2014 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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The European Union Committee of Experts on Rare Diseases (EUCERD) was established in 2009 and its mandate ended in 2013. It is replaced from 2014 by the Commission Expert Group on Rare Diseases. The EUCERD Joint Action continues to support the activities of the new Expert Group until 2015.

More information on the activities of the former European Union Committee of Experts on Rare Diseases and the EUCERD Joint Action 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) Joint Action: Working for Rare Diseases (N° 2011 22 01), which covers a three year period (March 2012 – February 2015).

The European Union Committee of Experts on Rare Diseases (EUCERD) was established in 2009 and its mandate ended in 2013. It is replaced from 2014 by the Commission Expert Group on Rare Diseases. The EUCERD Joint Action continues to support the activities of the new Expert Group until 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 2013. 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 Commission Expert Group 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 2013
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

Parts I – V also include a description of the methodology, sources and validation process of the entire report, and 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.

Each year, there are around 15 000 downloads of the different sections of the report combined.
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 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 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 has not been updated since 2001, 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 the 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 diseases.

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 diseases 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 organised 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 stakeholders 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 presented in December 2012 at the Ministry of Health in the presence of 200 stakeholders. The next step was for the document to be implemented by the stakeholders, from January to February 2013. Their comments were evaluated and included in the document in March 2013 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.

In January 2013, UNIAMO FIMR organized in Rome a meeting with patients’ representatives focused on the discussion of the Draft Plan for Rare Diseases. The contributions were forwarded to the Ministry of Health.

In April, UNIAMO FIMR started organising the second EUROPLAN Conference 2012-2015, by setting the Steering Committee and activating the thematic working groups through face to face meetings and a virtual web platform set up ad hoc. The working groups included a broad representation of the key stakeholders.

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, 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.

**Rare Diseases Interregional Board**

In 2006, the Health Commission, constituted by the Health Representatives of all Italian Regions, has established a permanent Interregional Board on Rare Diseases. Members are experts officially appointed by every Regional Government.

The Board meets regularly, at least 6 times per year, in order to share best practices and promote a progressive harmonisation of the health policies for RD patients, which, in the decentralized Italian scenario, have been developed so far by the Regional Governments. In these years, among others, the following issues were addressed: methods adopted for the identification of Centres of expertise at regional/interregional level, set-up and maintenance of regional-interregional RD registries, access to therapies for RD patients, shared care pathways and diagnostic-therapeutic protocols for RD patients, innovative tools for patients’ management (i.e. telemedicine).

The Board officially represented the Regional Governments’ position in the first Italian Europlan Conference and in the context of several RD-related events promoted by patients’ associations.

Since its establishment, the Board has produced, in collaboration with the Health Ministry and the ISS, a proposal of a list of RD to be added to the national list issued in 2001, and has worked on the elaboration of formal agreements between the State and the Regions leading to the definition of a common minimum data set to be transferred from regional/interregional Registries to the national Registry. Other documents produced by the Board were focused on the regional/interregional governance of the RD care networks and on

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the position of the Regions with respect to the laws’ proposals on rare diseases under discussion at the Italian Parliament.

In particular, in 2013, the Board has carried out an inventory of all the Centres for rare diseases, officially labelled at regional-interregional level since 2001. The inventory aimed, in particular, at exploring the RD Centres’ compliance with the criteria adopted by Eucerd. Following this activity and the experience of the “A Community for RD” project, promoted by UNIAMO, a collaboration with Age.na.s (the Agency for the Regional Health Systems) has started. The aim is to analyse the methods used for the identification of RD Centres, in particular those developed by some Regions, based on the integrated analysis both of patterns of hospitalization of RD patients and regional Registries’ data.

In 2013, the Interregional RD Board has produced an inventory of all the patients’ organizations dealing with rare diseases active at national, interregional, regional and local level. For each association updated information regarding diseases followed, number of patients represented, officially appointed representatives, ongoing projects, territorial diffusion and contact details, has been collected and shared.

In 2013, the Health Commission officially adopted two other documents elaborated by the RD Interregional Board: one dealing with the identification of common regional modalities and pathways for the delivery of home cared therapies to RD patients; another one, addressed in particular to AIFA, containing the Regions’ proposals regarding the main open issues in the field of the drug provision to RD patients. The contents of both these documents have been shared with the Interregional Pharmaceutical Board, in which all Regional Pharmaceutical Services are represented. Furthermore, the collaboration with the Pharmaceutical Interregional Board has lead to the production of a list of off-label drugs and drugs marketed abroad for rare diseases, partially refundable by AIFA to Regions, which normally cover with their budget these costs.

