The Italian National Centre for Rare Diseases: where research and public health translate into action

Domenica Taruscio, Linda Agresta, Annalisa Amato, Giuseppe Bernardo, Luana Bernardo, Francesca Braguti, Pietro Carbone, Claudio Carta, Marina Ceccarini, Federica Censi, Simona Coppola, Patrizia Crialese, Marta De Santis, Stefano Diemoz, Carlo Donati, Sabina Gainotti, Gianluca Ferrari, Giovanna Floridia, Claudio Frank, Rosa Giuseppa Frazzica, Amalia E. Gentile, Orietta Granata, Yllka Kodra, Manuela Latrofa, Paola Laricchiuta, Armando Magrelli, Cristina Morciano, Agata Polizzi, Stefania Razeto, Marco Salvatore, Antonella Sanseverino, Daniele Savini, Paola Torreri, Fabrizio Tosto, Flavia Villani, Giorgio Vincenti, Luciano Vittozzi

Italian National Centre for Rare Diseases, National Institute of Health, Rome, Italy

Introduction

The Italian National Centre for Rare Diseases (CNMR) is the result of a strategic approach, which the National Institute of Health (ISS) has been developing for more than 10 years, to deal with the public health challenges associated with rare diseases (RDs).

The CNMR was formally established within the ISS in 2008[1]. Its mission is to promote and develop experimental research and public health actions, as well as to provide technical expertise and information on RDs and orphan drugs, for the prevention, treatment and surveillance of these diseases. It is also the national focal point for information and communication for patients suffering from one of several thousand RDs, and for their families, collaborating with the national organisations of patients suffering from RDs.

The Centre employs a wide range of scientific and technical expertise from various fields (medicine, genetics, molecular biology, epidemiology, public health, psychology, sociology etc.) and holds a network of national and international collaborations, which allow the development of a sound and integrated approach to RDs. The CNMR provides expert advice to the Italian Ministry of Health (MOH), to the National Health Council, to the National Health Service (NHS), and collaborates with the Regions, which are responsible for the provision of health services in the Italian devolved health system. Expert advice on RDs is also provided at EU and at international level.

Since its establishment, the Centre has developed into a lively and propulsive hub for experimental research, public health, information, communication and training on RDs in Italy, and for patient empowerment. In addition, it has contributed to networks and scientific boards at national, European and international level and has implemented a number of strategic projects on RDs. The Centre is in continuous evolution in order to follow closely the pace of science and research, the emerging needs of patients, the solicitations of policy makers, and the demands of the health system.

The Italian National Centre for Rare Diseases European and national frame of reference

Before introducing the Centre's present configuration and its activities in detail, it is worthwhile to clarify some general issues concerning RDs and the institutions responsible for RD policy, programmes and actions at the European and at the National level, which provide the foundations for the CNMR work. The Centre maintains relations with them as well as with other qualified national, European and international institutions for the realisation of its activities in the field of RDs.

General considerations on rare diseases

RDs are characterised by low prevalence (by European Union (EU) definition less than 5/10,000 in the general population) but represent a considerable public health burden due to their high number and to their complex management. According to the European Commission[2], the number of existing RDs is estimated at between 7,000 and 8,000, affecting, altogether, 6-8% of the general population. RDs are distinguished by specific clinical and etiopathogenetic characteristics, but their social and health burden share a number of common features. Most of them set out at birth or during infancy, while the rest appear in adulthood. RDs are chronic, multisystem conditions often associated with reduced life expectancy and a relevant mortality rate in childhood, a severe disabling course, high medical expenses and poor quality of life.

Their low prevalence rate is the main cause of a poor awareness among health care professionals and often of inadequate levels of care expertise. These can result in delayed diagnosis, misdiagnosis or even un-diagnosis, difficulties in assessing and adopting the appropriate disease management, and in problems related to

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the psychological and economic impact on patients and their families. In addition, the limited market represented by the single conditions does not make the development of new drugs and treatments attractive to the pharmaceutical industry. As a consequence, *orphan drugs* are expensive and seldom available; furthermore, their efficacy and safety usually cannot be thoroughly assessed, due to the lack of a large patient population.

The Italian legislative support for rare diseases

Since 1998, RDs have been recognised as a health priority in each of the 3-year Italian national health plans, though a national plan/strategy for RDs has not yet been formalised by the MOH. Meanwhile, a coordinated and comprehensive framework of actions was defined by Ministerial Decree (D.M.) n. 279/2001[3], which established a national network of selected clinical centres for prevention, surveillance, diagnosis and treatment of RDs, a National Registry for RDs (RNMR), and defined the exemptions for the costs of medical care for a number of RDs.

Accordingly, disease related services are free for citizens affected by a RD in the list (see Annex 1 D.M. n. 279/2001). A major shortcoming is that not all RDs and groups of diseases are included in the inventory and that it is not regularly updated, although a revision is expected in the near future.

Since 2001, Regions have established regional registries, centres for the diagnosis and treatment of RD patients and regional coordination centres, in order to manage the activities, including the exchange of information among centres and to provide expertise and data to the regional RD registries. Regional registries send the epidemiological data to the RNMR, established at the CNMR in 2001, in accordance with Article 3 of the D.M. n. 279/2001. The RNMR is supported by public funds; it is web-based, in compliance with the legal and ethical requirements, and it is a population-based registry, although the regional coverage is still heterogeneous. The RNMR collects the data ("common data set") coming from the regional registries and it is the tool for epidemiological surveillance of RDs and for the national and regional planning of RD measures.

The European framework for the Italian National Centre for Rare Diseases activities

The European Union and the Council of the European Union

The RDs gained political concern at the EU level in the early 1990s. In fact, in November 1993, the European Commission (EC) published the "*Commission communication on the framework for action in the field of public health*" (1993)[4], defining the framework for action by the Community and describing the role of the Community Institutions and the Member States (MS).

After this publication, the Commission opened a wide consultation in the Union on public health issues. In December 1993 the Commission invited experts to submit a proposal describing how they would seek to formulate draft policy proposals in some of the areas indicated in the framework document. In consultation with the Commission, five priority areas were identified, among them also "*An EU programme for management of rare diseases*".

