



Overview Report on the State of the Art of Rare Disease Activities in Europe

2016 Version

RD-ACTION WP6 Output



Co-funded by
the Health Programme
of the European Union

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In certain sections, especially those describing the origins of rare disease policies in Europe, the RD-ACTION-led State of the Art resource has retained text generated by Prof. Aymé and Ms Rodwell under the EUCERD Joint Action, and thus they should be considered co-authors of the current document.





Disclaimer:

The findings and conclusions in this report are those of the contributors and validating authorities, who are responsible for the contents; the findings and conclusions do not necessarily represent the views of the European Commission or national health authorities in Europe. Therefore, no statement in this report should be construed as an official position of the European Commission or a national health authority.

Background to the State of the Art of Rare Disease Activities in Europe:

The Report on the State of the Art of Rare Disease activities in Europe is a well-established resource providing valuable, detailed information for all stakeholders in the field of rare diseases and orphan medicinal products. It highlights activities and progress at both the European Union (EU) and Member State (MS) levels. Under the EUCERD Joint Action the report was produced by the INSERM team in Paris, in [five volumes](#). This was a substantial report, downloaded 15,000 times per annum and divided into five volumes. Under the subsequent Joint Action, RD-ACTION (2015-18) production of the State of the Art resource moved to Newcastle University and it was agreed that two versions of the 'Overview report' (the current document) would be produced in the project lifetime: this overview report will be complemented by Member State-specific webpages under the main RD-ACTION site, detailing activities at the national level.

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1. Political framework

Since the 1990s, rare diseases have been a policy priority at both European Union (EU) and Member State (MS) level. A number of countries led the way in the decade leading up to the first European legislative text concerning rare diseases, the Orphan Medicinal Product Regulation of 16 December 1999¹, and the ensuing Commission Communication (2008) and Council Recommendation (2009). Sweden, for example, established the first centres of expertise for rare diseases in 1990 and a rare disease database and information centre in 1999; Denmark established an information centre in 1990 and then centres of expertise for rare diseases in 2001; in Italy, a decree on rare diseases came into force in 2001; and in France, Orphanet was established in 1997 with the support of the French Ministry of Health as the portal for information on rare diseases and orphan medicinal products, followed by the first national plan/strategy for rare diseases in Europe (2004). A number of other countries (Bulgaria, Greece, Portugal and Spain) elaborated a national plan/strategy for rare diseases at the very same time as EU policy in the field was defined through the Commission Communication and Council Recommendation.

By the end of 2016, the situation has changed in many positive respects. For instance:

- ✓ **24 countries have adopted a national plan or strategy for rare diseases,² compared to only 4 in 2008, and the focus has moved more from ‘adopting’ to actually implementing and evaluating the success of these first (and in some cases second and moving to third) incarnations.**
- ✓ **2016 saw the approval and official ‘birth’ of the long-awaited European Reference Networks for rare diseases – 24 ERNs are now operational, an unprecedented success.**
- ✓ **Collaboration between the ‘healthcare’ and ‘research’ domains is increasing, and will continue to grow, in part due to the dual focus of the ERNs.**
- ✓ **Patient organisations such as EURORDIS continue to grow and play leading roles in initiatives such as Joint Actions, Tender and Projects driving forwards progress.**
- ✓ **Both EURORDIS and Orphanet (the global database for rare diseases) celebrate their 20th anniversaries in 2017.**

¹ http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf

² The Council Recommendation of 2009 <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF>: asked MS to “elaborate and adopt a plan or strategy as soon as possible, preferably by the end of 2013 at the latest, aimed at guiding and structuring relevant actions in the field of rare diseases within the framework of their health and social systems

Although there has been progress there is still much to do to ensure that people suffering from a rare disease can obtain the right diagnosis and best possible treatment throughout the EU. A number of recommendations exist, pertaining to specific topics – the degree to which these are implemented on the ground, and the extent to which life is changing for the better at patient-level, still needs to be explored. Member States have much to learn from one another, in terms of what works, and how to address some of the shared challenges pertaining to rare diseases. It may well be the case that, as opposed to seeking a ‘one size fits all’ approach to the 28 European MS, a focus on regional cooperation or shared approaches based upon a country’s size, situation, wealth, language etc. is the most realistic approach to identifying and embedding good practices.

1.1 Political framework at European Level

1.1.1 Key policy documents

The key ‘foundation’ documents which have inspired so much activity and progress in the European rare disease policy sphere are often identified as the **Commission Communication on Rare Diseases: Europe’s challenges [COM(2008) 679 final]** and the **Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02)**. Though ‘soft law’ both of these policy documents have been hugely influential in uniting European level and Member State level activities, and in shaping the work of bodies such as the rare disease Joint Actions and the Expert Groups/Committees in the field.

In 2014 the European Commission published an **Implementation report**³ on both the Council Recommendation and Commission Communication, addressed to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions. This report was based on the information provided by the Member States, and stakeholders were asked to consider the extent to which the proposed measures are working effectively, whilst also envisaging further actions required to improve the lives of patients affected by rare diseases and those of their families. The report concludes that overall, the objectives of the Communication and the Council Recommendation have been reached: “both have served to strengthen the cooperation between the European Union, the Member States and all the relevant stakeholders” (p15)

The Implementation Report, as above, highlights the following actions, to continue supporting Member States:

- Maintain the EU’s coordinative role in the development of the EU policy on rare diseases and to support Member States in their activities on the national level.
- Continue to support the development of high quality National Rare Diseases Plans/Strategies in the European Union.
- Provide continued support for the International Rare Disease Research Consortium and initiatives developed under its umbrella.
- Continue to ensure proper codification of rare diseases
- Work further to decrease inequalities between patients with rare diseases and patients suffering from more common disorders and to support initiatives promoting equal access to diagnosis and treatment.
- Continue to promote patients empowerment in all aspects of rare disease policy development

³ http://ec.europa.eu/health/sites/health/files/rare_diseases/docs/2014_rarediseases_implementationreport_en.pdf

- Continue activities increasing public awareness about rare disease and EU activity in this field.
- Make use of the Directive 2011/24/EU on the application of patients' rights in cross-border healthcare to bring together European Reference Networks on rare diseases. Support the development of the tools facilitating cooperation and interoperability of the European Reference Networks for rare diseases.
- Stimulate development and use of eHealth solutions in the area of rare diseases.
- Implement and continue support for the European Platform on rare diseases registration.
- Continue playing a global role in the rare diseases initiative and collaborating with important international stakeholders.⁴

The **Directive on the Application of Patients' Rights in Cross-Border Healthcare (Directive 2011/24/EU)**⁵ has played a key role in the development of European Reference Networks, or ERNs, which has particular importance to rare diseases. This is the Directive which clarifies the circumstances under which patients can seek care in a country other than that of usual residence, and article 12 provided the basis for the ERNs

1.1.1.1 The Commission Expert Group on Rare Diseases (2014-2016)

The Commission Expert Group was formed in 2013 in accordance with Commission Decision (2013/C219/04)⁶ (revoking the previous Decision setting up the European Union Committee of Experts of Rare Diseases (EUCERD)). The Commission Expert Group on Rare Diseases (CEGRD) was chaired by the European Commission and the main stakeholder groups represented were as follows:

- Member States' competent authorities
- Patient organisations in the field of rare diseases
- European associations of producers of products or service providers relevant for patients affected by rare diseases
- European professional associations or scientific societies acting in the field of rare diseases
- Individuals appointed in a personal capacity as experts having public health or scientific expertise at Union level in the field of rare diseases.

Between 11th February 2014 and 29th November 2016 (the final meeting of the CEGRD) the Group met 8 times, in Luxembourg. Certain activities of the CEGRD, like the EUCERD before it (see below) were supported by a Joint Action, RD-ACTION. The agendas, flash reports and Minutes are available here - https://ec.europa.eu/health/rare_diseases/expert_group_en

The CEGRD adopted several sets of Recommendations between its first meeting on 11-12 February 2014 and its final meeting on 28-29th November 2016:

⁴ <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52014DC0548&from=GA> (p16)

⁵ <http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A32011L0024>

⁶ http://ec.europa.eu/health/rare_diseases/docs/dec_expert_group_2013_en.pdf

- ***The Recommendation on ways to improve codification for rare disease in health information systems***⁷ adopted at the 3rd meeting on 12-13th November 2014
- ***Rare Disease European Reference Networks: An Addendum to the EUCERD Recommendations of January 2013***⁸ adopted during the 5th meeting 10-11th June 2015
- ***Recommendations on cross-border genetic testing of rare diseases in the European Union***⁹ adopted at the 6th meeting on 12th November 2015
- ***Recommendations to Support the Incorporation Of Rare Diseases Into Social Services***,¹⁰ adopted at the 7th meeting on 5-6th April 2016

The agendas for the eight meetings covered a broad range of topics, of relevance to the rare disease field, **and increasingly incorporated presentations from beyond the ‘traditional’ rare disease sphere**, delivered by colleagues from different Directorates General: DG RTD presented the IRDiRC¹¹ (International Rare Disease Research Consortium) initiative, RD-Connect,¹² and H2020 funding streams; the Joint Research Centre (JRC) presented the progress relating to rare disease registration; DG EMPL presented EU Policy on social services. Additionally, topics such as Structural Funds, reimbursement of orphan medicinal products (OMPs), pharmaceutical legislation, Medicines Adaptive Pathways to Patients (MAPPs), and rare cancers all featured in the meetings.

The final meeting ended with the announcement that, with the mandate of the CEGRD now expired, discussions would be taking place internally in the European Commission, regarding the future of Expert Groups in general. As of early January 2017, no updates have been received.

1.1.1.2 European Union Committee of Experts on Rare Diseases (EUCERD) (2010-2013)

The EUCERD¹³ was formed on 30 November 2009 (EC decision 2009/872/EC) with the aim of assisting the European Commission to prepare and implement community activities in the rare disease field. A major strength of the EUCERD lay in its multistakeholder composition, which enabled it to function as an effective platform to discuss and debate the key topics and concerns of the whole rare disease community. The Committee successfully garnered the cooperation of not only Member State representatives but also the European Commission, patients, experts and representatives from industry. The group was able to foster exchanges of relevant experience, policies and practices in the field of rare diseases’ which in turn enabled the EC and Member States to develop and administer activities and recommendations. Over its three years the EUCERD was very successful and prolific, and was ably supported by a dedicated Joint Action (the EUCERD Joint Action) which, along with other expert stakeholder bodies, organised workshops to generate draft reports and sets of recommendations which could then be further elaborated and submitted for discussion and adoption by the EUCERD. Key topics on the EUCERD Agenda included the following:

- Centres of Expertise
- European Reference Networks

⁷ http://ec.europa.eu/health/sites/health/files/rare_diseases/docs/recommendation_coding_cegrd_en.pdf

⁸ http://ec.europa.eu/health/sites/health/files/rare_diseases/docs/20150610_erns_eucerdaddendum_en.pdf

⁹ http://ec.europa.eu/health/sites/health/files/rare_diseases/docs/2015_recommendation_crossbordergeneticstesting_en.pdf

¹⁰ http://ec.europa.eu/health/sites/health/files/rare_diseases/docs/recommendations_socialservices_policies_en.pdf

¹¹ <http://www.irdirc.org/>

¹² <http://rd-connect.eu/>

¹³ http://ec.europa.eu/health/rare_diseases/expert_group/index_en.htm

- Patient registration and data collection
- Access to Orphan Medicinal products for rare diseases
- RD National Plans/Strategies
- Newborn screening
- Codification of rare diseases
- Cross-border genetic testing

The EUCERD adopted 5 sets of Recommendations over its lifetime, on the topics of indicators for national plans/strategies, registries, European Reference Networks, centres of expertise, and improving informed decisions based on the clinical added value of orphan medicinal products:

- ***EUCERD Recommendations on Core Indicators for Rare Disease National Plans/Strategies***,¹⁴ adopted 6th June 2013
- ***EUCERD CORE Recommendations on Rare Disease Patient Registration and Data Collection***,¹⁵ adopted 5th June 2013
- ***EUCERD Recommendations on European Reference Networks for Rare Diseases***,¹⁶ adopted on 31st Jan 2013
- ***EUCERD Recommendations on the Clinical Added Value of Orphan Medicinal Products (CAVOMP) Information Flow***,¹⁷ adopted September 2012
- ***EUCERD Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases in Member States***,¹⁸ adopted October 2011

For an excellent summary of the EUCERD achievements and added value, see

<http://ojrd.biomedcentral.com/articles/10.1186/1750-1172-9-30>

Document Description	Date Adopted	Notes	Link to Document
Quality Criteria for Centres of Expertise for Rare Diseases	October 2011		http://www.eucerd.eu/?post_type=document&p=1224
Improving Decisions based on the Clinical Added Value of Orphan Medicinal Products (CAVOMP) Information Flow	September 2012		http://www.eucerd.eu/?post_type=document&p=1446
European Reference Networks for Rare	January	Addendum adopted June	http://www.eucerd.eu/?post_type=document&p=1224

¹⁴ http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_Indicators_adopted.pdf

¹⁵ http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_RDRegistryDataCollection_adopted.pdf

¹⁶ http://www.eucerd.eu/?post_type=document&p=2207

¹⁷ http://www.eucerd.eu/?post_type=document&p=2207

¹⁸ http://www.eucerd.eu/?post_type=document&p=1224

Diseases	2013	2015	ument&p=2207
Rare Disease Patient Registration and Data Collection	June 2013		http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_RDRegistryDataCollection_adopted.pdf
Core Indicators for Rare Disease National Plans/Strategies	June 2013		http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_Indicators_adopted.pdf
Potential Areas of European Collaboration in the field of New Born Screening (Opinion)	July 2013		http://www.eucerd.eu/wp-content/uploads/2013/07/EUCERD_NBS_Opinion_Adopted.pdf
Ways to Improve Codification of Rare Diseases	November 2014		http://ec.europa.eu/health/rare_diseases/docs/recommendation_coding_cegrd_en.pdf
Cross-Border Genetic Testing of Rare Diseases in the EU	November 2015		http://ec.europa.eu/health/rare_diseases/docs/2015_recommendation_crossbordergenetictesting_en.pdf
Support the Incorporation of Rare Diseases into Social Services and Policies	April 2016		http://ec.europa.eu/health/rare_diseases/docs/recommendations_socialservices_policies_en.pdf

Fig. 1 Summary of EUCERD/Expert Group Recommendations and Opinions

1.1.1.3 Joint Actions in the field of Rare Diseases

EUCERD Joint Action

It was primarily the European Commission Communication “Rare Diseases: Europe’s Challenge” (11 November 2008), and the Council Recommendation on an action in the field of rare diseases (8 June 2009) which prompted the creation of the EUCERD Joint Action (EJA). The Joint Action’s mandate was to assist the European Commission in the formulation and implementation of activities within

the rare disease community, and to foster exchanges of relevant experience and policies and practices between MS and stakeholders. The EJA was coordinated from Newcastle University, UK, by Professor Kate Bushby. It began in March 2012 and ran through to Autumn 2015, supporting the activities and mandate of the EUCERD until the end of 2013 and from 2014, supporting the activities of the CEGRD.

