

ITALY

EUROPLAN NATIONAL CONFERENCE

FINAL REPORT

27-28 January 2014, Rome

FOREWORD

The EUROPLAN National conferences are aimed at fostering the development of a comprehensive National Plan or Strategy for Rare Diseases addressing the unmet needs of patients living with a rare disease in Europe.

These national plans and strategies are intended to implement concrete national measures in key areas from research to codification of rare diseases, diagnosis, care and treatments as well as adapted social services for rare disease patients while integrating EU policies.

The EUROPLAN National conferences are jointly organised in each country by a National Alliance of rare disease patients' organisations and EURORDIS – the European Organisation for Rare Diseases. For this purpose, EURORDIS nominated 10 EURORDIS-EUROPLAN Advisors - all being from a National Alliance - specifically in charge of advising two to three National Alliances.

EUROPLAN National conferences share the same philosophy, objectives, format and content guidelines. They involve all stakeholders relevant for developing a plan/strategy for rare diseases. According to the national situation of each country and its most pressing needs, the content can be adjusted.

During the period 2008-2011, a first set of 15 EUROPLAN National Conferences were organised within the European project EUROPLAN. Following the success of these conferences, a second round of up to 24 EUROPLAN National Conferences is taking place in the broader context of the Joint Action of the European Committee of Experts on Rare Diseases (EUCERD) over the period March 2012 until August 2015.

The EUROPLAN National Conferences present the European rare disease policies as well as the EUCERD Recommendations adopted between 2010 and 2013. They are organised around common themes based on the Recommendation of the Council of the European Union on an action in the field of rare diseases:

1. Methodology and Governance of a National Plan;
2. Definition, codification and inventorying of RD; Information and Training;
3. Research on RD;
4. Care - Centres of Expertise / European Reference Networks/Cross Border Health Care;
5. Orphan Drugs;
6. Social Services for RD.

The themes “Patient Empowerment”, “Gathering expertise at the European level” and “Sustainability” are transversal along the conference.

Table of Contents

A. INTRODUCTION	2
B. Network (of Centres)	5
1. Network governance, definition and assessment of the Centres	5
2. Network governance. Guaranteeing the continuity of care from the Centres of the Network to the territory	7
3. E-Health	8
4. Care abroad – Cross-border health care	9
5. HORIZONTAL THEMES	9
C. Surveillance, information flow, classification and coding	11
6. Surveillance system: registries and information flow	11
7. Nomenclature, classification and coding.....	14
8. HORIZONTAL THEMES	14
D. Patient’s management (social services and orphan drugs included).....	16
9. Multidisciplinary approach, pathways and treatment continuity.....	17
10. Diagnostic Therapeutic Care Pathway.....	18
11. Individual Therapeutic Assistance Plan	19
12. Social services for rare diseases	19
13. Drugs and orphan pharmaceutical therapies for rare diseases, use of “off-label”, pharmacovigilance.....	20
E. Research activity and orphan drugs.....	21
14. Resource, infrastructure, research projects and fund governance supporting research into rare diseases.	24
15. Needs and Priorities of the research activity into Rare Diseases.....	25
16. The participation of Centres/“Presidi” Centres/“Presidi” , researchers and patient associations into Rare Diseases research projects.	25
17. International and European cooperation for Rare Disease research.....	26
18. HORIZONTAL THEMES	28
19. Supporting the development of orphan drugs.....	30
20. Access to the treatment	30
21. HORIZONTAL THEMES	33
F. Information and training.....	34
22. Awareness on rare diseases	34
23. Information on rare diseases.....	36
24. HORIZONTAL THEMES	38
25. Training.....	39
26. HORIZONTAL THEMES	41
G. Prevention (screening policies i.e. diagnostic assistance pathways for rare diseases diagnoses through screening).....	43
27. Pre-conceptional and pre-natal screening	43
28. Neonatal screening.....	44
29. Diagnostic and genetic tests.....	45
30. Primary Prevention.....	46
31. HORIZONTAL THEMES	47
Annex I - CORE INDICATORS for Monitoring National Plans/Strategies	50
Annex II – Programme of the Conference (in Italian)	56

A. INTRODUCTION

EUROPLAN European project for the development and implementation of national plans for rare diseases – EUCERD Joint Action for Rare Diseases

The European project EUROPLAN for the development and implementation of national plans for rare diseases was co-funded by the European Commission (DG- SANCO). In the period 2008-2011 EUROPLAN laid the foundation for the development in the EU countries of a national plan/strategy for rare diseases to be adopted by 2013, according to the Recommendations of the Consilium on a European action in the field of rare diseases (2009 / C 151 / 02).

In this three-year period 2012-2015, EUROPLAN is an integral part of EUCERD Joint Action, Work Package 4, coordinated by the Italian National Institute of Health (ISS), National Centre for Rare Diseases.

The main objective of this second round of EUROPLAN is to give a boost to the work of development and implementation of plans or other sets of coordinates and unified strategies to respond to the needs of health and social care for the RD patients and their families. All the stakeholders are involved in this project, especially the involvement of policy makers has a great importance.

As in EUROPLAN 2008-2011, the strategy is on two levels is maintained: the effort within each EU country, together with the coordination at European level.

The Italian Draft National Plan on RD

On December 18, 2012, after a long process of elaboration, the former Ministry of Health has submitted to the associations of patients a draft National Plan for Rare Diseases 2013-2016. At the same time the Health Ministry opened a public consultation on the draft plan to patient associations, scientific societies and to the national network of Centres/“Presidi” Centres/“Presidi” for rare diseases

The Second Italian National Conference – Rome, January 27-28

One of the most important moments in the project EUROPLAN is represented by the national conferences, which mark some of the milestones of the project. After the extraordinary success of the previous edition, UNIAMO FIMR non-profit organisation felt it was important, to give a new boost to a faster adoption of a national plan for rare diseases, to promote a Second National Conference EUROPLAN. On April 23, 2013, in Rome, the federation UNIAMO resumed the Steering Committee, which started its works for the previous conference.

Date and Venue: January 27- 28, 2014, at the auditorium of the Bambino Gesù Children Hospital –Rome

More than **160 people** actively involved in the work groups in the face to face meetings and the remote work representing bodies / institutions / organisations /patients’organisation/ societies involved.

The operating procedures:

- Activation of thematic working groups prior to the realization of the Conference in January 2014 to facilitate the analysis and discussion on the issues concerned;
- Involvement also of other bodies / organisations in addition to those represented in the Steering Committee (SC).

SC meetings held on April 23, 2013, May 21, 2013, June 25, 2013, September 9, 2013 to define date, venue, relevant topics for the national context and to identify the representatives in every WG.

After the Conference, on February 17-21, 2014, at the Ministry of Health a feedback meeting was held to revise the outcomes of the event.

WGs meetings were held on December 4-5, 2013 at different Institutional sites, in addition to remote work through the use of a virtual IT platform set up ad hoc by UNIAMO FIMR.

The 6 thematic working groups reflected the Chapters of the Italian Draft National Plan for Rare Diseases:

- a) Network
- b) b1) monitoring system: records and information flow
b2) nomenclature, classification and coding
- c) Diagnostic and care paths (including Social Services and Orphan Drugs)
- d) Research and Orphan Drugs
- e) e1) Information
e2) Training
- f) Prevention

Organiser : UNIAMO F.I.M.R. Onlus

Steering Committee :

- Ministry of Health
- Ministry of Labour and Social Policy
- Interregional Table for Rare Diseases -Coordination Health Commission of the State - Regions and Autonomous Provinces
- ISS /National Centre for Rare Diseases
- Agenas National Agency for Regional Health Services
- AIFA National Drug Agency
- CARD Scientific Society of territorial health and social activities
- EUCERD
- Farindustria Association of pharmaceutical companies
- Federsanità Anci National Association of Italian Municipalities for Health Issues
- FIMMG - Italian Federation of General Practitioners - Telethon Foundation
- Orphanet Italy
- SIGU - Italian Society of Human Genetics
- SIMG - Italian Society of General Practitioners SIP - Italian Society of Pediatrics
- SIMGePed - Italian Society for Genetic Diseases Pediatric and Congenital Disabilities

Other participating agencies :

- Assobiotec
- Inter-Parliamentary Group for Rare Diseases
- NOMOS Center of Parliamentary Studies Ltd
- O.Ma.R Observatory for Rare Diseases
- SIE - Italian Society of Endocrinology
- SIN - Italian Society of Neurology
- SIMMESN - Italian Society of Neonatal Screening Study and Metabolic Diseases
- Military Chemical Pharmaceutical Plant
- UPFARM - Professional Pharmacists Union for Orphan Drugs

Technical Support:

- Sinodè Ltd.

B. Network (of Centres)

Focus group		
Members:		
Angelasio	Angela	AGENAS National Agency for Regional Health Services
Angelelli Cafiero	Giulietta	UNIAMO F.I.M.R. onlus
Baraldo	Gedeone	Lumbardy Region
Bartuli	Andrea	S.I.P. Italian Society of Pediatrics
Berni	Cecilia	Tuscany Region
Caproni	Marzia	Tuscany Region
Ciampa	Serena	Orphanet Italia
Congiu	Maria Elena	Ministry of Health - Department of health planning
Cordiali	Rosanna	Regione
Cristoferi	Filippo	Cerimas Centre for Research and Studies in Health Management
Di Lallo	Domenico	Lazio Region
Di Gioia	Massimo	Regione
Gasperoni	Silvia	Regione
Lamanna	Alessandro	AGENAS National Agency for Regional Health Services
Manea	Silvia	Veneto Region
Marcheselli	Maria	UNIAMO F.I.M.R. onlus
Mazzocanti	Maria	Marche Region
Memo	Luigi	SIMGePeD Italian Society of Pediatric Genetic Diseases and Congenital Disability
Minelli	Flavio	EUCERD
Mollo	Emanuela	ISS Italian National Health Institute
Paci	Sabrina	SIMMESN Italian Society for the Study of Inborn Metabolic Diseases and Neonatal Screening
Patisso	Maria Concetta	Umbria Region
Rizzo	Cristiano	SIMMESN Italian Society for the Study of Inborn Metabolic Diseases and Neonatal Screening
Sanna	Guido	FIMMG Italian Federation of General Practitioners
Scarcella	Carmelo	Federsanità Anci National Association of Italian Municipalities on Health Issues
Silvano	Giuseppe	UNIAMO F.I.M.R. onlus
Sorrentino	Dina	Basilicata Region
Torricelli	Francesca	Tuscany Region

1. Network governance, definition and assessment of the Centres

State of the Art

In Italy, a single definition used to define Rare Disease Centres, i.e. “Presidi”, having legislative value. The Centres are identified in each Region by the competent Regional authorities in their territory among the National Health System structures, as provided for by Ministerial Decree 279/2001 establishing the “National Network for Rare Diseases”.

According to the Agreement undersigned between the State and Regions in 2007, the Network of Centres/“Presidi” selected by the Regions represents the National Network.

In the following years, in parallel with the debate at European level, the reflection about the specific features of such Centres/“Presidi” should have, has continuously developed leading to the present definition of Centres/ “Presidi”. They are characterised by:

- possible presence in the same Centre/“Presidio” of several operative units contributing, in parallel or in sequence, to diagnosis and patient management;

- selection of the Centre/"Presidio" according to objective and assessable criteria and transparent processes leading to binding acts;
- assessment of the Centres' activity based on two elements: a complex review of the quality perceived and the systematic collection of the main outcome and results indicators.

Presently, in order to select their Centres/"Presidi", most of the Regions have applied or are applying the criterion of the number of patients followed, calculated on the basis of the regional information flows or from the information systems specific to rare diseases. At present, the method followed to use the above objective elements is different according to groups of Regions. Experimental studies are being carried out in order to develop a model and its tools to assess the quality of Centres/"Presidi" and the outcome indicators.

Some rare disease patients, some associations and some professionals are complaining about the difficulty to have simple and immediate access to the information concerning the number of designated Centres/"Presidi" for specific diseases. This difficulty is mainly due to:

- the lack of knowledge about the existing information tools (e.g. Region websites and National Centre for Rare Diseases -Italian National Institute of Health –ISS- website);
- the succession over time of different Regional Resolutions;
- the possible lack of alignment between what provided for by the Regional Resolution and the service actually provided (e.g. latency period between the adoption of the Resolution and the actual Centre implementation; poor quality of the activity carried out; ...).

In general, there is the need to strengthen the network governance dynamics whose crucial pivots are the Centres identified by the Regions.

Proposals to be included in the National Plan for Rare Diseases

1. The Centres/"Presidi" selection, without prejudice of the regional autonomy concerning the implementation of such indications within specific organisational models, shall be based on optimum evidence-based criteria, and shall not be self-declared: the first shared criterion is the number of patients followed and defined by the number of diagnosis and care plans, using information flows sent by the "Presidi" and by regional registers to the RNMR (National Register for rare Diseases) and the other information flows.
2. The regular assessment of the Centres/"Presidi" shall be carried out involving patients associations and the other stakeholders in the network with a special attention to:
 - a. quality perceived;
 - b. outcomes.
3. The network is made by the Centres/"Presidi" Centres/"Presidi" but also by hospital and territorial services (health, health and social, social, educational services, ...) located near the place where the rare disease patient lives.
4. The list of active Centres/"Presidi" Centres/"Presidi" shall be constantly monitored and updated according to the Regional Resolutions and made simple and promptly accessible to the potential beneficiaries.
5. The information sources presently existing both at national (e.g. ISS Italian National Institute of Health) and regional level, via web and via phone, shall be properly divulged and interconnected (*see also group e) Information and Training*).
6. The Centres of Expertise to be part of the ERNs (European Reference Networks) shall be selected among those Centres /"Presidi" already identified in the Regions.

7. As for the overall network governance, the activation/ formalization of a National Committee has been proposed with the inclusion of all the actors involved in the rare disease field, including RD patients' associations. Such Committee should have the task of developing strategic policies and proposals to be implemented in the field of diagnosis, assistance, research, social protection and promotion, training, information and information system; it shall indicate the priorities for the use of financial resources dedicated to rare disease patients, also by taking into account monitoring data and assessment.
8. With a view to guarantee greater equity across the national territory, the National Committee shall address, as first action of its mandate, , the proposal to update of the **Essential Levels of Assistance (LEA¹)**. The LEA comprise all of the activities, services and benefits that the National Health Service (NHS) provides to all citizens for free or by paying a fee, regardless of income and place of residence.
9. It is necessary to implement both managerial and tariff modifications with the aim to overcome the present critical state of the tariff system and of the intra-hospital organisation, elements that make the survival of Centres as described above particularly difficult(see also group c) *Diagnostic-assistance path*).
10. To implement the above measures it is necessary to have dedicated resources.

2. Network governance. Guaranteeing the continuity of care from the Centres of the Network to the territory

State of the art

The different Regions have adopted different organisational methods to guarantee the continuity of care at territorial level thanks to their organisational autonomy. At present, there are still some difficulties to guarantee the continuity of care provided by the Centres/"Presidi" to the territory and to the place where the rare disease patient lives: for rare disease patients this is one of the system's weaknesses.

In particular, it is pointed out the difficulty to conciliate different cultures and approaches that distinguish the different nodes of the network: focus on the pathology, as for the specialised/hospital assistance, and focus on the protection level of the socio-health assistance needs, when it comes to the primary/territorial assistance.

Proposals to be included in the NPRD

1. Through suitable forms of organisation (e.g. Rare Disease Help Desk), developing the guidance and coordination services for patients and family members, on the one hand, and for health

¹ The LEA have been defined at the national level with the Decree of the President of the Council of Ministers of 29 November 2001 , which entered into force in 2002. The reform of Title V of the Italian Constitution also establishes the possibility for Regions to use their own resources to provide additional services or functionality (but never less) to those included in the LEA.

