolution of Italian regulatory and institutional context; the steps towards planning and implanting the National Registry; a description of regional/interregional registries; the data quality assessment; the methodological models for estimating epidemiological indicators. The National Registry provides a tool for epidemiological surveillance of rare diseases and evaluating health care programs. The Registry has a strong legal support and its aims are connected with the exemptions from the costs associated with the delivery of care; is a web-based registry in compliance with the legal and ethical requirements; is a population-based registry, although the regional coverage is heterogeneous; provides important public health indicators. The National Registry is linked to other interregional, regional and international registries.

A congress on the National Registry and Regional and Interregional Registries for rare diseases was held in Rome on 22 February 2012, to illustrate the results, to discuss and agree among all actors on actions to improve further the performance of the National Registry.

The CNMR is also providing support to spontaneous independent registries promoted by patients and run by clinicians: in the last years the Italian Registry of Paroxysmal Nocturnal Haemoglobinuria and Cystic Fibrosis have been established, with the assistance of CNMR. Registry initiatives for rare diseases will be a focus of the future National Plan for Rare Diseases.

Italy also participates in European registries such as EUROCAT, EIMD, EURO-WABB, EuroWilson, TREAT-NMD, HAE-registry, RBDD, AIR and EURO CARE CF.

Neonatal screening policy

In Italy, neonatal screening is mandatory for cystic fibrosis, congenital hypothyroidism and phenylketonuria (Law 104, 5 February 1992). Some Regions perform screening of additional diseases including adrenal hyperplasia, biotinidase deficiency, maple-syrup urine disease, and galactosaemia. Other Regions, including Tuscany, Sicily and Emilia Romagna, adopted wider neonatal screening programs to include a number of metabolic disorders, based on the guidelines developed by scientific societies. According to SIMMESN (Società Italiana per lo Studio delle Malattie Metaboliche Ereditarie e lo Screening Neonatale⁵), about one fifth of the Italian newborn population underwent an expanded screening in 2011. UNIAMO F.I.M.R. sent a position paper on this subject as Memorandum for the XII Social Affairs Commission of the Chamber of Deputies on Draft Law No. 5,440 Conversion into law of Decree-Law of 13 September 2012, n. 158 laying out “urgent measures to

³ <http://www.uniamo.org/>

⁴ <http://www.iss.it/binary/publ/cont/undici20WEB.pdf>

⁵ www.sismme.it/it/documents/rt_screening/rt_screening_2011.pdf

promote the development of the country by a higher level of protection of health”, calling for a gradual expansion of neonatal screening programs for all rare diseases for which there is evidence of appropriateness and not just to rare diseases for which a cure already exists. However, it will be mandatory to define a common set of standards, procedures and methodologies at the national level to ensure an effective, fair and appropriate disease screening as well as to assure adequate health and social post screening management.

At European level, the “Tender on EU newborn screening practices” had the aims of identifying and evaluating all aspects deemed relevant to the implementation of a public health action in newborn screening (NBS), taking into consideration the views of professionals, patients and health authorities. This project, funded by European Commission DG SANCO, was coordinated by CNMR-ISS, with the intent to support actions at the Community level, to identify the strategies which the European Commission could adopt to promote the establishment and improvement of NBS programmes in EU. All relevant documents elaborated by the Tender and the final reports are available at the www.iss.it/cnmr website. In line with the results obtained during this Tender, in 2011 the Italian Ministry of Health funded a project on neonatal screening aimed at harmonising access to health services in the Italian Regions. The project, coordinated by the CNMR-ISS, is carried out in collaboration with the Ministry of Health, the Italian Agency for Regional Health Services (Age.Na.S), the Tavolo Interregionale Malattie Rare, and two Italian Scientific Societies (SISMMESN and SIGU).

Genetic testing

In an international context, Italy is one of the few countries to monitor genetic test use (this survey was implemented in the 1980s), and recently this monitoring has expanded to include clinical and laboratory activities carried out by Medical Genetic Institutes and also private laboratories since 2009^{5,6}. This census, promoted by SIGU, surveys the services provided by Italian Medical Genetic Centres and involves the NHS bodies, the IRCCSs (Excellence Centres for Healthcare and Research), the University Institutes, the CNR (Research National Council) laboratories, and private laboratories. Data collection takes into account the typology of the Institutes, number and functions of the laboratory staff, cytogenetic analyses, genetic-molecular and immunogenetics analyses, and clinical activities, including genetic counselling. Certified quality systems adopted by the Institutes and the adequacy of some genetic tests have been also checked.

The survey concerning the 2011 data was carried out in 2012. The census was made possible thanks to the collaboration of the Bambino Gesù Children Hospital, Orphanet-Italy, and SIGU. On the whole, 517 services hosted by 268 Hospitals or Institutions were surveyed, including 145 clinical genetic services, and 153 cytogenetic, 198 molecular genetics and 21 immunogenetics laboratories. The 53% of services are located in the Northern regions, the 20% in the Central regions, 17% in the Southern regions, and 10% in Sicily and Sardinia. About 74% of these services were accredited and 55% certified.

The CNMR-ISS is in charge of carrying out the National External Quality Control Scheme for genetic tests. This scheme includes molecular and cytogenetic tests and has been addressed to public laboratories which provide genetic tests. This activity is dependent on a Steering Committee, composed of experts who evaluate the results of cytogenetic and molecular genetic tests. All strategies used for the project have been discussed and determined through a consensus by the Steering Committee. In 2009, this scheme was extended also to private genetic laboratories. A Steering Committee, composed of experts, evaluates the results of cytogenetic and molecular genetic tests. All strategies used for the project have been discussed and determined through a consensus by the Steering Committee. In 2009, a fee for participation was introduced by a national decree for all participant public and private laboratories. At the end of each trial of external quality control, each laboratory receives its own results. In addition, the CNMR-ISS organises a national Conference to illustrate the main results. To date eight rounds have been completed and overall 112 laboratories have been monitored in the context of the National External Quality Control Scheme. In particular, as regard molecular genetics, in 2012, national experts have assessed laboratory performance on genotyping, interpretation, and reporting of test results for a total of 404 different DNA samples sent to 68 public and private laboratories. In addition, 75 laboratories participated in one or more schemes of constitutional or cancer cytogenetic quality control.

The CNMR-ISS is a member of the management board of the European Molecular Genetics Quality Network (EMQN⁶), a not-for-profit organisation promoting quality in molecular genetic testing by establishing, harmonising and disseminating best practice. EMQN provides external quality assessment to labs worldwide in collaboration with other organisations, including EuroGenTest, CF Network, ESP, UKNEQAS for Molecular Genetics, RCPA QAP, and the EAA.

⁶ <http://www.emqn.org/emqn/Home>

Genetic tests for 1042 genes and 1107 diseases are registered in the Orphanet database⁷.