The Joint Action was established to address the following goals:

- Enhancing the visibility and recognition of Rare Diseases;
- Contributing to the development and dissemination of knowledge on Rare Diseases, from specialised research, through the support of the healthcare professionals and the empowerment of patients;
- Contributing to improvement in access to quality and care, from diagnosis, through to care and social support and innovative therapies.

The EJA built upon the achievements of previous European initiatives within the rare disease field. These included the European Commission Rare Disease Task Force, Orphanet, the Europlan project, and the outputs of several rare disease networks that had received funding from the European Union in the past. The project had a very broad scope, and was structured around five main work areas:

- The implementation of plans and strategies for rare diseases at the national level
- The standardisation of rare disease nomenclature at international level
- Mapping the provision of specialised social services and integration of rare diseases into mainstream social policies and services
- The leveraging of the value of EU networking for improving the quality of care for rare diseases
- The integration of Rare Disease initiatives across thematic areas and across Member States

The objectives, largely corresponding to these goals, were as follows:

- Enhanced visibility of RD and wider dissemination of related activities and knowledge
- Accelerated implementation of the inter-sectoral national action plans for rare diseases
- Adequate and established definition, classification and codification of rare diseases
- Wider recognition of the value and support to the development of specialised social services
- Identification of actions allowing to improve the access to higher-quality healthcare, covering the entire continuum, from diagnosis to care and rehabilitation, in particular through linking national dedicated structures with all European Reference Networks;
- A model for sustainable action in the area of RD, across thematic areas and geographical barriers, providing a framework for recognition of rare diseases and sharing knowledge and expertise.

Across its lifespan, the EJA organised 18 workshops involving many stakeholders in the broad discussions required to generate policy documents. Key outputs were 4 sets of draft Recommendations on the topics of registries, ERNs, National Plans/Strategies for Rare Diseases, and codification. The ERN Recommendations of 2013 were enriched with a Joint-Action-drafted Addendum in early 2015. Furthermore, significant work undertaken in the EJA on a) the integration

of RD to social policies and b) cross-border genetic testing for rare diseases, subsequently evolved into additional Recommendations issued by the CEGRD after the project had ended.

Besides the draft sets of Recommendations (presented for EUCERD and CEGRD revision and adoption) the EJA created many other outputs, including the following deliverables:

- Deliverable 5: Capacity Building Report for Rare Disease National Plans/National Strategies in EU Member States
- Deliverable 6: Relevant coding and classification of Rare Diseases in International nomenclatures
- Deliverable 7: Report on Guiding Principles for social care for rare diseases and EUCERD Recommendations in the Social Field
- Deliverable 8: State of the Art Report in Healthcare Systems and good practices in Rare Diseases
- Deliverable 10: Proposals for the sustainability of rare disease network tools and resources

The deliverables may be found here – http://www.eucerd.eu/?page_id=3029

The project also produced 3 volumes of the State of the Art report, 25 national European conferences with over 3000 participants. The final meeting of the EUCERD Joint Action, presenting the outcomes and future perspectives, was held on 15th September 2015 in Luxembourg.¹⁹ The support to the elaboration of policies in the field of rare diseases and improvement of the codification of rare diseases provided by the EJA continued in the scope of RD-ACTION (2015-2018).

RD-ACTION

RD-ACTION, 'Data and Policies for Rare Diseases' is the current Joint Action in the field of Rare Diseases, and merges the foci of two previous Joint Actions: the EUCERD JA and the Orphanet JA. RD-ACTION is coordinated overall by Ana Rath in INSERM, and the Policy & Integration workstream (WP6) is coordinated by Kate Bushby from Newcastle University. RD-ACTION unites 34 beneficiaries and 30 collaborating partners from 40 countries, with a total budget of 8.3 million Euros.

The general objectives of RD-Action are to:

- Support the further development and sustainability of the Orphanet database, the biggest global repository of information on RD
- Contribute to solutions to ensure an appropriate codification of RD in health information systems
- Continue implementation of the priorities identified in Council Recommendation 2009/C151/02 and the Commission Communication (COM 2008 679) on RD, with a view to ensuring the sustainability of the recommended priority actions and to support the work of the Commission Expert Group on Rare Diseases (CEGRD).

RD-Action has 6 workpackages which cover the following areas:

1. Coordination – led by Ana Rath (INSERM)
2. Dissemination – led by Yann Le Cam (EURORDIS) and Domenica Taruscio (ISS)
3. Evaluation – led by Till Voigtlaender (MUW)
4. Orphanet, the European database for Rare Diseases – led by Ana Rath (Inserm)

¹⁹ For more on the EUCERD JA, see <http://www.sciencedirect.com/science/article/pii/S1769721216302439>

5. Steering, maintaining and promoting the adoption of Orphacodes across MS – led by Stefanie Weber (DIMDI)
6. Policy Development for Rare Diseases and Integration – led by Kate Bushby (UNEW)

1.1.2 Work Programmes at European Level

- **A Community action programme on Rare Diseases**, including genetic diseases, was adopted for the period of 1 January 1999 to 31 December 2003 with the aim of ensuring a high level of health protection in relation to rare diseases. As the first EU effort in this area, specific attention was given to improving knowledge and facilitating access to information about these diseases.
- As a consequence, rare diseases were included as a priority in the **Second Programme of Community Action in the Field of Health 2008-2013**²⁰. The DG Health and Consumers work plans for the implementation of the Public Health Programme include main lines of action and priorities in the field of rare diseases every year.
- The **Third Programme of Community Action in the Field of Health 2014-2020** entitled **Health for Growth** also cited rare diseases as a priority.
- At European level, research²¹ on rare diseases has been addressed under the **EU Framework Programmes for Research and Technological Development** (FP) since the early 1990s. In the previous Framework Programme (FP7 2007-2013²²) the Health Theme of the "Cooperation" Specific Programme, was designed to support multinational collaborative research in different forms. FP7 was succeeded by Horizon 2020²³ the Framework Programme covering the period 2014-2020.

1.2 Political framework at Member State level

At Member State level, there is a great heterogeneity in the state of advancement of national policies, plans or strategies for rare diseases. The Council Recommendation on an action in the field of rare diseases (8 June 2009) recommended that MS elaborate and adopt, by the end of 2013, a national plan or strategy for rare diseases. Significant progress has been made towards this goal:

- 24²⁴ countries have adopted a NP/NS for rare diseases at some stage.
- 18 of these countries adopted NP/NS which were time-bound (i.e. they were approved covering certain years of activity).
 - The following 15 countries have time-bound NP/NS which were still apparently active at the end of 2016: **Austria; Croatia; Czech Republic; Estonia** (see note, below); **Finland, France**²⁵; **Hungary; Ireland; Italy; Lithuania; Netherlands; Portugal; Romania; Slovak Republic; Slovenia**

²⁰ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:271:0001:0011:EN:PDF>

²¹ For more on rare disease research, see the IRDiRC 'State of Play' resources - <http://www.irdirc.org/reports-guidelines/state-of-play-reports/>

²² http://cordis.europa.eu/fp7/home_en.html

²³ http://ec.europa.eu/research/participants/data/ref/h2020/legal_basis/fp/h2020-eu-estabact_en.pdf

²⁴ This figure includes the Estonian Rare Disease Development Plan 'An action plan for 2015-2017', developed as part of the main National Health Plan 2009–2020. The authors are awaiting the official Estonian update to determine the status of this document further.

²⁵ The 2nd plan was extended but was due to expire at the end of 2016 -discussions were ongoing as to the feasibility and content of a 3rd NP

- The following 3 countries adopted time-bound NP/NS which had expired by the end of 2016 and appear not to have been replaced/renewed: **Bulgaria, Greece, Latvia**
- The following countries adopted NP/NS which appear to be 'ongoing' (i.e. according to the 2016 SoA data received, do not cover specific time periods): **Belgium, Cyprus, Denmark, Germany, Spain, UK**
- Four EU MS appear not to have adopted a NP/NS by the end of 2016: **Luxembourg, Poland, Malta and Sweden**

Switzerland and Norway also now have a RD plan or strategy.

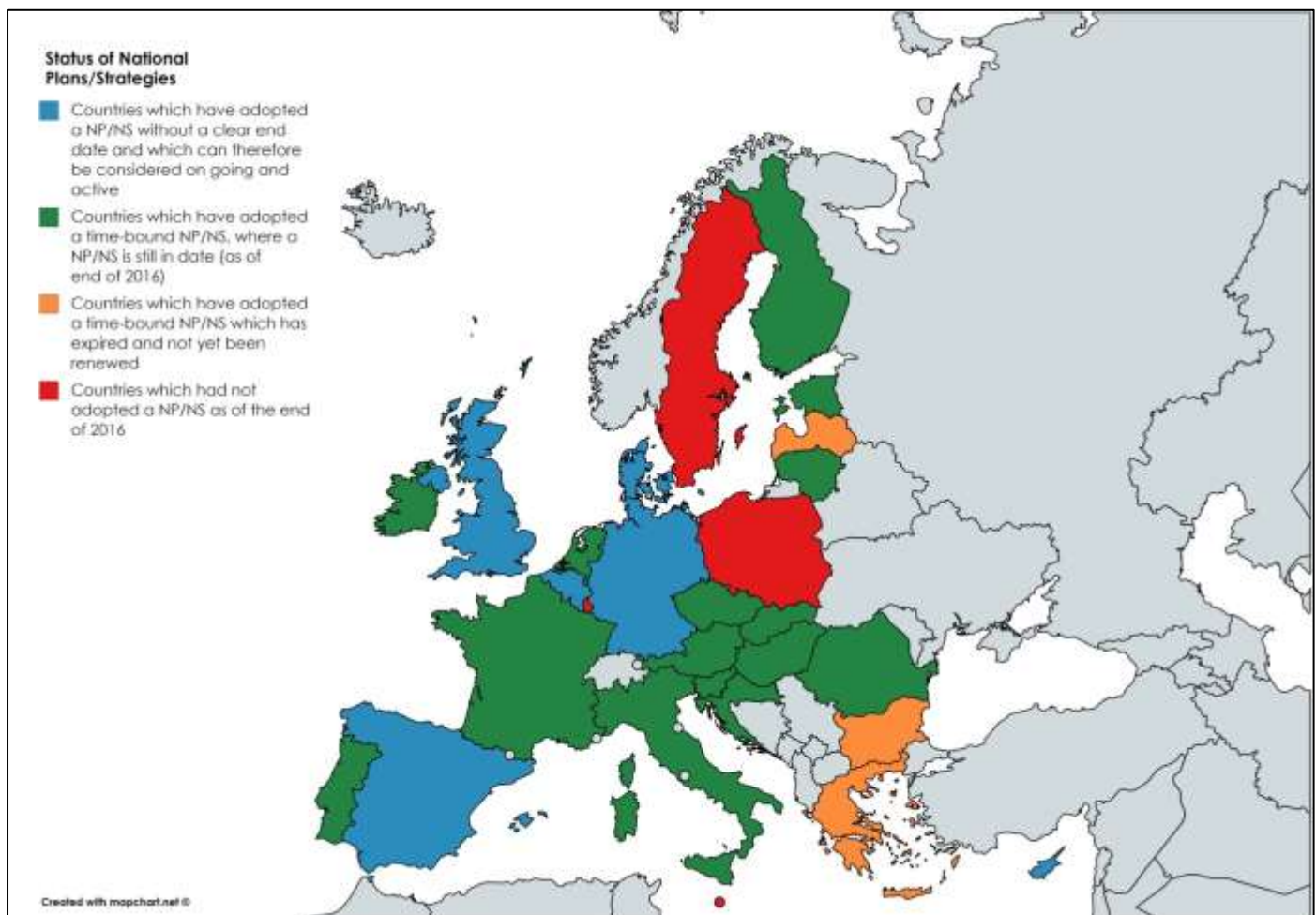


Fig. 2 – Status Quo of National Plans and Strategies for Rare Diseases in EU MS, as of end of 2016.