In 2013, two working groups have been established in the context of the Interregional Board on RD. They will conclude their mandate in early 2014 with the approval of two documents representing the state of the art and the Regions’ position and proposals on the following two issues: expanded newborn screening and telemedicine. Both these documents will be submitted in 2014 for final approval to the Health Commission.

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 (covering around 5000 entities) 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 assigned 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. In the years, there has been an effort towards progressive harmonization. Some Regions have shared a common methodology to identify Centres, based on the combined analysis of patterns of hospitalization of RD patients and on regional registries’ data. Furthermore, formal agreements between Regions have lead to the creation of interregional networks of Centres, working in collaboration for the definition of common diagnostic and therapeutic protocols. Around 215 centres (Presidi) 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, to provide information on RD to patients and health professionals and to collaborate with patients’ organisations.

In 2011, UNIAMO FIMR² 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. In December, Age.Na.s, the National Agency for Regional Health Services, together with UNIAMO FIMR visited in Milan five Centres (Presidi) to assess the validity of this model.

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 CNMRS – 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: estimation of incidence and prevalence;

² http://www.uniamo.org/
temporal and geographical distribution of cases and diseases at national level; 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 a minimum set of data from Regional registries, according to an Agreement between the State and the Regions, signed in 2007. Since 2001, each Italian Region established its own registry for rare diseases. These registries collect epidemiological information provided by accredited Centres for rare diseases (Presidi) and, in many cases, by other sources of data (i.e. territorial network of services, pharmaceutical services), and every year they send the agreed common minimum 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 some are aimed at evaluating health services and diagnostic procedures, while others are information systems developed to support the delivery of services to RD patients, collecting at the same time epidemiologic as well as clinical data on registered patients. Agreements were established between regional administrations in order to create some interregional registries. Each interregional system has its informatics infrastructure, acting as a network connecting different centres and health professionals involved in the management of patients with rare diseases. Piedmont has developed a system shared with Aosta Valley Region, covering an area of about 4.5 million inhabitants. Veneto Region has developed since 2001 an information system, currently adopted by other 8 Italian Regions (Autonomous Provinces of Bolzano and Trento, Emilia-Romagna, Liguria, Umbria, Campania, Apulia and Sardinia – this last one under implementation), globally reaching a covered area of about 25 million inhabitants. Other Regions have developed their own system for collecting data (i.e. Lombardy, Tuscany, Marche, Friuli Venezia Giulia, Sicily and Lazio). The remaining Regions (Molise, Abruzzo, Calabria, Basilicata, for a total of about 2.5 million inhabitants) currently use the software developed by the National Registry at ISS.

In November 2011, the CNMR-ISS published the first Report on “National Registry and Regional/Interregional Registries for rare diseases”¹, 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, including 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 connected with 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. On 25 February 2013, a second congress on the National Registry and Regional and Interregional Registries for rare diseases was held in Rome, aiming at sharing the state of the art of patient registries in Italy. Over the last few years, data collection for the National Registry of Rare Diseases was improved, reaching a territory coverage of the 97% in 2012 (compared with 62% of 2009), due to the improvement of the surveillance system both at national or regional level. Publication of the second ISTISAN Report on National Registry and Regional/Interregional Registries for rare diseases is in progress.

The CNMR also provides support to spontaneous independent registries promoted by patients and run by clinicians: in the last few years the Italian Registry of Paroxismal 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.

The CNMR coordinates EPICARE, a project co-funded by the DG-SANCO, which involves several EU and non-EU countries. The project’s general objective is to build consensus and synergies to address legal, ethical and technical issues associated with the registration of RD patients and to elaborate a proposal for an EU web-based multi-disease platform. This tool, based on sharing of information and resources, aims at increasing the sustainability of registries, promotes the use of standards and registry quality procedures, and provides an effective way of disseminating the results (www.epicare.eu).

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

¹ http://www.iss.it/binary/publ/cont/undici20WEB.pdf
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 Neonatale), about one fifth of the Italian newborn population underwent an expanded screening in 2011. UNIAMO FIMR sent a position paper on this subject as a Memorandum for the XII Social Affairs Commission of the Chamber of Deputies, on Draft Law No. 5440 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 only for rare diseases for which treatments are available. 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 implementation 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 Interregional Rare Diseases Board (Tavolo Interregionale Malattie Rare), and two Italian Scientific Societies (SISMESN and SIGU).