Specifically for RD and as stated in the draft NPRD "... *The standard (Ministerial Decree 279 /2001) does not define the services entitled to cost exemption, but provides for those RDs present in the list attached to the MD, the right to "exemption for all services included in the LEA needed to confirm the diagnosis, appropriate for the monitoring of the disease and to prevent further aggravation "*.

The scope of MD n. 279/2001 does not apply to the " pharmaceutical car , nor the "prosthetic assistance and economic benefits, which are regulated by other specific rules, even for the people exempted. However, many of the Regions whose economic and financial situation allow for the introduction of "additional assistance levels", have independently arranged for the free supply of drugs in group C and other products not classified as drugs, to citizens affected by RD residing in its territory .

The renewal of the discipline of the RD in the LEA implies that the legal instrument and the procedure for the update are those defined by law for the modification of the essential levels, that is a Decree of the President of the Council of Ministers, in consultation with the Minister of Economy and Finance, in agreement with the State-Regions Conference".

professionals, on the other, in order to favour the access to the rare disease network (*see also group e) Information and Training*);

2. Defining criteria and methods to ensure a standardised and consolidated level of care for people having complex needs at the local level, i.e. by the competent Local Health Unit (ASL) that is the one closest to the patient's place of residence). The coordination and liaison (with the nodes of the network) must be guaranteed (*see also group c) Diagnostic-assistance pathways*);
3. Developing dynamic and operative managing mechanisms of the rare disease network in order to guarantee the continuity of assistance (*see also group C) Diagnostic-assistance pathways*);
4. In particular, for ultra-rare diseases, for which it is not possible to have a Centre/"Presidio" in each Region, it is even more important to clearly identify the common working method/integration between the Centre and the territory of residence of the patient;
5. Guaranteeing methods and dynamics in the network governance that favours appropriate care in the transition from paediatric to adult age.

3. E-Health

State of the art

E-health can be a tool to share the clinical case with national or international Centres of Expertise allowing the patient to have a specialist consultation while remaining in his/her own territory. It can be the tool to favour the dialogue between centres and peripheral local structures. E-health can also be used to share expertise among health professionals with a view to a widespread cultural growth. Together with the e-health there must be also a structured network of territorial care and support, permitting, when possible, to manage the patient in his/her area of residence.

This kind of approach is mentioned in the guideline documents below and in the decision-making process on this issue:

- Draft memorandum on the telemedicine national guideline adopted on 20 February 2014 upon proposal of the Ministry of Health
- Document drawn up by the interregional Group for Rare Diseases about tele-counseling for rare diseases.

Proposals to be included in the National Plan for Rare Diseases

With reference to the official guideline documents, it is especially underlined the importance of:

1. Telemedicine for territorial integration and continuity of care;
2. Communication tools (telematic systems included) for the provision of advice among the Centres in the assessments of clinical cases;
3. A fee system of remuneration of the time spent by clinicians for the different forms of remote exchange advice with peers;
4. Diffusion of tools for information sharing (e.g. sharing, management and e-accessibility);
5. Completion and full implementation of the Electronic Health File;

6. Adoption, in the whole national territory, of the electronic medical record specific to the rare pathology each patient is affected; upon patient’s request, they are accessible by each “Presidio” or physician consulted.

4. Care abroad – Cross-border health care

State of the art

It is in the process of implementation, a legislative Decree has transposed the European Directive for the cross-border health care (Directive 2011/24/UE) aimed at providing the patient with the possibility to access the health services in all EU Union Countries.

Proposals to be included in the National Plan for Rare Diseases

Within this framework, for rare diseases it is clear the need to determine and further specify correct implementation policies. Particularly:

1. Art. 9 on preventive authorisation in case of rare disease provides that the patient’s request may be subject to expert assessment: for this reason it is desirable a clear definition of the assessment procedures and criteria. Such aspect is functional to a correct definition of the assessment systems in order to guarantee equity and uniformity in the national territory;
2. Establishing the National Body (as laid out in art. 13 paragraph 2 of the Directive) ensuring that Ministry and Regions are represented on an equal basis;
3. Giving greater diffusion and visibility to the National Contact Point and creating a network with Regional Contact Points to guarantee the connection among sources of information relevant to rare diseases;
4. The Centres of Expertise involved in the ERNs (European Reference Networks) shall be selected among the Centres / “Presidi” already identified by the Regions.

5. HORIZONTAL THEMES

- **Sustainability: what actions may be adopted by the National Plan for RD to favour the Centres’ medium-long term sustainability?**

-Funding channels of the network of Centres

-How to ensure medium-long term sustainability with respect to the above issue?

--Improvement of the effectiveness of public spending

--Raise of additional resources

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In the National Health System there exists the concept of financing according to the function; in some Regions the “Rare disease” function has been identified and has been allocated dedicated funds (e.g. Lazio Region).

- **Empowerment²: which actions may be included in the PNMR to support the empowerment, in its different elements concerning the Centres Network?**

Individual
•
Organisational
<ul style="list-style-type: none"> • Supporting expertise sharing among centres/professionals (professionals mobility among the Centres) • Involvement of representatives of the rare disease patients' associations in the Regional Coordination Groups on Rare Diseases.
Community
<ul style="list-style-type: none"> • Wide dissemination of information regarding the access to the Centres/"Presidi" throughout the territory.

- **Best practices (particularly significant experience to support the proposals): what experiences may be reported within the Centres 'network'?**

<ul style="list-style-type: none"> • Orphanet-Italy with the cooperation of the Interregional Technical Board since 1° January 2013 has been developing a mapping of the Centres/"Presidi"; • UNIAMO /FIMR, with the support of Agenas, the National Agency for Regional Healthcare, and the cooperation of all stakeholders of the rare disease network, is developing and experimenting a model for the quality assessment of Centres/"Presidi". The project «Community 2» is proposed as a good practice both for the assessment of Centres and empowerment; • The Tuscany Region is working on a model for the definition of indicators inspired to the methodology already used for the Tuscany Network for Rare Cancers, to the EUCERD recommended quality criteria on Centres of Expertise, as well as assessment forms developed from those used by Orphanet ; • The Regions in the Northeast area have defined common criteria and objectives for the identification of the Centres/"Presidi" and has promoted the mutual acknowledgment of the Centres, which is done by issuing "twins" Resolutions. In addition, they agreed to jointly extend the provision of extra-LEA services (LEA, Essential Levels of Assistance) ; • The Consortium of Regions for Rare Diseases (composed of 8/9 Italian Regions) has promoted and adopted an electronic medical record for rare diseases that record each phase of the patient's pathways and that can be used for handling medical prescriptions (<i>compare also the with Group B</i>); • The Tuscany Region has implemented a Centro di Ascolto Malattie Rare (Listening Centre for Rare Diseases) as listening and guidance centre for patients and physicians. It also developed a Tuscany Region Rare Disease website for the guidance within the network (<i>compare also with Group E</i>). • e-pilots on the use of of the Electronic Health File are being carried out (<i>compare also with Group B</i>). • Involvement of the representatives of rare disease patients associations in some Regional Coordination Groups for Rare Diseases.

² "Empowerment is a process generated by **social action** through which **people, organisations and communities acquire competence** on their life to change their social and political environment and to increase equity and life quality" (N. Wallerstein, 2006)

C. Surveillance, information flow, classification and coding

Focus Group

Members:

Baldovino	Simone	Piedmont Region
Benedicenti	Francesco	Regione
Bragagnolo	Paola	Sinodè Consultancy agency for welfare issues
Censi	Federica	ISS Italian National Health Institute
Del Zotti	Michele	UNIAMO F.I.M.R. onlus
Di Giacinto	Martina	Orphanet Italia
Di Rocco	Maja	S.I.P. Italian Society of Pediatrics
Gainotti	Sabina	ISS Italian National Health Institute
Giuffrè	Mario	SIMGePeD Italian Society of Genetic Diseases Pediatric and Congenital Disabilities
Kodra	Yllka	ISS Italian National Health Institute
Pediconi	Federica	Marche Region
Polizzi	Agata	ISS Italian National Health Institute
Reale	Emanuela	AGENAS National Agency for Regional Health Services
Romano	Corrado	SIGU Italian Society of Human Genetics
Salvatore	Marco	ISS Italian National Health Institute
Scopinaro	Annalisa	UNIAMO F.I.M.R. onlus
Sozio	Maria Pia	UNIAMO F.I.M.R. onlus
Spada	Marco	SIMMESN Italian Society for the Study of Inborn Metabolic Diseases and Neonatal Screening
Taruscio	Domenica	ISS Italian National Health Institute
Tosto	Fabrizio	ISS Italian National Health Institute
Venzi	Mietta	FIMMG Italian Federation of General Practitioners

6. Surveillance system: registries and information flow

State of the Art

In order to contribute to the planning of national and regional interventions, aimed at safeguarding rare disease patients and implementing surveillance, since 2001 a monitoring system for rare diseases is active in Italy, that is based on the local population registries making reference to a single register that, through a constant national information flow, permits to have specific estimates on rare diseases thus assessing the overall phenomenon. The National Register for Rare Diseases (RNMR) was created at the Italian National Health Institute (art. 3, Ministerial Decree n. 279/2001) and implemented thanks to the State-Regions Agreements signed in 2002 and 2007. With the Agreement undersigned by the State, Regions and the Autonomous Provinces of Trento and Bolzano on March 10, 2007 the Regions committed themselves to create regional or interregional Registers, to assign them the necessary resources and to update the RNMR with a flow of data according to a number of variables (*dataset*) defined by the same Agreement; such dataset contains important personal data for patient enrolment and on the specific disease. Before being sent to National Register of RD such information is previously validated by the people in charge/referents of Regional Registers.

The Regional/interregional registries, created in 2001 in several Regions according to diverse timings and methods, are differentiated by type of organisation, the information collected and the purposes that the regional/provincial administrations assign them. Some of them have mainly an epidemiologic purpose and support the regional planning, in addition to the flow of information that the Regions are by law required to feed into the National Registry of RD; other registers are structured with the aim of supporting care

activities and coordinating the rare disease patients management by collecting and making available information to services' providers and operators involved in the diagnostic-therapeutic interventions included in the individual care pathways.

This processes and projects sharing led to the creation of interregional conventions and agreements that led to the creation in the country of two distinct "interregional" territorial areas duly recognised: the first one including Piemonte and Valle d'Aosta regions, the second one including Veneto, the Autonomous Provinces of Trento and Bolzano, Friuli Venezia Giulia, Emilia Romagna, Liguria, Puglia and Campania regions. The administrations involved in the two interregional networks share the same policy regarding the accreditation and functioning of the Centres/"Presidi", the therapeutic protocols and the care pathways. They represent two virtuous examples of best practices valorisation and sharing, notwithstanding the differences among the regional realities. Such result was achieved by the interregional group for rare diseases created in 2006 within the Health Commission of the Regions and the Autonomous Provinces Conference.

The above-described situations also present some critical aspects, among them:

- *dataset* completeness and updating in the different Regions;
- the rigidity of the list of pathologies, as under MD 279/2001, according to which the National Register of RD is structured; the list updating, required by law every 3 years, has not been implemented yet with a consequent inequality among rare disease patients and an overall underestimation of epidemiological data for rare disease. The lack of updates and the difficulty in its revision represent a significant limit for the system. The new scientific findings are very frequent and it would be useful to develop a dynamic and prompt method to include new RD to better fulfil the objectives and ensure a greater equity as for the assistance of rare disease patients³;
- the lack of regular feedback between people in charge of entering data (physicians operating in the Centres/"Presidi" identified by Regions, enabled to register the diagnosed cases and in charge of rare disease patients management) and those in charge of registers;
- it is important not to omit the problem concerning the economic sustainability and the motivations of those contributing to the register by entering data (to be associated with the previous point).

The difficulties concerning rare diseases codification (see the following point) make a study to estimate the costs borne by the health system to treat the single pathologies particularly difficult.

Together with the National Register of RD and the regional Registers, there are also additional registers, often concerning the same patients: the registers run by patient associations, registers for specific diseases and databases (e.g. bio-banks), all of them important tools for the clinic research on rare diseases, to improve patients' care management, plan patients' health and assess the social, economic and quality of life outcomes. When a new orphan drug is put on the market, the disease's registries can be very useful to carry out retrospective studies and to identify the disease course. Due to the proliferations of isolated experiences, it is pointed out the need to share a data collection methodology in order to share and compare it with other information flows.

It is essential to include also the registry of drugs subject to monitoring by AIFA (Italian Medicines Agency), bio-banks, etc.: there is a potential problem of information flow rationalization destined to worsen over time due to the technological development. It would be useful to consider also the possibility of integration and harmonisation, especially where registers are structured as patient management system.

Proposals to be included in the NPRD

³ The discussion has pointed out that there are rare diseases that are not included in the list in the Annex to the Ministerial Decree 279/2001, and vice versa, some non-rare pathologies are included in that Annex.

1. Enhancing and disseminating the existing good practices as for regional/interregional registers for rare disease in order to make them more complete, to improve their quality, epidemiological data promptness, thus reducing their costs.
2. For a population registry it would be appropriate to:
 - i) Favour the rationalisation of information flows concerning rare disease patients by promoting the interoperability also via data-linkage, among the different registers and flows (in particular among regional/interregional and national registries for rare disease, registries of drugs under AIFA monitoring, the flows of patients benefiting from social assistance exemption, civil population registries, Hospital Discharge Cards, outpatients flow under art. 50 (monitoring of waiting lists), mortality regional registries);
 - ii) Recognising and defining the role of patients and associations in the case reporting.
3. Identifying a system for quality guarantee and related indicators for the data both in regional/interregional registers and for the National Register, also to favour a greater standardisation of data collection.
4. Creating a mixed technical group among the National Centre for Rare Disease/Italian National Institute of Health (ISS), Regions, patients' representatives for the solution of technical problems concerning registries. This Group should also define and implement actions to guarantee the (mandatory) data forwarding to the National Register of RD by regional/interregional registers by organizing regular meeting sessions.
5. Supporting the operators involved in the compilation of regional/interregional and national registries for rare diseases through adequate training programmes (ECM system), economic incentives and involvement in publications and studies according to registries' data, participation to 1 or 2 dedicated meetings a year and to the national meeting organized by the ISS.
6. Ensuring the annual publication and public presentation in a meeting of the data collected from regional/interregional and national registers for rare diseases specifying the Centres/"Presidi" contributing to the registry.
7. Recommendation in the National Plan for Rare Disease aiming at the creation of coordination committees internal to the regional registries involving also the rare disease patients' representatives.
8. Creating a multi-stakeholder working group for the definition, experimentation and validation of good practices guidelines on informed consent as for the participation in the registries.
9. Extending data collection for to the National Register of RD, to a greater number of rare diseases; planning regular updates of the list according to the Ministerial Decree 279/2001.
10. Developing guidelines for the implementation of pathology-based registers.
11. Increasing awareness and training of patients to render them a stimulus for health professionals involved in the registry compilation (bottom up approach) (*Note: issue considered for the training of rare disease patients and for their associations 'representatives*).