More information on the status of NP/NS will be available via the dedicated output 'state of the art of national plans and strategies for rare diseases in Europe' (Summer 2017)

1.3. Political framework in other world regions

Outside of Europe, an increasing number of countries have developed a political framework in the field of rare diseases. Quite often, these initiatives concern the regulation of orphan medicinal products. Policies for orphan medicinal products emerged as early as 1983 in the United States with the adoption of the Orphan Drug Act, followed by Japan and Australia in 1993 and 1997.

Europe followed suite in 1999 with the implementation of a common EU policy on orphan medicinal products via **Regulation (EC) N° 141/2000**. The Council Recommendation on an Action in the Field of Rare Diseases (2009) asked all European MS to elaborate and adopt as soon as possible, but by the end of 2013 at the latest a national plan or strategy for rare disease designed to guide and structure RD activities within the framework of the health and social systems. France set an important precedent here, with the adoption of its first French National Plan for Rare Diseases in 2008. Considered a model by other Member States, the number of European countries having adopted a NP or NS rose to 24 in 2016. More importantly still, countries around the world were inspired to contemplate the elaboration of national plans/strategies for rare diseases. Below, one can find a few examples of existing political frameworks in the field of rare diseases in other world regions outside of Europe.

IMPORTANT –This country-specific information is based primarily upon the updates and articles appearing in the OrphaNews newsletter. It is not intended to be exhaustive, but is merely designed to provide an over view of the most relevant rare disease activities in the following countries.

A) North America

i. USA

In the USA, a rare disease is defined as a condition with a prevalence of fewer than 200,000 affected individuals in the United States, as per the **Rare Diseases Act²⁶ of 2002**.

Research: A flagship of the US rare disease policy framework is the Office of Rare Diseases Research²⁷ (ORDR) established in 1993 within the Office of the Director of the National Institutes of Health (NIH). The mission is to promote cooperation within the NIH to advance research in the field of rare diseases, and also to support cooperation with the regional centres of excellence around clinical research, training, diagnostics, prevention, control, and treatment of rare diseases. On 6 November 2002, the President established the Office in statute (**Public Law 107-280, the Rare Diseases Act of 2002**).

In 2003 the ORDR, established the Rare Diseases Clinical Research Networks²⁸.

The Undiagnosed Diseases Network²⁹ was launched in 2008 and is funded by the NIH Common Fund. Coordinated by the Department of Biomedical Informatics at Harvard Medical School, it operates via

²⁶ <http://history.nih.gov/research/downloads/PL107-280.pdf>

²⁷ <http://www.ncats.nih.gov/research/rare-diseases/ordr/ordr.html>

²⁸ <http://rarediseases.info.nih.gov/research/pages/41/rare-diseases-clinical-research-network>

²⁹ <https://undiagnosed.hms.harvard.edu/>

a shared cloud portal through which patients can apply and researchers and clinicians can collaborate. The Undiagnosed Diseases Network International is a new initiative, using this model, designed to:

- Improve the level of diagnosis and care for patients with undiagnosed diseases through the development of common protocols designed by a large community of investigators.
- Facilitate research into the aetiology of undiagnosed diseases, by collecting and sharing standardized, high-quality clinical and laboratory data (including genotyping, phenotyping, and documentation of environmental exposures).
- Create an integrated and collaborative community across multiple Countries and among laboratory and clinical investigators prepared to investigate the pathophysiology of these newly recognized and rare diseases

In October 2015 the FDA announced it had awarded 21 new clinical trial research grants totalling more than \$23 million over the next four years, to boost the development of products (drugs, biologics, medical devices, or medical foods) for patients with rare diseases.³⁰ These new grants were awarded to principal investigators from academia and industry working on both national and multinational trials. The grants were awarded through the Orphan Products Clinical Trials Grants Program.

In early 2016, the NIH National Human Genome Research Institute (NHGRI) announced³¹ plans to create new Centres for Common Disease Genomics (CCDG) and to support the next phase of the Centres for Mendelian Genomics (CMGs created in 2011) Pending the availability of funds, the plan was to fund the CMG programmes (specifically for rare diseases) via approximately \$40 million over a four year period. NHGRI also announced the intention to fund a new Coordinating Centre for approximately \$4 million over four years to facilitate research collaborations among the programme grantees, and to contribute to data analysis and program outreach.

The NIH in February 2016 released its strategic fiscal plan for 2016-2020 which placed a heavy focus on funding research and development in the field of rare diseases. The plan sought to help and support those patients within the NIH Clinical Centre's Undiagnosed Diseases Program.

Orphan Drug Legislation

The US was the first country world-wide to pass legislation on 'orphan drugs' – the 1983 'Orphan Drug Act'³² defined the term with regards to the prevalence (frequency) of the disease for which it is indicated within the American population. In the US, the concept of 'orphan drug' supersedes pharmaceutical or biological products to also cover medical devices and dietary products. The OOPD³³ (Office of Orphan Products Development) within the FDA (Food and Drug Administration) is in charge of promoting the availability of safe and efficacious products for the treatment of rare diseases in the US. The receipt of 'orphan' status allows the drug sponsor to benefit from incentives for the development of these products, up to the point of marketing approval. The measures apply to all stages of the drug development process, and include:

- Tax credits on clinical research;
- Technical assistance during the elaboration of the application file necessary for marketing approval
- Simplification of administrative procedures (reduction of the waiting period and reduction in registration fees);

³⁰ <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm525468.htm>

³¹ <https://www.nih.gov/news-events/news-releases/nih-genome-sequencing-program-targets-genomic-bases-common-rare-disease>

³² <http://history.nih.gov/research/downloads/PL97-414.pdf>

³³ <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm>

- Marketing exclusivity for 7 years after the marketing approval is granted.

In July 2012, President Barack Obama signed into law the **U.S. Food and Drug Administration Safety and Innovation Act** (FDASIA), which was hailed by the USA's National Organization for Rare Disorders as *"the most ground-breaking measures for rare disease patients and their families since the Orphan Drug Act of 1983"*. The Act ushered in several significant changes including *"accelerated patient access to new medical treatments; the development of Humanitarian Use Devices, or medical devices for small patient populations; accelerated development of "breakthrough therapies"—those that show early promise; enhanced consultation with rare disease medical experts; a rare paediatric disease priority review voucher incentive program; and resolution of conflict-of-interest issues related to FDA advisory committee participation"*³⁴

Also in 2012, Congress introduced the **Ultra-orphan Life-saving Treatments Act of 2012 - or ULTRA Act-** which was designed to promote the discovery and development of safe and effective drugs and biologics to treat ultra-rare diseases (those affecting 6000 or fewer). It was intended to open-up the Accelerated Approval pathway to drugs for extremely rare conditions. The legislation was supposed to empower the FDA to consider the full scope of existing scientific data when reviewing surrogate endpoints for use under the Accelerated Approval pathway, instead of requiring prior clinical data which is nearly impossible to collect for ultra-rare diseases.

In 2013, the rare disease community in America celebrated thirty years of the Orphan Drug Act. This same year the FDA made a number of minor revisions³⁵ to the Act to bring its definitions up to date and to eliminate ambiguity. The consultation process began in October 2011.

- One of the key was to redefine an orphan subset: *"use of the drug in a subset of persons with a non-rare disease or condition may be appropriate but use of the drug outside of that subset (in the remaining persons with the non-rare disease or condition) would be inappropriate owing to some property(ies) of the drug, for example, drug toxicity, mechanism of action, or previous clinical experience with the drug"*.
- Another important clarification concerned the issue of whether an orphan drug would retain its designation -and hence the special marketing protection- if it had more than one indication which meant it finally treated more than 200,000 patients. The final ruling was that as long as each patient population for which the drug is indicated is less than 200 000, the drug would still have the protections under the Orphan Drug Act. This, however, does not extend to distinct stages of the same disease (for example, cancer), unless an acceptable justification is provided.
- The FDA also attempted to address so-called "evergreening" of drugs, where some companies try to obtain extended periods of patent exclusivity exceeding the approved 7 years by changing a component of the drug, or simply changing the dose. However, no resolution was obtained on this as according to the FDA some dose changes may be *"eligible for their own seven-year period of orphan exclusive approval"* due to its advanced nature.
- The final rule also removed language which implied that clinical superiority would require direct comparison with approved drugs. FDA also urged sponsors to include only *"relevant"* in-vitro laboratory data, and *"clinical experience"* in their application, except in cases of *"well-documented case histories or significant human experience with the drug"*.

Early in 2017,³⁶ the Centre for Drug Evaluation and Research (CDER) at the FDA, which oversees the approval of small molecules and antibodies, reported the approval of 22 novel drugs in 2016 (either as new molecular entities under New Drug Applications or as new therapeutic biologics under

³⁴ <http://www.orpha.net/actor/EuropaNews/2012/120901.html>

³⁵ <http://www.gpo.gov/fdsys/pkg/FR-2013-06-12/pdf/2013-13930.pdf>

³⁶ <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM536693.pdf>

Biologics License Applications). 9 of these 22 novel drugs (41%) were approved for rare or 'orphan' diseases.

Patient Alliance

2013 also marked the 30 year anniversary of the patient organisation NORD (the National Organization for Rare Disorders), which made pioneering efforts to increase awareness about rare diseases and continues to provide support to the stakeholders in the rare disease community.

Rare Diseases Registration: The ORDR launched a pilot project in 2012 to establish the Global Rare Diseases Patient Registry and Data Repository (GRDR)³⁷. The goal was to establish a data repository of de-identified patient data, aggregated in a standardised manner, to enable analyses across many rare diseases and to facilitate various research projects, clinical studies, and clinical trials. This should facilitate drug and therapeutics development, and improve the quality of life for the many millions of people who are suffering from rare diseases. By 2016, the GRDR had agreed Common Data Elements (CDEs) organized into 10 categories that include required and optional elements, and has launched consent forms and information resources.

ii. Canada

The Canadian Organization for Rare Disorders (CORD) released Canada's first **Rare Disease Strategy on Parliament Hill on May 25, 2015**, which was the result of cross-Canada consultations and contributions from a wide range of stakeholders, including governments, researchers, individual patient organizations, policy experts et. al.³⁸ The Strategy's main priorities are as follows:

- the implementation of the federal Orphan Drug Regulatory Framework
- a tailored evaluation and funding approach to ensure timely and equitable patient access to orphan drugs
- definition of Centres of Excellence, to generate and support research and patient care, which could be linked through a new Canadian Partnership for Rare Diseases or reference network.
- dedicated and increased research funding for rare diseases, potentially through Public Private Partnerships, and allocated resources for patient organizations and ORPHANET
- adoption of a national program for Newborn Screening with clear guidelines for adding new diseases based on evidence and international best practices

Meanwhile, Canadian stakeholders are still awaiting the federal **Orphan Drug Regulatory Framework** promised by the Federal, Provincial and Territorial Health Ministers. The Initial Draft Discussion Document for a Canadian Orphan Drug Regulatory Framework was released publicly on 13 December 2012 for review and comment but nothing concrete has yet been emerged on the policy level.

³⁷ <http://www.ncats.nih.gov/grdr>

³⁸ http://www.raredisorders.ca//content/uploads/CORD_Canada_RD_Strategy_22May15.pdf

On the research and diagnostics front, an important global matchmaking portal, **PhenomeCentral**, was created in 2014 and is co-led by Michael Brudno and Kym Boycott. PhenomeCentral³⁹ was developed by the Centre for Computational Medicine at the Hospital for Sick Children in Toronto, Canada, and was launched on Rare Disease Day 2014. PhenomeCentral is a novel online system that securely and effectively allows data-sharing to match patients with similar genotypes and phenotypes, no matter where they live in the world. The aim is to connect clinicians and scientists worldwide working on similar cases, thereby speeding up the discovery of genes responsible for rare disorders. PhenomeCentral is funded by the **Canadian Institutes of Health Research (CIHR)**, **Genome Canada**, the **Ontario Genomics Institute**, as well as the **Natural Sciences and Engineering Research Council (NSERC)** through the Collaborative Health Research Program. Global partners of PhenomeCentral include the NIH Undiagnosed Diseases Program in the United States, CARE for RARE Australia, Finding of Rare Disease Genes (Canada), RD-Connect (Europe and Australia), and the International Rare Disease Research Consortium (IRDIRC).