National alliances of patient organisations and patient representation

In Italy, UNIAMO F.I.M.R is the National Alliance of Rare Disease Patient Organisations. Member of EURORDIS and established in 1999, UNIAMO gathers over 100 patient organisations representing more than 600 rare diseases. UNIAMO publishes a newsletter and organises regular meetings and conferences. The goal of this Federation is to serve as a reference and representative voice for rare diseases, bringing opinions of patients and their families in the public health decision-making processes at regional and national level. It is committed in the protection of patients' rights and improvement of the quality of life of rare disease patients and their families. UNIAMO is currently organising Regional Delegations: a coordination of territorial groups in order to develop or strengthen the relationship of solidarity and cooperation between member organisations and to foster, at local level, initiatives and policies promoted by the Federation. The Federation participates in the regional boards on Rare Diseases of Apulia, Liguria, Lazio and Lombardy regions. In addition, UNIAMO F.I.M.R. has played an important role in the Lombardy Region, in particular during the discussion of rare disease diagnostic and therapeutic pathways, having been enrolled by patients lacking reference associations on the territory.

In 2012, a framework agreement was signed by UNIAMO F.I.M.R. with the Telethon Foundation Onlus-CTFO, to promote access to TNGB genetic biobanks by members of the associations' federation.

In October 2012, the Ministry of Welfare recognised UNIAMO F.I.M.R. as an Association of Social Utility.

There is no public funding scheme for activities of the patients' organisations, but national governmental institutions (e.g. the Welfare Ministry) and local institutions support specific actions. Grants for activities of patients' organisations are coming mainly from private sponsorship, charities and income tax donations. UNIAMO's goals for 2010-2012 were reached taking advantage from these funds, which have granted continuity to the Federation's activities, and sustained several projects:

- "Knowing to assist", carried out in collaboration with Farindustria and Scientific Societies, is aimed at training general practitioners and paediatricians regarding rare diseases. The project is based on a covenant of understanding signed by several Institutions. The project will cover the whole Italian territory by 2013.
- "Galeno Help" results from a memorandum of understanding between UNIAMO F.I.M.R. and the professional pharmacists' federation (UPFARM), with the intention of giving practical support to patients who need drugs which are difficult to find. Many of these drugs can be prepared in the galenic laboratories of the pharmacies in a personalised manner. "Galeno Help-Pharmacist helps for rare disease patients" is a national service offering the possibility to quickly and easily find the nearest participating pharmacy.
- "Mercury", funded by the Ministry of Labour and Social Affairs in cooperation with the signatories of the aforementioned covenant of understanding, has been designed to train the general practitioners and paediatricians in rare diseases. The major goal of the project is to implement and enhance the web site "Malatirari.it" and turn it into a platform to meet the rare disease community's needs along the complex path from a suspected case to diagnosis of rare disease. The site will become a virtual place where information based on direct experience can be shared by patients, relatives and health professionals involved in the diagnosis and treatment of these diseases. In 2012 the data were implemented with an area dedicated to health professionals, with a restricted access.
- "The Atlantis Code" is aimed at fostering the culture of research in rare diseases. Developed in partnership with the Telethon Foundation, it involves rare disease patient organisations in the attempt to identify research priorities and provide answers to the patients' needs. Three seminars were organised. The outcomes of this survey were matched up with the results of a similar investigation carried out by EURORDIS at European level.
- "Momo" intends to bring together, with a unique voice, the demands of different groups of rare disease patients at Regional level. For this purpose, regional UNIAMO delegations were created in the context of a progressive regionalisation of the federation.
- "A Community for Rare Diseases", is aimed at developing a model to assess the quality of expertise centres for rare diseases in Italy. Since many Regions are reorganising their network of expertise centres, it was felt important to share similar inclusion criteria. Participants were the Ministry of

⁷ Information extracted from Orphanet in December 2012.

Health, the Ministry of Labour and Social Affairs, ISS, Regions, local health authorities, Orphanet Italy, expert centres, municipal districts, general practitioners, primary care paediatricians, biobanks and patients organisations. On September 20, 2012 an agreement was signed with Age.Na.S., the National Agency for Regional Health Care Services, for the implementation of the second phase of the project which will assess some previously defined centres of expertise, with a major emphasis on the geographic distribution of a selected group of centres dedicated to distinct diseases (e.g. haemoglobinopathies).

- "Diaspro Rosso", a pilot project concluded in 2012, has provided an accurate, effective and efficient model for detecting the care needs and the social-economic costs for families with patients affected by rare diseases. The model will be presented to the institutional actors as a decision-making tool to be used to develop policies on social health based on concrete data.
- "Dumbo" was aimed at developing a model for the social reporting of patients' organisations. This model was illustrated to the Associations' members in several meetings and UNIAMO F.I.M.R. used it to present its first Social Report.

In September 2006, the National Council for Rare Diseases (the "Consulta") was established as a national independent representative body and its activities were hosted by the CNMR-ISS. It was originally composed of 34 members (one for each participating rare disease patient organisation), which was then lowered to 28; these members were elected by 264 rare disease patient organisations' representatives. The Consulta aimed at identifying the priorities in the field of rare diseases, to define the problems, to recognise solutions for the patients and their families, to involve rare disease patients in the legislative bodies' decisions, and to strengthen the links between RD organisations and the society. By the end of 2010, the Consulta⁸ constituted itself as a private legal organisation which keeps on executing the tasks entrusted by the Minister of Health and affords some of the daily problems of rare disease patients.

The Council for Neurodegenerative Diseases was established by the Ministry of Labour, Health and Social Affairs, through a Ministerial Decree (27 February 2009). The Council brings together patients organisations for neurodegenerative diseases, such as amyotrophic lateral sclerosis, muscular dystrophy, spinal muscular atrophy, advanced stage muscular dystrophy and locked-in syndrome, experts on these disorders, and representatives from Regions and the Ministry of Health. Based on the final document produced by the Council, a proposal for an agreement among State and Regions on health care pathways has been drawn up and is currently assessed by the Regions.

The Veneto Region issued a call in March 2010 for the provision of contributions to Social Promotion Associations, for projects and initiatives identified in several areas of interest, including initiatives aimed at increasing the awareness and knowledge of rare diseases. Several of these projects have been funded in 2011.

In November 2012, the MIR (Movimento Italiano dei Malati Rari) was established by 15 patients' associations.

Sources of information on rare diseases and national help lines

Orphanet activity in Italy

Since 2001, a dedicated Orphanet team was established in Italy, which is hosted by the Bambino Gesù Children Hospital in Rome. This team is in charge of collecting data on rare diseases-related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations, networks) for entry into the Orphanet database. This group was designated in 2010 by the Ministry of Health as the official Orphanet team for Italy. The Orphanet portal is available in Italian and the team also maintains the Orphanet Italy national website⁹.

On the occasion of the tenth anniversary of Orphanet Italy, an updated Italian Directory of Services, *Annuario Orphanet delle Malattie Rare 2011*, was presented at the Ministry of Health. In attendance was Italian Health Minister, as well as the Director of the Paediatric Hospital Bambino Gesù, hosting the Italian Orphanet headquarters; Orphanet country coordinator and Scientific Director at Paediatric Hospital Bambino Gesù; President of Farindustria, which financed this second book; and President of UNIAMO F.I.M.R.

In December 2011, the Italian Minister of Health, Prof. Renato Balduzzi, presented the "Relazione sullo stato sanitario del paese 2009-2010" (Report on country sanitary status 2009-2010). For the very first time, the Italian Ministry of Health identified Orphanet as a reference source for rare diseases and orphan drugs, stressing the relevance of the joint action established between the Ministry of Health and Orphanet-Italia.