7. Nomenclature, classification and coding

State of the art

In Italy the official definition given by the European Union is applied: a rare disease is a clinic condition with a prevalence not higher than 5 cases every 10.000 people. Such apparently clear definition does not mirror a much more critical picture. Many rare diseases, in fact, are difficult to detect and trace within the health and social systems due to the difficult classification and coding, due to the inadequacy of the system currently used (e.g. ICD9-CM used in Italy for the SDO – Hospital Discharge Sheets - and ICD10 used by ISTAT- Central Statistics Institute- to encode deaths) and because of specific rare disease features such as heterogeneity of pathologies, diagnostic inaccuracy, numerous synonyms and groups of pathologies etc. etc. At the moment, few rare diseases are associated to a unique and specific code; some rare diseases are coded within group of pathologies including common and rare diseases, many are not included in the system because not associated to a code. In the attempt to give its contribution on this issue, the ISS (the Italian National Health Institute), with the cooperation of some regions (e.g.: Lazio, Lombardia, Piemonte, Puglia, Veneto), the Health Ministry, ISTAT-Central Statistics Institute, the WHO Collaborative Centre, specialists from different sectors, scientific societies and Orphanet are taking part into a European Project to improve rare diseases' coding and classification. Such process should lead to a new ICD11 version in 2015. The ORPHA code is presently used to classify all the diseases present in the Orphanet database and in the Public Hospitals in France.

The problem concerning the classification is crucial and should be distinguished from the attribution of the exemption code (list attached to Ministerial Decree 279/2001). It should be characterised by other criteria permitting (as provided for by art. 5 Legislative Decree 29 April 1998, n. 124) to correctly assess the care needs of the patients, such as, the clinical severity, the level of disability as well as the cost for the treatment. All the mentioned aspects should be constantly monitored.

Proposals to be included in the NPRD

1. Promoting the divulgation of ORPHA Codes⁴ and ICD 11 (when issued) in information flows in order to give a greater data standardisation in line with the European level.

8. HORIZONTAL THEMES

- **Sustainability: what action may be included in the National Plan for RD to favour medium-long term sustainability of the rare disease system as for rare disease registries, nomenclature and coding?**

-Funding channels of the network of Centres

-How to ensure medium-long term sustainability with respect to the above issue?

--Improvement of the effectiveness of public spending

--Raise of additional resources

--

- Optimisation of patients registration (avoiding duplications)
-

⁴ The adoption of ORPHA code could facilitate the transition to ICD 11, being the ORPHA code the template currently used for ICD review and SNOMED CT expansion.

<p>How to use the Structural Funds programmed for 2014-2020 in the best way? Indicate if an investment objective on rare disease has been provided to strengthen the Centres network within the reference national strategic framework (and within the regional framework) for the Structural Funds. Indicate the Operational Programmes in which the projects for rare diseases may be included.</p> <p>HORIZON 2020</p> <ul style="list-style-type: none"> •
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- **Empowerment⁵: what action may be planned in the NPRD to support empowerment, in its different aspects, as for rare disease registries, nomenclature and coding?**

<p>Individual</p> <ul style="list-style-type: none"> • Patient’s contribution to information collection: in pathology registers, patients may include perceived data in specific sections. • Patients involvement as incentive to the registration of their own data by health professionals. •
<p>Organisational</p> <ul style="list-style-type: none"> • Regular notice to all the stakeholders involved in rare diseases data collection to be integrated in the registries (aggregate data). • Promoting interoperability among different information systems. •
<p>Community</p> <ul style="list-style-type: none"> • •

- **Best practices (particularly significant experiences to support the proposals): what experiences may be mentioned as for rare diseases registries, nomenclature and encoding?**

<p>Registers</p> <ul style="list-style-type: none"> • RD Connect • GUID (Global Unit Identifier) <p><i>Rare diseases registers</i></p> <ul style="list-style-type: none"> • Rare diseases regional and/or wide area rare registers • Rare disease national register <p><i>Register by pathology</i></p> <ul style="list-style-type: none"> • Cystic Fibrosis Register • SLA Register • EUROCAT congenital anomalies Register • Parent Project Register • Ipinet <p>Rare Disease nomenclature and encoding</p> <ul style="list-style-type: none"> • ORPHA code (Orphanet)
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⁵ “Empowerment is a process generated by **social action** through which **people, organisations and communities acquire competence** on their life to change their social and political environment and to increase equity and life quality” (N. Wallerstein, 2006)

D. Patient’s management (social services and orphan drugs included)

Focus group about specific issues

c) Diagnostic Assistance Pathways

Members:

Annicchiarico	Giuseppina	Apulia Region
Bembi	Bruno	Friuli Venezia Giulia Region
Bianchi	Amedeo	Federsanità Anci National Association of Italian Municipalities(for health issues)
Bombardieri	Stefano	Tuscany Region
Bona	Gabriele	UNIAMO F.I.M.R. onlus
Bordugo	Andrea	SIMMESN Italian Society for the Study of Inborn Metabolic Diseases and Neonatal Screening
Bussotti	Alessandro	Tuscany Region
Cerilli	Micaela	AGENAS National Agency for Regional Health Services
Da Riol	Rosalia Maria	Friuli Venezia Giulia Region
De Santis	Marta	ISS Italian National Health Institute
Di Gregorio	Adriana	CARD Confederation regional associations of social health districts
Donati	Carlo	ISS Italian National Health Institute
Esposito	Antonella	UNIAMO F.I.M.R. onlus
Facchin	Paola	Veneto Region
Gabaldo	Michela	Telethon Foundation
Giannetti	Giovanna	Health Ministry
Guarnieri	Marta	Tuscany Region
Iorno	Tommasina	UNIAMO F.I.M.R. onlus
Leuzzi	Vincenzo	SIMMESN Society for the Study of Inborn Metabolic Diseases and Neonatal Screening
Macchia	Francesco	Nomos Lab
Macchiaiolo	Marina	SIP Italian Society of Pediatrics
Marinelli	Pietro	UNIAMO F.I.M.R. onlus
Nenna	Giorgio	UPFARM Professional Pharmacists Union
Paganin	Carla	TELETHON
Piano	Patrizia	F.I.M.M.G. Federazione Italiana Medici Medicina Generale
Polizzi	Agata	ISS Istituto Superiore Sanità
Porchia	Stefania	SINODE’ Consultancy Agency for Welfare Issues
Roccatello	Dario	Piedmont Region
Romano	Corrado	SIGU Italian Society of Human Genetics
Rottoli	Paola	Tuscany Region
Ruotolo	Roberta	Orphanet Italia
Settesoldi	Daniela	AIFA National Drug Agency
Simi	Paolo	Tuscany Region
Zampino	Giuseppe	SIMGePeD Italian Society of Pediatric Genetic Diseases and Congenital Disabilities

The working group, before dealing with the critical aspects concerning the national context and the proposals to be included in the NPRD, has considered important to develop a definition of “patient’s management” consistent with the legislation enforced, with the definitions agreed by the multi-stakeholder pathways developed during these years, as well as the model organisation of the rare disease patients care organisation to be applied in all Italian territories.

Patient’s management DEFINITION:

All the coordinated interventions addressing the care needs of every individual, taking into account family and life environment, in order to give dynamic answers, as needs vary over time.

CRUCIAL ELEMENTS FOR PATIENT’S MANAGEMENT:

The management network consists of different pivotal elements working in synergy, in particular:

- Centres/ “presidi” for rare disease patients identified by the Regions;

- Hospitals and territorial services (health, social-health (e.g. districts), social, educational, ...) close to the place where rare disease patients live.

WORKING METHOD: Coordination

- 1) Within the Centre/"presidio" for multidisciplinary aspects;
- 2) Between Centre/"presidio" and the territorial structures close to the place where the rare disease patient live;
- 3) Within the territory with a multi-sector approach (health, social, education, workplace, leisure time ,...).

TOOL:

Drawing up and updating "Integrated Individual Therapeutic Care Plans", shared with the network; they are drawn up through Integrated Assessment Units.

9. Multidisciplinary approach, pathways and treatment continuity

State of the art

- Presently in many Italian areas is very difficult to guarantee the treatment continuity among the different nodes in the network.
- There are still many differences among territories, still not able of guaranteeing an equal treatment for patients living in different Regions, especially those Regions involved in a "repayment plan", i.e. having exceeded the ceiling for healthcare-related expenditures. These regions can not provide extra LEA (Essential Levels of Assistance – see footnote pag. 9) services. Therefore it is necessary that LEA are updated as soon as possible. It is also crucial to review the repayment plan regulation (possible reinvestment of the resources saved).
- The so-called Diagnosis-Related Groups (DRG), supporting diagnosis and disease cure, have a nosological base without taking into account the differences among patients and the complexity of specific pathologies.
- For many pathologies there are no Centres/"Presidi" and there is a lack of references when patients pass from paediatric to adult-oriented assistance.

Proposals to be included in the NPRD

1. Eliminate the conditions making difficult the multidisciplinary work within Centres and those making not advantageous for a structure to deal with rare diseases through:
 - The support of managerial experimentation permitting to overcome the budget logic organised according to the single operative unit and guaranteeing an organisational, infrastructural, and economic assessment of healthcare pathways within the hospital structures dealing with rare disease patients. The aim of managerial experimentations is to define methods and/or identify good practices for budget sharing among different the operative units involved.
2. Increase the economic resources permitting to the Centres/"Presidi" to operate through:
 - Modification of tariffs, agreed with NHS for every service provided, according to the complexity of the patient followed.
 - Additional economic recognition to the Centre/"Presidio" for the function performed in the field of rare diseases.

- Economic recognition of counselling activities performed in favour of other hospitals, centres or local services providers (an agreement on this matter is being defined by the Interregional Technical Board for Rare Diseases).

10. Diagnostic Therapeutic Care Pathway

Diagnostic Therapeutic Care Pathway (PDTA) DEFINITION:

The Diagnostic Therapeutic Care Pathways (PDTA) are a tool for clinical management used to define the best assistance process in order to meet the specific health care needs on the basis of recognised recommendations (guidelines) adapted to the local context.

The PDTA purpose is to favour the integration among operators, to reduce the clinical variability, to contribute to the diffusion of evidence-based medicine, to promote a correct use of the resources and to assess the services provided through indicators.

PDTA have to clearly describe the tasks, “who does what”, within the specific context, how the nodes of the network of care are linked up, which are the rules allowing patients to access the different nodes in a simple and clear way, how to render the system equal by defining the basic conditions for the patient to access certain services .

The PDTA must guarantee a minimum quality level for all patients (“no less, no more than”) leaving a certain degree of discretion to the physician who has the final responsibility for the pathway according to the patient’s characteristics.

State of the art

- The issuing by the Regions of the **Diagnostic Therapeutic Care Pathways (PDTA)** is still very fragmented: some regions adopted many PDTA while in others PDTA have not been developed yet.
- There is a lack of comprehensive and shared knowledge about which Regions have developed PDTA and for which pathologies.
- Difficulties in the Regions facing a “repayment plan”, to ensure the extra-LEA services (i.e. services and benefits considered beyond the statutory “Essential Levels of Care”) indicated in many PDTA ⁶

Proposal to be included in the NPRD

1. Guaranteeing that all Regions develop their PDTA and put in place a monitoring system.
2. Activating working groups for the comparison among the PDTA developed in different Regions in all possible appropriate places and events. In case of differences in guaranteeing the services and interventions considered appropriate by national or international guidelines on pathologies, it will be necessary to identify ways to align measures, thus guaranteeing an equal treatment for the patients in the different regional territories.

⁶ The Essential Levels of Care” (LEA) comprise all of the activities, services and benefits that the National Health Service (NHS) provides to all citizens for free or by paying a ticket, regardless of income and place of residence. LEA were defined at the national level with the Decree of the President of the Council of Ministers of 29 November 2001, which entered into force in 2002. reform of Title V of the Constitution also establishes the possibility for regions to use their own resources to provide additional services or functionality (but never less) than those included in the LEA. This implies that LEA may differ from region to region (provided that those defined at the national level are guaranteed throughout the Italian territory).

3. In the PDTA, the extra-LEA elements crucial for the different patients, must be defined, also by reviewing the services/functionalities presently guaranteed by LEA but for which there are no evidence of effectiveness. Therefore it is necessary to fully review the LEA at national level.

11. Individual Therapeutic Assistance Plan

State of the Art

Present weaknesses in the network: difficulty in sharing the Individual Therapeutic Care Plan among the different stakeholders in the network, in particular among Centres/"Presidi" and territorial services.

Proposals to be included in the NPRD

1. Adopting an approach based on the Individual Therapeutic Care Plan as tool to meet all the patients and families's needs, also guaranteeing the continuity of therapeutic care from paediatric to adult age. The responsibility for the Individual Plan is of all those subscribing it.
2. Divulging the Electronic Health Dossier⁷ at national level to facilitate the information sharing among the different nodes of the network.
3. Acknowledging the concept of "complexity" also for the sake of local health-social services through:
 - The identification of specific monitored services recognising the complex condition (e.g. grant of home services, protected discharge, etc.) to be assessed from an economic point of view;
 - The need of integrating services e.g. with the Service of job placement, school ...
4. Stimulating organisational experimentations aimed at overcoming the separation between hospital and territory, thus facilitating mobility between hospital and local services' personnel in both directions.
5. Implementing counselling and support activity carried out by the Centres/"Presidi" towards the territory.
6. Paying attention to the continuous training of personnel both at the Centres/"Presidi" and at the local level in order to support integration (*see Group E) Information and training*).

12. Social services for rare diseases

State of the art

- In Italy, the provision of social services is linked to the degree of disability and the consequent loss of autonomy of the individual. In case of loss of autonomy, the rare disease patients can be included in the category of disabled people and have access to social and social-health services.

⁷ A EHC is intended as a set of data and health or socio-health digital documents consequent to present and past clinical events concerning the assisted patient. Its main purpose is facilitating the access to care, offering a service for the integration of the different professional competences, providing a sound information database contributing to the improvement of all the assistance and cure activities in compliance with the rules for the personal data protection.

The date of 30 June 2015 has been designated as the time limit for the Regions and Autonomous Provinces to establish the EHC. By 30 June 2014, the Regions and the Autonomous Province shall submit the project plan for the creation of the EHC. The Agency for Digital Italy makes available to the Regions, by 31 December 2015, a central national infrastructure for the EHC interoperability. Determined that the implementation of the EHC is included in the obligations which Regions and Provinces Autonomous are committed to access the integrative financing provided by the National Health Service (art. 12 of the decree-law 18 October 2012, n. 179 converted, by modifications, by the Law dated 17 December 2012, n. 221 on «Further urgent measures for the Country growth», as amended by art. 17, paragraph 1, of the decree-law dated 21 June 2013, n. 69 converted by amendments into the law dated 9 August 2013, n. 98 on «Urgent measures for the economy revitalisation»).

- The real problem for the patients is the difficulty to know the opportunities available in their own territory, considering that the organisation of social and socio-health services is very fragmented and the responsibilities are different according to the territory.
- There is a need to receive clear-cut recognition of the loss of autonomy for the patients and to be correctly managed by the social services providers.
- There is a generalised shortage of resources for social and social-health services.

Proposals to be included in the NPRD

1. When discharged by the Centre/“Presidi”, patients shall receive all the documents and correct information to access the territorial social services; the Individual Therapeutic Care Plan shall include also social and health interventions.

13. Drugs and orphan pharmaceutical therapies for rare diseases, use of “off-label”, pharmacovigilance

State of the art (off-label)

- The use of off-label drugs for rare diseases is widespread but there is a lack of traceability regarding the use of such drugs not contemplated in the indications. By ignoring that such molecules are used out of indications to treat some rare diseases, it may happen that some of these drugs are recalled from the market because the pharmaceutical companies are no longer interested in marketing such active principles for the approved therapeutic indication. Often the use of off-label drugs is not supported by clinical experimentations.
- The list of off-label drugs used is different among the Regions
- Difficulty to authorize the use of off-label drugs due to the lack of clinic experimentations and/or solid scientific evidence.