In November 2013, a hearing at the Senate took place concerning a proposal to reorganise and rationalise the different regional health care systems in the field of newborn screening in order to harmonize the regional activities. Existing regional differences in neonatal screening policies can be explained because the screening of additional diseases, besides the diseases cited in law to be tested (cystic fibrosis, congenital hypothyroidism and phenylketonuria) represents an extra-LEAs (Essential Levels of care) service for citizens. So, the cost of the screening of additional diseases is completely at the charge of the Regions. To appropriately tackle this issue, in 2013 the Interregional Rare Diseases Board has established a working group in order to elaborate a document describing the state of the art, specific health policies developed by the Regions in this area and some proposed future actions. This document will be presented for approval to the Health Commission in early 2014. It clearly advocates the common definition of the diseases, the screening of which should be included into the LEA list, in order to overcome regional differences. Furthermore, it underlines the necessity to consider expanded newborn screening as a part of broader and comprehensive care pathways developed for patients affected by the diseases screened.

The Stability Law of December 2013 (art. 1, paragraph 229) has granted the experimental widening of national neonatal screening of metabolic disorders with €5 million.

Genetic testing

Italy is monitoring genetic test use since the 1980s, and this monitoring has expanded recently to include clinical and laboratory activities carried out by Medical Genetic Institutes and also private laboratories since 2009. This census, promoted by SIGU (Italian Society of Human Genetics), 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

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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.

In 2013, the Working Group on Cytogenetic of the SIGU approved and disseminated a set of guidelines for cytogenetic diagnosis, which came 20 years after the previous set of guidelines in this area.

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 (EMQN²), 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.

Genetic tests for 1101 genes and 1165 diseases are registered in the Orphanet database⁶.

National alliances of patient organisations and patient representation

In Italy, UNIAMO FIMR 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 FIMR 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 FIMR 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, as patients' representative, in the institutional tables dedicated to rare diseases in Lombardy, Lazio, Puglia and Campania. In addition, UNIAMO FIMR 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 not officially represented by any territorial association.

In 2012, a framework agreement was signed by UNIAMO FIMR 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 FIMR 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.

In 2013, within the “Conoscere per assistere” project addressed to general practitioners (GPs) and paediatricians (PLS), supported by Farmindustria, UNIAMO FIMR, in collaboration with the federation of paediatricians and general practitioners (FIMP, FIMMG), and scientific societies of physicians (SIP, SIMG, SIMGEPED, SIGU) organized 3 training courses in Florence (April), Potenza (May), and Turin (October). The

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² http://www.emqn.org/emqn/Home

¹ Information extracted from Orphanet in February 2014.
major topics of these courses included: how to suspect a rare disease, how to manage the transition of rare
disease patients from paediatric into adult age.

In July-September 2013, on behalf of Eurodis, the President of UNIAMO FIRM worked as a member of
the Commission established by the Ministry of Health charged of evaluating the so-called Stamina protocol (a
non-scientifically sound treatment for many rare diseases, based on stem cells).

In 2013, UNIAMO FIRM was confirmed as a member of the board of the Biobank Network settled by
Telethon Foundation, and of the Interregional Rare Disease Committee.

In 2013, UNIAMO FIRM coordinated the project “Determinazione Rara”, an advanced national training
programme for the proactive enrolment of patients in research trials, based on workshops with clinicians,
researchers and biobankers.

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 taking into account some modifications proposed by the Interregional Board on Rare Diseases. The final
version of the Agreement has been signed in 2011. Following this Agreement some Regions have developed
interregional collaboration for the definition of common health-care pathways, supported by the parallel
development of specific modules within the existing RD information systems with the aim of supporting the
prescription, made by clinicians working in Centres of expertise, and the delivery not only of drugs, but also of
medical devices (i.e. eye-gaze systems). An Agreement between the State and the Regions has been signed in
2013 regarding the development of specific and comprehensive care pathways for patients affected by
Hededitary Haemorragic Disorders, based on the activity of the already labelled regional-interregional Centres
for HHD and involving other professionals working in the RD care networks, as well as in other care settings.

In November 2012, the MIR (Movimento Italiano dei Malati Rari) was founded 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 maintains also the Orphanet
Italy national website9 and a Facebook page10.

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 Farmindustria, which financed this second book, and President of UNIAMO FIRM.

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

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9 www.cndmr.it
10 http://www.orphanet-italia.it/national/IT-IT/index/homepage/
10 https://it-it.facebook.com/OrphanettItalia
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-Italy.

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.

In November 2011, Orphanet Italy set up a partnership with the company Genzyme who provides financial support for the translation in Italian of the bi-monthly newsletter OrphaNews.

In January 2013, in the perspective of implementing the Orphanet database, Orphanet Italy launched a survey and set up a collaboration with the Italian Inter-regional Technical Board for Rare Disorders to collect data on the Centres of Reference officially recognized and established by Regions. All regional coordinators of the Italian National Network for Rare Diseases were involved in this process and more than 700 Centres of Reference for rare diseases were identified in Italy and registered in the Orphanet database.