Subsequently, four key policy documents have been emanated by the EU and these have paved the way to current RDs developments in Europe; the CNMR has aligned to it. Following are the cited documents.

a. *The Orphan Medicinal Product Regulation*[5]
   This text defines the criteria for orphan designation in the EU and described the incentives to encourage the research, development and marketing of medicines to treat, prevent or diagnose RDs.
b. *The Commission Communication on Rare Diseases: Europe's challenge*[2]
   This document, which was adopted on 11 November 2008, proposes an overall strategy to support MS in diagnosing, treating and caring for RD patients in Europe. This Communication focuses on three main areas: i) improving recognition and visibility of RDs, ii) supporting policies on RDs in MS for a coherent overall strategy, and iii) developing cooperation, coordination and regulation for RDs at EU level.
c. *The Council Recommendation on an action in the field of RDs*[6]
   This document was adopted on 8 June 2009 and comprises twenty recommendations gathered into seven main areas. The seven themes are: plans and strategies in the field of RDs; adequate definition, codification and inventorying of RDs; research on RDs; centres of expertise and European reference networks; gathering the expertise on RDs at European level; empowerment of patient organisations; sustainability.
d. *Directive 2011/24/EU on the application of patients' rights in cross-border healthcare*[7]
   This Directive was approved on 28 February 2011 and is particularly important for RD patients, because of scarce and scattered resources for diagnosis and care of these disorders. The Directive is meant to facilitate the access of EU citizens to cross-border health care and to encourage the cooperation between EU Member States in the field of health.

The European Union Committee of Experts on Rare Diseases

The European Union Committee of Experts on Rare Diseases (EUCERD) was formally established by

the European Commission Decision[8] on 30 November 2009, replacing the European Commission's Rare Diseases Task Force (RDTF). Its mission is to assist the EC in the cooperation and consultation efforts with the specialised bodies in the MS, the relevant European authorities dealing with research and public health action and other relevant stakeholders operating in the field of RDs. Recently, the EUCERD has been replaced by the Commission Expert Group on Rare Diseases[9].

The CNMR participated regularly to the RDTF and EUCERD meetings, and will continue to take part to the activities of the newly established Commission Expert Group on Rare Diseases.

The role of patient organisations in the Italian National Centre for Rare Diseases work

National, European and international patient organisations, representing the voice of the RDs community, play a key role in the activities carried out by the CNMR as highlighted in the following sections.

The Italian organisations of patients with rare diseases

The role of patient organisations in the field of RDs is crucial. Driven by the need to share difficulties and problems, and by a desire to see their rights recognised, they encourage targeted policies, research and specific interventions for health and social care. In recent years, much of the progress in inter-institutional relations and between institutions and patients are attributable to the efforts of these organisations. Their work comprises a body of knowledge complementary to that of the doctor. For this reason, it becomes increasingly important to have a constructive and cooperative relationship between patients and social and health professionals. This collaboration allows the former to reach such a level of empowerment that enables them to take an active part in the decision making processes that affect them, and the latter to make strides in research and take effective charge of the patients, improving their quality of life.

Of the several patient organisations present in Italy, some have chosen to carry on their battle individually, others have opted to join umbrella organisations at national and international level. In Italy there are currently three major leagues:

- the Italian Federation for Rare Diseases - UNIAMO[10], connected to the European Organisation for Rare Diseases - EURORDIS[11];
- the National Council for RDs[12];
- the Italian Movement for Rare Patients (MIR)[13].

The European Rare Diseases Organisation

The European Rare Diseases Organisation (EURORDIS) is a non-governmental patient-driven alliance of patient organisations and individuals active in the field of RDs. It was founded in 1997 for the promotion of research on RDs and the commercial development of *orphan drugs*. EURORDIS is dedicated to improving the quality of life of all people living with RDs in Europe. It represents more than 606 RDs organisations in 56 different countries (of which 25 are EU MS), covering more than 4,000 RDs[11].

The CNMR works closely with EURORDIS, particularly with regard to the implementation of the European Project for Rare Diseases National Plans Development (EUROPLAN) and European Platform for Rare Disease Registries (EPIRARE) projects and for other patient centred activities.

The International Rare Diseases Research Consortium

The International Rare Diseases Research Consortium (IRDiRC)[14] was launched in 2011 by the European Commission and by the US National Institutes for Health Research to foster international collaboration in the RDs field. The Consortium's goal is to team up researchers and organisations investing in research to deliver 200 new therapies for RDs and to diagnose most RDs by the year 2020.

These are some the ambitious challenges on IRDiRC agenda to be addressed through collaborative actions:

- establish and provide access to harmonised data and samples;
- perform the molecular and clinical characterisation of RDs;
- boost translational, preclinical and clinical research.

The collaboration will also be required to harmonise the policies related to research utilisation, standardisation and dissemination. Each organisation will use its own funding mechanism to support RDs research.

The CNMR participates in some IRDiRC research projects and research, including the Interdisciplinary Committee, and chairs the Working Group on Registries and Natural History of RDs.

The frame of action of the National Centre for Rare Diseases

The history of the CNMR dates back to the institution of the National Registry[3] for Rare Diseases in 2001, which was the first nucleus of the Centre. In fact, when the National Registry was instituted, the first building stone of the CNMR was also laid. On it, through the years, the CNMR has steadily evolved into a dynamic and vital centre for research and action, for prevention, diagnosis and treatment of RDs, for patient's empowerment and public awareness, through information and communication tools. In order to meet old and new challenges posed by RDs, the Centre has

developed its institutional activities along six main pillars: 1) experimental research; 2) public health; 3) projects; 4) information and communication; 5) training and empowerment; 6) networks and collaborations.

1. Experimental research on Rare Diseases

The CNMR plays an important role in the coordination and promotion of experimental research on RDs in Italy, has participated in the Advisory Committee for European Research and is an active Work package (WP) leader of E-Rare project (see later). In 2003, a bilateral Italian and US agreement between the ISS and the US National Institutes of Health (NIH) was undersigned with the purpose of developing and increasing research in a number of fields, including RDs. In this respect, the CNMR has assured the implementation of a national programme of scientific research projects mainly based on the study of pathogenetic mechanisms, diagnosis, treatment and clinical management of RDs. On 16 December 2013, the agreement with the NIH was renewed until 2016.

Within this international context, the CNMR carries out scientific research projects on selected RDs using advanced technologies (e.g. bioinformatic methodologies, high resolution melting, micro-RNA platform and CGH array). These studies are focused on a better comprehension of the molecular mechanisms underlying the pathogenesis of RDs, as well as the identification of specific biological markers involved in both RDs and rare cancers. The Centre is involved in collaborative studies on pathological conditions related to RDs[15-24].