Proposal to be included in the NPRD

1. Off-label drugs, whose effectiveness is supported by scientific evidence, shall be assessed for a possible inclusion⁸ in the list as under L. 648/96, with a special attention by AIFA (the National Medicine Agency) on rare diseases as under L. 648/96.
2. The administration of off-label drugs shall be regulated so as to be included in the Individual Assistance Therapeutic Plan for traceability.
3. Creating a negotiating table between AIFA (National Medicine Agency) and other bodies (Regions).
4. Strengthening the pharmacovigilance systems to encourage the detection of adverse effects reported by the patients, by monitoring the Individual Assistance Therapeutic Plans.
5. Inviting patients and physicians to report such effects.

⁸ Reference to L. 648/1996

E. Research activity and orphan drugs

Focus Group		
Members:		
Ambrosini	Anna	Telethon Foundation
Andria	Generoso	Campania Region
Bernini	Matteo	Tuscany Region
Bianchi	Fabrizio	Tuscany Region
Borzacchiello	Camillo	Military Chemical Pharmaceutical Establishment
Brandi	Maria Luisa	Italian Society of Endocrinology
Carta	Claudio	ISS Italian National Institute of Health
Caruso	Giuseppe	FARMINDUSTRIA Association of pharmaceutical companies
Ceccarini	Marina	ISS Italian National Institute of Health
Daina	Erica	Regione Lombardia
Dallapiccola	Bruno	Orphanet Italia
De Angelis	Raffella	UNIAMO F.I.M.R. onlus
Federico	Antonio	SIN Italian Society of Neurology
Frank	Claudio	ISS Italian National Institute of Health
Gambineri	Eleonora	Tuscany Region
Giglio	Sabrina	Regione
Lamanna	Alessandro	AGENAS National Agency for Regional Health Services
La Marca	Giancarlo	SIMMESN Italian Society for the Study of Inborn Metabolic Diseases and Neonatal Screening
Larizza	Lidia	SIGU Italian Society of Human Genetics
Maggi	Enrico	Tuscany Region
Magrelli	Armando	ISS Italian National Institute of Health
Mannelli	Massimo	Tuscany Region
Menegatti	Elisa	Regione
Muscolo	Luisa	AIFA Italian Medicines Agency
Neri	Rossella	Regione
Parenti	Giancarlo	SIMMESN Italian Society for the Study of Inborn Metabolic Diseases and Neonatal Screening
Pizzera	Bianca	EUCERD past component
Ragghianti	Benedetta	Regione
Reale	Emanuela	AGENAS National Agency for regional Health Services
Renieri	Alessandra	Regione
Salvatore	Marco	ISS
Spinelli	Nicola	UNIAMO F.I.M.R. onlus
Tarani	Luigi	SIMGePeD Italian Society of Pediatric Genetic Diseases and Disability
Torreri	Paola	ISS Italian National Health Institute
Zambruno	Giovanna	Past Component EUCERD
Zinnato	Giovanni	UNIAMO F.I.M.R. onlus
Zuccotti	Gian Vincenzo	SIP Italian Society of Pediatrics

D1. RESEARCH

State of the Art⁹

The best way to increase and spread knowledge on rare diseases is through basic and clinical research. If we take into account the Old Continent, the overall volume of research work is considerably low, above all in relation to the high number of diseases and their heterogeneity. This is why it is particularly important to awaken industry and researchers' interest towards researching on rare diseases.

⁹ On the basis of what shared during the meeting, this first phase is totally drawn from the latest NPRD draft.

This need, however, clashes with the harsh reality of a scanty number of experts, slender available resources and a general low interest due to the minimum social impact. Industries, in fact, regard it as nothing more than a niche market and thus basic research is mainly delegated to Universities. It is therefore necessary to overcome a number of bottlenecks. Firstly, the limited number of patients requires collaborative research at both national and international level, as well as the need to venture in experimental clinical projects designed for few patients. Secondly, given the scanty availability of highly technological platforms, there is a great need for innovation investments. Last but not least, rare diseases are hard to classify. Their peculiar and highly heterogeneous nature makes it difficult to identify their phenotype and very often rare diseases are not documented properly. Their natural history is seldom known, in fact, and more generally, clinical research in this field is totally disregarded.

Conversely, thanks to technological development and the so called genetic revolution's progress, the objective set by the *International Rare Diseases Research Consortium* (IRDiRC) to develop 200 new therapies for rare diseases as well as diagnostic tests for most of them by 2020, does not seem to be unreachable.

Here follow the current main public financing sources for the research into rare diseases.

a) national: thanks to the institutive law of the National Medicines Agency, AIFA, a national fund has been created for the use of orphan drugs in rare diseases as well as drugs representing a hope for the cure waiting to be marketed. Such fund is nourished by 5% of pharmaceutical companies' annual expenditures in promotional activities intended for health operators. The 2012 fund amounted to €32m. 50% is allocated for orphan drugs purchase, while the remaining 50% is devoted to no profit research on general drugs (independent research). Up to 2008, a minor part of the fund has been devoted to rare diseases research and namely from 2005-2007 one section of AIFA's calls, has been devoted to rare diseases and orphan drugs so to increase knowledge on their safe use and effects (over the mentioned three years, AIFA has allocated over €13m). In 2008, though, the authority upon the calls was transferred to the Health Ministry and no reserve fund for rare diseases has been created ever since. Notwithstanding, the same year, AIFA contributed to the calls for rare diseases by financing 12 studies with €3m.

E-Rare: a programme included in the framework of European Research Framework Programmes FP6 and FP7, E-Rare meant to enhance cooperation and coordination of research activities carried out at regional and national level within Member States and Associates, through the creation of research networks and the publication of annual international joint research calls. Italy has taken part to the first call together with 5 Countries and to the second with 9. Over the last two years, access to E-Rare funds has been granted only to IRCCS – *Scientific Institutes for Hospitalization and Treatment* .

b) European: since 1990, Europe has determined that researching rare diseases is a top priority within the *EU Framework Programmes for Research and Technological Development (FP)*. In Framework Programmes FP5, FP6 and FP7, Italy has taken part to 107 projects focusing on RD (last update, March 2013).

c) International: created in 2011, IRDiRC is intended to foster international cooperation to research rare diseases and together with the EC and the *US National Institutes of Health*, many Countries have joined the consortium, including Italy. In order to carry out a number of ambitious plans, some crucial steps will have to be taken. Amongst them: enhancing clinical activity to make homogeneous sampling and data available; secondly, implementing cross-border research, and lastly, streamlining regulatory and ethical procedures.

Together with public financing, other funds have been raised and made available through calls by patients' associations and private no-profit Foundations , such as Telethon Italia.

Finally, there are also further initiatives directly promoted by for-profit companies.

The European Context

On 8 June 2009, the EU Council in its Recommendation “an action in the field of rare diseases”, identified RD research as a top priority. It is well known, in fact, how this kind of research is crucial to innovation not only limited to the biological and genetic fields, but also with regards to biotechnological and pharmaceutical industry’s progress. Currently, about 20% of all innovative medicinal products licensed to be marketed in Europe are developed for rare diseases, this is why the EC has addressed Member States with a series of recommendations featuring the following priorities: identify ongoing studies and available resources devoted to researching rare diseases; coordinate activities both at a regional and national level; identify needs and priorities for basic, clinical, translational and social research as well as related promotional activities; foster interdisciplinary cooperation; take part to European and national research projects; include financial allocations for Rare Disease research projects within national plans and strategies; promote joint research activities with third Countries to enhance information exchange and knowledge sharing.

In its 2013 annual report, the EU Committee of Experts for Rare Diseases (EUCERD)¹⁰ has identified n. 5811 RD research projects carried out in Italy among which: n. 4036 into basic research (69% research projects into: mutations, gene expression profiles, genotype-phenotype correlation, in-vitro functional studies, animal models, human physiopathology studies); n. 676 into clinical research (12% observational clinical studies and epidemiology studies); n. 480 pre-clinical experimentations (8% gene therapies, cell therapies, drug and vaccine processing, sanitary ware and appliance development); n. 450 research projects on new protocols, diagnostic approaches and biomarker development (8%); n. 169 (3%) into health sociology, health economy, public health and health services studies.

Such a considerable basic research activity is justified by the huge impact that these studies are likely to have on common diseases, which often refer to rare diseases to be understood (for instance if we think of the Mendelian diseases such as hereditary hyper-cholesterolemia or Alzheimer and Parkinson diseases, which have determined the development of drugs for the cure of the respective common pathologies).

Furthermore, the real number of these studies is certainly underestimated as above all industrial data is difficult to access. However, a study carried out in 2011 by the *Rare Disease Platform*, identified n. 581 orphan designations potentially useful to treat 343 rare diseases affecting over 8 million European citizens. The same study had identified n. 666 ongoing clinical experimentations intended for 312 rare diseases.

The National Context

The complex nature of the problems caused by rare diseases makes it hard to set priority criteria within the research activity. All the related fields, in fact, (e.g. epidemiological and clinical field, basic research, treatments intended for life-quality improvement and social services) need to be further researched in order to provide patients and their needs with new answers.

Moreover, the number of publications and data provided by bibliometry indicators attest to the Italian researchers’ expertise to produce competitive scientific results concerning rare diseases. Such achievements are even more significant given the limited financial resources made available to this end. According to a study carried out by CERM Research Centre, in 2009, Italy’s contribution accounts for 10% of all scientific publications in these matters. Therefore, it can be stated that our country does boast a certain tradition in researching rare diseases which pivots upon our ability to consolidate a network of national and international relations.

¹⁰ (<http://www.eucerd.eu/upload/file/Reports/2013ReportStateofArtRDActivities.pdf>).

In 2011, Orphanet-Italy registered n. 654 research projects into rare diseases including: n.143 studies on the detection of disease-genes or their mutational analysis; n. 71 genotype-phenotype correlation studies; n.117 in-vitro functional studies; n. 73 human diseases' animal models; n. 79 human physiopathology studies; n. 40 pre-clinical gene therapies; n.18 cell therapies, n. 14 drug and vaccine development studies; n. 34 research projects on new diagnostic or biomarker detecting protocols, and n.36 observational clinical studies. Furthermore, 110 clinical trials, 80 registries, and 42 networks have been classified.

For a long time in the past, another critical issue has been represented by the inadequacy of the monitoring and evaluation instruments available to quantify results, above all when research activities were financed through public funds. To this end, since the '90s, Telethon Italia's contribution has been the decisive factor for introducing meritocratic and scientific assessment standards, until then hardly ever accepted by the Italian biomedical research community.

Concerning the research into rare diseases, a further issue relates to financial resources which are usually allocated irregularly and often do not grant access to funds in the right timing as laid down in the call's announcement. Italy has been lacking of a centralised system connecting funds and research works' achievements, a role that is now starting to be played by the National Agency for the evaluation of research and university studies, (ANVUR). The Agency is called to carry out a number of tasks, such as: assessing the level of university, private and public research institutes' activities benefiting from public funds; addressing judgement activities usually referred to universities and research institutes' internal evaluation boards, as well as assessing the efficiency and effectiveness of incentives and financing public programmes intended for innovation and research activities. To this end, some cooperation between the Agency and the National Health System should be enhanced to monitor and learn about research activities directly or indirectly linked to rare diseases.

Ministerial Decree dated July 15th 1997, charges sponsors with the obligation to insure those taking part to clinical trials from any tort liability risk resulting from said participation, and charges the ethical Committee with supervising on the effective existence of the adequate insurance cover. On July 14th 2009, a subsequent Ministerial Decree pinpointed the minimum requirements for clinical trial participants' insurance policies. It established that an insurance policy should bear a specific mention as to compensation terms in case of damages caused by the participation to experimental activities for the entire duration of trials, that such tort liability policy must also cover tester and promoter from any involuntary damage caused by accident and/or arising from negligence, unskilfulness or carelessness, as long as it occurred over the period indicated in the same decree.

The Workshop has debated over the following priorities:

14. Resource, infrastructure, research projects and fund governance supporting research into rare diseases.

Italy does not have a national programme nor a dedicated fund for research on rare diseases, and unfortunately, the current scenario does not enable to think that anything will change in the short, medium term. The complexity of the Italian institutional system, if not duly governed even through an authority supervising research funds – similarly to England and Germany – may cause waste of energy as well as resources. Over the last years, in fact, the resources dedicated to researching rare diseases have decreased steadily, the timings for delivering of funds have become less reliable and no whatsoever continuity has been granted. Although in the last two years, access to E-Rare funds has been solely reserved to IRCCS (*Scientific Institutes for Hospitalisation and Treatment*), in 2013 the allocated funds have been cut off by 16% and no research project in the frame of that same year's public calls, has been financed. Needless to say, all this entails a number of issues in terms of

research sustainability, which by definition, should not be almost solely financed by private citizens or associations' initiatives (Telethon Foundation and other associations are the perfect example).

Research on rare diseases not only lacks a national programme, but it also has to face the absence of a definite *governance* strategy to run research activities and manage the related fund allocations. And, as already mentioned, such chaotic situation is the cause of scattered, unreliable financing.

The absence of a *governance* strategy prevents information exchange and knowledge sharing on rare diseases. Besides the initiatives promoted by Telethon foundation and Orphanet-Italy, there is no list or any other information source about research groups committed to rare diseases nationally, nor an official register of research projects into rare diseases.

15. Needs and Priorities of the research activity into Rare Diseases

In Italy, over two thirds of the research done into rare diseases is basic research. The research activity stems from a series of medical and social inputs occasionally determined also by those associations which often bear the financial costs of the projects. With the exception of *one-off* initiatives, in Italy there is no organisation in place to define priority needs in researching rare diseases, and/or reliable sources to finance quality projects. Therefore, *policy makers* should be made aware about the effectiveness of research activities - patients associations could play a major role in doing so - to actually change the current opinion according to which, research expenditure is viewed more as a cost rather than an investment for our future.

16. The participation of Centres/“Presidi” Centres/“Presidi” , researchers and patient associations into Rare Diseases research projects.

The involvement of Centres in research on rare diseases is affected by the critical upstream of the process of identification of the Centres, which is uneven between Regions. With few positive exceptions, the adopted criteria do not follow EUCERD recommendations and are not always specified in order to ensure the effective availability of case studies and expertise appropriate, with the consequence of penalising up to ignore the need to contribute to research on rare diseases. While in more qualified Centres, research is considered an integral part of the clinician's activity, it is more difficult to obtain an adequate level of integration of researchers into the clinical services.

Given the absence of a national programme of research on rare diseases, no programme of recruitment of researchers for research on rare diseases is available, which is another critical element for the system of rare diseases. Although appreciated, the effort made by the patient organisations in support of research activities is likely, in turn, to run fragmentation and dispersion, which is why it would be necessary to activate, even through the Federation UNIAMO, an even greater exchange between them organisations representing people with rare diseases as well as foster a greater connection with international experience.

The contribution that people with rare disease and their representatives can provide in research is still significant and their involvement should be further promoted through the institutionalisation of their participation in the decision-making bodies that direct the use of funds to support research in order to help define the research priorities in a perspective that properly takes into account the needs of the person with a rare disease and promotes empowerment.

The opportunity for direct contact and exchange between researchers and people with rare diseases must also be positively evaluated, such as those that are carried out through the 'laboratories' open day' and the various meetings and training initiatives, including those that provide for the enhancement of the contribution of patients and their associations in research.

17. International and European cooperation for Rare Disease research

The rarity of individual diseases and the scarcity of resources available for research on rare diseases should address researchers, patients and their organisations towards international large-scale projects. For this it is essential to promote a "culture of research" among researchers and patients. The resources are also important for European Reference Networks (ERN) and for the participation in key programmes to support collaborative research on rare diseases at European level, such as E-RARE.