**Official information centre for rare diseases**

The Ministry of Health organised a specific section for Rare Diseases¹¹, 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 website¹² 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 public at large. 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 Network of National Registries of 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 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 CNMR-ISS web page¹³. 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 made 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”).

Some Regions (Veneto, Lombardy, Tuscany, and others) have established help line services to provide information on rare diseases, dedicated health services and provisions to patients, families, professionals, and the public at large.

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¹¹ [http://www.salute.gov.it/malattieRare/malattieRare.jsp](http://www.salute.gov.it/malattieRare/malattieRare.jsp)
¹² [www.iss.it/cnmr](http://www.iss.it/cnmr)
¹³ [www.iss.it/cnmr](http://www.iss.it/cnmr)
Other sources of information on rare diseases

Information for patients and health professionals is available from 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 offered by patient organisations, although they are heterogeneous in their coverage.

The website www.malatirari.it set up by UNIAMO FIMR, 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. On December 2011, OrphaNews-Italia13 was launched by national Orphanet team. This online bulletin offers a complete translation into Italian of the contents of OrphaNews-Europe, and is available from Orphanet-Italy homepage and from the Orphanet Italian country site. OrphaNews-Italia is published online on a regular basis, one week after the publication of the English version. At the end of 2013, 38 issues were published and the total number of registered readers was 4031.

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, 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. RARE-BestPractices is a platform for sharing best practices for the management of rare diseases. This project brings 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. The overall aim of the project is to improve the care of patients by disseminating globally best practices for the management of persons with rare diseases. The CNMR acts as coordinator of 14 partners across Europe, all with strong commitment in research on rare diseases, public health and evidence based medicine. The project’s aims to provide reliable informative resources for the rare disease community by creating a collection of methodologically trustworthy and up-to-date guidelines for the management of rare disease; to develop a standard methodology suitable for the development of RD guidelines; to set up training activities and training tools targeted at key stakeholders for the production of high quality rare disease guidelines. Other key elements of the platform are the identification of mechanisms to address the limitations of the evidence, set priorities for rare disease research and propose improvements in pre-approval and post-marketing studies.

RARE-Bestpractices has supported the creation of a new international open access, online, peer-reviewed journal: “Rare Disease and Orphan Drugs” (RARE Journal - http://rarejournal.org/rarejournal). RARE is a science journal, published three times per year focusing on relevant aspects of public health, health policy and clinical research on rare diseases.

About 85 Percorsi Diagnostici-Therapeutici-Assistenziali-PDTA (Diagnostic Therapeutic Care guidelines), dedicated to diagnosis, treatment and clinical management of rare diseases, have been developed since 2010 by the Lombardy Region14.

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

13 http://malattierare.marionegri.it/content/view/111
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 diseases15.

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 makers16. 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 looking 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. 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.

In 2013, the CNMR organised a course (using cooperative learning method) for the “W Ale - Alessandra Bisceglia” Foundation volunteers, aiming to set up and carry out a specific helpline to inform health operators, social workers, patients and their families, and the public at large, on congenital vascular malformations and related disabilities. The W Ale helpline will start in 2014, in collaboration with the Italian national helpline for rare diseases “Telefono Verde Malattie Rare”.

The CNMR coordinates the “Story Telling on Record” (S.T.o.Re. – www.storeproject.eu): a 2-year European partnership funded in the Lifelong Learning Programme (Leonardo da Vinci Multilateral Partnerships August 2013 -July 2015). The project involves 7 partners from 6 countries and foresees 4 partners’ meetings and a final conference in Italy. The objective is to design an action-research that includes training participants, giving them the knowledge and the skills necessary to design, test and train people in the use of Integrated Medical Records (IMRs), and organise courses on the use of IMRs for health care system personnel, in the rare and chronic diseases. The results of this project will be disseminated through a dedicated website, scientific reports and two booklets (toolkits in English and in the partners’ languages, tailored to patient organisations and to health institutions and professionals).

The CNMR carried out the first International Summer School “Rare Diseases and Orphan Drug Registries” (ISS, Rome - 16-20 September 2012). The course took the participants through the main concepts and practical steps to be undertaken in the establishment and management of a rare diseases registry, to ensure its usefulness, soundness and sustainability. The course provided basic notions on the methodology of observational studies with a view to the specificity of rare disease registries, on the selection of data elements with a focus on the interoperability of rare disease registries, on quality assurance, and on the technical and legal tools to be adopted for protecting patients’ data confidentiality. The course consisted of frontal presentations followed by small group exercises, using the cooperative learning method.