In order to overcome the problems of the low number of patients with RD, a transnational collaboration with multidisciplinary approaches is highly desirable. In this respect, the CNMR has taken part in the activities of E-Rare, a EU funded project described in the Projects section.

2. Public Health actions on Rare Diseases

The CNMR develops a number of public health activities in the field of RDs, from public health research on matters of relevance to its mission (e.g. epidemiology, service accessibility, identification of patients' needs) to policy. Through the coordination of the EU co-funded EUROPLAN project, it assists European States in defining needs and developing national plans for RDs, in accordance with the EU Recommendations. Following is a description of the main Public Health activities undertaken by the Centre to deal with the RDs emerging needs and interests.

Primary and secondary prevention

Since 2004, the Centre has coordinated the *Italian Network for folic acid promotion in the primary prevention of congenital anomalies*, which comprises more than 200 public and private organisations, such as local health authorities, patients organisations, scientific societies, research institutes and communication experts. In 2004, it developed and delivered the "*Official Recommendation for the peri-conceptional supplementation of folic acid*"[25] and is currently working for the widest application of this Recommendation[26]. Subsequently, the Italian Medicines Agency (AIFA) decided to offer 0.4 mg folic acid supplements free of charge to all women planning a pregnancy.

In 2008, the CNMR was part of the Scientific Cooperation Working Group (ESCO WG), established by the European Food Safety Authority (EFSA) for the study on the *"Analysis of risks and benefits of fortification of food with folic acid*", and was co-author of the final report published in November 2009[27].

The CNMR participates to the European surveillance of congenital anomalies (EUROCAT) Joint Action 2011-2013 (see later) as coordinator of the WP on "*Primary prevention of Congenital Anomalies*". This WP has joined efforts with EUROPLAN in order to provide the "*EUROCAT-EUROPLAN Recommendations on policies to be considered for the primary prevention of congenital anomalies in National Plans and Strategies on Rare Diseases*"[28]. The document represents the first comprehensive set of recommendations for the primary prevention of congenital anomalies in the EU.

The Centre played an important role in the coordination of the EU Tender on EU New-born Screening (NBS) Practices. The tender delivered a report on the practices of neonatal screening for RDs implemented in all the MS and established by the European Network of Experts on New-born Screening (EUNENBS). After consultation of EUNENBS members, 70 expert opinions were finalised into an Expert Opinion Document, to actively support the discussion for the development of European policies in the field of NBS of RDs[29-31].

Currently, the CNMR is working on a national project to expanded new-born screening, funded by the National Centre for Disease Prevention and Control (CCM) of the MOH, under their 2011 programme. Its aim is to overcome different implementation strategies at regional level, regarding the expanded new-born screening, through a national model based on principles of uniformity, coherence, effectiveness and portability[32].

The Registries

Following is the presentation of the National Registry for Rare Diseases (RNMR) and the Disease-specific Registries conducted by the CNMR.

The National Registry for Rare Diseases

The RNMR was established in 2001 by Ministerial Decree (M.D.) 279/2001[3] and is run by the CNMR in collaboration with the regional registries. It collects epidemiological information useful to determine the dimension of the issue and the potential risk factors, to support clinical research and to foster the definition of diagnostic criteria.

The general objectives of the RNMR are indicated in the Article 3 of the M.D. 279/2001; they were reasserted in two Agreements between the State and the Regions, in 2002[33] and 2007[34]:

1 - planning and evaluating health care programmes (services utilization, patients' mobility…);
2 - diseases surveillance (estimation of prevalence and incidence, geographical and temporal distribution of RDs).

The RNMR is structured into three levels, reflecting the Italian Healthcare System: local, regional and national level. The local level refers to clinical centres identified in each Region, which are the primary source of data flow. From here, patients' demographic and clinical data are collected and transmitted to the regional level. This is the intermediate level of data flow and is composed by regional registries. Each regional registry has a different organisational structure, different objectives, and, as a consequence, different types of information (variables) collected. Meanwhile, a common data set to be communicated from the regional registries to the RNMR was defined in line with the CNMR's mandate. This set includes socio-demographic as well as disease data for each patient: patient's identification code, birth date and place of birth, gender, place of residence; live-dead condition (with death date); diagnosis; RDs clinical centre where the diagnosis has been made; date of disease onset; date of diagnosis; orphan drug treatment used.

The RNMR collects data on the conditions afferent to the list of RDs (see Annex 1 M.D. n. 279/2001). In 2012, the RNMR, in collaboration with Regional Registries, prepared it first annual report[35].

The RNMR future strategies include supporting the development of new clinical registries on specific RDs in order to better understand their natural history. Furthermore, the RNMR plans to strengthen the collaboration and networking among existing disease specific registries at national, as well as, at International level. For example, the RNMR is currently collaborating with the National Registry of Congenital Coagulopathies, established at the ISS, on Inherited Bleeding Disorders[36,37].

Meanwhile, the RNMR is working towards the improvement of quality of data collection at national and regional level. Accordingly, the Centre has collaborated with the EU Task Force on RDs of the EC Health and Consumers Protection Directorate General, whose goal is to revise the classification and codification of RDs in the ICD system. Its objective is to ensure that RDs are traceable in all health information systems, including national and international registries.

Disease specific Registries

The following Disease specific registries are maintained by the CNMR.

Cystic Fibrosis Registry

The Italian Cystic Fibrosis Registry (ICFR) collects demographic and epidemiological data on Cystic Fibrosis (CF) patients from the Italian CF Regional Centres. Anonymous data are collected using a specific common set of variables and definitions; these data are also forwarded to the European CF Patients Registry. Each participating centre is identified through a specific code. Use of data for scientific purposes is possible only after application and approval by a scientific committee and a representative of each regional centre. An Annual Report is elaborated by the scientific committee and a detailed description of CF patients (demography, diagnosis, genetics, etc.) is published. The ICFR sends the core data to the European Registry.

The Italian Database for Paroxysmal Nocturnal Haemoglobinuria

The Italian Database for Paroxysmal Nocturnal Haemoglobinuria (IDPNH) was set up in 2010 through the cooperation of the CNMR staff, haematologists and representatives of the patient organisation. The database, which interfaces with the RNMR, includes all patients with a diagnosis of PNH established according to international criteria. The IDPNH main objective is to enhance the knowledge of the natural history of the disease and to obtain information on short and long-term follow-up, particularly on how patients respond to available treatments.

A set of variables are collected: personal data, clinical data, diagnostic tests, other laboratory data, blood transfusion treatment, drug treatment, pregnancies and quality of life. The IDPNH is web based and personal data are encrypted according to national regulations on the protection of personal data. A national expert on PNH validates the complete data set for each individual patient.