Proposals to be included into the NPRD

1. Charge the National Committee for the overall network control (*as under Group A) Network*), also with the governance of rare diseases research activity. To this purpose, the Committee should set some guidelines for the definition of solid criteria for research financing, in order to grant transparency to the selecting process and the monitoring activity of projects' results. The definition of research priorities should consider not only genetics but also the impact of the needs of new knowledge.
2. Create an expertise and infrastructure network among the RD research 's main actors, also through better identification of Centers to promote the connection of basic research to translational research.
3. Put in place experimental strategies to overcome the difficulties entailed by the low number of patients: epidemiological research activities and training of specialists (statistic and epidemiology experts) to support clinical testers.
4. Promote actions to foster interaction amongst researchers, patients and public opinion:
 - Enhance interaction between patient associations and researchers through meetings, courses and advertising campaigns, to create a safe environment where the "culture of research" can be shared and spread;
 - By means of patient associations, share knowledge about "the scientific method" applied to clinical trials, for patients, citizens, family members and their representatives ("scientific community") to learn about it;
5. Promote mobility of researchers and clinicians at intra-company and inter-company and international level.
6. Encourage the recruitment of young researchers thus boosting RD research through the creation of intra-corporate or inter-corporate coordination centres in the fields of research, assistance and training, within large corporations/Institutes.
7. Create calls devoted to studies of trial readiness, outcome measures, analysis of the phenotype, registers and fields of research to support the development of European Reference Networks for collaborative research on rare diseases at supranational level.
8. Streamline procedures and provide necessary support to increase the number of Level I clinical trials in Italy. To this purpose, and to uphold ethical principles, it would be necessary to unify and improve local, regional, national regulations.

9. Promote the creation of a collaborative strategy among rare diseases research's main actors, namely patients, physicians, researchers, companies, public institutions and private agencies of research funding, with the creation of consortiums that also include private companies.

18. HORIZONTAL THEMES

- **Sustainability:** what actions may be included in the NPRD to favour medium/long-term sustainability of of rare disease system, with regard to the research activities?

<p>- Finance channels of the research projects?</p> <p>- How to guarantee the medium/long-term sustainability for research?</p> <p>--Improving public spending effectiveness</p> <p>--Raising additional resources</p> <p>--</p>
<ul style="list-style-type: none"> • Guaranteeing method and continuity of finances for rare diseases research. • Reintroducing a financing reserve in favour of rare diseases research in the calls indicated in the AIFA fund (independent research, until 2008 managed by AIFA, a competence that later transferred to the Ministry of Health). • Identifying some procedures stimulating clinical research (i.e. Tax deductibility of investments).
<p>How to use the Structural Funds programmed for 2014-2020 in the best way?</p> <p>Indicate if an investment objective on rare disease has been provided to strengthen the Centres network within the reference national strategic framework (and within the regional framework) for the Structural Funds.</p> <p>Indicate the Operational Programmes in which the projects for rare diseases may be included.</p>
<p>HORIZON 2020</p> <ul style="list-style-type: none"> •

- **Empowerment:** what actions may be included in the NPRD to assist the empowerment, in its different parts, with regard to the research activities for rare diseases?

<p>Individual</p>
<ul style="list-style-type: none"> • Enhancing the contribution of patients in producing information about the disease (so called “knowledge from experience”). • Fostering projects aiming at developing knowledge and experiences to be shared among patients and researchers.
<p>Organisational</p>
<ul style="list-style-type: none"> • Institutionalise the presence of representatives of patients' organisations in decision-making bodies for the allocation of resources for research. • Developing research about the social impacts of rare diseases.

Community

- Promoting in the studies the use of questionnaires to measure the benefits for patients in the different processes they are involved in (genetic counselling, genetic test, follow-up, treatment), the level of satisfaction in the relationship between clinician and patient and “self-care” pathway in all chronic conditions
- Promoting the presentation of particularly complex and educationally important clinical case, stimulating the debate among experts in scientific magazines and on the web

Empowerment of “Open Access” tool and promotion of the use of “Open AIFA” (*The Italian Medicines Agency has launched the “OPEN-AIFA” dedicated to the institutionalisation of meetings with all of its stakeholders in order to ensure a direct and transparent dialogue. Patient organisations, representatives of civil society, pharmaceutical companies and any other interested person may submit a reasoned request to participate in the meetings that will be held on a monthly basis*)

- **Good practices (particularly important experiences supporting the proposals): what experiences can be indicated in the field of research for rare diseases?**

Research

For further Information about the research projects for rare diseases:

- Telethon Foundation
- Orphanet Italia
- Project: “Il Codice di Atlantide” promoted by UNIAMO FIMR in 2010-2011 to investigate the contribution among the associations of people with rare disease and research

To exchange information between researchers and patients:

- Open-day labs
- European Night of the Research
- The lab “Insieme @ttivamente per la ricerca” promoted by UNIAMO FIMR in 2012-2013
- The initiative “Determinazione Rara” promoted UNIAMO FIMR nel 2013-2014 www.uniamo.org

D2. ORPHAN DRUGS**19. Supporting the development of orphan drugs****20. Access to the treatment***State of the art*

The need to reduce the time necessary for the definition of the pricing and reimbursement of medicines, in order to improve access to orphan drugs, is shared by all stakeholders of the sector that are trying to deal with the authorities responsible at national and EU level. They also support dialogue between AIFA (the National Medicines Agency) and sponsors of orphan drugs' development. On this matter, the policy of EMA (European Medicines Agency) also provides for the patients involvement in the drug development process.

AIFA has always tried to guarantee full access to orphan drugs and in its advisory role to the Government recommended that special attention be given to companies producing such drugs. In fact, the Budget Law 2014 establishes that orphan drug producing companies are exempted from the obligation to compensate the budget overrun of hospital pharmaceutical expenditure. Indeed, when this budget overrun is related to the budget of companies producing orphan drugs, the obligation to redress the budget excess is shared among all holders of Marketing Authorisation, with the exception of those producing orphan drugs. To date (January 2014), 67 orphan medicinal products were granted marketing authorisation, 47 of which authorised and merchandised in Italy. Among the 20 unavailable drugs, 8 products are being assessed by AIFA, while, as for the other products, 9 have not been assessed yet and 3 have never applied for pricing and reimbursement in Italy.

In addition, to accelerate the availability of orphan drugs in the territory, the so-called "Balduzzi Law" (law 189/2012, art. 12, par. 3) has determined that a pharmaceutical company can apply for pricing and reimbursement to AIFA as soon as the CHMP (Committee for Medicinal Products for Human Use) at the EMA release positive opinion, thus even before the European Commission has issued a marketing authorisation for the drug in question.

Finally, Decree 69/2013, Art. 44 (provisions for the classification of orphan medicinal products and medicinal products with exceptional therapeutic relevance) establishes that AIFA, for the purposes of classification and reimbursement by the National Health Service, assesses orphan drugs applications (and applications drugs with exceptional therapeutic relevance), as a priority, i.e. giving them priority over pending applications. In such cases, the assessment delay is reduced to one hundred days (so-called «*authorisation fast track* »).

Moreover, if a marketing authorisation holder failed to submit an application within thirty days from the issuance of marketing authorisation for an orphan drug or a drug with exceptional therapeutic relevance, AIFA calls on the holder to submit an application for classification and reimbursement within the following thirty days. After expiry of this period, information is given in the AIFA website and the drug is classified as "group C, not negotiated", group D drugs being those not reimbursed by the National Health System.

CAVOMP (Clinical Added Value for Orphan Medicinal Products) is recognised as an important supporting process for properly deciding about the added value of an orphan drug, even if it could encounter some difficulties during the implementation phase. Positive is also the assessment concerning the "MOCA" project (Mechanisms for Coordinated Access to ODs)", promoted by the European Commissioner Tajani in 2010 and supported by some EU Member States to discuss the value of new orphan drugs on the basis of a transparent framework of common values at European level. It is important to mention the active

participation of AIFA in this process. This project focused on the elements that essential to favour a dialogue among the stakeholders (Member States, pharmaceutical companies, representatives of patients, clinical specialists) and increase the exchange of knowledge/experience among all the people involved. This mechanism relies on a high-level cooperation that is aimed to contributing to generate evidence and contribute to collect all the information produced. Such evidence and information shall be collected in a unique repository to avoid duplication of work and to facilitate the orphan drugs assessment for decision-makers. After a first phase of MOCA, in June 2013, the foundations have been established to start a new pilot project that puts into practice what defined in the first phase of the project.

Differently from other European countries, Italy shows a certain degree of institutional sensibility and gives access to pharmacological treatments for rare disease patients, not only through centralised authorisation, but also with further legislative instruments. The procedure of centralised authorisation is the main avenue for access to orphan medicinal products; as alternative, in the absence of a marketing authorisation, a patient can obtain the drug through one of the following procedures:

- Law 648 of 1996, that allows for the use of a drug on a national basis;
- Law 326 of 2003, art.48 (AIFA Fund), Ministerial Decree dated 8 May 2003 (therapeutic use of a drug undergoing clinical research), and Law 94 of 1998 (former “Di Bella Law”) that, differently from Law 648/1996, regulate the drug prescription for the individual patient, on an ad hoc basis.

In particular, Law 326/2003, Art. 48 (AIFA Fund), provides for the establishment of a National Fund devoted to rare disease orphan drugs and drugs “representing a hope for treatment”, still waiting to be placed on the market, and for particular and severe pathologies (art. 48 paragraph 19 letter a, Legislative Decree 30 September 2003 no. 269 converted by Law no. 326 of 24 November 2003). This Fund is fuelled by 5% of annual costs for promotion activities of the pharmaceutical companies that are intended to physicians (for seminars, workshops, etc.). The 2012 Fund amounted to approximately 32 million Euros. The use of the AIFA fund is dedicated :

- a) 50% , to purchase of orphan drugs for rare diseases and drugs not yet authorised, but representing a hope for the treatment of severe pathologies; and the remaining 50% of the fund
- b) 50% to research on the use of drugs: comparative clinical trials between medicines aimed to show the therapeutic added value, and additional studies on the appropriateness and information.

As far as the purchase of the above-mentioned drugs is concerned, the applications to access the fund are forwarded to AIFA, through Regions and Centres dealing with rare diseases, or by specialised structures identified by the Regions, together with the description of the diagnosis and of the therapeutic plan. Even the applications coming directly from the individual Centres and sent in copy to their own Region, may be accepted by AIFA to grant the access. To access the fund it is necessary to submit a formal request, to produce supporting scientific literature and a short clinical report with the therapeutic plan for each patient. The financing application must be supported by the indication of the dosage for each cycle, number of cycles and unit costs of the medicinal product. The application is then assessed by the Technical Scientific Consultative Commission of AIFA after verifying the compliance with the conditions provided for by the law. The product purchase by the pharmaceutical companies is reimbursed by AIFA, according to the quantities specified by the applying physicians. The cost and the number of patients that accessed AIFA fund in 2012 amounts to 901.130 €.

The Italian National Medicines Agency (AIFA), because of its specificity, covers all aspects of the life cycle of a medicinal product, from the marketing authorisation to the product enhancement within the clinical practice. Since its creation, AIFA given its contribution to scientific advice initiatives, with multi-dimensional characteristics and/or on a multi-national scale. At the same time in 2011, it has formalised its activity of provider of scientific advice at national level, also in relation to HTA.

Despite the provisions mentioned above, in recent years there have been, with increasing frequency, emergency situations related to the sudden lack of essential drugs on the market for the treatment of rare

diseases or infrequent pathologies. The Italian National Institute of Health and AIFA intervened to protect the right to therapy for rare disease patients by asking the Military Chemical Pharmaceutical Factory (Stabilimento Chimico Farmaceutico Militare) in Florence to produce drugs no longer available. The presence on the Italian territory of a public, no-profit plant for drug production able to face rapidly citizens' needs, allowed to solve several critical shortages of medicines (i.e. Mexiletina, Penicillamina). This role of the Military Chemical Pharmaceutical Factory, that is available as State Pharmaceutical Shop in case of drug shortages, was provided for by in the Cooperation Agreement signed with AIFA on 31 March 2012.

Proposals to be included in the NPRD

1. Improving and speeding up the national procedures to establish drug pricing and reimbursement thus improving the access to orphan drugs
2. Establishing, through the suitable regulatory measures, specific procedures to guarantee the functioning of the Military Chemical Pharmaceutical Factory of Florence
3. Promoting adoption of CAVOMP (exchange of knowledge for the assessment of orphan drugs clinical added value)
4. Helping the organisation of clinical trials for limited populations thus favouring the creation of cooperation groups among researchers, national and international networks, and the development of dedicated web-sites to increasingly involve people in clinical studies.

21. HORIZONTAL THEMES

- **Sustainability:** what actions can be included in the NPRD to assist the medium/long-term sustainability of rare diseases system, with regard to the orphan drugs?

<p>- Finance channels of the orphan drugs? - How can we ensure the medium/long-term sustainability with regard to the matter in hand? -- Improving efficiency of costs -- Raising additional resources --</p> <ul style="list-style-type: none"> • Making thorough studies on the real costs for treatment/therapy taking into account efficacy and safety (monitoring registers, functional to this target) • Increasing accuracy by defining the expected quantifiable improvement parameters that, if not achieved, lead to the treatment suspension • Associating monitoring registers to the procedures for a qualified refunding (Risk sharing, cost sharing and payment by results) in order to increase the accuracy of prescription.
<p>How to use at best the Structural Funds programmed for 2014-2020? Indicate if an investment objective on rare disease has been provided to strengthen the Centres network within the reference national strategic framework (and within the regional framework) for the Structural Funds. Indicate the Operational Programmes in which the projects for rare diseases may be included.</p> <ul style="list-style-type: none"> • HORIZON 2020 • AIFA is considering how to implement the use of the Fund of 5% (eg drawing up a list of rare diseases to be shared with the Regions)... ..

- **Empowerment:** what actions can be included in the NPRD to support the empowerment, in its different parts, with regard to orphan drugs?

<p>Individual</p> <ul style="list-style-type: none"> • Promoting the training of people with RD and of their representatives about drugs in rare diseases • Promoting projects like “Determinazione rara” run by UNIAMO FIMR and encouraging contacts among the associations of patients with all other stakeholders in the field of rare diseases • Promoting meetings with regulatory authorities for information/suggestions (i.e. OPEN AIFA) • Diffuse the AIFA toll free number (drugs line) to facilitate contacts by phone or via e-mail of citizens, patients and health workers
<p>Organisational</p> <ul style="list-style-type: none"> • Involvement of patients’ representatives in the drug reimbursability assesment processs •
<p>Community</p> <ul style="list-style-type: none"> • Participation in the MOCA (Mechanism of Coordinated Access to Orphan Pharmeceutical Products) •

- **Good practices (particularly important experiences supporting the proposals):** what experiences can be indicated in the field of orphan drugs?