In late 2014, Canadian basic research for rare diseases received a boost: the Canadian Institutes of Health Research (CIHR), in partnership with Genome Canada, awarded CAD 2.3 million to the Canadian Rare Diseases Models and Mechanisms (RDMM) Network to investigate molecular mechanisms of rare diseases. The aim of the RDMM network is to investigate biological mechanisms underlying rare diseases at the genetic level in model organisms such as yeast, worms, flies, fish, and mice to gain insights on rare disease mechanisms and advance our knowledge towards elucidating molecular mechanisms of treatment options in some cases. The RDMM Network comprises basic science researchers studying gene function in model systems and clinical scientists discovering novel disease genes in Canada.

The Canadian Organization for Rare Diseases was one of the founding members of Rare Disease International – a global voice for rare disease patients – which launched on 24 May, 2015.

B) South America

Although Latin American countries have come relatively “late to the game” in terms of legislation surrounding rare diseases, there are efforts underway to adopt strategies relating to orphan drug legislation similar to those in the EU and US, to support drug development in the region. *F1000 Research* published a review⁴⁰ which contrasts the market access issues associated with orphan drug status in Europe and the United States with the legislation in five Latin American (LA) countries that have made strides in this regard: Mexico, Brazil, Colombia, Chile and Argentina.

i. Argentina

In 2001 the Geiser (Grupo de Enlace, Investigación y Soporte - Enfermedades Raras) Foundation was established, as the first NGO for rare diseases. Geiser also encourages and supports other countries to take action, such as Chile, Uruguay, Brazil, Panama and Mexico, where rare diseases laws are also being elaborated.

³⁹<https://www.ncbi.nlm.nih.gov/pubmed/26251998> and <https://www.phenomecentral.org/About>

⁴⁰<https://f1000research.com/articles/4-57/v1>

Over the last five years, Argentina has adopted specific policies and legislation to improve the care and research for rare diseases. On 29th June 2011 the first national legislation for rare diseases was endorsed by the Argentinian Senate and House of Representatives. This legislation - **Law No. 26.689**⁴¹ - defines rare disease as conditions affecting no more than 1 per 2000 (i.e. it adopts the EU definition). It stipulates that the health system and public/private social security schemes must provide specific support for patients with a rare disease and calls for specific actions such as:

- the establishment of a national patient registry
- establishment of a Newborn screening programme
- the creation of a central coordinating committee.

The extent to which the law is being implemented is being monitored with interest by the rare disease stakeholder community in Argentina. An important step in the development and marketing of orphan medicinal products occurred in 2012, when the drug and food regulatory agency (ANMAT) created a commission for the evaluation and authorization of drugs for rare conditions: **Decree 4622/2012**⁴² mandates intensive post-marketing surveillance for orphan drug approval.

Argentina is making use of telemedicine methods to support training and education in rare diseases: in May 2015 the National Programme for Rare Diseases and Congenital Defects of the Ministry of Health of Argentina launched an interactive course on Rare Diseases aimed at strengthening the diagnosis of low prevalence diseases. The course duration is six months and it is intended for paediatricians, family medicine and GP residents of public hospitals. The training will be conducted through online discussion of clinical cases and biweekly telemedicine meetings⁴³.

ii. Peru

Peru established its first national law concerning patients with rare diseases in the Summer of 2011. **Law 29698**⁴⁴ promotes treatments for rare conditions and includes a national strategy encompassing diagnostics, surveillance, prevention, care, and rehabilitation. While Peru has not developed a precise definition based on prevalence, this legislation – resulting from the efforts of the Geiser Foundation, Peruvian rare disease patient groups, and policymaker Michael Urtecho - was considered a big step forward for rare disease patients in Peru.

On July 22 2011, the Ministry of Health issued **Ministerial Resolution No. 579-2011 / MINSA**, stating that the last day of February each year should be celebrated as the ‘National Day of Rare or Orphan Diseases in Peru’.⁴⁵

In 2014 the MoH published a list of 399 rare and orphan diseases, divided into four groups according to the priority and difficulties of addressing the conditions.⁴⁶

⁴¹ <http://servicios.infoleg.gob.ar/infolegInternet/anexos/185000-189999/185077/norma.htm> and <http://www.fundaciongeiser.org/wp-content/uploads/2011/11/Boletin-oficial-Ley-en-Argentina.pdf>

⁴² <http://www.alua.org.ar/DISPOSICION%20%204622-2012%20ANMAT.pdf>

⁴³ See <http://www.cibersalud.gob.ar/>

⁴⁴ <http://www.orpha.net/actor/EuropaNews/2011/doc/PeruLaw.pdf>

⁴⁵ <http://www.minsa.gob.pe/erh/index.html>

⁴⁶ <http://lainfo.es/en/2014/02/23/published-list-of-399-rare-diseases-in-peru/#more-3953>

Several activities were organised in 2016, around the date of Rare Disease Day, to support the implementation of the rare disease Law. On 29th February 2016 the Peruvian Congress organised sessions entitled *Management for the 'humanisation' of rare diseases* and *A Multidisciplinary approach: bio, psychosocial*. In March 2016, the MoH held a seminar to discuss the implementation of the measures stipulated in the Law 29698.⁴⁷

iii. Colombia

The first **Orphan Disease Law – Law 1392-** was ratified in Colombia in July 2010, and guarantees medical care and social protection for people with a rare disease.

In 2011 the Colombian Federation of Rare Diseases (FECOER) was established⁴⁸ and since then has been a strong voice of patient advocacy for the rights of people with rare diseases. Also in 2011, a second relevant piece of legislation, **Law 1438**, was adopted, defining an orphan disease as a condition which is chronically debilitating and life-threatening and affects no more than 1 per 2000 people. The ministry of Health and Social Protection maintains a list of all conditions considered rare, ultra-rare and Orphan in Colombia.⁴⁹ In 2013 the Ministry conducted a census of patients with orphan diseases, in which 13,168 cases were reported.

In 2015, the passage of the Statutory Health Law confirmed that access to healthcare was a fundamental right. The law opened the possibility of access to treatments still in development and also to treatments not yet registered in Colombia, both of which have significant ramifications for rare diseases. On the OMP front, an important step came in 2015 when Mercosur -an important Latin American trading bloc- created a platform for the joint acquisition of high cost medicines, including orphan medicinal products. Colombia is *not* signed up to Mercosur, however joint purchases are open to any country that wishes to participate, and it is a route to obtaining high-cost medicines with significant discounts.⁵⁰

iv. Brazil

The first Ibero-American Congress on Rare Diseases (CIADR), organised by the Associação MariaVitoria (AMAVI), was held on 25 September 2013 in Brasília, Brazil. This event was the first of its kind in Brazil with more than 1500 participants from all sectors including academia, government, industry and patient associations. The focal topic of this conference was the need to create public policies for a population of up to 16 million Brazilian citizens.

A working group meeting took place after the CIADR Congress on 25 October 2013 to discuss the creation of a specific policy to benefit rare diseases patients. This meeting was attended by 30 stakeholders from different sectors. The working group expressed a strong interest in creating a policy that will help to establish reference centres for rare diseases. Additionally, the Minister of

⁴⁷ : <http://www.rarediseaseday.org/country/pe/peru>

⁴⁸ <http://www.fecoer.org/>

⁴⁹ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4367080/> and <https://cuentadealtocosto.org/site/index.php/patologias/9-patologias/24-enfermedades-huerfanas/?template=cuentadealtocostocontenido>

⁵⁰ <https://decisionresourcesgroup.com/drg-blog/rare-diseases-a-colombian-perspective/>

Health has committed to the creation of a Technical Group for Rare Diseases, which was finalised during the event of World Rare Disease Day on 2 February 2012, in Brasilia.

In 2014, the Ministry of Health published **Ordinance No. 199**,⁵¹ a '**Policy for the Integral Attention to Subjects with Rare Diseases**'. The policy defines a rare disease as a condition affecting up to 65 in every 100,000 individuals, or 1.3 per 2,000 individuals. The policy defined the two main axes, genetic and non-genetic rare diseases. In addition, it divides the genetic rare diseases into the following: congenital anomalies & late-onset diseases; intellectual disability; and metabolic disorders. The policy mandates several provisions for public health (SUS) provision of specialised health services for rare disease patients, including the following:

- Where possible, patients should be treated at a reference centre: in the absence of appropriate Centres of Reference for rare diseases, the executive branch can create the necessary centres, or enter into agreements with federal, state and local government agencies or institutions, with a view to providing these services.
- The Policy clarifies the criteria for the Reference Centres for Rare Diseases, which include an ability to evaluate patients, to perform genetic testing procedures, to diagnose, treat and offer genetic counselling to patients, to follow the principles of evidence-based medicine and to adhere to MoH protocols for identified rare diseases.
- The Policy defines an annual plan of action and financial and logistical support.
- It proposes the establishment of a national database/registry.

Another area of focus is the creation of rare diseases protocols/guidelines. The Brazilian HTA Body, CONITEC, launched a public consultation in 2015 and approved a list of 43 rare diseases deemed the most 'frequent and important' rare diseases in Brazil. CONITEC also agreed to elaborate 12 Clinical Protocols and Therapeutic Guidelines for rare disease treatments before the end of 2015⁵².

C. Asia

i. Japan

Japan holds the distinction of having the oldest programme for rare disease research and care in the world. Established in 1972, the **Medical Care Program for Specific Diseases** encompasses 'Nanbyo' (Intractable Diseases) and the closely-related 'Tokutei Shikkan' (Specified Rare and Intractable Diseases)⁵³. Japan's Nanbyo programme includes any troubling, untreated disorder, though the vast majority of conditions it accepts – determined by a consultative committee - are rare. While historically infectious diseases such as cholera or tuberculosis were once considered Nanbyo, today the intractable diseases are defined as those *"...that have resulted from an unidentifiable cause and, without a clearly established treatment, have a considerably high risk of disability"* and *"...that chronically develop and require a significant amount of labour for the patient's care, causing a heavy burden on other family members of the patient, both financially and mentally"*. Requests for inclusion can come from medical professionals as well as the patient organisations. Diseases taken

⁵¹ http://bvsms.saude.gov.br/bvs/saudelegis/gm/2014/prt0199_30_01_2014.html

⁵² <https://www.ihs.com/country-industry-forecasting.html?ID=1065999046>

⁵³ <http://www.nanbyou.or.jp/english/index.htm>

up under the programme receive funding for research and allow patients full health coverage. Currently, of the 130 disease groups covered under the Nanbyo programme for clinical research, 56 diseases in the Tokutei Shikkan programme receive specific subsidies from public funding. Some 650,000 patients benefit from medical expense support in Japan.

On 1 October 1993, the Japanese government revised the pharmaceutical law by introducing special provisions relative to research and development of orphan drugs, including financial subsidies for clinical and non-clinical research, exclusive marketing rights for 10 years, and tax credits for research as well as reduction in corporate tax, in addition to priority review, fast track approval, free protocol assistance and user-fee waivers. According to these new provisions, **orphan drug status can be granted to a drug, provided it fulfils the following two criteria:**

- The disease for which it is intended must be incurable. There must be no possible alternative treatment (or the efficacy and expected safety of the new drug must be excellent in comparison with other available drugs.)
- The number of patients affected by this disease in Japanese territory must be less than 50,000, which corresponds to a maximum incidence of 4 per 10,000-.

The Japan Intractable Disease Information Center was established as a collaborative effort of the Ministry of Health, Labour and Welfare and the Japan Intractable Diseases Research Foundation aimed at disseminating information about rare diseases in Japan.

In 2013, the committee for the rare and intractable diseases in Japan generated a proposal for intractable disease for the Commission for Specific Disease Control under the Health Science Council. This proposal was accepted on 31 January 2013. The objective of the proposal was to reform the current policies on intractable disease by improving the quality of the development of effective treatment methods, introducing a fair and stable medical expense subsidy system, and enhancing awareness among the public. To accomplish these objectives, the committee recommends increasing the number of reimbursed intractable disease treatments from 56 to 300, and to provide comprehensive long-term care and social support for patients with intractable disease. To ensure fairness, the committee recommends narrowing the subsidy beneficiaries only to patients facing a severe disruption to lifestyle. The committee also placed great importance on strengthening research and promoting comprehensive and strategic study of intractable diseases.

On 10th March 2014, the Japanese Ministry of Health, Labour and Welfare and the Japanese Pharmaceutical and Medical Devices Agency joined the EMA and the FDA in organising a worldwide orphan medicine designation workshop, held at the EMA offices. The workshop aimed at enhancing efficiency and avoiding ambiguity between the agencies and sponsors by highlighting 3 areas: the process of granting orphan medicine designation in each jurisdiction; the post-designation incentive programmes (accessible after receipt of designation); and the grants available through the FDA, European Commission and NIBIO (Japan) intended to boost research and development in the therapeutic management of rare diseases. In Japan, the National Institute of Biomedical Innovation (NIBIO) provides grants after a product is granted an orphan drug designation. Only Japanese companies are eligible to apply for this grant which is available for a maximum of 3 years and contributes half of the actual costs required to develop the drug. It is possible to obtain five major incentives for the development of orphan drugs in Japan, including subsidy payment, guidance and

development, preferential tax treatment, priority review and extension of the re-examination period.

Japan is increasingly investing in innovative medicine and research. In late 2015, Japan's cabinet allocated ¥82.5 billion to the Ministry of Health, Labor and Welfare to launch several initiatives which included promoting the development of innovative drugs, developing an information database for pharmacovigilance, and strengthening the capacity of the Pharmaceutical and Medical Devices Agency (PMDA).