The experience gained in the management of an institutional/epidemiological registry that collects data on all RDs - the RNMR - and in the management of research oriented registries, collecting data on single diseases (CF and PNH), has provided the CNMR with the track record that facilitated its selection for the coordination of the EPIRARE project and, as

well, for the WP on RD registries of the RD-Connect project. The two projects are aimed at building research infrastructures for exchange of data, with a focus, respectively, on epidemiology (EPIRARE), "omics" and translational research (RD-Connect). Both projects are presented in the specific Projects section.

Quality Assurance on genetic tests and external quality assessment programmes

The CNMR participated in the Organisation for Economic Cooperation and Development (OECD) Panel of experts for the preparation of Guidelines for quality assurance in molecular genetics tests and in the EU funded project "*Multi-National External Quality Assay (EQA) programmes in Clinical Molecular Diagnostics*"[38,39]. The CNMR is a member of the European Molecular Genetics Quality Network and takes part in the EU funded EuroGentest excellence network, which aims at the standardisation and harmonisation of the quality of genetic testing in the EU MS.

Since 2001, the CNMR has coordinated the National External Quality Assessment programme for genetic testing that covers molecular genetics (Fragile-X syndrome, Beta-Thalassemia, FAP (*APC* gene) and Cystic Fibrosis) and cytogenetics (prenatal, postnatal and oncological diagnosis) tests[40,41].

Since 2009, this activity is institutional and laboratories pay a fee to participate in each scheme[42]. Participation is voluntary and is open both to public and private laboratories.

All submissions are assessed and reviewed by assessors, using previously agreed marking criteria. In molecular genetics, assessment takes into account genotyping, interpretation and reporting. In cytogenetics, assessment reviews banding quality, karyotype reconstructions, completeness/accuracy of the analysis, International System for Human Cytogenetic Nomenclature (ISCN), written description of the result, interpretation, completeness/accuracy of the report and reporting times.

At the end of each round, participant laboratories receive a report with marks and comments; a web-utility has been developed to share documents and information among ISS/CNMR, the assessors and the laboratories. Up to now, nine rounds have been completed and, for the 9th round, a category of poor performance has been defined. In 2013, the number of participating medical genetics centres was 94; the number of participating cytogenetics and molecular genetics laboratories was 69 and 77 respectively. Each year the CNMR organises the annual Meeting on "*Quality assessment of genetic testing*", inviting relevant speakers, laboratories and assessors for a joint discussion on the aggregated results obtained.

A specific external quality control scheme for the sweat test, a "gold standard" for the diagnosis of CF[43], has been set up and the first Italian pilot experience, to be carried out by the CNMR, is under way. In fact, it is of critical importance that sweat testing is carried out accurately, with precise measurement of relevant analytes, in order to have the most accurate discrimination of results.

Guidelines

The CNMR is involved in developing guidelines for the management of RDs. Guidelines are produced in collaboration with the Italian National Guideline System (SNLG) and with relevant stakeholders - research organisations, governmental bodies and institutions of the Italian National Health System.

In order to disseminate and promote the adoption of guidelines on RDs, the CNMR selects and makes available on its website guidelines prepared by national and international organisations. Moreover, an International Summer School on the development of guidelines on RDs is organised by the CNMR yearly. The CNMR actively participates in the international debate on the quality of existing guidelines, on their development and on the role of guidelines for RDs. In 2012, an international workshop with worldwide experts was organised to stimulate the debate on these themes. The FP7 project "*RARE-Bestpractices*", led by CNMR, was conceived in the mainstream of such debate and it is detailed in the Projects section.

Narrative Medicine

Narrative Medicine (NM) is considered a complementary approach to classic medicine, practiced with narrative skills of recognizing, absorbing, interpreting and being moved by the stories of illness. Treating by the narrative competencies, it is conducted through the doctor's and patient's understanding of the origin of the illness following the background of the problems, the reason of the illness and the whole body approach[43-46].

Since 2005, NM has emerged among the activities of the CNMR with the objective to disseminate its application on RDs, among social and health professionals, patients with RDs and their families, and patient organisations. In order to achieve its objective, a number of national and international activities were organised by the "national laboratory of narrative medicine" of the CNMR:

- *Documentation*: research, analysis, monitoring of national and international literature in Open Source publishing;
- *Research*: study of narratives relating to patients with RDs, relatives, health professionals, patient

organisations. Following are some examples: the pilot study "*General practitioners and rare diseases: knowledge, skills and needs*" at national level; the first funded project "*Rare diseases and Narrative Medicine: integrations and contributions in Public Health projects, quality of life, accessibility to social and health services and training*" (in the NEPHIRD context), at European level and, recently, the European project "*Story Telling on Record*" (S.T.o.Re.).

- *Communication and training*: activities addressing NHS workers, RD patients and their familiars. The CNMR organised the National Congress on "*Narrative medicine and rare diseases*" (2009, 2010, 2011) and the First International Congress "*Narrative medicine and rare diseases*" (2012).

There are several approaches and methods in NM. In order to clarify its definition, methodology and practical utility (experiences and examples of application), the CNMR promoted the Italian Consensus Conference (CC) aimed at (a) developing recommendations (addressed to professionals working in the medical, social and health care sectors) for the implementation of NM at the clinical level, with regard to rare and chronic degenerative diseases and (b) identifying indicators useful to evaluate their implementation. The CC celebration day will be held in June 2014 together with the Second International Congress on "*Narrative medicine and RDs*". The CC document will be ready in Autumn 2014 and will be addressed to health professionals working in the Italian social and health care sectors.

A number of activities have their roots in the NM Laboratory, such as the communication project "*Controvento - Upwind*", which includes a theatre piece, a book based on RD patients' stories and the National Competition "*The Flight of Pegasus*".

The National competition "The Flight of Pegasus"

"*The Flight of Pegasus*" is a literary art contest, sponsored by the CNMR. All participants are invited to tell their own experiences through writings, poems, drawings, photos and paintings. The main objectives are: (a) to provide a space for expression and visibility for people with RDs, as well as for all citizens, through various artistic and literary channels, and (2) to promote and disseminate the knowledge of RDs in all its aspects, by means of targeted communication and awareness campaigns. The results show the diverse viewpoints with which the disease is faced: isolation and neglect, indifference and difficulty of diagnosis and treatment, but also strong willpower and courage, sharing and tolerance.