⁸ www.cndmr.it

⁹ <http://www.orphanet-italia.it/national/IT-IT/index/homepage/>

In May 2011, Orphanet Italy signed a collaboration agreement with *Fondazione Cesare Serono* linking the two web sites in order to spread information on rare diseases to a broader public.

From September 2011 onwards the Italian Society of Anesthesia, Analgesia and Intensive Paediatric Care (SIAATIP) collaborates with Orphanet Italy to develop the "Orphanet Emergency" guidelines, designed to improve the hospital emergency management of rare diseases, through recommendations about the care of patients who need medical treatment under emergency.

Official information centre for rare diseases

The Ministry of Health organised a specific section for Rare Diseases¹⁰, providing several information, including the list of rare diseases present in the ministerial decree 279/2001.

The CNMR-ISS plays a key role in disseminating information on rare diseases through the official website¹¹ and the Italian national helpline for rare diseases "Telefono Verde Malattie Rare". The website (in Italian and English), updated weekly, is addressed to health operators and institutions, social workers, associations, patients and their families and, in general, the wide public. The site has been structured on two levels: the central site containing general information, and satellite websites containing specific projects and different topics, including Registries (Italian National Registry for Rare Diseases, Italian National Registry for Orphan Drugs, Italian National Registry for Congenital Anomalies), Orphan drugs, Guidelines, Narrative medicine, Folic Acid Italian Network, European projects, Genetic Tests, Patient Organisations. The section "Centres for rare diseases in Italy" lists all Centres accredited by Regions for diagnosis and treatment, which can be searched by disease, code number, Region, etc. Moreover, all contact details of the Regional Coordination Centres are available.

Help line

The Italian national helpline for rare diseases "Telefono Verde Malattie Rare" (no. 800.89.69.49) was set up at CNMR-ISS on February 2008, and is funded by the Ministry of Health. This helpline collaborates with all stakeholders, including the Ministry of Health for legislative and regulatory issues, and it is advertised on the CNMR-ISS web page¹². The line is free and available five days per week (from 9 am to 1 pm). From abroad it is possible to access the line information by using the e-mail address tvmr@iss.it. A group of psychologists, sociologists and medical doctors trained and experienced on telephone counselling, public health policies and management of rare diseases are involved in this activity. The aim of the service is to inform health operators, social workers, patients and their families, and the public at large, on rare diseases (including exemptions from the costs of medical care in Italy), and to address them to the national/Regional network of specialised centres. *Ad hoc* literature researches are performed for specific questions. Information about patient organisations, orphan medicinal products and clinical trials running in Italy and abroad are also provided. A web based system is used for data collection and to provide information, also using national and international databases (e.g. Orphanet, PubMed, ClinicalTrials.gov, etc.). The Italian national helpline for rare diseases is a member of the European Network of Rare Disease Help Lines.

In 2012, the CNMR-ISS started collaborations and training activities for regional help lines (i.e. Contact Centre of Tuscany Coordination Centre for rare diseases) and with Patients' Associations (i.e. Foundation "W Ale –Alessandra Bisceglia").

Other sources of information on rare diseases

Information for patients and health professionals is also provided by websites run by Centres for rare diseases present in some Regions. A specific e-mail address (esenzioni@sanita.it) at the Ministry of Health provides information on issues concerning LEA services and co-payment exemption for rare disease patients. Online Regional information is also available. Other services are run by patient organisations and are largely heterogeneous in their coverage.

The website www.malattirari.it set up by UNIAMO F.I.M.R., provides both general information on legislative and administrative issues and orphan medicinal products, and, at regional level, specific information managed in collaboration with patients' organisations and health professionals.

Many regions have developed their ones websites dedicated to rare diseases, as well as help lines for health operators and patients.

¹⁰ <http://www.salute.gov.it/malattieRare/malattieRare.jsp>

¹¹ www.iss.it/cnmr

¹² www.iss.it/cnmr

On December 2011, OrphaNews-Italia¹³ was launched by the national Orphanet team. This online bulletin offers a complete translation into Italian of the contents of OrphaNews-Europe, and is available from the homepage of Orphanet-Italy and also from the Orphanet Italian country site. The issues of OrphaNews Italia are published online on a regular basis, one week after the publication of the English version. At the end of 2012, 18 issues had been published with a total number of 2465 registered users.

Best practice guidelines

The Ministry of Health and ISS are involved in the National Guidelines System (NGS), which is officially entitled to issue guidelines and to make available any other document drawn up by the Consensus Conferences carried out by NGS. Guidelines published by CNMR-ISS, as part of NGS, include those for Down's syndrome, alternating hemiplegia, hereditary epidermolysis bullosa. Guidelines for tuberous sclerosis and aniridia are under development.

In order to promote the development of high quality best practice guidelines and their use in Italy and across Europe, CNMR-ISS organised national and international training courses (9-11 July 2012) providing participants (health care professionals, policy makers, patients) with the opportunity to learn about the core methodology used to develop best practice guidelines. In addition, CNMR-ISS encourages international debate on the role and quality of best practice guidelines in the field of rare diseases. In particular, a workshop on Clinical Practice Guidelines on Rare Diseases was organised on 23-24 February 2012, aimed at sharing experiences and knowledge and discussing critical methodological issues due to the specificity of rare diseases.

In 2012, CNMR-ISS, 13 institutional partners and one SME have been awarded with a grant by the European Commission, under the Seventh Framework Programme (FP7/2007-2013) for a four-year research project entitled RARE-BestPractices (www.rare-bestpractices.eu), commencing in January 2013. This project will bring together a team of experts in the area of clinical practices guideline, systematic review, health technology assessment, health policy, rare disease epidemiology and public health.

About 85 *Percorsi Diagnostico-Terapeutico-Assistenziali-PDTA* (Diagnostic Therapeutic Care guidelines) dedicated to diagnosis, treatment and clinical management of rare diseases have been developed since 2010 by the Lombardy Region¹³.

The working group of the National Committee for Bioethics (CNB) and the National Committee for Biosecurity, Biotechnology and Life Sciences (CNBBSV) published two reports in 2010 dealing respectively with the issues related to the long storage of biological samples obtained by neonatal screenings, and susceptibility testing and personalised medicine. In 2011, the CNB drafted a document relating to orphan medicinal products for people with rare diseases¹⁴.

Training and education initiatives

In Italy, a second level Master degree in rare diseases is organised by the University of Turin. Rare diseases are present in the undergraduate training and post-graduate courses of the Optional Integrated Degree Course of Medicine and School of Specialisation at the Universities of Padua, Siena and Pisa.

The CNMR-ISS organises residential courses and learning activities dedicated to the empowerment of patients, health professionals and policy makers¹⁵. This program is included within the project "Rare diseases: from monitoring to training" funded by the Ministry of Health.