The second International Summer School “Clinical Practice Guidelines on Rare Diseases” was organised by CNMR (ISS, Rome, 8-12 July 2013). The course took the participants through the development process of clinical practice guidelines, by providing the basics of clinical practice guideline and evidence synthesis approaches. The course format consisted of brief presentations followed by individual or small group exercises 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 FIMR through the projects “Knowing to assist” and “Mercury”, see the “National alliances of patient organisations and patient representation” section).

15 http://www.governo.it/bioetica/pdf/Maklattie_rare_25112011
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 15 April 2013, the Orphanet team held a training course in Rome for health professionals from the Bambino Gesù Children Hospital, aimed at teaching them how to use the Orphanet resources.

In 2013, the ISS Press Office and CNMR, in cooperation with the Italian Ministry of Health, developed “Con gli occhi tuo” (through your eyes): a communication project addressed to schools, aiming to implement inclusion practices for fragile children in the classrooms and to raise awareness of rare diseases as a public health issue. The project was developed in collaboration with the Ministry for Education, University and Research, the Italian Federation of Rare Diseases UNIAMO FIMR, the Bambino Gesù Children Hospital and with the support of the centre for Health Pastoral Care, Diocese of Rome. The project will include a web-based video tale and a guidebook for teachers (aimed to enable teachers to repeat the experience in other schools, using cooperative learning techniques). The project results will be disseminated in the Rare Disease Day 2014.

**National rare disease events in 2013**

Since February 2008, UNIAMO FIMR 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 Farmindustria, the Serono Foundation and Novartis. Awareness was 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.

In 2013, a gala evening was organised in Rome on 27 February by UNIAMO FIMR, followed by a dedicated conference entitled “Health is solidarity: a common commitment to fight against rare diseases” in collaboration with ISS, the Diocese of Rome, and Rome’s medical school. The congress was the opportunity to reflect on advances in the field and priority issues. A Play/Decide session on cross-border healthcare and other relevant issues was organised also by UNIAMO FIRM at Sapienza University in Rome with the participation of students from faculties of medicine and nursing. A flash-mob was also organised to mark the day.

Other events in 2013 included: MaRE UNIAMO FIMR meeting (Rome, 29 January 2013), The National Registry and Regional and Interregional Registries of Rare Diseases meeting (Rome, 25 February 2013), UNIAMO workshop on quality evaluation of centres of expertise (Rome, 1 March 2013), O.Ma.R Prize for Journalism on Rare Diseases and Orphan Drugs (Lake Garda, 11 March 2013), AMMI Convention on Rare Diseases (Rome, 22 March 2013), Rare Diseases and Congenital Disorders seminar (Arezzo, 9 November 2013), International Conference on del22q Rome, 24-25 May 2014, DEBRA International Congress, Rome, 20 September 2013.

**Hosted rare disease events in 2013**

Amongst the events announced in Orphanews Europe were: EUCERD Joint Action Europlan Workshop on Key Indicators for National Plans/Strategies for Rare Diseases (Rome, 25 March 2013), DEBRA International Congress (Rome, 20 September 2013), International Meeting on Angelman Syndrome (Rome, 11 October 2013), 2nd International Workshop Rare Disease and Orphan Drug Registries (21-22 October 2013, Rome), 5th European Symposium on Rare Anaemias (15-16 November 2013, Ferrara), Second Symposium on ATP1A3 in Disease Genotype/Phenotype Correlations, Modelling and Identification of Potential Targets for Treatment (23-24 September 2013, Rome), International Summer School on Rare Disease and Orphan Drug Registries (16-20 September 2013, Rome), Haemophilia Centres Certification System Across Europe (11 July 2013, Rome), 5th International Meeting on Pulmonary Rare Diseases and Orphan Drugs (8-9 February 2013, Milan), International Summer School on Clinical Practice Guidelines on Rare Diseases (8-12 July 2013, Rome).

**Research activities and E-Rare partnership**

**National research activities**

In Italy, there are efforts to coordinate research between Regions, Italian Drug Agency (AIFA)\(^2\), Ministry of Health and ISS. Funds for rare diseases research are granted by Ministry of Health, ISS, AIFA and Ministry of

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\(^2\) [http://www.agenziafarmaco.gov.it/](http://www.agenziafarmaco.gov.it/)
Education, University and Research, Telethon, patient organisations and a few charities. The last Health Ministry call for projects for rare diseases 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 granted for a maximum of €300,000, with the therapy costs funded separately. From 2008 onwards rare diseases and orphan medicinal product research are 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 2013 Telethon was able to fund 230 research projects on rare genetic diseases, thanks to the fundraising activities in 2012.