After years of activity, the most important outcome is the creation of a national network with all the participants, providing a real exchange of ideas, knowledge sharing and updating. The sixth award ceremony has taken place at the ISS on 25 February 2014, close to the Rare Disease Day.

Orphan drugs

CNMR has instituted the *National Register of Orphan Drugs* to collect, for a limited time period after their marketing, data of selected drugs newly authorised for the treatment of RDs, for the assessment of their appropriateness and safety. From 2001 to 2009 and from 2012-up to now, the CNMR has been the Italian member of the Committee of Orphan Medicinal Products (COMP) at the European Medicines Agency (EMA).

Rare Diseases and organ transplantations: a new frontier

Organ transplantation in RDs patients represents a new area of research for the CNMR, both for its clinical aspects, and for potential public health implications.

Since the literature has very few data on this topic, the CNMR is carrying out a statistical survey, in collaboration with the Italian National Transplant Centre, with the aim of assessing the number of cases of RDs patients receiving organ transplantation, defining the type of RD and the transplantation carried out, together with the evaluation of the outcome.

According to the preliminary data, 1,306 patients with RDs have undergone an organ transplantation over the period 2008-2012. This figure represented 8.9% of the total of the patients undergoing a transplant surgery in the same period (14,821 patients). The organs transplanted were mainly kidneys, livers, hearts, or lungs (71% of all the latter cases had RDs, mostly CF).

The data on organ survival in RDs recipients show that, 5-6 years after the surgery, the cumulative survival is better for the RD patients compared with patients with other diagnoses. The reasons for this result are currently under study. However, some hypotheses are already being explored: are the results due to a better selection of the cases, when the patient is not yet in a severe condition, or to the fact that the transplantation represents a cure for some diseases?

3. Projects

A number of national, European and international projects on RDs are undertaken yearly by the Centre. Following are some of the projects still under way or recently closed.

European Platform for Rare Disease Registries

European Platform for Rare Disease Registries (EPIRARE, www.epirare.eu)[47], is a project co-funded by the EU Commission, DG-SANCO (2011-2014). It

is a feasibility study addressing regulatory, ethical and technical issues, associated with the registration of RD patients. The feasibility of a minimum data set common to all RDs designed to inform policy-makers is also being assessed by the project.

The project carried out two surveys among registry and database holders and one among patients. The first was meant to explore the conditions and needs of existing RDs registries and to define the services and the contents that they would expect from a European platform.

The second survey among registry holders was dedicated to assess the feasibility of a set of Common Data Elements (CDEs) from the existing RDs registries, by exploring the data elements that are currently collected by these registries.

The survey among patients was dedicated to understand their needs and expectations from registries and from the implementation of a common EU framework for the registration of RD patients.

In the framework of EPIRARE, particular interest and concrete actions have been devoted to monitor and influence the debate in the EU Parliament on the draft of the Regulation on General Personal Data Protection and an on-line petition was launched on this matter[48]. The work of the EPIRARE project resulted in two publications until now[49,50].

ERA-Net for Research Programmes on Rare Diseases

ERA-Net for Research Programmes on Rare Diseases (E-RARE: 2006-2010, 2010-2014)[51] is a project funded by FP7, dedicated to transnational coordination of research programmes on RDs (www.e-rare.eu).

E-Rare 2, which follows the successful implementation of E-Rare-1 (2006-2010), aims at deepening and extending the cooperation among partners interested in the funding mechanisms for research on RDs. It works through the systematic exchange of information, the yearly launching of joint calls, the assessment of the funding strategies and the strategic activities for the sustainable development and the extension of the network.

In order to reach this goal, the E-Rare Consortium has gathered 17 funding agencies/ministries from 14 European and Associated countries. Since 2007, E-Rare has launched and completed five joint transnational calls for research projects on RDs whereby 249 research groups belonging to 53 research consortia have been supported for an investment of € 37,5 million.

In particular, the CNMR coordinates the WP dedicated to update and expand the analysis on the state of the art of RD research funding in Europe and in selected countries outside Europe, in order to map the current situation in these countries. The map will reveal the existing opportunities and the unmet needs throughout Europe.

E-Rare-2 activities contribute to reducing the fragmentation of research and of resources through the coordination and the transnational funding of excellent research projects on RDs. This project has now become a key reference point in the landscape of European Transnational research funding on RDs.

European Network for Surveillance of Congenital Anomalies Joint Action

The European Network for Surveillance of Congenital Anomalies (EUROCAT) Joint Action (JA), was funded by the Public Health Programme 2008-2013 of the European Commission, to take place on the period January 2011-December 2013 (www.eurocat-network.eu)[52].

This JA combines funding of the EU and MS in order to secure a sustainable, high quality and easily accessible information system on Congenital Anomalies (CA). Its main objectives were the improvement of surveillance and the identification of strategies for primary prevention of CA, involving 36 Associate and 9 Collaborating Partners, and was structured into 9 WPs.

The CNMR has coordinated the WP7, which focused on the effectiveness of CA primary prevention. The central aspect was the role of folic acid in the incidence of CA but other potential risk factors have been investigated. Risk factors studied were: use of drugs in pregnancy, effects of maternal infection and vaccination, chronic diseases, environmental factors, alcohol and smoking, and other maternal lifestyle issues. These issues were translated into the "*EUROCAT-EUROPLAN Recommendations on policies to be considered for the primary prevention of congenital anomalies in National Plans and Strategies on Rare Diseases*" as specified in the section on Primary and Secondary Prevention[28].

European Project for Rare Diseases National Plans Development

The European Project for Rare Diseases National Plans Development (EUROPLAN, www.europlanproject.eu)[53-57], which comprises two phases: EUROPLAN I (2008-2011) and EUROPLAN II (2012-2015), is co-funded by the EU Commission (DG-SANCO) and is coordinated by the CNMR.

Its goal is to promote and implement National Plans or Strategies (NP/S) for RDs, and to share relevant experiences within Countries, linking national efforts with a common strategy at European level. This "double-level" approach ensures that progress is globally coherent and follows common orientations throughout Europe. Its main objective is to establish an international and interactive network of stakeholders (mainly policy makers) to speed up the elaboration and

the implementation of NP/S for RDs, through scientific and technical assistance, workshops and the active participation of patient organisations (EURORDIS and National Alliances).