Stimulating the growth of Genomic medicine in Japan is also a key part of this strategy: in 2016, Japan's Agency for Medical Research and Development (AMED) launched an Initiative on Rare and Undiagnosed Diseases (IRUD). This is a nationwide consortium designed to support the networking of patients, medical doctors at hospitals and community clinics, and researchers. A particular focus is placed on exploiting the information obtained by genome analysis to provide diagnoses to patients with rare and undiagnosed diseases. The IRUD follows the model of the Undiagnosed Diseases Program in the US NIH and the Deciphering Developmental Disorders project in the U.K. A major goal is the establishment of a genome database of people with rare diseases.⁵⁴

ii. Singapore

Singapore was also an 'early adopter' in terms of orphan drug policies, as demonstrated by the **Medicine Order ('Orphan drugs Exemption')** which came into force at the end of 1991. This important legislation provided a definition of orphan drugs and of the legal framework for imports into Singapore. A rare disease is defined in Singapore as a life-threatening and severely debilitating illness affecting fewer than 20,000 persons. An orphan drug is a medicinal product which has been identified by any doctor or dentist as an appropriate and essential remedy with no effective substitute for the treatment of a rare disease. The product should not hold a previous product licence under the Medicine Act and should be approved by the competent Health Authorities either from the country of origin or from any other country where the orphan drug has been used. Orphan drugs importers must maintain proper records, including:

- The quantity imported or supplied;
- The date of reception or supply;
- The name and address of the person for whom the orphan drug is provided.

In addition, any other drug imported must be kept in a hospital and be under the charge and control of a 'custodian' who must be a physician, dentist or pharmacist appointed by the hospital. Any doctor or dentist who requires an orphan drug for the treatment of their patient suffering from a rare disease may request the custodian to provide them with the drug. So far, there have been no other incentives, such as marketing exclusivity or subsidies in the orphan drug policy. To date, there is no national strategy or plan for the management of rare diseases in the health and social systems of Singapore.

⁵⁴ <http://www.amed.go.jp/en/program/IRUD/>

The Rare Disorders Society (Singapore) was established in 2011 as an alliance open to patients with any rare diseases. Singapore provides a national newborn screening programme for more than 25 rare metabolic disorders.⁵⁵ In February 2015, Singapore hosted the first Rare Disease Asia Conference in February 2015. The conference united 25 patient organisations from 13 countries.

iii. Taiwan

Taiwan adopted its **Rare Diseases Control and Orphan Drugs Act** in 2000⁵⁶. This watershed legislation comprised 36 articles, covering many topics: the acquisition of orphan drugs; R&D; manufacturing orphan drugs; diagnosis and treatment of rare diseases; prevention of rare diseases; cooperation with international rare disease organisations; and the subsidised supply of specific pharmaceuticals and special nutrients. It specifies a 10 year marketing exclusivity period in Taiwan for pharmaceuticals approved as orphan drugs.

Rare diseases are defined in Taiwan as conditions with a prevalence of less than 1 person in 10 000, which are difficult to treat and are genetic in origin. To be *officially* recognised as having a rare disease, patients can apply through their doctors or medical institutions by presenting a rare disorders report sheet (including suspected cases), abstract of the disease, and related medical essays to the Bureau of Health Promotion, Department of Health, Executive Yuan to proceed with the application. Patients that have been acknowledged officially as having rare diseases can apply for reimbursement for the medical expenses incurred in a local medical centre, or regional teaching hospitals. Expenses include diagnosis, treatment, drugs, and special nutritional supplements. The reimbursement cap is 70% of actual expenses but families that qualify for low-income status can receive reimbursements up to 100% for drugs and nutritional supplements for the patient.

In late 2014, Taiwan **amended** its **Rare Diseases Control and Orphan Drugs Act** and the Nursing Personnel Act (which also aims to provide additional assistance for rare disease patients, particularly those in a care facility). The changes to the act were designed to guarantee the government's financial backing of supportive and palliative care for people with rare diseases which is not covered by the National Health Insurance (NHI) in Taiwan. The amendments were also geared towards accelerating the review process for required medications to be covered by the NHI, and to establish an emergency drug supply mechanism to combat drug shortages.

iv. South Korea

Although there is currently no specific rare disease legislation in place in South Korea, nor a national plan or strategy for rare diseases, a number of actions have been initiated by the Ministry of Health and Welfare. This includes the establishment of a non-profit organisation Orphan Drug Centre in 1999, supported by the Korean Food and Drug Administration (KFDA which became the Ministry of Food and Drug Safety in 2013), which supplies medications for rare diseases. The KFDA has also

⁵⁵ <https://www.singhealth.com.sg/DoctorsAndHealthcareProfessionals/Medical-News/2007/Pages/Expanded-Newborn-Screening-Using-Tandem-Mass-Spectrometry.aspx>

⁵⁶ http://www.tfrd.org.tw/english/laws/upload/20080328098114_01.html

defined, in an official notice, rare diseases as diseases affecting less than 20,000 people in Korea and which lack appropriate treatment and substitution treatment modalities. An Orphan Drug guideline was established in 2003 which stipulates exclusive marketing rights for 6 years in order to encourage research and development of orphan drugs.

The Ministry of Health established a Genetic and Rare Disease Centre in 2004 which deals with the subsidies for medical expenses related to rare diseases, organises national reference centres (established in 2006) and research in the field of genetic and rare diseases. The Rare Disease Centre also acts as an information centre, and provides a helpline⁵⁷ service for patients: the centre has produced information on around 800 diseases which is regularly updated.

From its inception in 2012, the Korean Rare Disease Knowledge Base (KRDk)⁵⁸ is a web-based, research oriented data repository which seeks to provide the following: comprehensive information for rare disease research; disease review; information on clinics and a laboratory directory; a mutation database; a patient registry, and biobank. Modelled on the genetic database GeneTests (www.genetests.org), this database enables fast querying and prevents the appearance of redundant data. The database uses Orphanet as the main resource for information on rare disease, genetic data and reviews. Most recently, Rare Genomics Korea was initiated to help rare disease patients in South Korea, using a similar model to that of RG USA. The goal is to develop Next Generation Sequencing-based diagnostic services for undiagnosed rare disease patients.

v. China

China has no formal definition of a rare disease: on 17th May 2010 a group of medical experts proposed that a rare disease be defined as a disease affecting 1 person in 10 000, covering genetic diseases in infants. Organisation of care for rare diseases has not yet been formally included in the national health system and special legislation on orphan medicinal products has not been established; current legislation only sets forth general criteria for the acceleration of regulation and approval of specialised drugs, such as those for rare diseases⁵⁹.

On Rare Disease Day 2013, the China Rare Diseases Prevention and Treatment Alliance was launched in Jinan, China. This Alliance is helping to implement a vast pilot project, the Chinese Pilot Project on Rare Diseases Prevention and Treatment (2013BAI07B02), focusing on the provision of better resources for 20 focal rare diseases. 17 medical institutions from 13 provinces in China (covering an estimate population of 0.7 Billion) are involved. The goals may be summarised as follows:⁶⁰

- First overarching goal: organizing experienced medical centres specializing in the 20 focal rare diseases and building their capacity to develop and use guidelines and pathways
 - develop medical guidelines and clinical pathways for those 20 rare diseases

⁵⁷ <http://helpline.nih.go.kr/cdchelp/index.gst>

⁵⁸ <http://www.snubi.org/software/raredisease/>

⁵⁹ *Intractable and rare diseases research in Asia*, P Song et al, BioScience Trends, 2012 ; 6(2):48-51

⁶⁰ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3937133/>

- pilot these rare diseases medical guidelines and clinical pathways in approximately 100 provincial or municipal medical centres within the national collaborative network.
- Submit the revised medical guidelines and clinical pathways to committees of experts from the MOH and Chinese Medical Association for review, to be further applied in hospitals nationwide
- 2nd overarching goal: establish a patient registry and data repository for 20 example rare diseases through the national rare diseases network
 - The inpatient medical records from the medical centres of the network dating from 2003 to 2012 will be retrospectively reviewed to identify cases of the 20 example rare diseases.
 - Newly diagnosed patients with the 20 focal diseases will be prospectively registered from 2013–2016.
 - A data repository of de-identified patient data will be created, using Common Data Elements (CDEs) and standardized terminology.
 - In addition to the above, a web-based open-source patient registry system will be released to the public, as a service to the patient organizations and others, to allow and encourage them to establish additional rare disease patient registries.
- Third overarching goal: establish a molecular genetic testing centre for rare diseases. Initially, nine single gene and seven NGS-based panel analyses covering 15 example rare diseases will be developed to support molecular genetic diagnostic services.

An important step in the development of rare disease policies in China was the launch -on 14 September 2013, during the 1st Chinese Rare Disease Symposium- of the Chinese Rare Disease Research Consortium (CRDRC). More than 20 universities, colleges and institutes and 50 specialists are now members of this consortium. The stated goals of the CRDRC include the following:

- the creation of a national registry for rare diseases in China – 30 million RMB (around 4 million USD) has been pledged towards this
- provision of access to harmonized data and samples
- contribution to the identification of 5-30 rare disease genes per year (and subsequently making genetic testing based on these genes available for patients)
- performing translational research with newly identified genes and facilitating development of therapeutic strategies
- provision of funding support for rare disease research in China by forming an alliance with the China Natural Science Foundation, the Ministry of Science and Technology, and the MoH.
- seeking to launch a Rare Disease Research Institute in China to centralize the rare disease research efforts in China.

Despite these positive initiatives, in 2014 it emerged that China's Food and Drug Administration (CFDA) has imposed regulatory constraints on the provision of clinical genetic tests.⁶¹ The scope of the ban is unclear: there is a blanket ban on prenatal DNA testing, for instance, but the exact scope of what falls inside the ban is ambiguous (e.g. is screening for cancer permitted?).

On 7-9th November 2014 China hosted the 2nd International Rare Diseases Research Consortium (IRDiRC) conference in Shenzhen. The event was organised by IRDiRC in partnership with BGI, to bring together rare disease stakeholders from all over the world to discuss and share experiences and expertise. This international conference was attended by more than 600 participants representing Europe, North America, Australia and Asia.

On 26th December 2015 China's Social Assistance Foundation (CSAF) launched the 'China Child Rare Disease Aid Fund'. This is a special fund for children and young people with rare disease, designed to help them cope with their illnesses and at the same time establish a support system around them.⁶²

In 2016, several articles were published, concerning rare disease policies in China.⁶³ These articles demonstrate increasing concerns over the availability of OMPs in China. Another article from 2016 concluded that *"orphan drugs approved in the U.S., EU and Japan had 37.8 %, 24.6 % and 52.4 % market availability in China, respectively."* There is a particular concern that of the drugs which are available in China, many are not reimbursed and in fact it is argued by the authors that 22 orphan drugs for 14 rare diseases available in China were unaffordable for the most of residents in China. To redress this situation, the authors recommend that a *"social security mechanism for rare disease patients should be established and specific payment pattern for orphan drugs should be set up."*⁶⁴

D. Australasia

i. Australia

An **Australian orphan drugs policy** was established back in 1997, which aimed to ensure the availability of a greater range of treatments for rare diseases. The Australian Orphan Drugs Programme helps manufacturers to overcome the high cost of marketing drugs which have proved to be commercially unviable because of small patient population. Orphan designation is intended for drugs which aim to treat diseases with a prevalence of no more than 2000 patients/subjects in the Australian population (around 18 million inhabitants).

The main characteristics of the orphan drug policy in Australia are:

- A legal framework for orphan drug designation ;
- Waiver of application and evaluation fees and no annual registration fees ;
- A five-year exclusivity period

⁶¹ <http://www.phgfoundation.org/blog/15702/> and <http://www.forbes.com/sites/shuchingjeanchen/2014/03/03/china-cracks-down-on-dna-testing-2/#3e52d5d17407>

⁶² <http://www.orpha.net/actor/EuropaNews/2015/150117.html>

⁶³ <http://ojrd.biomedcentral.com/articles/10.1186/s13023-015-0361-3>; <http://ojrd.biomedcentral.com/articles/10.1186/s13023-015-0333-7>

⁶⁴ <http://ojrd.biomedcentral.com/articles/10.1186/s13023-016-0392-4>

The Federal Government in Australia usually funds treatments and therapies via the PBS (Pharmaceutical Benefits Scheme). However, treatments for rare diseases do not meet the criteria for inclusion in the PBS as they do not meet its cost effectiveness standard. Many RD treatments are instead funded by another scheme, the Life Saving Drugs Program (LSDP). This program was set up in 1995 on the back of an Act of Grace as a means of providing much-needed treatments to people living with very rare conditions. As of October 2016, the LSDP funds **12 medications for the treatment of 8 rare** conditions, for which patients must meet an entrance criteria. This programme is carefully managed, via advisors for each specific condition listed.

The Orphan Drug Policy included a provision to allow the Australian Therapeutic Goods Administration (TGA) to use information from the US FDA Orphan Drugs Program as part of the Australian evaluation process. In 2014 an agreement was also made with the EMA that the two agencies would share the workload for marketing-authorisation applications of orphan drugs, and support scientific exchange to facilitate the evaluation of such medicines. The two regulatory bodies announced that they would henceforth be sharing full assessment reports related to marketing authorisations of orphan drugs. Ultimately however, both regulators will independently determine the suitability of every medicine to be authorised in their respective markets.