Orphan drugs

- “Determinazione Rara” project promoted by UNIAMO FIMR in 2013-2014 www.uniamo.org
- Decree law 69/2013, art.44 (*regulations for the classification of orphan drugs with exceptional therapeutic relevance, so called «authorising fast track »*)

F. Information and training

Focus group

Members:

Agostini	Maurizio	FARMINDUSTRIA Association of pharmaceutical companies
Aminoff	Dalia	UNIAMO F.I.M.R . onlus
Astolfo	Romano	SINODE’ Consultancy Agency for Welfare Issues
Caruso	Ubaldo	SIMMESN Italian Society for the Study of Inborn Metabolic Diseases and Neonatal Screening
Chessa	Luciana	SIGU Society of Human Genetics
Cocchi	Guido	SIP Italian Society of Pediatrics
Collet	Stefania	O.MA.R OSSERVATORIO MALATTIE RARE
Coratella	Giuseppe	CARD Confederation regional associations of social health districts
Corbetta	Carlo	SIMMESN Italian Society for the Study of Inborn Metabolic Diseases and Neonatal Screening
Crapanzano	Andrea	F.I.M.M.G. Italian Federation of General Practitioners
Dagna Bricarelli	Franca	Liguria Region
Daturi	Alessia	Telethon Foundation
Donzelli	Gianpaolo	Regione
Faranda	Ivana	Ministry of Labour and Social Policies
Frazzica	Pina	ISS Italian National Institute of Health
Gentile	Lia	ISS Italian National Institute of Health
Giannico	Marcello	Federsanità Anci National Association of Italian Municipalities on Health Issues
Lapadula	Velia Maria	UNIAMO F.I.M.R onlus
Laricchiuta	Paola	ISS Italian National Institute of Health
Morciano	Cristina	ISS Italian National Institute of Health
Mingarelli	Rita	Orphanet Italia
Nasta	Loredana	UNIAMO F.I.M.R. onlus
Piccinocchi	Gaetano	SIMG Italian Society of General Medicine
Razeto	Stefania	ISS Italian National Institute of Health
Reale	Emanuela	AGENAS National Agency for Regional Health Services
Saba	Franco	Federsanità Anci National Association of Italian Municipalities on Health Issues
Selicorni	Angelo	SimGePed Italian Society of Genetic Diseases Pediatric and Congenital Disabilities
Sensi	Flavio	Federsanità Anci National Association of Italian Municipalities on Health Issues
Severi	Irene	Tuscany Region
Valanzuolo	Ines	UNIAMO F.I.M.R onlus

22. Awareness on rare diseases

State of the art

Over the years, several awareness actions addressing a multiplicity of rare diseases have been implemented by a range of heterogeneous and numerous stakeholders (Ministry, Regions, National Centre of Rare diseases (CNMR-ISS), Local Health Units/Hospitals, associations of patients, professionals and their federations, scientific societies, pharmaceutical societies , etc.). These actions are to be understood as actions aiming at calling and stimulate the attention of the stakeholders - citizens, politicians, health professionals, in relation to rare diseases. they to arouse a reaction, a behavioural change, that often

originate spontaneously and according to the networks of local and personal relationships, but that sometimes fail to build a network where to share efficiently actions and results, within a framework of common direction. All this risks to create a leakage of the investment squandered by promoters of the single companies. In addition to initiatives now recognised as “Rare Disease Day”, there are many other initiatives at both national and local level, but they are often linked to the sensitivity of the individuals and do not represent the structural components of the system, with the consequent risk of fragmentation and uneven coverage. Another critical point is the difference in the correct awareness as for targets and objectives that are not always clearly identified and shared¹¹, thus making it more difficult to assess the effectiveness of the promoted initiatives.

Proposals to insert into NPRD

1. The National Committee for Rare Diseases (as identified by workshop A) shall guarantee cooperation and coordination of all the activities and information aimed at increasing awareness about rare diseases at national level. For this purpose a dedicated staff person shall be identified with the task of monitoring communication and creating stable relationships with the contact people in charge of communication in the different organisations. Through such cooperation, s/he shall draw up a strategy to communicate on rare diseases. S/he should also be responsible for fundraising to boost communication (television and radio advertisements, advertisements at the cinemas, etc.), in order to get a greater visibility for rare diseases.
2. The National Committee for Rare Diseases shall:
 - promote the knowledge of positive experiences (good practices) implemented at local and/or national or international level, such as events/initiatives aimed at improving awareness and whose validity and effectiveness have been proved;
 - ensure better interconnection among initiatives aimed at increasing awareness on rare diseases, their objectives and the relevant organising processes, in order to include all the initiatives promoted by different stakeholders in a coherent system. In particular:
 - Continuing initiatives (all year long), will be promoted and integrated;
 - Rare Disease Day may become the event aimed at giving greater visibility to a series of relevant initiatives covering a longer time span;
 - All involved stakeholders should give visibility to their different initiatives in favour of Rare Diseases.
3. Awareness/information initiatives and the relevant information material:
 - shall consider the target audience of the different media and suggest tailored, appealing messages ,thus reaching the desired visibility (i.e. valorisation of narrative medicine – it is a medical approach that recognizes the value of people's narratives in clinical practice, research and education) could be adequate for large diffusion magazines);
 - shall represent opportunities to spread knowledge on the information tools available (Toll Free Number for Rare Diseases provided by the CNMR-ISS, Centres of Regional Coordination, UNIAMO FIMR website and phone number, etc.);
 - shall consider schools and new technologies as places /tools to build experience and create awareness about rare diseases.

¹¹ For example, towards rare disease patients and their families, the objective could be facilitating knowledge and access to the existing information tools; for health professionals the objective could be promoting a greater attention for the rare disease culture, as for the policy makers the objective could be obtaining greater funds and/or services etc.; for the population at large, knowing rare diseases as a public health priority;

4. Ask for NHS services, social services, General Practitioners and paediatricians, covering homogeneously and extensively the whole national territory, to implement awareness initiatives for rare diseases, thus spreading the message to the entire population.
5. Promoting an integrated and coordinated action with all stakeholders in the field of rare diseases towards directors and politicians at different institutional level, including by enhancing existing tools, such as the Regional Commissions for Rare Diseases).

23. Information on rare diseases

State of the art

All research carried out in these last years underlines how difficult it is for rare disease patients and their family members to get useful, verified and updated information. At the same time, healthcare professionals find it difficult to access information, in many cases limited and often diluted inside scientific publications. Therefore, information can be considered one of the greatest critical issue for rare diseases. Notwithstanding, in Italy there is a variety of information sources about rare diseases handled by different actors, many of which prefer the web as diffusion support (i.e. Orphanet website, Supplement to the News of ISS “Rare Diseases and Orphan drugs” run by CNMR-ISS, www.malafirari.it run by UNIAMO FIMR). In fact, this apparent wealth hides different problems: to this day, a clear and organic map of available information sources does not exist, and for some sources, it is not well known how often they are updated; there are wide margins of overlapping with a consequent waste of employed resources, etc. The main potential users of information (a rare disease patient and/or his/her relatives) risks in this way to be alone and disorientated in a jungle of information sometimes difficult to assess as for quality, especially if it does not come from institutional sources. This adds to the complexity of the Italian institutional organisation that for some aspects, such as social protection, involving also rare disease patients, implies a very complex scenario due to devolvement to Regions of relevant powers and responsibilities. Finally, we have to bear in mind that health professionals are to be included among the possible recipients of information on rare diseases, not only about specific pathologies, but also about system organisation, centres/supervision centres, etc.).

At present the Toll Free Number for Rare Diseases (TVMR - 800 896949) run by CNMR-ISS is working at national level and is addressed to rare disease patients and/or their relatives, to health and social professionals. Besides, the help lines of different Regions are working at local level, just like other telephone lines and ad hoc info desks spread across the territory that are managed by patient associations.

The workshop also pointed out the need for a help-line or an information point specifically addressed to health professionals.

Also in this case, the existing instruments differ in purpose and operational modalities and, consequently, for the support they are able to offer to users, as well as for the degree of coverage, thus leading to unequal treatments. Together with these institutional information services, it is important to remember “Telethon info-line”.

Proposals to insert into NPRD

1. The National Committee on Rare Disease (identified in workshop A) shall promote a mapping of information sources currently available and validated on rare diseases and their work towards a better indexing and visibility in the web, thus enhancing the information produced by the various stakeholders;
2. Promoting awareness among potential users of existing information sources (people with rare diseases; providers of healthcare, educational and social services; pharmacies, ...);

3. Providing a specific training of personnel involved in information diffusion (both on the phone and at the help desk);
4. Promoting the use of a system for evaluating the quality of information and the impact that this may have;
5. Strengthening the provision of information on rare diseases by help-lines for healthcare professionals;
6. Activating/empowering/qualifying regional info desks, including those providing support on the phone, in order to favour a greater territory coverage. Objectives and functions of the different instruments shall be clearly distinguished. In this way it would be possible to strengthen the cooperation with the TVMR (the national help line service provided by the CNMR-ISS);
7. Supporting the procedure for establishment of a European number “116” for Help Lines on rare diseases.

24. HORIZONTAL THEMES

Sustainability: what actions may be included in the PNMR to support medium/long-term sustainability of rare disease system, for what concerns a greater awareness, information and help-line?

<p>Finance channels to support awareness initiatives, information dissemination and help-line (public, private, ...)</p> <ul style="list-style-type: none"> - How can we ensure the medium/long-term sustainability with reference to the subject? - Improving efficiency of costs - Raising additional resources - <ul style="list-style-type: none"> • Encouraging a greater synergy and integration among the existing initiatives •
<p>How to use at best the Structural Funds programmed for 2014-2020? Indicate if an investment objective on rare disease has been provided to strengthen the Centres network within the reference national strategic framework (and within the regional framework) for the Structural Funds. Indicate the Operational Programmes in which the projects for rare diseases may be included.</p> <ul style="list-style-type: none"> • •

Empowerment: what actions may be included in the NPRD to assist the empowerment, in its different parts, for what concerns a greater awareness, information and help-line activities?

<p>Individual</p> <ul style="list-style-type: none"> • The patients contribution to produce information about their pathology (so called “knowledge from experience”)
<p>Organisational</p> <ul style="list-style-type: none"> • The contribution of associations of patients to produce information about the pathology <p>...</p>
<p>Community</p> <ul style="list-style-type: none"> •

Good practices (particularly important experiences supporting the proposals): what experiences may be indicated in the field of awareness, information and help lines?

<p>Awareness</p> <ul style="list-style-type: none"> • Rare Disease Day (28 February) organised by UNIAMO FIMR with the support of Farindustria • (health professionals) The Italian Society of Pediatrics is to establish a prize for the best thesis on rare diseases to be delivered within its national congress • (for journalists) Press Prize O.Ma.R (Rare Disease Observatory) dedicated to rare diseases and rare cancers • (for children) Video-fairy tale aimed at school teachers. The project, sponsored by the ISS,
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concerns rare diseases and is to be used in schools. It is promoted by the Ministry of Health in cooperation with different institutions and with UNIAMO FIMR

- (open to all) “Il volo di Pegaso” - Artistic-literary Competition about rare diseases, promoted by CNMR-ISS
- (for young people) DNA Day in schools promoted by the Italian Society of Human Genetics

Information and help-line

- Orphanet
- Toll Free Number for Rare Diseases (national help-line) of CNMR-ISS
- Supplement “Rare diseases and Orphan Drugs” to the Bulletin of ISS
- Reference number for Rare Diseases of different Regions
- Telethon Info-line
- O.Ma.R. – Rare Disease Observatory – an official national press agency, completely dedicated to the world of rare diseases and rare cancers
- “UniStem” - University of Studies of Milan, Research Center about stem cells. The centre’s mission is to complete, coordinate and promote access to information related to the study of stem cells and their applicative potential.
- Book and DVD “Emergency in genetic-metabolic rare diseases. A support to the medical and nursing personnel”, edited by the Italian Society of Pediatric Genetic Diseases and Disability (SIMGePeD)

25. Training

State of the art

Training is a crucial aspect in the field of rare diseases.

In Italy, the basic medical training, as well as the specialist, is mainly the responsibility of universities that manage university courses and specialisation schools; Regions may provide further training offer. Professional updating (not only ECM, Continuous Medical Education) for healthcare professionals is organised at national and regional level (Ministry of Health, ISS, Regions and professional associations, scientific societies, ...). Besides, RD patients associations promote strong educational activities for people with rare diseases aimed to consolidate patients’ awareness and knowledge on their disease (even though certification of these training activities is still a pending issue).

Rare diseases have not yet not significantly entered the basic and specialist educational courses (for the latter, with some exceptions, as some initiatives have been put in place by few individuals on a voluntary basis). Even for this reason, it is seriously difficult, above all for General Practitioners and paediatricians, who are the first contact of the patient with the National Health Service/Regional Health Service, to interpret complex symptomatology and to formulate a diagnostic suspicion, with the consequent delays in diagnosis and therapy. Therefore, in order to increase health professionals awareness and knowledge about rare diseases, it is necessary to take suitable educational actions to be delivered during basic and specialist training courses. However, such an approach risks to produce results in the long term; for this reason, such courses shall be also accompanied by refreshers and other measures such as, for example, information actions.

A further complex point is to strike the right balance between the high number of rare pathologies and the need for synthesis required for updates and educational activities. Even more complex is the handling of the low number of cases of ultra-rare pathologies for which reports made by patients and their representatives can be even more important to, help develop, together with physicians and other workers, knowledge and competences on their pathology.

Finally, also in this field the workshop stressed the need for better coordination and for planning of shared initiatives, so far often fragmented and not coordinated.

Proposals to be included in the NPRD

Training of health and social-health professionals

1. Promoting a joint action targeting on the Conference of Rectors of Italian Universities (CRUI-) and – the Ministry for University and Research (MIUR) with all stakeholders, aimed to introduce rare diseases among the curricular subjects of university studies for health professionals. In the meantime, promoting specific courses on rare diseases (i.e. among the so called «elective courses» entitling students to 3 training credits).
2. Promoting rare diseases classes among the subjects of compulsory trainings promoted by ASL (Local Health Units).
3. Promoting the introduction of rare diseases among the subjects of ECM (Continuous Medical Education) framework annual training plans.
4. Promoting through the ISS, Medical Associations, Federations and scientific societies refresher courses for GPs on rare diseases, also using distance-learning, especially with reference to:
 - diagnostic suspicion;
 - organisation of networks for rare diseases;
 - specific clinical contents;
 - effective communication.
5. Promoting training of social and social-health workers, as well as personnel of Social-Health Districts and schools;
6. Involving rare disease patient in educational initiatives addressed to health professions (so called «knowledge of experience»).

Training rare disease patients

7. Providing for and supporting training for people with rare diseases and their representatives:
 - To promote their empowerment throughout the care process;
 - To encourage competent participation in the decision-making fora on rare diseases, in awareness-raising and information.

Training for caregiver, family members, volunteers

8. Providing for and supporting training aimed to caregivers, rare disease patient's family members and volunteers, paying particular attention to their first-hand experience.

26. HORIZONTAL THEMES

- **Sustainability:** what actions may be included in the NPRD to support medium/long-term sustainability of rare disease system, for what concerns a greater awareness, information and help-line?

-Finance channels to support awareness initiatives, information dissemination and help-line (public, private, ...)

- How can we ensure the medium/long-term sustainability with reference to the subject?

- Improving efficiency of costs

- Raising additional resources

-

- Encouraging a greater synergy and integration among the existing initiatives
-

How to use at best the Structural Funds programmed for 2014-2020?

Indicate if an investment objective on rare disease has been provided to strengthen the Centres network within the reference national strategic framework (and within the regional framework) for the Structural Funds.

Indicate the Operational Programmes in which the projects for rare diseases may be included.

-
-

- **Empowerment:** what actions may be included in the NPRD to support the empowerment, in its different parts, for what concerns training activities?

Individual
<ul style="list-style-type: none"> • Enhancing the role and contribution of the person with rare diseases and his/her family members during the treatment process. •
Organisational
<ul style="list-style-type: none"> • Enhancing the contribution of rare disease patients and their associations during the training courses, including those dedicated to health professionals, in relation to their specific pathologies.
Community
<ul style="list-style-type: none"> •

- **Good practices (particularly important experiences supporting the proposals):** what experiences may be indicated in the field of training?¹²

Training of health professionals

- The project “Knowing to assist”, developed by UNIAMO and addressed to family

¹² For a more comprehensive list of such experiences, it is necessary to refer to the experiences reported in the final report of the First National Conference of EUROPLAN.

doctors/paediatricians, has been planned in agreement with different actors (FIMG, FIMP , SIP, SIMGePeD and SIGU and supported by Farindustria); it focused on diagnostic suspicion, quality of care and the transition from paediatric to adult age.