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

**Participation in European research projects**

Italian research teams participate/participated in 123 rare disease related FP7 projects and coordinated 27 projects.

**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. Italy took part in the 5th Joint Transnational Call in 2013 with Italian teams participating in 4 out of the 12 selected consortia.

**IRDiRC**

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

**Orphan medicinal products**

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.

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18 [http://www.quotidianosanita.it/cronache/articolo.php?&articolo_id=1144&cat_1=1&cat_2=0](http://www.quotidianosanita.it/cronache/articolo.php?&articolo_id=1144&cat_1=1&cat_2=0)

19 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.

20 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.
**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 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, 55 out of the 72 orphan medicinal products approved by EMA are launched on the market. The cost of 49 of them is fully paid by NHS, based on a therapeutic indication, while 6 of them are reimbursed under special circumstances (Law 648/96) and (Law 326/2003 art.48). The other EMA approved drugs have a pending request at AIFA by the companies in charge of pricing and reimbursement. 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 available.

**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 Commission.

**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.

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 patient. 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.

**Other initiatives to improve access to orphan medicinal products**

Italy also has an off-label, compassionate use procedure, regulated by Law 648/96 (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 authorised. A Ministerial Decree of 8

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24 Orphan Drugs in Europe: Pricing, Reimbursement, Funding & Market Access Issues, Donald Macarthur (2011) p.83
26 KCE reports 112B: Politiques relatives aux maladies orphelines et aux médicaments orphelins – 2009 p.50.
May 2003 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 Decree 223/1998, 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%”.

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 use.

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 Italy.

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.

**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 patient, 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 €250, 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.

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28 EMINET Initial investigation to assess the feasibility of a coordinated system to access orphan medicines, C. Habl, F. Bachner (2011) p54.
29 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
DEVELOPMENT OF RARE DISEASE ACTIVITIES IN 2013 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 conference was organised 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 stakeholders 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 presented in December 2012 at the Ministry of Health in the presence of 200 stakeholders. The next step was for the document to be implemented by the stakeholders, from January to February 2013. Their comments were evaluated and included in the document in March 2013 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.

In January 2013, UNIAMO FIMR organized in Rome a meeting with patients’ representatives focused on the discussion of the Draft Plan for Rare Diseases. The contributions then forwarded to the Ministry of Health.

In April, UNIAMO FIMR started organising the second EUROPLAN Conference 2012-2015, by setting the Steering Committee and activating the thematic working groups through face to face meetings and a virtual web platform set up ad hoc. The working groups included a broad representation of the key stakeholders.

Rare Diseases Interregional Board
In 2013, the Health Commission officially adopted two other documents elaborated by the RD Interregional Board: one dealing with the identification of common regional modalities and pathways for the delivery of home cared therapies to RD patients; another one, addressed in particular to AIFA, containing the Regions’ proposals regarding the main open issues in the field of the drug provision to RD patients. The contents of both these documents have been shared with the Interregional Pharmaceutical Board, in which all Regional Pharmaceutical Services are represented. Furthermore, the collaboration with the Pharmaceutical Interregional Board has lead to the production of a list of off-label drugs and drugs marketed abroad for rare diseases, partially refundable by AIFA to Regions, which normally cover with their budget these costs.

In 2013, two working groups have been established in the context of the Interregional Board on RD. They will conclude their mandate in early 2014 with the approval of two documents representing the state of the art and the Regions’ position and proposals on the following two issues: expanded newborn screening and telemedicine. Both these documents will be submitted in 2014 for final approval to the Health Commission.

Registries
On 25 February 2013, a second congress on the National Registry and Regional and Interregional Registries for rare diseases was held in Rome, aiming at sharing the state of the art of patient registries in Italy. Over the last few years, data collection for the National Registry of Rare Diseases was improved, reaching a territory coverage of the 97% in 2012 (compared with 62% of 2009), due to the improvement of the surveillance system both at national or regional level. Publication of the second ISTISAN Report on National Registry and Regional/Interregional Registries for rare diseases is in progress.

Neonatal screening policy
In November 2013, a hearing at the Senate took place concerning a proposal to reorganise and rationalise the different regional health care systems in the field of newborn screening in order to harmonize the regional activities. Existing regional differences in neonatal screening policies can be explained because the screening of additional diseases, besides the diseases cited in law to be tested (cystic fibrosis, congenital hypothyroidism and phenylketonuria) represents an extra-LEAs (Essential Levels of care) service for citizens. So, the cost of the screening of additional diseases is completely at the charge of the Regions. To appropriately tackle this issue, in 2013 the Interregional Rare Diseases Board has established a working group in order to elaborate a document
describing the state of the art, specific health policies developed by the Regions in this area and some proposed future actions. This document will be presented for approval to the Health Commission in early 2014. It clearly advocates the common definition of the diseases, the screening of which should be included into the LEA list, in order to overcome regional differences. Furthermore, it underlines the necessity to consider expanded newborn screening as a part of broader and comprehensive care pathways developed for patients affected by the diseases screened.