The CNMR and ISS External Relations Office have developed in several Regions a project for training the general practitioners (GP) and paediatricians to look for rare diseases, in order to reduce delay in diagnosis, to manage patients' care appropriately in the framework of the Italian rare diseases network, and to improve communication skills. To reach this goal, the courses employ an interactive method, Problem-Based Learning (PBL). PBL is an instructional approach that uses a problem as a didactic initial stimulus; learning is achieved by working in small groups assisted by a trained PBL facilitator at the explanation or solution of the problem. The GPs' and paediatricians' participation to the courses has been active and all professionals got positive results in learning assessment questionnaires; ratings reported in satisfaction questionnaires were mostly positive. The training showed that PBL enhances participant activity and provides the opportunity to practice skills, so that they can produce changes in professional practice, and, ultimately, in health care outcomes. In order to improve the training model, patient organisations were involved in new courses, in collaboration with the "W Ale - Alessandra Bisceglia" Foundation, aiming at training GPs and paediatricians on congenital vascular malformations.

¹³ <http://malattierare.marionegri.it/content/view/111>

¹⁴ http://www.governo.it/bioetica/pdf/Maklattie_rare_25112011

¹⁵ <http://www.iss.it/cnmr/appu/index.php?lang=1&tipo=56&anno=2011>

A workshop on Clinical Practice Guidelines on Rare Diseases was organised on 23-24 February 2012, for sharing experiences, knowledge and discussing some methodological related to the specificity of rare diseases.

A major role in educating medical doctors is carried out by patients' organisations (e.g. UNIAMO-F.I.M.R. through the projects "Knowing to assist" and "Mercury", see the "National alliances of patient organisations and patient representation" section).

The Italian Telethon Foundation and Orphanet-Italy joined their respective competences and contact networks in October 2012 to meet the patients' needs and support health professionals via a training course entitled "e-patients, e-parents, e-doctors: le malattie rare via web – opportunità e rischi". Suited for all stakeholders of the rare disease community, this event provided an opportunity to discuss web services and social networks as tools for professionals, patients and their families. During the course, health professionals, journalists, and IT experts presented their experiences to guide the community in using the web as a tool to break the isolation rare diseases can impose. A round table was animated by communication experts on the responsible use of Internet.

On 16 April 2012, the Orphanet team held a training course in Rome for health professionals operating in the Bambino Gesù Children Hospital, aimed at teaching them how to use the Orphanet resources.

National rare disease events in 2012

Since February 2008, UNIAMO F.I.M.R. coordinates the Rare Disease Day events organised by its members throughout the national territory. It provides them with information leaflets, posters, gadgets, T-shirts and banners, created in collaboration with Farindustria, the Serono Foundation and Novartis. Awareness has been achieved through over one hundred local events, in squares, sports halls and schools and through many articles and interviews on rare diseases in newspapers and on TV. The cartoon "Mamma, cosa sono le malattie Rare? – Mum, what are rare diseases?" promoted by UNIAMO F.I.M.R. was shown on Mediaset TV Channels all through February. The Volley Major League collaborated with UNIAMO F.I.M.R. in distributing dedicated information leaflets on rare diseases during the matches where an awareness raising announcement was also made.

On 29 February 2012, the event "La solidarietà che costruisce" was organised at the Italian Senate to promote the Rare Disease Day in Italy, with the participation of several leading figures in the field of the rare diseases. This event raised awareness on the needs and actions in the field of rare diseases, and promoted dialogue between stakeholders and public institutions. During the event, Orphanet-Italy received a prize for its contribution in the "Mercurio" project (update of the malatirari.it web site) managed by UNIAMO F.I.M.R.

To mark Rare Disease Day, the Bambino Gesù Children Paediatric Hospital, in collaboration with Orphanet launched on 27 February 2012, a pilot project on rare diseases for middle schools. The "Virgilio" public school is hosting the project whose aim is to teach children the basics of familial inheritance. Professionals from Bambino Gesù Hospital will work together with teachers and pupils to produce papers, which will be evaluated in the context of a prize-awarding contest. The award ceremony will be held on Rare Disease Day 2013.

The CNMR-ISS presented two different events: a theatre play dedicated to rare diseases, inspired by real events, and the fourth edition of the event "Il Volo di Pegaso - Raccontare le malattie rare: parole e immagini" (Pegasus' Flight – Describing rare diseases through words and images), an art contest on rare diseases. The theatre play "Controvento" (Against the Wind) took place at the Quirino theatre in Rome on 27 February 2012 and the art contest prize-giving at the ISS on the same day. Another institutional event, on 29 February was the initiative "La solidarietà che costruisce" (Creating through solidarity): several leading figures in the field of the rare diseases discussed the topic "L'esperienza, il presente e il futuro per le Malattie Rare in Italia", while a white book "Una incompiuta: le Malattie Rare" was presented by the Senator Antonio Tomassini. Flash mobs were also organised to mark the Day with a closing speech by the Italian Minister of Health, Prof. Renato Balduzzi.

On 29 February 2012, the patient association MITOCON organised a round table focused on research, care and policy concerning rare diseases.

On 8 February 2012, in the Rome Campidoglio a press conference was held for the event "Stammi vicino" (Stay close to me), organised by EEC syndrome International Network Word Communication ONLUS. This event, aimed to foster communication on rare diseases through sport.

On 18 February 2012, on the occasion of the Del Monte Italian Cup final tour, before the beginning of the matches, particular attention was given to the importance of funding rare disease research.

On 4 June 2012, an international congress entitled "Narrative Medicine and Rare Diseases" was held in Rome at the ISS.

On 12 June 2012 a press conference was held at the Senate to mark the launch of the book "Malattie rare: alla ricerca di un approdo" (Rare Diseases: in search of a landing place). This book collects the results of the Public Consultation launched in March 2012 on website and includes interviews of the main Italian and European stakeholders belonging to the academic and institutional world, together with the experience of patients and their families. The aim was to provide input on the elaboration of the National Plan for Rare Diseases.

On 12 July 2012, a press conference was organised in Rome to launch the second edition of the project "MALattie raRE NOSTRUM", promoted by "Tender to Nave Italia", a non-profit foundation and the Bambino Gesù Children Hospital. The project aimed at making a group of children affected by rare diseases more independent, fostering sea and navigation as an education instrument.

From 1 September to 6 September 2012, the first edition of the project "GiRare Mangiando", an initiative of the non-profit organisation UNIAMO Goldin, was held in Venice. This project was designed to provide an information path of independent living for patients affected by metabolic rare diseases. Four young patients were given the opportunity to stay in an apartment in Venice owned by UNIAMO Goldin, profiting by the facilities of the Fantasia restaurant, managed by rare disease patients, and following a program of cultural activities on the territory. The young participants have been supported by the healthcare professionals of the Bambino Gesù Children Hospital.

On 18 September 2012, a conference entitled "The State of Art of Rare Diseases: Rare Diseases and Economic Development" was held in Rome at the Ministry of Health. The Conference focused on several issues related to rare diseases: diagnostic difficulties; lack of therapeutic options and structured care pathways; chronic and debilitating course of the disease; emotional impact due to feelings of isolation experienced when living with one of these diseases. The initiative aimed to identify goals and actions to support health services, industry production and drug companies.

Several dozens of events have been organised locally in all Italian Regions.