- Course “FAD” at Bambin Gesù Children Hospital, with the contribution of Farindustria.
- International Summer School of the National Centre for Rare Diseases-ISS on Methodology of Guidelines for rare diseases (*a number of the available places were reserved to representatives of associations of patients and their relatives*).
- International Summer School of NCRD-ISS on Registries for rare diseases and orphan drugs (*a number of the available places were reserved for representatives of associations of patients and their relatives*).

Training for rare disease patients

- Training initiatives promoted by UNIAMO FIMR Onlus (ex. «Determinazione rara»)
- «EUPATI» Project
- Empowerment initiatives addressed to patients promoted by the Thalassemia Patients’Organisation in Lombardy Region
- Meeting of the associations “FRIENDS OF TELETHON”

Training for caregiver and family members

- SAPRE, Early enabling for parents at the Operational Unit of Childhood and Adolescence Neuropsychiatry at Policlinico Hospital in Milan.
- Training courses on home assistance at the Centre for Advanced Simulation (robotics) of the School of Medicine, University of Genoa.

G. Prevention (screening policies i.e. diagnostic assistance pathways for rare diseases diagnoses through screening)

Focus Group

Members:

Barbon Galluppi	Renza	UNIAMO F.I.M.R. onlus
Calzolari	Elisa	Emilia Romagna Region
Carbone	Pietro	ISS Italian National Health Institute
Cerone	Roberto	SIMMESN Italian Society for the Study of Inborn Metabolic Diseases and Newborn Screening
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Dionisi Vici	Carlo	SIMMESN Italian Society for the Study of Inborn Metabolic Diseases and Newborn Screening
Festa	Sonia	Orphanet Italia
Florida	Giovanna	ISS Italian National Health Institute
Granata	Orietta	ISS Italian National Health Institute
Laringe	Matteo	SIMG Italian Society of General Practitioners
Petetti	Federica	AGENAS NATIONAL Agency for Regional Health Services
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Privitera	Maria Grazia	Ministry of Health - Department of Prevention
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Rozzi	Elisa	Regione Emilia Romagna
Rusticali	Bruno	AGENAS NATIONAL Agency for Regional Health Services
Scarano	Gioacchino	SIGU Italian Society of Human Genetics
Vaccarotto Pedron	Manuela	UNIAMO F.I.M.R. onlus
Volta	Matteo	Regione Emilia Romagna

27. Pre-conceptual and pre-natal screening

State of the art

According to the present legislation, pre-conceptual genetic counselling is free for all couples applying for it; prenatal counselling, if specific requirements are present, is free¹³.

There many differences between Regions as for the services provided by the NHS, both for the services delivered by public facilities and those delivered also by qualified private structures.

There are critical elements as for the implementation of the guidelines of the Agreement of the State-Regions Conference for the activities of medical genetics within the NHS and there are differences between the regional accreditation procedures.

At present, for certain metabolic diseases, it is possible to give prenatal diagnosis using methodologies that are only available in specialised centres abroad.

¹³ In the [Ministerial Decree dated 10 September 1998](#) (*Access protocols of laboratory analysis and diagnostic instruments for pregnant women and maternity safeguard*) analysis/ assessments (also genetic) that can be carried out for free before conception. In particular at point 4 Enclosure A “Free specialist analysis having a **preconceptional function** for a responsible maternity” of the Decree it is clearly mentioned the “genetic counselling” “in case of repetitive miscarriages or previous pathologies associated with pregnancy perinatal mortality and upon gynaecologist or genetist prescription”

Proposals to be included in the NPRD

1. According to the guidelines of the competent scientific societies minimum criteria shall be established that the facilities qualified to carry out studies for prenatal diagnosis shall observe (to be assessed by the State-Regions Conference).
2. Regional competent bodies shall comply with the in-force regulations about pre-conceptual and prenatal¹⁴ counselling. It shall be explicitly stated that targeted pre-conceptual studies and prenatal diagnosis that are exclusively available abroad (after verifying they are not available in the national territory) are covered by the NHS¹⁵.
3. Regional authorities must guarantee to the users a clear, accessible information and an updated list of reliable facilities that can be contacted at local level.
4. With reference to the pre-conceptual screenings, screening for some rare but “frequent” pathologies shall be guaranteed across the entire national territory, when validated diagnosis procedures exist.
5. Regions shall collect specific pre-conceptual and prenatal screening data by pathology in order to carry out epidemiological assessments.

28. Neonatal screening

State of the art

In the current legislation (Law 5 February 92 no. 104, item 6, letter g, and DPCM 9 July 1999) the mandatory character of neonatal screening for cystic fibrosis is not clearly specified; the consequence is that the screening for such a pathology is not homogeneously implemented across the national territory.

On 23 January 2014 a document was subscribed on occasion of the meeting of the Interregional Round Table on Rare Diseases (“guidelines on patient’s management and pathways in the screening process”). At present, the list of metabolic pathologies subject to wide neonatal screening is not homogeneous on the national territory.

The scenario is changing, waiting for the application of Paragraph 229 art. 1 Law 147/2013 providing for the definition of the list of pathologies for which the screening should be performed.

The information given to families on the entire screening pathway, the procedures for the collection of informed consent and its content, is poor, ineffective and uneven throughout the country.

It is necessary to improve training of healthcare professional involved in screening processes.

Proposals to be included in the NPRD

1. The list of rare pathologies included in the list of those for which neonatal screening is supported by the NHS shall be periodically re-assessed (approximately every 2 years) in line with new technical and epidemiologic knowledge. The pathologies to be included in the screening shall be chosen following evidence-based criteria.

¹⁴ See [Ministerial Decree dated 10 September 1998](#)

¹⁵ On the basis of the Directive on cross-border healthcare (Dir. 2011/24/EU).

2. It is essential to communicate on the screening process more efficiently, both for families and operators, in order to make information accessible on the whole national territory. It is also necessary to take into consideration language and cultural differences and to make contents and procedures on informed consent uniform.
3. The constituencies of the facilities to be designated for performing neonatal screening shall be reassessed according to the provisions of the relevant amendment of the “stability law”¹⁶, possibly in compliance with criteria based on experience resulting from the whole screening programme, including patient clinical management.
4. It is necessary that the competent bodies clarify the content of article 3 DPCM 9 July 1999 with regard to the compulsoriness of neonatal screening for cystic fibrosis.
5. The epidemiologic supervision of the pathologies subject to neonatal screening shall be organised, as well as their monitoring the assessment of the effectiveness of the activities performed, with aim to redirect future steps.
6. Information/communication campaigns concerning primary prevention and early diagnosis and screening programmes concerning secondary prevention must be implemented with different methods, considering also the ethnic-language-cultural aspects and the user social-economic status. Different studies have shown that the social-demographic aspects deeply influence the demand for healthcare. While doing prevention, it is important to reach out the whole interested population, in particular population groups with low social-economic status and/or recently immigrated because often excluded by these actions.

29. Diagnostic and genetic tests

Diagnostic laboratories

State of the art

Regions have provided an updated list of centres /“Presidi” for rare diseases or groups of diseases that take charge of patients and that are officially accredited by regional resolutions. These centres/“Presidi” have been identified and included in Orphanet, in accordance with and under the supervision of the Regional contact persons of the Round Table for Rare Diseases.

As for the lists of laboratories reported in Orphanet, the above database may not be exhaustive and it is not assessed by the Regions as for the real effectiveness of the facilities.

Some tests that are necessary for diagnostic confirmation and for monitoring hereditary metabolic diseases (included those subject to neonatal screening) are not included in the national nomenclature nor in the regional ones, if existing. Some rare diseases are not included in the enclosure A of MD 279/01 – list of RDs with cost exemption

Proposals to included in the NPRD

1. It is desirable that qualitative-quantitative standards are used, with the specific indicators developed by the Italian Society for Human Genetics (SIGU) for: clinical facilities dealing with medical genetics, labs of medical genetics and bio-banks.

¹⁶ Paragraph 229 art. 1 Law 147/2013

2. With reference to bio-chemical metabolic tests, it is necessary that competent scientific societies define qualitative-quantitative standards with specific indicators for reference clinical facilities.

Transmission of diagnostic and tele-counselling materials

Proposals to be included in the NPRD

3. It is necessary to guarantee across the whole national territory the principle whereby the patient should not move to undergo genetic tests, but biological samples shall be sent to diagnostic laboratories, with the sample staying under the responsibility of the sender.
4. For the sample preservation (following informed consent) it is necessary to create and/or develop bio-banks, for which common regulating procedures shall be defined.

30. Primary Prevention

State of the art

As far as rare diseases primary prevention is concerned, with reference to **risks connected to diet and life styles**, EUROCAT Recommendations for the primary prevention of congenital anomalies have been established. In these Recommendations there is a short paragraph dedicated to this issue¹⁷.

In the Recommendations, beside the factors relevant to diet and life styles, also other risk factors for the prevention of congenital deformities are mentioned:

- 1- drugs administration during pregnancy and teratogen risk;
- 2- environmental pollutants and occupation-related exposures;
- 3- genetic risk connected to generative or family history of the couple.

In those Regions performing neonatal screening for metabolic diseases, the problem of mother's deficiency (nutritional or non-nutritional) of B12 vitamin has emerged.

Regarding the health of pregnant women, it is important to mention the "physiological pregnancy" guidelines, written under the aegis of the Ministry of Health within the activities of the national system of guidelines, issued in November 2010, updated in September 2011; the next update is planned for November 2014.

¹⁷ The Recommendations are available in English visiting the websites:

EUROCAT (http://www.eurocat-network.eu/content/EUROCAT-EUROPLAN-Primary-Preventions_Reccomendations.pdf)

EUCERD (http://www.eucerd.eu/wp-content/uploads/2013/03/Eurocat_Reco_PrimaryPrevention.pdf)

ISS (http://www.iss.it/binary/acid2/cont/Primary_Prevention_of_CA_Report_DT.pdf)

Recently these Recommendations have been translated into Italian and published in the ISTISAN Report 13/28 "Primary prevention of congenital anomalies: activities of the Network for Italian Promotion Folic acid" pages 175-178. http://www.iss.it/binary/publ/cont/13_28web.pdf

Proposals to be included in the NPRD

1. Ensuring that the guidelines on physiological pregnancy are updated by the end of 2014.
2. Promoting the products developed within the CCM (National Centre for Disease Prevention and Control) programme 2007, project “Implementation of strategies to encourage the ideal intake of folic acid for women in reproductive age and for the population at large”:
www.pensiamociprima.net
www.primadellagravidanza.it
3. Promoting the products developed within the project “Primary prevention of congenital defects with folic acid: risk/benefit assessment, result supervision and communication”.
4. Promoting the programme “Genitori più” that underlines 8 actions of proved efficacy for the prevention of the most important risks for the child’s body/psychological health since pre-conceptual phase: www.genitoripiu.it
5. Inserting in the labels and on packaging of commercial products specific pictograms to identify the reproductive risk.
6. Similarly, for alcoholic drinks, it should be possible to provide for the obligation to report the reproductive risk, by using specific pitograms illustrating the prohibition to drink alcohol during pregnancy.
7. Providing for the development of guidelines (periodically updated) for health professionals about the suitable use of drugs during pregnancy and alternative therapies.
8. Rationalising and regulating the national network of Teratologic Information Services (TIS).
9. Encouraging compliance with the provisions of the Decree July 9, 1999, Article 1, paragraph 4 concerning the epidemiological surveillance of adverse outcomes with particular reference to reproductive malformations, that should be implemented also through the integration of common healthcare information sources (Congenital Malformations registries, Certificates of attendance at birth, Hospital Discharge Data, Investigations of the National Institute of Statistics on abortions and voluntary abortions, etc..).
10. Supporting the use and the implementation of epidemiologic surveillance systems for rare diseases and congenital anomalies (at national/regional level) and providing for specific studies to monitor/assess the effectiveness of preventive actions, in view of orienting future actions.

31. HORIZONTAL THEMES

- **Sustainability: what actions MAY be included in the NPRD to SUPPORT the medium/long-term sustainability of the rare diseases system as for prevention activities?**

- The Stability Law n° 147 of 12.27.2013 in order to implement Article 1, paragraph 229, provide for an increase of 5 million euro per year (as of 2014) of the State contribution for financing (even on an experimental basis) extended newborn screening for inherited metabolic diseases.
- It is crucial that once the experimental phase comes to an end, further economic funds are allocated to guarantee neonatal screening to all new-born babies.

- **Empowerment: what actions may be included in the NPRD to support the empowerment, in its different parts, with regard to preventive activities ?**

Individual
<ul style="list-style-type: none"> • Primary Prevention <p>Knowledge, attitudes and behaviors of operators and users interested in using the already existing dedicated communication and information tools (information campaigns /fad)</p> <ul style="list-style-type: none"> • Secondary Prevention <p>Information leaflets issued by the birth centre of the competent Region (which should be also disseminated to bordering Regions – already existing processes: informed consent on the newborn screening).</p>
Organisational
<p>Paragraph 229 art. 1, Stability Law n. 147 of 2013</p> <ul style="list-style-type: none"> • In order to favor the broadest uniform application across the national territory of early neonatal diagnosis and to identify of the optimal constituencies, proportional to the birth rate, a coordination center on neonatal screening is established at the Age.na.s. (National Agency for Regional Health Services), composed by: the General Director of Age.na.s with the function of coordinator; three members appointed by Age.na.s, of which at least one expert with medical-scientific experience in this area; a member of the associations of people with metabolic-hereditary diseases ; a representative of the Ministry of Health; a representative of the Permanent Conference for the Relations between State, Regions and the Autonomous Provinces of Trento and Bolzano. • A Round Table to implement the Directive on Cross-border Health Care has been created.

- **Good practices (particularly important experiences supporting the proposals): what experiences may be indicated in the field of prevention?**

- Project “Implementation of strategies to encourage an ideal folic acid intake in women in reproductive age and in the population at large”:
www.pensiamociprima.net
www.primadellagravidanza.it
- Project “Primary Prevention of congenital defects with folic acid: risk/benefit assessment, result supervision and communication outcomes”:
www.iss.it/cnmr/acid
- Programme “Genitori Più” that underlines 8 actions of proved efficacy for the prevention of the most important risks for child physical /psychological development in pre-conceptional phase:
www.genitoripiu.it
- European Projects providing information material about diseases subject to screening (ex.: EIMD, registers and guidelines for metabolic diseases, E-HOD for homocystinuria and methylation defects).
- Free OPBG-FAD (Bambin Gesù Children Hospital e-Learning “Diagnostic/assistance pathways for diseases subject to neonatal screening” defined in the CCM project “Development of diagnostic-

assistance pathways diseases subject neonatal screening” (7-hour lesson) addressed to health professionals and granting ECM credits.

- EMILIA-ROMAGNA REGION: Use and sharing of information material and informed consent and dissent models already predisposed by the Regions.
- ISS - leaflet about folic acid translated into 11 languages and multilingual Leaflet (11 languages in synthetic version) about the Prevention of Congenital Anomalies (DTN and other MC) through pre-conceptual supplementation with folic acid, developed in 2011 within the CCM project *“Primary prevention of congenital defects with folic acid: risk/benefit assessment, results supervision, training and communication”*.
- Italian National Health Institute ISS – free FAD (e-learning) about primary prevention of Consultant of MC (60-hour lesson). The course, granting ECM formative credits for different professional profiles, was developed in 5 modules in 2009 and was implemented in 2011 by the CNMR in cooperation with FAD Group of the External Relations Department of ISS, thanks to a grant of the Ministry for Health, Innovation Department, Drugs and Medical Devices General Direction.
- AISMME Association – television advertisement about neonatal screening for methabolic Diseases.