The Stability Law of December 2013 (art. 1, paragraph 229) has granted the experimental widening of national neonatal screening of metabolic disorders with €5 million.

**Genetic testing**

In 2013, the Working Group on Cytogenetic of the Italian Society of Human Genetics (SIGU) approved and disseminated a set of guidelines for cytogenetic diagnosis, which came 20 years after the previous set of guidelines in this area.

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. To date eight rounds have been completed and overall 112 laboratories have been monitored in the context of the National External Quality Control Scheme.

**National alliances of patient organisations and patient representation**

In Italy, UNIAMO FIRM 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. In 2013, within the “Conoscere per assistere” project addressed to general practitioners (GPs) and paediatricians (PLS), supported by Farmindustria, UNIAMO FIRM, in collaboration with the federation of paediatricians and general practitioners (FIMP, FIMMG), and scientific societies of physicians (SIP, SIMGEPED, SIGU) organized 3 training courses in Florence (April), Potenza (May), and Turin (October). The major topics of these courses included: how to suspect a rare disease, how to manage the transition of rare disease patients from paediatric into adult age.

In July-September 2013, on behalf of Eurordis, the UNIAMO FIRM President worked as a member of the Commission established by the Ministry of Health charged of evaluating the so-called Stamina protocol (a non-scientifically sound treatment for many rare diseases, based on stem cells).

In 2013, UNIAMO FIRM was confirmed as a member of the board of the Biobank Network settled by Telethon Foundation, and of the Interregional Rare Disease Committee.

In 2013, UNIAMO FIRM coordinated the project “Determinazione Rara”, an advanced national training programme for the proactive enrolment of patients in research trials, based on workshops with clinicians, researchers and biobankers.

An Agreement between the State and the Regions was signed in 2013 regarding the development of specific and comprehensive care pathways for patients affected by Hereditary Haemorrhagic Disorders, based on the activity of the already labelled regional-interregional Centres for HHD and involving other professionals working n the RD care networks, as well as in other care settings.

**Sources of information on rare diseases and national help lines**

**Orphanet activity in Italy**

In January 2013, in the perspective of implementing the Orphanet database, Orphanet Italy launched a survey and set up a collaboration with the Italian Inter-regional Technical Board for Rare Disorders to collect data on the Centres of Reference officially recognized and established by the Regions. All regional coordinators of the Italian National Network for Rare Diseases were involved in this process, and more than 700 Centres of Reference for rare diseases were identified in Italy and registered in the Orphanet database.

**Guidelines**

In 2012, CNMR, 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. RARE-BestPractices is a platform for sharing best practices for the management of rare diseases. This project brings 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. The overall aim of the project is to improve the care of patients by disseminating globally best practices for the management of persons with rare diseases. The CNMR acts as coordinator of 14 partners across Europe, all with strong commitment in research on rare diseases,
public health and evidence based medicine. The project’s aims to provide reliable informative resources for the rare disease community by creating a collection of methodologically trustworthy and up-to-date guidelines for the management of rare disease; to develop a standard methodology suitable for the development of RD guidelines; to set up training activities and training tools targeted at key stakeholders for the production of high quality rare disease guidelines. Other key elements of the platform are the identification of mechanisms to address the limitations of the evidence, set priorities for rare disease research and propose improvements in pre-approval and post-marketing studies.

RARE-Bestpractices has supported the creation of a new international open access, online, peer-reviewed journal: “Rare Disease and Orphan Drugs” (RARE Journal - http://rarejournal.org/rarejournal). RARE is a science journal, published three times per year focusing on relevant aspects of public health, health policy and clinical research on rare diseases.

Training and education initiatives
In 2013, the CNMR organised a course (using cooperative learning method) for the “W Ale - Alessandra Bisceglia” Foundation volunteers, aiming to set up and carry out a specific helpline to inform health operators, social workers, patients and their families, and the public at large, on congenital vascular malformations and related disabilities. The W Ale helpline will start in 2014, in collaboration with the Italian national helpline for rare diseases “Telefono Verde Malattie Rare”.