Hosted rare disease events in 2012

Amongst the events announced in *Orphanews Europe* were: 15th Biannual Meeting of the European Society for Immunodeficiencies (Florence, 3-6 October 2012), EpiRare International Workshop: Rare Disease and Orphan Drug Registries (Rome, 8-9 October 2012), Goldrain Courses in Clinical Cytogenetics and Prenatal Genetic Diagnosis (Goldrain, 15-21 September 2012) .

Research activities and E-Rare partnership

National research activities

In Italy, there are efforts to coordinate research between Regions, Italian Drug Agency (AIFA)¹⁶, Ministry of Health and ISS. Funds for rare diseases research are provided by Ministry of Health, ISS, AIFA and Ministry of Education, University and Research, Telethon, patient organisations and a few charities. The last Health Ministry call for projects for rare diseases¹⁷ had a total budget of €8 million. The call for projects was published in 2008 and 13 projects were granted in 2010.

A bilateral agreement between Italy (ISS) and USA (NIH) was established with the purpose of developing and increasing research in different fields, including rare diseases since 2002. This agreement is still active.

AIFA issued calls to fund independent researches on the development of orphan medicinal products. In particular, AIFA financed a three-year initiative, launched in 2005, to support clinical research on drugs of interest to the NHS where commercial support is inadequate: one of the concerned areas was the field of rare diseases and orphan medicinal products. Three topics were included in the clinical research area concerning rare diseases: the benefit-risk profile of orphan medicinal products designated by EMA; the benefit-risk profile of off-label drug use (and in particular generics); the benefit-risk profile of drugs for non-responders to standard treatments. Projects in these topic areas were funded for up to a maximum of €300,000, with the therapy costs funded separately. From 2008 onwards rare diseases and orphan medicinal product research is being funded by the Ministry of Health, within the general health research call, with a specific budget reserved for rare diseases research. A specific call to fund research projects on rare diseases was issued by the Ministry of Welfare in 2009.

In 2012 Telethon was able to fund 260 research projects on rare genetic diseases, thanks to the fundraising activities in 2011.

¹⁶ <http://www.agenziafarmaco.gov.it/>

¹⁷ http://www.quotidianosanita.it/cronache/articolo.php?&&articolo_id=1144&&cat_1=1&&cat_2=0

Foundations and associations promote campaigns funding genetic research or research on specific diseases. Voluntary funds can be collected through general taxation.

Participation in European research projects

Italy participates, or has participated, in European rare disease research projects including: AAVEYE, ADIT, ANTIMAL, BIG HEART, BIOMALPAR, BIO-NMD, CELL PID, CARDIOGENET, CUREHLH, CUREFXS, CLINIGENE, CONTICANET, CSI-LTB, DYSCERNE, DRUGSFORD, DEMCHILD, EUROPEDICAT, EUROMOTOR, ESPOIR, EUROSARC, ENRAH, EURADRENAL, EUCILIA, EUCLYD, EMSA-SG, EUROBONET, EUROGROW, EUROLAMINOPATHIES, ENCCA, EUROPAPNET, EUROBNFS, EURENOMICS, EURO-CGD, EURO-SCAR, EUROTRAPS, EURPIFNET, EUROSD, EPINOSTICS, ERMION, EUROGEBETA, EURORETT, EUROPSPA, EUMITOCOMBAT, EURAMY, EURAPS, EUREGENE, EURO CARE-CF, EUROPEAN LEUKEMIA NET, EUROSCA, EUROWILSON, GENESKIN, GENOMIT, INHERITANCE, IMMOMECE, INTRALL, IPF-AE, HAE III, GRIP, IMPACTT, FIGHTHLH, HMA-IRON, HSCR, KINDLERNET, NEUROMICS, MTMPATHIES, LEISHMED, LIGHTS, MALARIA AGE EXPOSURE, MANASP, MITOCIRCLE, MOLDIAG-PACA, MCSCS, MILD-TB, MM-TB, MYELINET, MYORES, MTMPATHIES2, NANOMYC, NEUROKCNQPATHIES, NEUROPRION, NEURO PROMISE, NEUROSIS, NMD-CHIP, NSEURONET, OSTEOPEPE, OPTATIO, OVERMYR, PEROXISOMES, PNSEURONET, PROTHETS, PODONET, PEMPHIGUS, RARE-BESTPRACTICES, RD PLATFORM, RDCONNECT, RISCA, READ-UP, SIOPEN-R-NET, SKIN-DEV, SPASTICMODELS, SME MALARIA, STEM-HD, TAMAHUD, TUB-GENCODEV, TARGETHERPES, TIRCON, VITAL, WHIPPLE'S DISEASE, WHIM-Thernet and WHIMPATH.

E-Rare

Italy, represented by ISS, is a partner of the E-Rare project and took part in all three Joint Transnational Calls. Italy participated in 12 of the 13 consortia selected for funding by the first call. In the second E-Rare transnational call, Italy participated in 8 of the 16 consortia/projects selected for funding with a budget of about €1 million. Italy participated in the 3rd Joint Transnational Call in 2011 and Italian teams have been funded to participate in 7 of the selected consortia. Italy did not take part in the 4th Joint Transnational Call in 2012.

IRDiRC

The ISS and Italian Telethon Foundation are committed members of IRDiRC.

Orphan medicinal products^{18,19}

AIFA is the main body in charge of the introduction of orphan medicinal products into the Italian market. The National Registry of Orphan Drugs includes data on diagnosis and follow-up of patients treated with orphan medicinal products. These drugs are authorised at central level by EMA (European Medicines Agency) and reimbursed by NHS. The National Registry of Orphan Drugs, established by AIFA and managed in collaboration with the National Centre for Rare Diseases, surveys forms for each rare disease and its related drugs, and collects, checks and analyses data sent by Regional Centres authorised to distribute these drugs. The goal of the registry is to have a nationwide coverage, to address all Italian Centres qualified to distribute and prescribe orphan medicinal products.

Orphan medicinal product committee

There is no specific orphan medicinal product committee at national level in Italy.

Orphan medicinal product incentives

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 collects €45 million each year: 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

¹⁸ This section has been written using information from the KCE reports 112B: *Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009* pp.49-53.

¹⁹ This section has been written using the Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. 2005 Revision pp.15-16.

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.

Orphan medicinal product market availability situation

In Italy, 47 out of the 72 orphan medicinal products approved by EMA are launched on the market. The cost of 44 of them is fully paid by NHS, based on a therapeutic indication, while 3 of them are reimbursed under special circumstances (Law 648/96). The other EMA approved drugs have a pending request at AIFA by the companies in charge of pricing and reimbursement²⁰. A list of orphan medicinal products with European marketing authorisation and the date of their publication in the Official Gazette concerning their marketing in Italy is available²¹.

Orphan medicinal product pricing policy

Prices of all medicines for reimbursement by the NHS, including hospital-only drugs, are set by AIFA. Two interministerial committees are involved in this process, the Pricing and Reimbursement Committee and the Technical-Scientific Commission¹⁵.