In recent years, Australia has also taken steps towards a national strategy for rare diseases. In 2010, a draft of a proposal for a national strategy was made available for consultation on the website of the Australian Paediatric Surveillance Unit. The proposal served as a platform and a framework from which to develop strategies for implementing elements identified by a National Rare Diseases Working Group which are concentrated in eight central priorities:

- Raise awareness of the burden of rare diseases on patients, families, health professionals and the community;
- Provide educational resources and networking opportunities for health professionals to allow them to better identify and manage rare diseases;
- Improve health care for people with rare diseases through access to diagnostic tests, new drugs and other treatments, improved primary care and specialised services;
- Promote research on rare diseases through advocacy for targeted research funds and development of national and international multidisciplinary research partnerships;
- Increase knowledge of the epidemiology and impact of rare diseases in Australia through research;
- Develop and disseminate information to educate patients, parents, carers and the general public, about rare diseases that is relevant in the Australian context;
- Develop an umbrella organisation to support people affected by any rare disease by linking existing organisations to facilitate the coordinated development of integrated peer support networks, contact among families and contact among rare diseases interest groups;
- Advocate to government in partnership with families, for people affected by rare diseases.

A rare disease symposium, entitled *Awakening Australia to Rare Diseases: Global perspectives*, was held in Western Australia on 18-20 April 2011⁶⁵. Building on the work initiated by the Australian Paediatric Surveillance Unit and the National Rare Disease Taskforce, the symposium was an important step in the process of developing a rare disease strategy in Australia. Decisions taken included an endorsement to develop a National Plan; an agreement to form a single overarching advocacy group for rare diseases in Australia; an agreement on the need for national rare disease registries; and an agreement on the need to explore how service delivery could be improved.

In Western Australia, the DoH established the Office of Population Health Genomics (OPHG) to translate new genomics knowledge into the public health system. In 2013 the OPHG working with the DoH began the process of developing a scoping paper to analyse the need for a national rare disease strategy in the country. Unfortunately, the Australian Health Ministers Advisory Council failed to collectively support the recommendation of the Scoping paper, namely that Australia develop a National Rare Diseases Plan: although Western Australia and Northern Territory confirmed their written support, the other states and territories were not in favour.

Nonetheless, the OPHG pushed forwards and adopted the *WA Rare Diseases Strategic Framework 2015-2018* (RD Framework). The strategy was the result of myriad stakeholder consultations and extensive community engagement. It is focused around 4 priorities:

- advance rare diseases planning in Western Australia and Australia;
- promote a person-centric approach throughout WA Health for people living with a rare disease;
 - contribute to a high-quality health system for people living with rare diseases;
 - foster world-class research on rare diseases

Specific actions were launched, regarding a trials centre for innovative treatments for rare diseases, national registries, screening policies and models, and actions around epidemiology. Western Australia health officials are encouraging other jurisdictions to participate in the Orphanet portal.

The 2015-16 Victorian Budget in Victoria, Australia earmarked AUD 25 million to develop a state-wide genomic sequencing programme. The funding has been allocated to the Melbourne Genomics Health Alliance which comprises of the Royal Melbourne Hospital, Royal Children's Hospital, University of Melbourne, Walter and Eliza Hall Institute, Murdoch Children's Research Institute, CSIRO and Australian Genome Research Facility. The Alliance will ensure that up to 2500 children and adults receive early diagnoses of their conditions.

A report⁶⁶ by the McKell institute (2014) concluded that Australia's system of funding rare diseases, conducted by the Life Saving Drug Program (LSDP), is in need of reform. This informative report highlights several challenges involved in bringing treatments for rare disease patients in Australia. The report identifies several problem areas including the fact that there is no common definition for rare diseases in Australia. The report also highlights that only two therapies, Kalydeco for Cystic Fibrosis, and Soliris for Atypical Hemolytic-Uremic Syndrome, are currently approved under Australia's current program for rare disease therapies. Additionally, the report emphasises that Australian rare disease patients wait considerably longer than other western countries to access

⁶⁵ <http://www.ojrd.com/content/7/1/50/abstract>

⁶⁶ <https://mckellinstitute.org.au/app/uploads/McKell-Institute-Funding-Rare-Disease-Therapies-in-Australia-Nov-2014.pdf>

drugs, which sometimes could be as long as 8 years. The report makes five recommendations to overhaul the current program commencing with the formulation of a national strategy for rare diseases. Also recommended is flexibility in the analysis of cost-effectiveness and assessment of new therapies for rare diseases.

ii. New Zealand

The New Zealand Organisation for Rare Diseases (NZORD)⁶⁷ and groups within its network are promoting earlier diagnosis, improved clinical care and disability support, and greater efforts to research health interventions and therapies. In 2012, a proposal was submitted to the National Health Committee for the development of a rare diseases action plan for New Zealand. NZORD decided to investigate the continuing challenges faced by those within the rare disease field. In September 2015 the Patient Support Group survey was launched with the General Practitioner Survey commencing in February of 2016. Overall, both surveys indicated that improvement was required, and in particular there is a need to improve educational resources which could aid both patients and medical specialists.

2016 witnessed the first successful Rare Disease Day event, organised by NZORD, and the launch of SWAN (Syndromes Without a Name). In June 2016, the New Zealand bread industry made significant progress with folic acid fortification (proven to be a safe method of improving maternal health and significantly reducing neural tube defects.)

New Zealand's pharmaceutical management agency [PHARMAC](#), established a rare disease pilot⁶⁸ in 2014, using a NZD 5 Million fund to subsidise high cost treatments for rare diseases, which approved 10 medicines for funding.

E. Russia, Ukraine and Kazakhstan

i. Russia

The All-Russian Society of Rare Diseases was created in 2012 on the initiative of patients, their families and experts. To date, it represents more than 400 patients from 47 regions of Russia with 63 rare diseases.

- The All-Russian Society of Rare (Orphan) Diseases is a member of the international organization for rare diseases, EURORDIS
- It has representatives who take part in international conferences on rare diseases
- [The society] is also a member of the East-European rare disease associations
- The Russian Federation has participated in Rare Disease Day since 2009, involving the general public and stakeholders alike. Events have varied from photo and children's art

⁶⁷ http://www.nzord.org.nz/_data/assets/pdf_file/0004/56695/NZORD-2016-Annual-Report.pdf

⁶⁸ <https://www.pharmac.govt.nz/medicines/how-medicines-are-funded/medicines-for-rare-disorders/>

exhibitions, to roundtables and a drive for signatures advocating for rare diseases. In 2015, an open meeting in Moscow called for greater legislative changes to defend patient rights under the Ministry of Health.

- The Russian Federation has two National Alliances, the National Association of Patients with Rare Diseases "GENETICA" and the Russian Association of Rare Diseases

ii. Ukraine

Ukraine adopted the Law "On Amendments to the Basic Laws of Ukraine on Health to ensure the prevention and treatment of rare (orfannyh) diseases" on April 16 2014. It entered into force on January 1, 2015. The Ministry of Health of Ukraine is instructed to:

- determine and approve the list of rare diseases and provides the official publication of the list;
- in the manner prescribed by the Cabinet of Ministers of Ukraine, create and maintain of the state register of citizens who suffer from rare disease;
- determine the measures necessary to ensure the prevention of rare diseases and establish the procedure of medical care to citizens who suffer from these diseases.

The law defines rare diseases as conditions which threaten human life or have a chronic progression, reduce life expectancy, and have a prevalence in the population not more than 1: 2000.

Ukraine has had a National Alliance 'NGO Rare Diseases of Ukraine' since 2014. Associations in Ukraine have participated in Rare Disease Day since 2008, using the occasion to launch publicity campaigns in major cities and hold conferences to progress Ukraine's National Plan on rare diseases. They also aired a television show based on rare diseases on national television. In 2015, a campaign entitled "Orphan but not rightless" included a photography exhibit in the lobby of the Parliament building in Kyiv, a public demonstration, and a call-to-action letter written by rare disease patients which was presented to the Prime Minister.

iii. Kazakhstan

As per the **Regulation Order of the Ministry of Health n°735 of 18 Nov 2009**, a medicinal product may be considered an orphan drug if it is used "rarely or in less than 10 000 individuals" living in Kazakhstan. As such, the product can be included on the List of Orphan Drugs if:

- Scientific knowledge level at the time of filing application for state registration does not allow to obtain complete information, or
- Obtaining additional information would contradict generally accepted principles of medical ethics.

A positive decision on the registration of orphan drugs is contingent on commitments made by the applicant to:

- Carry out a specific study program (which will be the basis for annual re-evaluation of the benefit-risk ratio);
- Ensure the administration of the medicinal product under strict medical supervision;
- Immediately inform the governmental body of any adverse effects, and measures taken.

During the period in which these commitments are being fulfilled, the MOH will re-evaluate the benefit-risk ratio on an annual basis. The instructions on the therapeutic indications and other information on the registered orphan drug must contain a note on the missing data.

Inclusion of a product on the List of Orphan Drugs will allow the government to allocate funds for state procurement of the product. The Scientific centre of paediatrics and paediatric surgery (SCP&PS) is aiming to establish a national register of rare disease patients in Kazakhstan.⁶⁹

⁶⁹ <https://www.mzsr.gov.kz/en/node/334964>

2. Expert services in Europe

2.1 Centres of expertise in Member States

The concept of Centres of Expertise is of major relevance to the rare disease field, as it encompasses a goal of mapping and understanding the existing rare disease expertise available in countries, but also exacts particular standards and quality criteria necessary in highly specialised care.

DG SANCO (as was) established the High Level Group (HLG) on Health Services and Medical Care as a means of taking forward the recommendations made in the reflection process on patient mobility. One of the working groups of this High Level Group, in collaboration with the EC Rare Diseases Task Force (RDTF), focused on reference networks of centres of expertise for rare diseases. In the context of this working group, a number of criteria for national centres of expertise for rare diseases were defined in 2006⁷⁰ based on the experience of countries with designation processes already in place.

Based upon this work, the EUCERD elaborated a set of recommendations which were adopted on 24 October 2011 as the ***EUCERD Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases in Member States***⁷¹.

The Council Recommendation on an action in the field of rare diseases (2009) asked Member States to “Identify appropriate centres of expertise throughout their national territory by the end of 2013, and consider supporting their creation”. This was deemed especially important, in the lead-up to the creation of European Reference Networks, which would be centred upon expert healthcare providers. Selection and endorsement of national centres to participate in ERNs would thus be facilitated for countries which had agreed formal processes for designating expertise in rare diseases.

The dedicated supplement on centres of expertise for rare disease will be available in summer 2016

2.2. European Reference Networks

The Concept

2016 marked a major watershed for cross-border healthcare in Europe – this was the year in which European Reference Networks (ERNs) matured from concept to reality. In the five years since the publication of the Directive on the Application of Patients’ rights in cross-border healthcare (Directive 2011/24/EU) the concept of an ERN –embedded in Article 12 of the aforementioned Directive- has slowly but surely taken shape, bringing European Member States closer to collaboration and innovation in rare diseases. Under the terms of Directive 2011/24/EU, Europeans are entitled to seek healthcare in a country besides the country of residence, under specific

⁷⁰ <http://www.eucerd.eu/upload/file/Publication/RDTFECR2006.pdf>

⁷¹ <http://www.eucerd.eu/upload/file/EUCERDRecommendationCE.pdf>

circumstances and by following pre-determined procedures. ERNs are Europe's answer to the urgent need for cross-border collaboration in rare diseases, and often the guiding principle is that the patient should not travel unless necessary; instead, the *expertise* should travel, virtually, to enable patients to receive the best possible diagnosis, treatment and care, regardless of where they happen to live, removing the traditional disadvantages of not having the good fortune to live near the specialists in their disease.

EUCERD Recommendations

The EUCERD adopted Recommendations on Rare Disease European Reference Networks on 31st January 2013. The document was the result of a long process of debate and analysis on the part of several stakeholder groups. (In the light of discussion of RD ERNs during the January 2012 EUCERD meeting, followed by a plenary session in June 2012, the EUCERD Joint Action (EJA) organised an expert workshop in September 2012. The outcome of this workshop was a draft set of Recommendations for review and discussion at the November 2012 EUCERD meeting. Following revision, the document was sent to all Members for written review, before a final version was submitted and adopted by EUCERD in January 2013.)

Legal Acts

Once the Recommendations were adopted, the EJA ensured cross-talk, as appropriate, with the Cross Border Healthcare Expert Group in order that the core content of the Recommendations might be considered when elaborating the Delegated and Implementing Acts. The European Commission published the Delegated Decision (2014/287/EU) and Implementing Decision (2014/286/EU) on 10th March 2014. The Delegated and Implementing Decisions were not intended to define or comprehensively address the specific needs of the RD field, but instead to stipulate transversal criteria for networks to fulfil in order to qualify as ERNs and for healthcare providers wishing to join an ERN. Therefore, further work was conducted in order to explore those areas of the EUCERD Recommendations warranting further attention from the EC Expert Group on Rare Diseases in the light of the Delegated and Implementing Decisions. An EJA workshop took place in Rome 28-29th October 2014, to affirm and highlight the importance of these RD-specific needs not defined in the legal Acts but nonetheless essential to support applications for ERNs in the field of RD.