Annex I - CORE INDICATORS for Monitoring National Plans/Strategies

The Working Groups of the Italian EUROPLAN Conference provided answers to the **21 Core Indicators** of the “EUCERD Recommendations on Core Indicators for National Plans or Strategies on Rare Diseases” (http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_Indicators_adopted.pdf).

The answers are reported below.

- **Methodology, Governance and Monitoring of the National Plan**

N°1 Existence of Regulations/Laws, or equivalent official national decisions that support the establishment and development of a Rare Diseases (RD) plan

This Indicator refers to the fact that National Plans/Strategies for Rare Diseases should be devised/regulated at national level in accordance with the Council Recommendation on RD, relevant Recommendations of the EUCERD e.g. those on Centres of Expertise and European Reference Networks, as well as relevant legislation (Regulation EC n° 141/2000 on Orphan Medicinal Products, Directive EU/2011/24 on Cross Border Healthcare, etc.).

The National Plan or Strategy is adopted via binding legislative acts, the exact nature or level of which may vary (regulation, laws, or other types of decisions). They may be established at the appropriate level of governance (federal vs. federated state level) depending on the country's system of government. It is therefore embedded in a legislative or operational framework

Short answer : **In progress /in development**

Detailed answer : **Expected adoption in the form of State Regions agreement**

N°2 Existence of a RD advisory committee

The Expert Advisory Committee refers to the existence of a coordination mechanism that oversees the development and implementation of the National Plan/Strategy for Rare Diseases. This body is composed of representatives of all relevant stakeholders, including patient representatives, national government, industry, treating physicians, payers, academia, etc.

Short answer: **No**

Detailed answer: **It is planned within the scheme of NPRD and provides representation of stakeholders**

N°3 Permanent and official patients' representation in plan development, monitoring and assessment

Patients are officially represented at all stages of plan development and governance, including its monitoring and evaluation.

Short answer: **No**

N°18 Existence of a policy/decision to ensure long-term funding and/or sustainability of the measures in the RD plan/strategy

The indicator verifies whether the financial commitment for rare disease care and treatment is clearly defined in a budget decision that supports the implementation of the National Plan/Strategy actions.

Short answer: **No**

Detailed answer : **The assistance of rare diseases is funded within the National Health Fund allocated to the Regions.**

N°19 Amount of public funds allocated to the RD plan/strategy

The indicator is the overall budget (in EUR) allocated per year to the National Plan/Strategy (excluding reimbursement of care and cost of standard care, excluding cost of orphan drugs). As with the previous indicator, this indicator aims to ensure that RD actions include appropriate provisions to ensure their sustainability over time. Efficient and effective actions for rare diseases depend on integrating scarce and scattered resources both nationally and within a common European effort

Detailed answer: **No funds provided in a dedicated and structured way. Over the years, ad hoc funding has been allocated through a bound share of the National Health Fund.**

• Definition, Codification. Information and Training

N.10 Existence of a national policy for developing, adapting and implementing clinical practice guidelines

The indicator checks the existence of a policy for developing, adapting and implementing clinical practice guidelines (CPGs) for diseases/groups of diseases (“Adapting” refers to adaption of supra-nationally based clinical guidelines to the local context).The cumulative production of protocols and clinical guidelines is an instrument for equity of access to care by rare disease patients across the European Union.

Short answer: **No**

N°11 Type of classification/coding used by the health care system

The adoption and the daily use of an internationally recognised, comprehensive, health care codification system is important for RD management and would encourage the harmonisation of disease nomenclature worldwide. This enables budgetary and management decisions to have a more solid basis and would constitute one relevant tool for Health Technology Assessment.

Short Answer : Type of coding system used **ICD-9 ICD-10 Exemption Code**

ORPHA Code is used in addition to national coding system **No**

N°12 Existence of a national policy on registry and data collection on RD

This indicator collects information on Member States’ support, at all appropriate levels, to rare diseases registries and databases for epidemiological, public health and research purposes, as well as on the role ensured by public authorities for the coordination and sustainability of data collection.

Short answer: **Yes**

Detailed answer: **YES, for national/centralised registry and data collection**

N°4 Adoption of the EU RD definition

The EU defines “rare diseases” as those with a prevalence of no more than 5 patients per 10.000 persons. This definition is laid down in Regulation EC n° 141/2000 on Orphan Medicinal Products, Directive 2011/24/EU on Cross Border Healthcare as well as in the Council Recommendation on an action in the field of rare diseases of 8 June 2009.

Short answer: **Yes**

Detailed answer: **YES, the NP/NS measures are applied using the EU definition**

N°8 NP/NS support to the development of/participation in an information system on RD

This indicator refers to the existence of a functional, RD-specific information system that is comprehensive and nation-wide (such as Orphanet). This indicator includes the participation in the Orphanet Joint Action and eventually the production of information packages in national language(s).

Short answer: **Yes**

Detailed answer: **YES, national YES, regional/s YES, participates in Orphanet JA and produces information in national language(s)**

N°9 Existence of Help lines for RD

The availability of help lines is fundamental for the diffusion of information and expertise on rare diseases. They have an important role in orienting patients towards a solution to the issues that directly or indirectly affect him/her as a result of the condition and are the only service that can offer social, psychological and information solutions to all of these needs. Professionals (including those working in emergency departments) may learn about resources and pathways to diagnose their patients or receive important information regarding the management of patients with a rare disease. This indicator aims to account for the national help lines on rare diseases, either aimed at patients or professionals (or both), including those not publicly funded.

Short answer :

Detailed answer

YES, supported by public funding

YES, only for professionals

YES, only for patients

YES, for both professionals and patients

YES, supported by private funding

YES, only for professionals

YES, only for patients

YES, for both professionals and patients

- **Research**

N°13 Existence of a RD research programmes/projects in the Country

This indicator aims to describe the status of RD research in the country, most notably whether a dedicated programme exists, or whether RD research is carried out by individual projects within the general research programme

Short answer: **No**

N°14 Participation in European and international research initiatives

Participation of national research agencies in international research initiatives (such as E-RARE – www.e-rare.eu, and IRDiRC – www.irdirc.org) is important to foster research on rare diseases a global level, by pooling resources and coordinating national research programmes to overcome the fragmentation of research on RD.

Short answer: **Yes**

Detailed answer: **YES, E-RARE YES, IRDiRC YES, others (specify) -RD Connect**

N° 20 Specific public funds allocated for RD research

This indicator aims to identify the policy decision(s) to allocate a portion of the national research budget specifically to RD research

Short answer: **No**

N°21 Public funds specifically allocated for RD research actions/projects per year since the plan started

This indicator verifies the total amount of public funds (in EUR) allocated to RD research projects or programmes

Short answer: **No**

- **Centres of Expertise and European Reference Network for RD**

N°5 Existence of a national policy for establishing Centres of Expertise on RD

This policy defines a strategy to identify and designate centres of expertise, aiming to improve the quality of health care by defining appropriate centres with experience on RD as well as pathways that reduce the diagnosis delay and facilitate both care and treatment for RD patients.

Short answer: **Yes**

Detailed answer: **YES, existing, fully implemented (D279/2001)**

N°6 Number of national and regional Centres of Expertise adhering to the national policy

Member States identify and appoint Centres of Expertise (CEs) throughout their national territory, and consider supporting their creation. The Centres of Expertise should adhere to the national policy.

It is to be remembered that the EUCERD adopted the “EUCERD Recommendations on Quality Criteria for Centres of Expertise” which are “intended to help EU Member States in their reflections or policy developments concerning

national plans and strategies for rare diseases when addressing the issue of organisation of healthcare pathways at national and European level". This indicator therefore also aims to count the number of Centres of Expertise that are compliant with the EUCERD recommendations.

Short answer: **No number**

Detailed answer : **All centers are in compliance with national policy (number) the assessment respect to the EUCERD criteria is in progress.**

N°7 Participation of national or regional centres of expertise in European Reference Networks

The information on the integration of national Centres of Expertise in European Reference Networks (ERNs) is essential to obtain the broader picture of RD care across Europe and enables the diffusion of expertise across the EU, regardless of the size/population of each country.

According to the "EUCERD Recommendations on European Reference Networks for Rare Diseases", different forms of affiliation to an RD ERN (association, collaboration) should be allowed to ensure inclusivity." Therefore this indicator aims to differentiate between full and associated membership of RD Centres of Expertise to RD ERNs.

However, it should be taken into account that it will take some time before ERNs are established. Therefore it should be expected that this Indicator will provide meaningful information only a few years after the adoption of these Recommendations

Short answer: **No number**

Detailed answer: **The National Centres are being assessed in order to identify those that will be part of the ERNs. Some Centres already have institutional collaboration at European level.**

- **Orphan Medicinal Products and Therapeutics for Rare Diseases**

N°15 Number of Orphan Medical Products (OMPs) with a European Union marketing authorisation and available in the country (i.e. priced and reimbursed or directly supplied by the national health system)

The actual availability of OMPs in the national market is essential to illustrate patients' access to treatment in their country. Moreover, with patient access to OMPs differing across Member States, the success of cross border healthcare depends on the harmonisation of access to diagnosis and treatment. Therefore, quantifying the drugs that are available in each country, either in ambulatory or in-hospital regimens, is also important to bridge the existing gap between Member States.

Short answer : **47**

N°16 Existence of a governmental system for compassionate use of medicinal products

The indicator aims to identify whether a system exists to provide medicines to rare diseases patients prior to approval of new drugs (so-called compassionate use).. The existence of such programmes is relevant for the assessment of overall RD care.

Short answer: **Yes**

- **Social Services for Rare Diseases**

N. 17 Existence of programmes to support in their daily life RD patients integration

Rare Diseases often lead to disability and a need for continuous care. Specialised Social Services are instrumental in providing patients with a full, rewarding life. Their existence and number demonstrate the political commitment of Member States to this mission. Examples of social services to integrate patients in their daily life and support their psychological and educational development are:

a) educational support for patients, relatives and caregivers;

b) individual support at school, for both pupils with rare diseases and teachers, including disease-specific good practices;

c) activities aimed to foster higher education for people with rare diseases;

d) supporting mechanisms to participate in work life for people with disabilities.

Short answer: **Yes**

Detailed answer: **YES, people living with RD can access general programmes for persons with a disability**

Annex II – Programme of the Conference (in Italian)

EUROPLAN 2012-2015 è il progetto europeo finalizzato allo sviluppo di Piani e/o strategie nazionali per le malattie rare co-finanziato dalla Commissione Europea (DG-SANCO) nell'ambito della più generale EUCERD Joint Action, della quale è responsabile l'Università di Newcastle. Il progetto EUROPLAN 2012-2015 è coordinato dal Centro Nazionale Malattie Rare dell'Istituto Superiore di Sanità e la Conferenza EUROPLAN II, promossa da Eurordis e UNIAMO FIMR Onlus in collaborazione con tutti i portatori di interesse del settore, si pone in continuità con l'esperienza realizzata con il progetto precedente (EUROPLAN 2008-20011) che ha posto le basi per lo sviluppo nei Paesi Membri di un piano nazionale per le malattie rare da adottare entro il 2013, secondo le Raccomandazioni del Consilium su una azione europea nel campo delle malattie rare (2009/C 151/02). Con questa iniziativa UNIAMO FIMR Onlus intende quindi portare un contributo fattivo al processo di adozione del Piano Nazionale Malattie Rare 2013-2016.

Metodologia:
Processo di empowerment "organizzativo" fra tutti gli attori coinvolti portatori d'interesse specifico per le Malattie Rare con l'attivazione dei seguenti gruppi di approfondimento tematico:

- Rete
- Sistema di monitoraggio (registri e flusso informativo); nomenclatura e codifica
- Percorso diagnostico assistenziale (inclusi Servizi Sociali Specializzati e farmaci orfani)
- Ricerca e farmaci orfani
- Informazione e formazione
- Prevenzione

www.euoplanproject.eu



Si ringrazia Pfizer per il contributo incondizionato all'iniziativa

UNIAMO
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Roma
27/28
gennaio
2014

27 lunedì gennaio		28 martedì gennaio	
Ministero della Salute via G. Ribotta		OPBG Ospedale Pediatrico Bambino Gesù via Ferdinando Baldelli 36	
partecipazione ad invito		partecipazione libera	
10,30	Arrivo e accreditamento partecipanti	8,30	Arrivo e accreditamento partecipanti
11,00	Inizio dei lavori per gruppi predefiniti a) Rete b) Sistema di monitoraggio (registri e flusso informativo); nomenclatura e codifica c) Percorso diagnostico assistenziale (inclusi Servizi Sociali Specializzati e farmaci orfani) d) Ricerca e farmaci orfani e) Informazione e formazione f) Prevenzione	9,00	Saluti e introduzione alla giornata Giuseppe Profiti , Presidente OPBG Bruno Dallapiccola , Direttore Scientifico OPBG On.le Paola Binetti , Gruppo Interparlamentare Malattie Rare
13,30	Colazione di lavoro presso la mensa della struttura ospitante	9,15	Il progetto EUROPLAN II nel quadro europeo sulle malattie rare I risultati dei gruppi di approfondimento tematico Simona Bellagambi , Eurordis Europlan Advisor Intervengono Domenica Taruscio , CNMR-ISS e Renza Barbon Galluppi , UNIAMO F.I.M.R. onlus
14,30	Ripresa dei lavori	9,30	La parola ai rappresentanti delle persone con malattia rara I risultati dei gruppi di approfondimento tematico A – Maria Marcheselli B – Michele Del Zotti C – Pietro Marinelli e Tommasina Iorrio D – Nicola Spinelli E – Velia Maria Lapadula F – Renza Barbon Galluppi
16,30	Elaborazione degli indicatori di valutazione di EUCERD	12,30	Dibattito
17,30	Chiusura dei lavori	13,30	Chiusura dei lavori Colazione di lavoro
17,45	Spostamento in albergo Barcelò Aran Mantegna	14,30	Debrief session (riservata ai responsabili del progetto EUCERD Joint Action, UNIAMO, Eurordis Europlan Advisor, CNMR-ISS, Ministero Salute, Alfa, Agenas, Rappresentante Regioni)
18,30	Incontro con i verbalizzanti e conduttori dei gruppi di approfondimento tematico		Moderatrice: Michela Vuga
20,30	Cena		

Soggetto organizzatore:
UNIAMO F.I.M.R. Onlus

Steering Committee:
Ministero della Salute
Ministero del Lavoro e delle Politiche Sociali
Tavolo Interregionale Malattie Rare
Coordinamento Commissione Salute della Conferenza Stato-Regioni e Province Autonome
ISS - Centro Nazionale Malattie Rare
Agenas
AIFA
CARD
Ce.Ri.S.Ma.S. (Centro di Ricerche e Studi in Management Sanitario)
EUCERD
Farmindustria
Federsanità Anci
FIMMG - Federazione Italiana Medici di Medicina Generale
Fondazione Telethon
Orphanet
SIGU - Società Italiana di Genetica Umana
SIMG - Società Italiana di Medicina Generale
SIMGePed - Società Italiana Malattie Genetiche Pediatriche e Disabilità Congenite
SIP - Società Italiana di Pediatria

Altri enti/organizzazioni partecipanti:
Assobiotec
Gruppo interparlamentare Malattie Rare
NOMOS Centro Studi Parlamentari srl
O.Ma.R Osservatorio Malattie Rare
SIE - Società Italiana di Endocrinologia
SIMMESN - Società Italiana Studio Malattie Metaboliche e Screening Neonatali
SIN - Società Italiana di Neurologia
Stabilimento Chimico Farmaceutico Militare
UPFARM - Unione Professionale Farmacisti per Farmaci Orfani

Supporto tecnico:
Sinode srl