EUROPLAN II builds on the achievements of the first project, whose goals was to elaborate tools and carry out activities to help EU Countries establish and implement NP/S in the field of RDs, coherent with the European Council Recommendations[6]. One of the tools developed during the first phase was the development of a set of 59 Indicators, as specified in the "*Report on indicators for monitoring the implementation and evaluating the impact of National Plans or Strategies for rare diseases*"[54].

In EUROPLAN II, WP 4 of the EUCERD Joint Action, foresees the participation of EURORDIS and Associated e Collaborating Partners from 33 Countries. EUROPLAN II, means to provide technical and scientific support to Countries with various geographical/economic concerns for the elaboration of their NP/S for RDs. This is meant to be achieved mainly through *capacity building* actions, which include training and continuing technical and scientific support for the sustainable development of the NP/S for RDs.

In order to achieve the project's objectives, a process has been undertaken that comprises a number of steps:

1. a survey was carried out to identify strengths and weaknesses in the definition of NP/S in each Country context.
2. A set of 21 Core Indicators was defined, out of the original list, and was selected on the bases of their usefulness and feasibility to monitor health and social planning. The selection was the result of a Delphi Method organised by the ISS, then easily integrated with those selected according to the participatory process established by EURORDIS. This work has contributed to the elaboration of the EUCERD "*Recommendations on Core Indicators for Rare Disease National Plans/Strategies*"[58].
3. Debrief sessions have been organised at the end of each national conference on RDs, to help local governments to focus on weak areas that need strengthening in order to develop effective NP/S. This is the first effective action for defining the collaboration and the other capacity building activities.
4. The next steps foresee the CNMR and its partners, along with the EU, providing the necessary support for the development of NP/S for RDs and furnishing all that is needed to guarantee its effective and timely sustainability.

EU Tender on EU Newborn Screening

EU Tender on EU Newborn Screening (NBS)[59] was launched by the European Commission in July 2009 in order to (1) report on the practices of neonatal screening for RDs implemented in all MS, including number of centres, to estimate the number of infants screened and the number of disorders included in the NBS, as well as the criteria adopted for the selection of the diseases to be screened; (2) identify the types of clinical pathways implemented in MS; (3) establish a network of experts to analyse the results and formulate final recommendation on the best practices, as well as on the core panel of NBS conditions that could be included in all MS practices, and (4) develop a decision-making matrix that could be used by member states' programmes to systematically expand (or contract) screening mandates.

The project, coordinated by the CNMR, was concluded in June 2011 with a consensus conference where the deliverables produced were approved by the members of the EU Network of Experts in NBS (EUNENBS), nominated by the RD competent authorities. The documents produced by the tender are available at: http://ec.europa.eu/health/rare_diseases/screening/index_en.htm and have given rise to a number of publications on scientific journals.

A platform for sharing best practices for the management of rare diseases

A platform for sharing best practices for the management of rare diseases (RARE-Bestpractices)[60] is is a four-year project (January 2013-December 2016), funded by the Seventh Framework Programme of the European Union (FP7/2007-2013) (www.rarebestpractices.eu).

The overall aim of the project is to improve the care of patients by disseminating globally best practices for the management of persons with RDs. The CNMR acts as coordinator of 14 partners across Europe, all with a strong commitment in research on RDs, public health and evidence based medicine.

The project main objectives are:

Regarding guidelines

- to provide reliable informative resources for the RD community by creating a collection of methodologically trustworthy and up-to-date guidelines for the management of RDs;
- to develop a standard methodology suitable for the development of RD guidelines;
- to set up training activities and educational tools targeted at key stakeholders for the production of high quality RD guidelines.

Regarding Health Technology Assessment of orphan drugs

- to ascertain cost-effectiveness assessment methods as well as criteria for funding decision making process of *orphan drugs* across European countries.

Other key elements of the platform will be the identification of mechanisms to address the limitations of the evidence, set priorities for RD research and propose improvements in pre-approval and post-marketing studies.

Moreover, RARE-Bestpractices is supporting the creation of a new international open access, online, peer-reviewed journal: "*RARE DISEASES AND ORPHAN DRUGS. An International journal of public health*" (RARE Journal). RARE Journal is a science journal, published three times per year with no publishing fees for readers and authors and focuses on important aspects of public health, health policy and clinical research on RDs. More details are provided at the website: http://rarejournal.org/rarejournal.

An integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research

An integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research (RD-Connect)[61] is a six-year project funded by the EC (7FP, 2012-2016) and the CNMR coordinates the WP on RD registries.

RD-Connect is building a global infrastructure connecting data from RD research into a central resource for researchers across the world. RD-Connect is developing an integrated platform in which "omics" data will be combined with registries, clinical phenotype information and biomaterial availability.

As therapeutic interventions are increasingly tailored towards the underlying genetic defects, patient registries need to include the genetic information of individual patients in a standardised way. Several clinical research networks, such as the one on CF, the one on Huntington disease and neuromuscular diseases, have concentrated efforts on a "new generation" of gene-specific patient databases. These include genotype data and detailed quality-controlled phenotype data and maintain the link with the patient within a secure ethical framework and in close collaboration with patient organisations. These initiatives have a much broader range of clinical utility than either locus-specific genetic databases (which are often anonymous and thus have no link to the patient for trial recruitment) or registries that do not collect genetic information and thus cannot facilitate cohort selection for trials.

These next-generation registries have facilitated numerous studies including clinical trials, generated investments by commercial partners, and resulted in better treatments. The WP2 coordinated by the CNMR directly answers the need to harmonise and standardise global databases and patient registries for RDs in order to maximise their utility for "omics" and other research.

Social Economic Burden and Health-related Quality of Life in Patients with Rare Diseases in Europe

Social Economic Burden and Health-related Quality of Life in Patients with Rare Diseases in Europe **(**BURQOL-RD;www.burqol-rd.com)[62] was a 3-year project under the 2nd Programme of Community Action in the Field of Public Health, commenced in April 2010 and ended in October 2013. It was funded by DG SANCO to generate a model to quantify the socio-economic costs and Health Related Quality of Life (HRQOL), of both patients and caregivers, for up to 10 RDs in different European countries.

The general objective of this project was to develop a disease based model capable of quantifying the socio-economic burden and the HRQOL of RD patients in Europe and of their caregivers. The model has to be adaptable and sufficiently sensitive to capture the differences in the distinct Health and Social Care Systems in the EU MS.

BURQOL-RD represents the most complete and realistic costing of the burden of RDs performed in European countries to date. The results of the project show that the healthcare costs of RDs are very substantial. However, other social costs are even higher, such as loss of labour productivity and that of formal or informal care, representing significant hidden costs that should be made apparent to society.