Orphan medicinal product reimbursement policy

In Italy drugs are catalogued in A and C classes, depending on their reimbursement. Costs of class A drugs are totally paid by NHS and free of charge for citizens, while class C drugs are paid entirely by patients. Many Regions in the last years have supplied class C drugs to their population, while other Regions, bound to strong budgetary limits and measures to contain their health care cost levels and trends, have been forced to not provide extra LEA services to their citizens, including C Class drugs. Reimbursement is granted for all orphan medicinal products which follow the centralised marketing authorisation procedure. Moreover, for all drugs which are not currently classified in class A, reimbursement is regionally based within “extra LEA services”, which means further services decided by the individual Regions and covered by their own economic resources. According to AIFA, the cost of orphan medicinal product raised in 2012 to about €735.00.000, with an 18.7% increase compared to 2011, and an increase of daily doses (DDs) per 1,000 habitants of 8.6%, corresponding to a figure of 0.28.

Some orphan medicinal products can only be dispensed if the details of the patient are entered into the National Registry of Orphan Drugs, containing information on diagnosis and follow-up of the patient²².

Other initiatives to improve access to orphan medicinal products

Italy also has an off-label, compassionate use procedure, regulated by Law 648/96²³ (a list of eligible drugs is annexed to this law). The Technical Committee of AIFA can include a given medication in the official list allowing it to be prescribed at the NHS charge, if for a specific disease there is no therapeutic choice. Three types of medical products can be included: innovative drugs for which the sale is authorised abroad, but not in Italy; drugs which have not yet received an authorisation, but have undergone clinical trials; and drugs to be used for a therapeutic indication different from the one which had been authorised²⁴. A Ministerial Decree of 8 May 2003²⁵ allows for the prescription (paid by the producer) of drugs not yet authorised, but subjected to phase II or III clinical trials for the same therapeutic indication, for which a favourable evaluation in terms of efficacy and safety is expected.

The off-label use of a drug at the expense of NHS is allowed and provided to hospitalised patients, as envisaged by article 3, paragraph 2 of Law Decree²⁶ 23/1998, when decided by a doctor on condition that this decision is made on a named patient basis, documented evidence is provided, and no other treatment is available. Medicines with non-approved indications are supplied through the “fondo AIFA 5%”.

²⁰ According to the Final Report of the Europlan National Conference, 11-13 November 2010.

http://download.EURODIS.org/europlan/2_EUROPLAN_Guidance_Documents_for_the_National_Conference/final_report_italy_europlan.pdf p16.

²¹ http://www.iss.it/binary/orfa/cont/Farmaci_orfani_in_Italia_Feb_2009.pdf (document accessed May 2011 and last updated in February 2009).

²² Orphan Drugs in Europe : Pricing, Reimbursement, Funding & Market Access Issues, Donald Macarthur (2011) p.83

²³ Law 23-12-1996 n. 648. Conversione in legge del D.L. 21 October 1996, n. 536, recante misure per il contenimento della spesa farmaceutica e la rideterminazione del tetto di spesa per l'anno 1996 (published in GU 23 December 1996, n. 300).

²⁴ KCE reports 112B: Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 p.50.

²⁵ Ministerial Decree 8 May 2003 *Uso terapeutico di medicinale sottoposto a sperimentazione clinica* (published in GU 28 July 2003, n. 173).

²⁶ Law Decree 17-2-1998 n. 23 Disposizioni urgenti in materia di sperimentazioni cliniche in campo oncologico e altre misure in materia sanitaria. (published in GU 17 February 1998, n. 39).

The Ministerial Decree 11/2/1997 allows the import of unauthorised orphan medicinal products on a patient basis: in this instance, the payer is the Region or the NHS, in the case of hospital or reference centre use²⁷.

At the end of 2010, an agreement between central Government and the Regions has established that 'potential/important therapeutic innovations' are automatically included on the regional formularies, so they should be available simultaneously and quickly across Italy¹⁵.

Other therapies for rare diseases

No specific information reported.

Orphan devices

No specific information reported.

Specialised social services

Respite care services, including "respite interventions" for families, either in residential or semi-residential structures, are included among the national LEA services and are mainly provided by governmental or accredited institutions, but are unevenly distributed within Italy and sometimes are provided by the private sector: full or partial reimbursement is offered and some patient organisations provide services free of charge. Lodging, meals and other housing services are to be paid for by patients, or by municipalities, in the case of low-income situations.

Therapeutic recreational programmes are provided, although unevenly, by local authorities' social services under the administration of the municipalities. The institutional framework is complex: at governmental level, this competence belongs to the Ministry of Social Affairs, but the legislative power in terms of social policies is under the exclusive responsibility of Regions (Constitutional Law no. 3 October 18, 2001). It is the competence of the State to determine the essential level of benefits relating to civil and social rights that must be guaranteed throughout the national territory; the municipalities are the holders of administrative functions relating to social interventions undertaken at local level (Law n.328 November 8, 2000). Some municipalities assure public services, but more often services are run by private bodies (companies or patient organisations) commissioned by social authorities.

Some summer camps are informally or formally organised by patient organisations (e.g. the Dynamo Camp in Tuscany). These services are sometimes fully reimbursed, or there is a partial contribution according to the family income.

Additional social and/or financial support is available for families and patients with disabilities (Law Decree n. 509, 23 November 1988). Services promoting social integration of patients with disabilities in schools and the workplace are provided by the Government. The provision of specialised social services is thus unevenly distributed at national level. The average per-capita social spending of municipalities varies from €30 to €250²¹, and it is not considered satisfactory because the rules of access to services and the sharing costs are different in Regions. Furthermore there is a reduction in available resources: in years 2008-2011 there was a 89% cut of the National Welfare Fund, down from €1 billion 200 million to €69 million, only covered in part by Regions and municipalities.

DEVELOPMENT OF RARE DISEASE ACTIVITIES IN 2012 IN ITALY

National plan/strategy for rare diseases and related actions

In 2011 a working group was established at the Ministry of Health in Rome to thoroughly analyse the issues related to the National Plan for Rare Diseases and to draft the preliminary document. On 23 February 2012, a

²⁷ EMINET Initial investigation to assess the feasibility of a coordinated system to access orphan medicines, C. Hahl, F. Bachner (2011) p54.

²¹ Istat 2008: *Gli interventi e i servizi sociali dei comuni singoli e associati*.

http://www3.istat.it/salastampa/comunicati/non_calendario/20110419_00/testointegrale20110419.pdf

conference was held at the Chamber of Deputies, and a white paper presented, with the aim of encouraging the government to put in place the rare diseases plan. Between March and April 2012 both Orphanet and UNIAMO organised public consultation on rare diseases with the aim of providing input from stakeholder into the process. The working group of the Ministry of Health preparing the draft of the national plan concluded in June 2012, and the document was sent by the Ministry of Health to AIFA for comments and subsequently again to the Ministry of Health for final assessment. The document was illustrated officially in December 2012 at the Ministry of Health in the presence of 200 stakeholders. The next step is for the document to be commented on by stakeholders. Their comments will be evaluated and implemented into the document by the Ministry of Health and sent for approval by the permanent Conference for relations between State, Regions and the autonomous provinces of Trento and Bolzano.

Registries

A congress on the National Registry and Regional and Interregional Registries for rare diseases was held in Rome on 22 February 2012, to illustrate the results, to discuss and agree among all actors on actions to improve further the performance of the National Registry.