Addendum to the Original Recommendations

At the November 2014 meeting of the EC Expert Group on Rare Diseases, it was agreed that although the Recommendations overall remained highly relevant and comprehensive, two topics should be revisited and elaborated at this stage: the grouping of RD into thematic networks and the necessity of a patient-centred approach to RD ERNs. Accordingly, the Addendum was drafted by the Joint Action for Rare Disease and was **adopted by the CEGRD** in June 2015. The Addendum does two things:

- 1) it defines what meaningful patient participation and engagement in ERNs should entail
 - To advise on planning, assessment and evaluation of Centres of Expertise and European Reference Networks based on their experience, with a consistent approach

- To ensure transparency to quality of care, safety standards, clinical outcomes and treatment options
- To promote and encourage a patient-centric approach in both delivery of clinical care, service improvement and strategic development and decision-making
- To ensure all ethical issues and concerns for patients are addressed, balancing patients' and clinical needs appropriately
- To ensure care is patient-centred and respects patients' rights and choice
- To ensure the application of personal data protection rules, compliance of informed consent and management of complaints
- To ensure feedback on patient experience and the active evaluation of patient experience

2) It seeks to ensure that all RD Patients could find a 'home' within a logical, manageable number of broad ERNs, a disease Grouping model was proposed:

- Rare immunological and auto-inflammatory diseases
- Rare bone diseases
- Rare cancers* and tumours
- Rare cardiac diseases
- Rare connective tissue and musculoskeletal diseases
- Rare malformations and developmental anomalies and rare intellectual disabilities
- Rare endocrine diseases
- Rare eye diseases
- Rare gastrointestinal diseases
- Rare gynaecological and obstetric diseases
- Rare haematological diseases
- Rare craniofacial anomalies and ENT (ear, nose and throat) disorders
- Rare hepatic diseases
- Rare hereditary metabolic disorders
- Rare multi-systemic vascular diseases
- Rare neurological diseases
- Rare neuromuscular diseases
- Rare pulmonary diseases
- Rare renal diseases
- Rare skin disorders
- Rare urogenital diseases

Status Quo as of early 2017

The European Commission launched the first call for ERNs in March 2016. The first call closed in June/July 2016 and 24 applications were submitted. RD-ACTION supported this process through creation of the 'matchmaker' resource, to ensure collaborative, not competing applications. Information about the 24 Networks, their scope and their priorities, is available here <http://www.rd-action.eu/european-reference-networks-erns/coordination-of-rare-disease-erns/> and here - http://ec.europa.eu/health/ern/policy_en

Network Name	Thematic Grouping	Coordinating HCP	Name of Coordinator	Website
BOND	Rare Bone Disorders	Istituto Ortopedico Rizzoli, ITALY	Luca Sangiorgi	ERN-BOND
CRANIO	Rare Craniofacial anomalies and ENT disorder	Erasmus Medical Centre, Rotterdam - THE NETHERLANDS	Irene Mathijssen	ERN-CRANIO
ENDO-ERN	Rare Endocrine Diseases	Leiden University Medical Centre - THE NETHERLANDS	Alberto Pereira	ENDO-ERN
EpiCARE	Rare and Complex Epilepsies	UCL Institute of Child Health - UNITED KINGDOM	Helen Cross	EpiCARE
ERKNET	European Rare Kidney Diseases Reference Network	Heidelberg University Hospital - GERMANY	Franz Schaefer	ERKnet
ERN-RND	Rare Neurological Diseases	University Hospital Tübingen - GERMANY	Holm Graessner	ERN-RND
ERNICA	Rare Gastrointestinal Diseases (Rare Inherited & Congenital Anomalies)	Erasmus Medical Centre, Rotterdam - THE NETHERLANDS	Rene Wijnen	ERNICA
ERN LUNG	Rare Pulmonary Diseases	Klinikum Goethe University Frankfurt - GERMANY	Thomas Wagner	ERN-LUNG
		MAGEC (Centre de		

To-date, three official ERN conferences have been organised by DG SANTE. The 3rd official European Reference Network (ERN) conference took place in Vilnius, Lithuania, on the 9th of March. The following day was dedicated to the kick-off meetings for the 24 thematic European Reference Networks (ERNs). This was a major event, involving approximately 600 delegates.

The development marks a major innovation in care for Europe's 30+ million rare disease patients: although pan-European structures exist in the *research* domain, this is the **first such enterprise in the health sphere**. Entering into 2017, Europe now moves from an era of *hypothetical* ERNs to the actual implementation of the Networks. It will likely take several years for the ERNs to truly reach their potential, and multistakeholder support -as well as political will and commitment- will remain essential over the coming months and years:

- Patients must continue to strive for meaningful input to *all* aspects of Network operations, which should be greatly facilitated by the [ePAGS](#) (European Patient Advocacy Groups), an initiative spearheaded by EURORDIS (which was instrumental in developing the concept of ERNs almost a decade ago);
- Member States must continue to explore how best to link ERNs with existing national structures and pathways for patients, to benefit fully from this new resource;
- The European Commission will hopefully continue to support the ERNs as hitherto, ensuring collaboration across the various units of DG Sante (and beyond) and maintaining its robust—indeed, often tireless— support for a true European innovation;

- [RD-Action](#), the Joint Action for Rare Diseases, will [continue to work with –and for- the ERNs](#), to support them in exploring and addressing their shared challenges around policy issues such as data-sharing, registration, clinical guidelines, therapy development etc.
- Last but not least, it is essential that 24 ERN coordinators are granted time and all possible support, to embrace the huge task of implementing these (brand new) Networks created across broad thematic areas (<http://www.rd-action.eu/european-reference-networks-erns/coordination-of-rare-disease-erns/>)

2.3 Expert Clinical laboratories

Expert clinical laboratories and diagnostic tests are part of quality healthcare in the field of rare disease. Major progress in gene identification has been translated into diagnostic tests. These tests are now being offered internationally, through both public and private sector genetic testing services. Physicians prescribing these tests and biologists receiving the samples need to know which tests are available, where they are performed and whether identified laboratories meet quality standards. To fulfil this need, Orphanet set up a database of medical laboratories in the field of rare diseases in 1997.

Data was originally collected in just 1 country back in 1997, 15 in 2003, 26 in 2006, 36 countries in 2011, 37 countries in 2012/2013 and 39 countries in 2016, with resources from the European Commission. In collaboration with the EuroGentest, a Network of Excellence (financed by DG Research and Innovation), information on quality management has been added to the Orphanet database in recent year. Information on genetic testing in Orphanet can be searched by disease name or by gene (symbol or name in English) as well as by laboratory or by professional. The information provided on laboratories included data on quality management. Information is freely accessible online and access to all data can be granted upon request. Indeed, the data in Orphanet was extremely valuable to the study (<http://www.nature.com/ejhg/journal/v24/n11/full/ejhg201670a.html>) which led to the generation of Recommendations in this are (see below).

The data presented in the Orphanet database concerns tests available in the clinical setting and thus does not reflect the research capacity of a country. Countries regulate to varying extents the number of tests available in the clinical setting, for quality and/or reimbursement reasons. At the beginning of 2017, the 1301 laboratories registered in Orphanet in Europe provided tests for **2897 genes (excluding panels of genes) and 3658 diseases**. The tests offered differs greatly from one country to another:

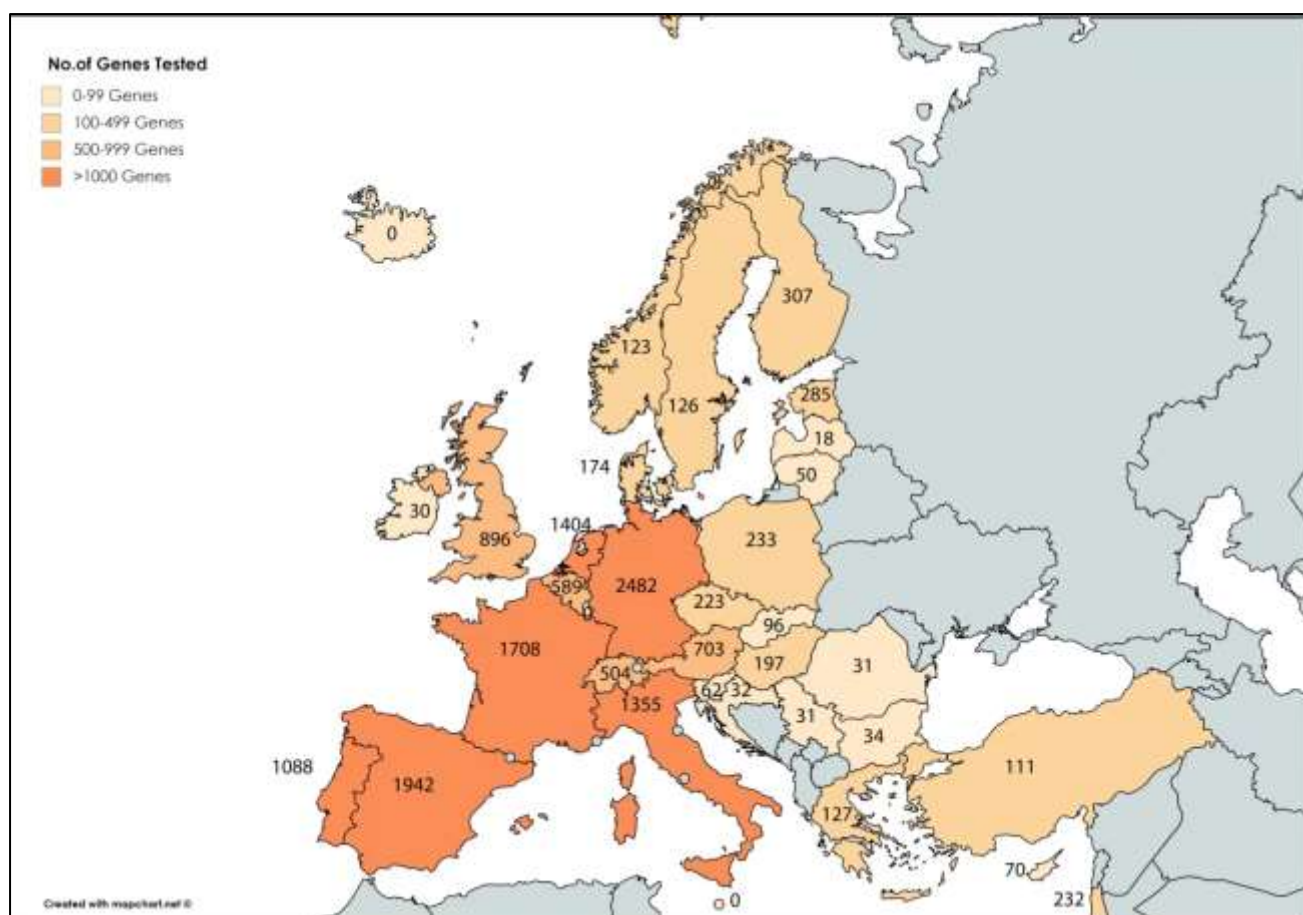


Fig. 3: number of genes tested in each European Country

Country	Diseases tested (excluding panels of genes)	Genes tested (excluding panels of genes)
AT	745	703
BE	547	589
BG	84	34
CH	542	504
CY	96	70
CZ	241	223
DE	2703	2482
DK	240	174
EE	157	285
ES	2224	1942
FI	249	307

FR	1682	1708
GB	972	896
GR	209	127
HR	51	32
HU	240	197
IE	59	30
IL	253	232
IS		
IT	1361	1355
LT	30	50
LU		
LV	18	18
MT		
NL	1319	1404
NO	139	123
PL	338	233
PT	1169	1088
RO	56	31
RS	29	31
SE	194	126
SI	74	62
SK	114	96
TR	163	111

As the table demonstrates, the variation in genetic testing offer between medium and small sized countries in Europe is substantial, and now ranges from 18 diseases and 18 genes (Latvia) to 2703 diseases and 2482 genes (Germany).

These figures alone demonstrate the need for a substantial cross-border exchange of specimens, as concluded by the EUCERD JA study above. Furthermore:

- 519 genes are tested in just one country;
- 1792 genes are tested only in 5 countries or fewer
- 2601 genes are tested in 10 countries or fewer⁷²

⁷² All of these figures refer to single tests, excluding panels. Since 2016, Orphanet has expanded its dataset to make it possible to enter NGS panels into the database. Data collection is underway, but a significant increase in the number of diseases and genes tested can be

In terms of the number of genetic diseases for which countries can test:

- 964 diseases can only be tested in a single country
- 2594 can only be tested in 5 or fewer countries
- 3357 can only be tested in 10 or fewer countries

In accordance with the 2015 Recommendations on Cross-Border genetic testing of rare diseases⁷³ Orphanet now annotates laboratory entries which have provided evidence of their Quality Assurance accreditation: as of January 2017, **263** labs currently have demonstrable quality assurance accreditations, across **20** countries.