The information generated by the BURQOL-RD consortium will help:

- policy makers design future policies in the area of RDs, which will ultimately have positive benefits for EU citizens' health, both of patients and of their caregivers;
- patient organisations and RD Federations to give more weight to their requirements when addressing health policy makers;
- scientific community to stimulate future research in the field of RDs transferring the protocols established to other RDs and to other countries.

Story Telling on Record

Story Telling on Record (S.T.o.Re. - www.storeproject.eu) is a 2-year European partnership funded in the Lifelong Learning Programme (Leonardo da Vinci Multilateral Partnerships August 2013 - July 2015). The project is coordinated by the CNMR, 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: (a) 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 (b) organise courses on the use of IMRs for health care system personnel.

The results of the project will be disseminated through a dedicated website, scientific reports and 2 booklets (toolkits in English and in the Partners' languages, tailored to patient organisations and to Health institutions and professionals).

4. Information and communication

The CNMR uses different channels for information and communication purposes.

The Institutional site

The CNMR holds a portal on RDs[63] which provides topics of interest to RD patients, to the scientific community and to anyone interested in RDs and includes a user friendly tool for searching disease-specific information.

National helpline for Rare Diseases

In order to provide quality information on RDs, a national telephone helpline for RDs (*TVMR*)[64] was established at the CNMR in February 2008. It is a public, toll-free service that can be reached by composing the phone number 800.89.69.49 or via e-mail at: tvmr@iss.it. The service is active 5 days per week, from 9 am to 1 pm.

A team of psychologists and medical doctors trained and experienced in telephone counselling, public health policies and management of RDs are involved. The main aim of the service is to gather and provide information, through an active and personalised listening, on several issues regarding RDs, such as exemptions from the costs of medical cares, clinical centres, national and international centres of expertise, coordination of care, clinical trials for specific conditions running in Italy and abroad, patient organisations, how to get in contact with other patients, access to drugs and special services. Medical information regards rare, ultra-rare and relatively "common" rare conditions and refers, as a source of data, to the international scientific literature and to the main European and international databases on RDs. The service is addressed to any individual with an interest in RDs: patients and their relatives, health care professionals, clinicians, researchers, and patient organisations. Information is accurate and up-to-date and is meant to support and encourage patients and family members to face and solve specific problems and needs related to RDs.

To date, more than 17,000 enquires (most of them phone calls) have been received and worked on. Calls are rather equally distributed over the different geographic areas of the country. Notably, one of the commonest purposes of calls and complaints is about undiagnosed diseases and/or on how to find the most appropriate specialist for a given suspected disease.

Since 2012, TVMR is part of a European network of email and telephone help lines for RDs coordinated by EURORDIS.

Publications

The CNMR produces every year a number of publications, including articles for national, European and international journals on the activities of the Centre, brochures, posters and other relevant material.

In order to expand its information strategy and highlight the broad range of national and international activities in the field of scientific research and public health, in 2007, the CNMR has initiated the publication of the Supplement of the ISS Bulletin on "*Rare diseases and orphan drugs*".

The journal provides an overview of the CNMR activities and, more generally, of all matters related to RDs, from research to patient organisations. Divided into several sections, the Bulletin is addressed to general practitioners, to the personnel responsible for public health at regional and national level, to patients, family members or patient groups and to all those interested in RDs.

The publication is distributed both in paper form, especially during scientific-informative events, and in a digital format, published in the website of the ISS and of the CNMR. The journal is also sent by e-mail to the CNMR mailing list.

5. Education, training and empowerment

Every year, the CNMR organises a number of education and training activities on RDs[65,66] directed to various stakeholders (patients and their families, patient organisations, physicians, nurse practitioners, paediatricians, residents of professional schools, etc.).

Training of patients and families

The CNMR is developing a programme of continuing education in RD patient identification, referral and management, addressed to GPs and other health professionals. The Centre has also carried out a number of courses, addressed to patient organisations, aiming at empowering RD patients, as well as their families, in the daily management of their disease.

Courses for the members of patient organisations

The CNMR has organised several training courses dedicated to the members of patient organisations. Among these it is worth mentioning:

1. "*Implementation and evaluation of a training programme on orphan drugs targeting patient associations and families of patients with rare diseases*" (2008-2010), a participatory *training of trainers* course on one of the major needs expressed by patients: *orphan drugs* (including

steps and challenges related to their development and commercialisation) and issues related to the accessibility of treatment for RDs. The course used Problem Based Learning (PBL) and the production of a Project work on the elaboration of a training and information programme on *orphan drugs* to be realised in the associations to which participants belonged.

2. The course on "*Parent Training on Prader-Willi syndrome*" was to engage the parents of children with PWS in order to improve their relationship with the children and children's behaviour, to increase the knowledge on PWS and to empower parents in managing their children. The intervention was offered to 32 parents coming from different Italian regions. The *Parent Training programme* consisted of twelve sessions of 2,3hours (from September 2008 to February 2009), and was conducted by two moderators: a psychologist and a parent with experience in parent training methods. Several questionnaires have been elaborated for the evaluation of the programme. Results from this study have suggested that parent training is a promising intervention for parents of children with behaviour problems. Thus, the next steps are to disseminate this intervention model to other RDs.

Training activities for the NHS personnel

In order to contribute to improving the quality of health care offered to patients with RDs, the CNMR - in collaboration with other institutions and organisations - has organised, for many years, educational interventions for health and social personnel of the NHS. One of the most interesting training activity at the national level was the course "*Rare diseases: diagnostic suspicion and effective communication*", intended for General Practitioners and Paediatricians. Designed originally for the personnel of a local health organisation in the province of Rome, the course was then replicated in other Italian regions. It used PBL and a "one day/one problem" approach, to make the training model flexible and usable in a variety of contexts.

Similar initiatives, targeted at clinicians and health professionals, also arise from the collaboration with organisations: an example is a course on congenital vascular malformations within the project "*Promoting the network for general practitioners and paediatricians*" (October 2013).

In addition to courses on RDs, training programmes on specific topics such as guidelines, narrative medicine, disease registries, helpline on RDs, have also been carried out. Furthermore, the CNMR's researchers offer numerous lectures on national and international projects, oral presentations and posters, in collaboration with institutions, scientific societies and/or patient organisations.

Advanced national and international courses and e-learning experience

Followig are some of the Centre's most significant experiences regarding advanced of training.