Neonatal screening policy

According to SIMMESN (Società Italiana per lo Studio delle Malattie Metaboliche Ereditarie e lo Screening Neonatale²⁸), about one fifth of the Italian newborn population underwent an expanded screening in 2011. UNIAMO F.I.M.R. sent a position paper on this subject as Memorandum for the XII Social Affairs Commission of the Chamber of Deputies on Draft Law No. 5,440 Conversion into law of Decree-Law of 13 September 2012, n. 158 laying out “urgent measures to promote the development of the country by a higher level of protection of health”, calling for a gradual expansion of neonatal screening programs for all rare diseases for which there is evidence of appropriateness and not just to rare diseases for which a cure already exists. However, it will be mandatory to define a common set of standards, procedures and methodologies at the national level to ensure an effective, fair and appropriate disease screening as well as to assure adequate health and social post screening management.

Genetic testing

In an international context, Italy is one of the few countries to monitor genetic test use (this survey was implemented in the 1980s), and recently this monitoring has expanded to include clinical and laboratory activities carried out by Medical Genetic Institutes and also private laboratories since 2009^{5,6}. This census promoted by SIGU surveys the services provided by Italian Medical Genetic Centres and involves the NHS bodies, the IRCCSs (Excellence Centres for Healthcare and Research), the University Institutes, the CNR (Research National Council) laboratories, and private laboratories. Data collection takes into account the typology of the Institutes, number and functions of the laboratory staff, cytogenetic analyses, genetic-molecular and immunogenetics analyses, and clinical activities, including genetic counselling. Certified quality systems adopted by the Institutes and the adequacy of some genetic tests have been also checked.

The survey concerning the 2011 data was carried out in 2012. The census was made possible thanks to the collaboration of the Bambino Gesù Children Hospital, Orphanet-Italy, and SIGU. On the whole, 517 services hosted by 268 Hospitals or Institutions were surveyed, including 145 clinical genetic services, and 153 cytogenetic, 198 molecular genetics and 21 immunogenetics laboratories. The 53% of services are located in the Northern regions, the 20% in the Central regions, 17% in the Southern regions, and 10% in Sicily and Sardinia. About 74% of these services were accredited and 55% certified.

The CNMR-ISS is in charge of carrying out the National External Quality Control Scheme for genetic tests. As regards molecular genetics, in 2012, national experts have assessed laboratory performance on genotyping, interpretation, and reporting of test results for a total of 404 different DNA samples sent to 68 public and private laboratories. In addition, 75 laboratories participated in one or more schemes of constitutional or cancer cytogenetic quality control.

National alliances of patient organisations and patient representation

In 2012, a framework agreement was signed by UNIAMO F.I.M.R. with the Telethon Foundation Onlus-CTFO, to promote access to TNGB genetic biobanks by members of the associations’ federation.

In October 2012, the Ministry of Welfare recognised UNIAMO F.I.M.R. as an Association of Social Utility.

²⁸ www.sismme.it/it/documents/rt_screening/rt_screening_2011.pdf

There is no public funding scheme for activities of the patients' organisations, but national governmental institutions (e.g. the Welfare Ministry) and local institutions support specific actions. Grants for activities of patients' organisations are coming mainly from private sponsorship, charities and income tax donations. UNIAMO's goals for 2010-2012 were reached taking advantage from these funds, which have granted continuity to the Federation's activities, and sustained several projects:

- "Knowing to assist", carried out in collaboration with Farmindustria and Scientific Societies, is aimed at training general practitioners and paediatricians regarding rare diseases. The project is based on a covenant of understanding signed by several Institutions. The project will cover the whole Italian territory by 2013.
- "Galeno Help" results from a memorandum of understanding between UNIAMO F.I.M.R. and the professional pharmacists federation (UPFARM), with the intention of giving practical support to patients who need drugs which are difficult to find. Many of these drugs can be prepared in the galenic laboratories of the pharmacies in a personalised manner. "Galeno Help-Pharmacist helps for rare disease patients" is a national service offering the possibility to quickly and easily find the nearest participating pharmacy.
- "Mercury", funded by the Ministry of Labour and Social Affairs in cooperation with the signatories of the aforementioned covenant of understanding, has been designed to train the general practitioners and paediatricians in rare diseases. The major goal of the project is to implement and enhance the web site "Malatirari.it" and turn it into a platform to meet the rare disease community's needs along the complex path from a suspected case to diagnosis of rare disease. The site will become a virtual place where information based on direct experience can be shared by patients, relatives and health professionals involved in the diagnosis and treatment of these diseases. In 2012 the data were implemented with an area dedicated to health professionals, with a restricted access.
- "The Atlantis Code" is aimed at fostering the culture of research in rare diseases. Developed in partnership with the Telethon Foundation, it involves rare disease patient organisations in the attempt to identify research priorities and provide answers to the patients' needs. Three seminars were organised. The outcomes of this survey were matched up with the results of a similar investigation carried out by EURORDIS at European level.
- "Momo" intends to bring together, with a unique voice, the demands of different groups of rare disease patients at Regional level. For this purpose, regional UNIAMO delegations were created in the context of a progressive regionalisation of the federation.
- "A Community for Rare Diseases", is aimed at developing a model to assess the quality of expertise centres for rare diseases in Italy. Since many Regions are reorganising their network of expertise centres, it was felt important to share similar inclusion criteria. Participants were the Ministry of Health, the Ministry of Labour and Social Affairs, ISS, Regions, local health authorities, Orphanet Italy, expert centres, municipal districts, general practitioners, primary care paediatricians, biobanks and patients organisations. On September 20, 2012 an agreement was signed with Age.Na.S., the National Agency for Regional Health Care Services, for the implementation of the second phase of the project which will assess some previously defined centres of expertise, with a major emphasis on the geographic distribution of a selected group of centres dedicated to distinct diseases (e.g. haemoglobinopathies).
- "Diaspro Rosso", a pilot project concluded in 2012, has provided an accurate, effective and efficient model for detecting the care needs and the social-economic costs for families with patients affected by rare diseases. The model will be presented to the institutional actors as a decision-making tool to be used to develop policies on social health based on concrete data.
- "Dumbo" was aimed at developing a model for the social reporting of patients' organisations. This model was illustrated to the Associations' members in several meetings and UNIAMO F.I.M.R. used it to present its first Social Report.

In November 2012, the MIR (Movimento Italiano dei Malati Rari) was established by 15 patients' associations.

Sources of information on rare diseases and national help lines

Help line

In 2012, the CNMR-ISS started collaborations and training activities for regional help lines (i.e. Contact Centre of Tuscany Coordination Centre for rare diseases) and with Patients' Associations (i.e. Foundation "W Ale – Alessandra Bisceglia").

Best practice guidelines

In order to promote the development of high quality best practice guidelines and their use in Italy and across Europe, CNMR-ISS organised national and international training courses (9-11 July 2012) providing participants (health care professionals, policy makers, patients) with the opportunity to learn about the core methodology used to develop best practice guidelines. In addition, CNMR-ISS encourages international debate on the role and quality of best practice guidelines in the field of rare diseases. In particular, a workshop on Clinical Practice Guidelines on Rare Diseases was organised on 23-24 February, 2012, aimed at sharing experiences and knowledge and discussing critical methodological issues due to the specificity of rare diseases.