The CNMR coordinates the “Story Telling on Record” (S.T.o.Re. – www.storeproject.eu): a 2-year European partnership funded in the Lifelong Learning Programme (Leonardo da Vinci Multilateral Partnerships August 2013 - July 2015). The project involves 7 partners from 6 countries and foresees 4 partners’ meetings and a final conference in Italy. The objective is to design an action-research that includes training participants, giving them the knowledge and the skills necessary to design, test and train people in the use of Integrated Medical Records (IMRs), and organise courses on the use of IMRs for health care system personnel, in the rare and chronic diseases. The results of this project will be disseminated through a dedicated website, scientific reports and two booklets (toolkits in English and in the partners’ languages, tailored to patient organisations and to health institutions and professionals).

The second International Summer School “Clinical Practice Guidelines on Rare Diseases” was organised by CNMR (ISS, Rome, 8-12 July 2013). The course took the participants through the development process of clinical practice guidelines, by providing the basics of clinical practice guideline and evidence synthesis approaches. The course format consisted of brief presentations followed by individual or small group exercises for sharing experiences, knowledge and discussing some methodological related to the specificity of rare diseases.

On 15 April 2013, the Orphanet team held a training course in Rome for health professionals from Bambino Gesù Children Hospital, aimed at teaching them how to use the Orphanet resources.

In 2013, the ISS Press Office and CNMR, in cooperation with the Italian Ministry of Health, developed “Con gli occhi tuoi” (through your eyes): a communication project addressed to schools, aiming to implement inclusion practices for fragile children in the classrooms and to raise awareness of rare diseases as a public health issue. The project was developed in collaboration with the Ministry for Education, University and Research, the Italian Federation of Rare Diseases UNIAMO FIMR, the Bambino Gesù Children Hospital and with the support of the centre for Health Pastoral Care, Diocese of Rome. The project will include a web-based video tale and a guidebook for teachers (aimed to enable teachers to repeat the experience in other schools, using cooperative learning techniques). The project results will be disseminated in the Rare Disease Day 2014.

National rare disease events in 2013
Since February 2008, UNIAMO FIMR 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 Farmindustria, the Serono Foundation and Novartis. Awareness was 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.

In 2013, a gala evening was organised in Rome on 27 February by UNIAMO FIMR, followed by a dedicated conference entitled “Health is solidarity: a common commitment to fight against rare diseases” in collaboration with ISS, the Diocese of Rome, and Rome’s medical school. The congress was the opportunity to reflect on advances in the field and priority issues. A Play/Decide session on cross-border healthcare and other relevant issues was organised also by UNIAMO FIRM at Sapienza University in Rome with the participation of students from faculties of medicine and nursing. A flash-mob was also organised to mark the day.
Other events in 2013 included: MaRE UNIAMO FIMR meeting (Rome, 29 January 2013), The National Registry and Regional and Interregional Registries of Rare Diseases meeting (Rome, 25 February 2013), UNIAMO workshop on quality evaluation of centres of expertise (Rome, 1 March 2013), O.Ma.R Prize for Journalism on Rare Diseases and Orphan Drugs (Lake Garda, 11 March 2013), AMMI Convention on Rare Diseases (Rome, 22 March 2013), Rare Diseases and Congenital Disorders seminar (Arezzo, 9 November 2013), International Conference on del22q Rome, 24-25 May 2014, DEBRA International Congress, Rome, 20 September 2013.

**Hosted rare disease events in 2013**

Amongst the events announced in Orphanews Europe were: EUCERD Joint Action Europlan Workshop on Key Indicators for National Plans/Strategies for Rare Diseases (Rome, 25 March 2013), DEBRA International Congress (Rome, 20 September 2013), International Meeting on Angelman Syndrome (Rome, 11 October 2013), 2nd International Workshop on Rare Disease and Orphan Drug Registries (21-22 October 2013, Rome), 5th European Symposium on Rare Anaemias (15-16 November 2013, Ferrara), Second Symposium on ATP1A3 in Disease Genotype/Phenotype Correlations, Modelling and Identification of Potential Targets for Treatment (23 - 24 September 2013, Rome), International Summer School Rare Disease and Orphan Drug Registries (16-20 September 2013, Rome), Haemophilia Centres Certification System Across Europe (11 July 2013, Rome), 5th International Meeting on Pulmonary Rare Diseases and Orphan Drugs (8-9 February 2013, Milan), International Summer School on Clinical Practice Guidelines on Rare Diseases (8-12 July 2013, Rome).

**Research activities and E-Rare partnership**

**National research activities**

In 2013 Telethon was able to fund 230 research projects on rare genetic diseases, thanks to the fundraising activities in 2012.

**E-Rare**

Italy took part in the 5th Joint Transnational Call in 2013 with Italian teams participating in 4 out of the 12 selected consortia.

**Orphan medicinal products**

**Orphan medicinal product reimbursement policy**

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.

**Other initiatives to improve access to orphan medicinal products**

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.
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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.
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