- Summer School on Guidelines

In order to improve knowledge and adoption of RDs guidelines, the CNMR has organised since 2012 the International Summer School on "*Clinical practices guidelines on rare diseases*". The one-week intense course means to provide participants with the methodological basis for the development of RD guidelines. It also gives an introduction of the commonly used standards for the assessment of existing guidelines.

The international team of trainers facilitates an informal and interactive learning environment, offering useful insights for discussion and stimulating the exchange of experiences between colleagues coming from different countries. The official language is English.

- Summer School on Registries

The first edition of the Summer School on RDs and orphan drug registries was in October 2013 and the second edition is planned to take place on 15-19 September 2014. The course takes the participants through the main concepts and practical steps that must be undertaken in the establishment and management of a RD registry to ensure its usefulness, soundness and sustainability. It provides basic notions on the methodology of observational studies, on the selection of data elements, on quality assurance and on the technical and legal tools that must be adopted to protect patients' data confidentiality. The course consists of frontal presentations followed by small group exercises. The official language is English.

- Distance learning

The CNMR has organised, in collaboration with the Distance Learning (FAD)[67-69] working group of the External Relation Office/ISS, a 5 modules training course on "*The prevention of congenital defects in the peri-conceptional and peri-natal: risk factors and protective factors for pregnancy*" supported by a specific project funded by the Italian MOH. The training used an interactive and experiential methodology - PBL - which is normally used in classroom training. Therefore, using PBL in FAD, presented aspects of training innovation[70]. More than 1,000 health professionals attended this e-learning course. One year after the training, a "*Follow-up skills questionnaire*" was administered to course participants to assess their perceived impact of the course on learning, on their professional practice,

on opinions and attitudes towards the improvement of the promotion of folic acid supplementation.

The data collected from the questionnaire shows an increased awareness and an improved quality of the participants professional practice, with more attention paid to health promotion and primary prevention. According to the data analysis, knowledge increased of about 30% and about 80% of the participants thought that the course provided a positive contribution to change their professional activities. Overall, the participants evaluated positively the learning experience, appreciating the opportunity to attend an e-learning programme with such an innovative methodology[71].

- *Capacity building activities*

Recently, the CNMR has initiated activities of capacity building in the framework of the EUROPLAN project, on request of the EU. *Capacity Building* is a conceptual approach to development that focuses on understanding the obstacles that inhibit governments from realizing their developmental goals, while enhancing their abilities that will allow them to achieve measurable and sustainable results.

Capacity building is a process and starts with the definition of needs and the obstacles that hinder progress in achieving the results. It includes all those actions that allow the Government to accomplish specific objectives and maintain the results over the time. Activities, tailored to each situation, include the training of human resources but are not limited to it. It comprises technical support and other strengthening efforts. The experience in *capacity building* that will be gained in the EUROPLAN II project will be useful for other active sectors of the Centre's areas of interest.

6. Networks and collaborations

The CNMR base most its work on networking and on effective collaboration at national, European and international level. Evidence of this effort is found in the description of the research activities, of the projects and of the many actions related to RDs. Furthermore, the CNMR participates, through its staff, in different national and international committees. Among these, it is worth mentioning the CNMR participation in:

- the Italian Clinical Trial Phase I Committee, which is the national committee that authorises Phase I clinical studies of new drugs;
- the Committee for Orphan Medicinal Products (COMP), at the European Medicines Agency (EMA);
- the EU Commission Expert Group on Rare Diseases.

Discussion and final considerations

RDs have undoubtedly been on the European agenda since the early 1990s. While a disease might be defined as "rare", the number of persons in Europe suffering from a RD is estimated to be between 27 and 36 million, or 6 to 8% of the European population.

Insufficient resources are dedicated to research for RDs and these, as well as expertise in these conditions, is fragmented across individual EU countries. Likewise, limited resources are devoted to improve ability and competencies in diagnosis, treatment and care of RDs patients throughout Europe. For this purpose, a number of documents and recommendations have been issued by the EU advising MS to take action in addressing RDs in their National context. In particular, a recommendation called on all EU MS to develop plans or strategies for RDs by 2013, in order to ensure universal access of RD patients to high quality care.

The Italian Government has taken factual steps in recognising the importance of RDs and has complied with some of the main Council Recommendations. Nevertheless, Italy has no National Plan for Rare Diseases yet[72], and this remains an open issue for this country. Likewise, the exclusion of some/most RDs from the list that would exempt individuals with RDs from paying for disease-related services creates inequities among the patients population. The low level of investments in scientific research, the insufficient number of specialised infrastructures and their uneven geographical distribution, along with the lack of knowledge of many RDs, make diagnosis and treatment difficult, delayed and costly. Often, RD patients have to migrate from one region to another, or even travel abroad, in search of a diagnosis or appropriate treatment.

Without any doubt, it can be stated that RD patients, in addition to the heavy burden of the disease, face heavy inequalities in the access to care and services. RDs do not only affect diagnosed people, but also their families, friends, caregivers and society as a whole. It is not uncommon for families of RD patients to end up impoverishing themselves in the effort to obtain a proper and timely diagnosis or an appropriate treatment for their diseased relatives. These open challenges require the utmost attention by the Government and by all stakeholders, both at Italian and at European level.

Particularly relevant is the action of patient organisations which, by voicing the real instances of RD patients, can be catalyst of more positive and rapid societal changes. Their consistent call for policies and programmes that aim at improving the quality of life of all people living with RDs should produce effective results. The Italian patient organisations are proactive and it is hopeful that their positive and determinate action can bring about a better future for Italian RD patients and for their families.

Since its establishment in 2008, the CNMR has developed and carried out a wide range of activities tackling old and new RD challenges in a comprehensive

and integrated manner. Innovation, enthusiasm, scientific rigour, quality, vision and hard work are the basic values on which the dynamic group of professionals, that constitute the CNMR, base their daily work. Their strategy is to gather essential elements of experimental research, acquire the newest and most relevant public health findings and translate both into effective and efficient actions for the prevention, surveillance, diagnosis and treatment of RDs in Italy. They also participate in the on-going research and action on RDs in Europe and at international level and thus contribute to improving the quality of life and the care of RD patients in Italy and elsewhere.

Keywords: rare diseases, orphan drugs, experimental research, public health, registries.

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Correspondence: Domenica Taruscio
Italian National Centre for Rare Diseases - Istituto Superiore di Sanità
Viale Regina Elena 299
00161 Rome, Italy
e-mail: domenica.taruscio@iss.it