In 2012, CNMR-ISS, 13 institutional partners and one SME have been awarded with a grant by the European Commission, under the Seventh Framework Programme (FP7/2007-2013) for a four-year research project entitled RARE-BestPractices (www.rare-bestpractices.eu), commencing in January 2013. This project will bring together a team of experts in the area of clinical practices guideline, systematic review, health technology assessment, health policy, rare disease epidemiology and public health.

Training and education initiatives

A workshop on Clinical Practice Guidelines on Rare Diseases was organised on 23-24 February 2012, for sharing experiences, knowledge and discussing some methodological related to the specificity of rare diseases.

The Italian Telethon Foundation and Orphanet-Italy joined their respective competences and contact networks in October 2012 to meet the patients' needs and support health professionals via a training course entitled "e-patients, e-parents, e-doctors: le malattie rare via web – opportunità e rischi". Suited for all stakeholders of the rare disease community, this event provided an opportunity to discuss web services and social networks as tools for professionals, patients and their families. During the course, health professionals, journalists, and IT experts presented their experiences to guide the community in using the web as a tool to break the isolation rare diseases can impose. A round table was animated by communication experts on the responsible use of Internet.

On 16 April 2012, the Orphanet team held a training course in Rome for health professionals operating in the Bambino Gesù Children Hospital, aimed at teaching them how to use the Orphanet resources.

National rare disease events in 2012

Since February 2008, UNIAMO F.I.M.R. coordinates the Rare Disease Day events organised by its members throughout the national territory. It provides them with information leaflets, posters, gadgets, T-shirts and banners, created in collaboration with Farindustria, the Serono Foundation and Novartis. Awareness has been achieved through over one hundred local events, in squares, sports halls and schools and through many articles and interviews on rare diseases in newspapers and on TV. The cartoon "Mamma, cosa sono le malattie Rare? – Mum, what are rare diseases?" promoted by UNIAMO F.I.M.R. was shown on Mediaset TV Channels all through February. The Volley Major League collaborated with UNIAMO F.I.M.R. in distributing dedicated information leaflets on rare diseases during the matches where an awareness raising announcement was also made.

On 29 February 2012, the event "La solidarietà che costruisce" was organised at the Italian Senate to promote the Rare Disease Day in Italy, with the participation of several leading figures in the field of the rare diseases. This event raised awareness on the needs and actions in the field of rare diseases, and promoted dialogue between stakeholders and public institutions. During the event, Orphanet-Italy received a prize for its contribution in the "Mercurio" project (update of the malatirari.it web site) managed by UNIAMO F.I.M.R.

To mark Rare Disease Day, the Bambino Gesù Children Paediatric Hospital, in collaboration with Orphanet launched on 27 February 2012, a pilot project on rare diseases for middle schools. The "Virgilio" public school is hosting the project whose aim is to teach children the basics of familial inheritance. Professionals from Bambino Gesù Hospital will work together with teachers and pupils to produce papers, which will be evaluated in the context of a prize-awarding contest. The award ceremony will be held on Rare Disease Day 2013.

The CNMR-ISS presented two different events: a theatre play dedicated to rare diseases, inspired by real events, and the fourth edition of the event "Il Volo di Pegaso - Raccontare le malattie rare: parole e immagini" (Pegasus' Flight – Describing rare diseases through words and images), an art contest on rare diseases. The theatre play "Controvento" (Against the Wind) took place at the Quirino theatre in Rome on 27 February 2012 and the art contest prize-giving at the ISS on the same day. Another institutional event, on 29 February was the initiative "La solidarietà che costruisce" (Creating through solidarity): several leading figures in the field of the rare diseases discussed the topic "L'esperienza, il presente e il futuro per le Malattie Rare in

Italia”, while a white book “Una incompiuta: le Malattie Rare” was presented by the Senator Antonio Tomassini. Flash mobs were also organised to mark the Day with a closing speech by the Italian Minister of Health, Prof. Renato Balduzzi.

On 29 February 2012, the patient association MITOCON organised a round table focused on research, care and policy concerning rare diseases.

On 8 February 2012, in the Rome Campidoglio a press conference was held for the event “Stammi vicino” (Stay close to me), organised by EEC syndrome International Network Word Communication ONLUS. This event, aimed to foster communication on rare diseases through sport.

On 18 February 2012, on the occasion of the Del Monte Italian Cup final tour, before the beginning of the matches, particular attention was given to the importance of funding rare disease research.

On 4 June 2012, an international congress entitled “Narrative Medicine and Rare Diseases” was held in Rome at the ISS.

On 12 June 2012 a press conference was held at the Senate to mark the launch of the book “Malattie rare: alla ricerca di un approdo” (Rare Diseases: in search of a landing place). This book collects the results of the Public Consultation launched in March 2012 on website and includes interviews of the main Italian and European stakeholders belonging to the academic and institutional world, together with the experience of patients and their families. The aim was to provide input on the elaboration of the National Plan for Rare Diseases.

On 12 July 2012, a press conference was organised in Rome to launch the second edition of the project “MALattie raRE NOSTRUM”, promoted by “Tender to Nave Italia” a non-profit foundation and the Bambino Gesù Children Hospital. The project aimed at making a group of children affected by rare diseases more independent, fostering sea and navigation as an education instrument.

From 1 September to 6 September 2012, the first edition of the project “GiRare Mangiando”, an initiative of the non-profit organisation UNIAMO Goldin, was held in Venice. This project was designed to provide an information path of independent living for patients affected by metabolic rare diseases. Four young patients were given the opportunity to stay in an apartment in Venice owned by UNIAMO Goldin, profiting by the facilities of the Fantasia restaurant, managed by rare disease patients, and following a program of cultural activities on the territory. The young participants have been supported by the healthcare professionals of the Bambino Gesù Children Hospital.

On 18 September 2012, a conference entitled “The State of Art of Rare Diseases: Rare Diseases and Economic Development” was held in Rome at the Ministry of Health. The Conference focused on several issues related to rare diseases: diagnostic difficulties; lack of therapeutic options and structured care pathways; chronic and debilitating course of the disease; emotional impact due to feelings of isolation experienced when living with one of these diseases. The initiative aimed to identify goals and actions to support health services, industry production and drug companies.

Several dozens of events have been organised locally in all Italian Regions.

Hosted rare disease events in 2012

Amongst the events announced in *Orphanews Europe* were: 15th Biennial Meeting of the European Society for Immunodeficiencies (Florence, 3-6 October 2012), EpiRare International Workshop: Rare Disease and Orphan Drug Registries (Rome, 8-9 October 2012), Goldrain Courses in Clinical Cytogenetics and Prenatal Genetic Diagnosis (Goldrain, 15-21 September 2012) .

Research activities and E-Rare partnership

National research activities

In 2012 Telethon was able to fund 260 research projects on rare genetic diseases, thanks to the fundraising activities in 2011.

E-Rare

Italy did not take part in the 4th Joint Transnational Call in 2012.

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²⁹ The contributors and validators of the report have contributed information which is accurate to the best of their knowledge. However, readers should take note that the contents of this report are illustrative and not exhaustive.

³⁰ All websites and documents were last accessed in May 2013.

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