3. Research and Registries

3.1 Rare Disease Registration

Data on any rare condition is extremely precious. No single country will see a sufficient number of patients with any very rare disease to fully understand the condition, in terms of its epidemiology (e.g. how many cases exists in any given population), the range of symptoms observed, the development of the disease over time, and the likely outlook for newly-diagnosed patients.

Registries collect information on patients afflicted by a particular disease or group of diseases. By combining data on as many patients as possible, at the regional, national, European or global level, the potency of the data increases exponentially; for example, if a particular symptom (e.g. hearing loss) is noted in 3 out of 5 patient cases collected by a clinician he or she may not feel confident in declaring this to be a typical accompanying feature of condition X. But if noted in 280 out of 300 patients, say, the observation becomes more statistically significant and the association with condition X is clearer. Registries, particularly when used by many different centres, enable researchers to accrue a so-called ‘critical mass’ of patients which would often otherwise be impossible.⁷⁴ Registries can serve many important purposes in the rare disease field; for example:

- By collecting data over a long period of time, registries can elucidate the **natural history** of a disease (i.e. how the symptoms develop and progress, what the prognosis might be, etc.);
- Registries can focus upon the **epidemiology** of the disease i.e. how the disease is caused/what are its origins and its impact in any given population (including its rarity). Such epidemiological information is very valuable in assessing disease threats and informing the appropriate planning of health services;
- They may reveal the most effective and efficient methods of **diagnosing** a particular condition;

observed in the case of France, where the collection of data is complete: in France, tests for 3217 diseases and 3755 genes including NGS panels are entered in the database, compared with tests for 1682 diseases for 1708 genes excluding NGS panels.

⁷³ http://ec.europa.eu/health/sites/health/files/rare_diseases/docs/2015_recommendation_crossbordergenetictesting_en.pdf

⁷⁴ EURORDIS (2013) The voice of rare disease patients: experiences and expectations of over 3,000 patients on rare disease patient registries in Europe. Available at: http://download.eurordis.org.s3.amazonaws.com/the-voice-of-rare-disease-patients.pdf?bcsi_scan_c221d61a0ea4ff4c=0&bcsi_scan_filename=the-voice-of-rare-disease-patients.pdf. Accessed 18 March 2016.

- Registry data can demonstrate the **efficacy of different management and therapeutic options**, presuming information on treatment regime and clinical outcomes is captured. For instance, the dosage of corticosteroids in neuromuscular patients can be compared with the degree of ambulation and mobility. The relative impact of different regimes of enzyme replacement therapy for patients with inherited metabolic diseases can be assessed with reference to liver and spleen volume, for instance;
- Registries -if established in a certain way⁷⁵- can support the **post-marketing surveillance** of (conditionally) approved orphan medicinal products. Increasingly, the safety and efficacy of medicinal products for rare diseases are granted less-traditional (i.e. 'adaptive') pathways to marketing authorisation, in which a drug may be conditionally approved for use based upon a relatively low volume of trial data (often unavoidable in the rare disease field), on the understanding that high-quality robust data will be captured for each patient prescribed that drug for perhaps 10-15 years.
- The correlation between certain genetic mutations and corresponding clinical presentation (phenotype) may be elucidated by registry data. Sometimes patients with the same condition and the same genetic mutation exhibit very different symptoms and experience the disease with varying severity: only by capturing this information routinely and robustly are researchers better able to understand rare conditions and their prognoses by correlating patients' genotypes and phenotypes (in other words, understanding how different combinations of genetic anomalies result in particular clinical presentations).⁷⁶
- Registries are a significant enabler for clinical research, for instance by supporting an assessment of the feasibility of conducting a trial in the first place, and later by facilitating the recruitment of patients. This is particularly useful when registries record an accurate genetic diagnosis (i.e. they stipulate the particular mutation responsible for causing the condition). As medicines and interventions become more personalised, clinical trials often target a specific mutation and therefore need to recruit a particular sub-set of patients. The existence of detailed genotypic information enables a sponsor to assess the number of trial participants they could potentially recruit, and where they are based. This sort of information is critical in supporting the pharmaceutical industry and academic communities to drive forward much-needed clinical research in the rare disease field.

⁷⁵ Hollak, C., Aerts, J.M.F.G., Ayme, S., and Manuel, J (2011) 'Limitations of drug registries to evaluate orphan medicinal products for the treatment of lysosomal storage disorders' *Orphanet Journal of Rare Diseases* 6:16 [DOI: 10.1186/1750-1172-6-16]

⁷⁶ Brookes, A., and Robinson, P. (2015) 'Human genotype-phenotype databases: aims, challenges and opportunities', *Nature Reviews Genetics* 16 [doi:10.1038/nrg3932]

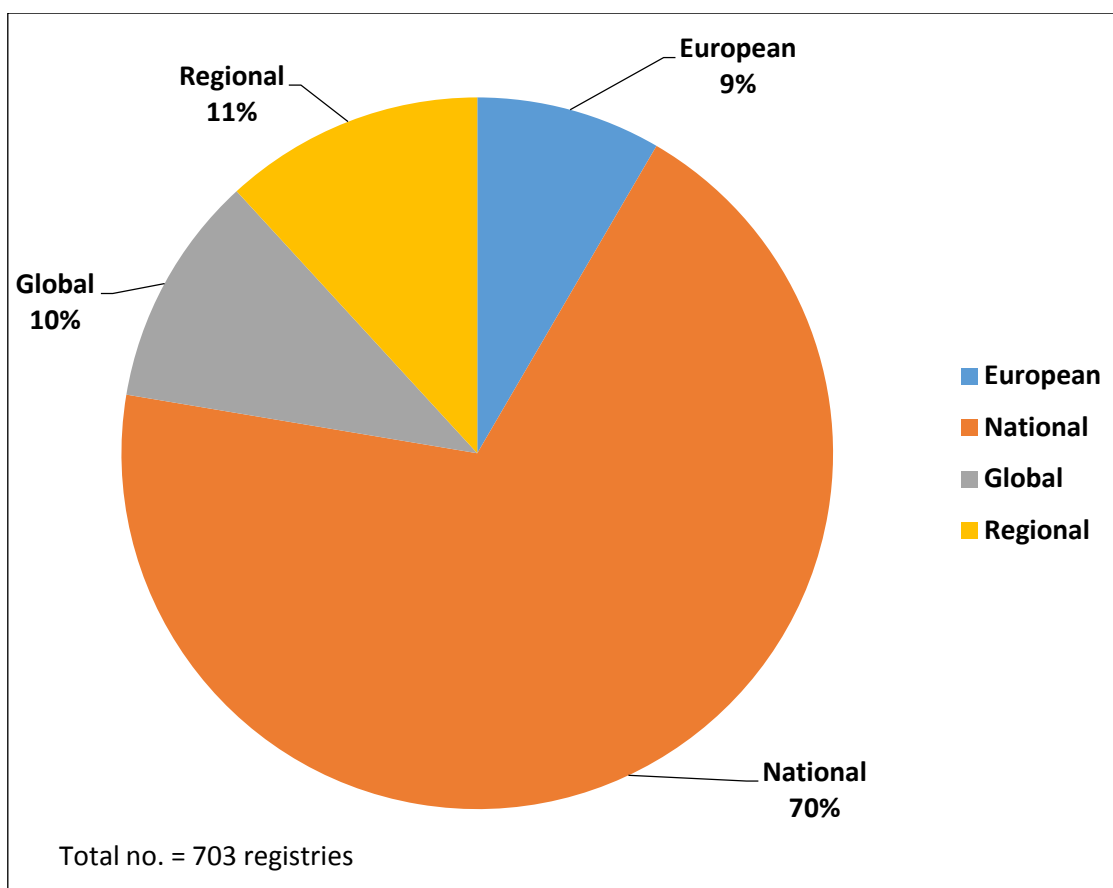


Fig 4: Distribution of European Rare Disease Registries by geographical 'scope', according to the Orphanet database

According to the May 2017 Orphanet Report Series report 'Rare Disease Registries in Europe'⁷⁷, there are 703 disease registries in Europe: 61 operate at the European level; 77 Global; 496 National and 69 Regional. Most of the registries are established in academic institutions. A minority of them are managed by pharmaceutical or biotech companies, with others being run by patient organisations. A full list, based upon the data contained in the Orphanet database, is available here - <http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf>

⁷⁷ <http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf>

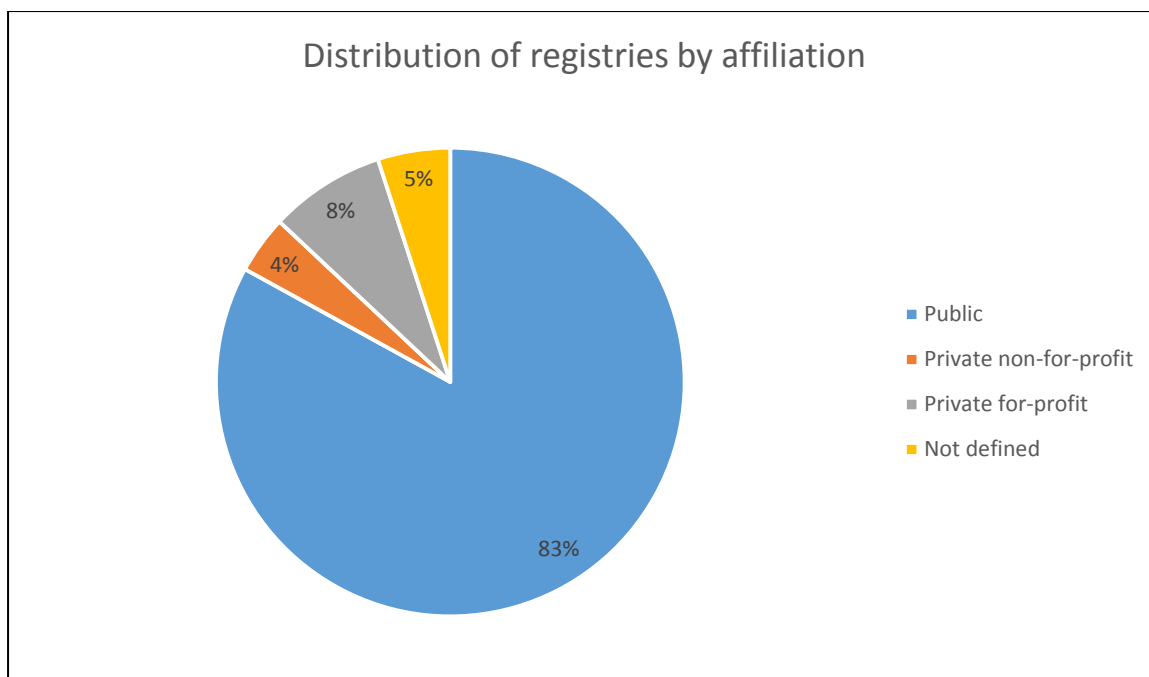


Fig. 5: Distribution of registries by affiliation – information from Orphanet Report Series May 2017
<http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf>

3.1.1 Summary of sample initiatives with particular relevance to Rare Disease Registration⁷⁸

EMA Patient Registries Initiative

EMA launched a new initiative for patient registries in September 2015, with a goal of facilitating interactions between registry coordinators and potential users of registry data, both at an early stage of therapy development and during the MA evaluation procedure and post-authorisation. The Initiative organised its 1st workshop in October, and the report is now available: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2016/08/event_detail_001315.jsp&mid=WC0b01ac058004d5c3. Multiple stakeholders discussed the challenges and barriers to collaboration around registry data and identified specific solutions. The Initiative is exploring issues such as quality requirements for safety and efficacy data in registries used to support Post-Marketing-Surveillance

EPIRARE -EPIRARE <http://www.epirare.eu/project.html> was coordinated by Domenica Taruscio at the ISS in Rome. The project was funded 2011-2014 to build consensus and synergies to address

⁷⁸ NB this is not intended to be exhaustive, but is merely a tool to aid discussion on registry and resources and initiatives with a cross-disease focus on rare diseases

regulatory, ethical and technical issues associated with the setting up and management of registries for Rare Diseases patients in the EU. A major focus was to contribute to prepare a platform for the registration of rare disease patients in Europe and to ensure the quality and best use of the registered data.

EUCERD Joint Action – The EJA was funded from 2012 to 2015 by DG SANTE (SANCO as was) and was coordinated by Kate Bushby in Newcastle University. The EJA and EPIRARE prepared a set of Recommendations on Rare Disease Registration and Data-Sharing http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_RDRegistryDataCollection_adopted.pdf for consideration and eventual adoption by the EUCERD. Under the Registries task of this project, led by Thomas Wagner, two additional outputs were generated A Minimal Data Set for Rare Diseases Registries (http://www.eucerd.eu/wp-content/uploads/2015/03/WP8_Registries_MDS.pdf) with modules of suggested data items depending on the purpose of the registry (4 broad types were posited – a basic registry, clinical (epidemiological), clinical research, or post-marketing registry; and a Thesaurus of Registry Terminology (http://www.eucerd.eu/wp-content/uploads/2015/03/WP8_Registries_Thesaurus.pdf))

FAIR Data principles - FAIR data is a concept, a set of principles, originating outside of the RD field but especially pertinent in domains which necessitate a significant level of data-sharing. FAIR is an acronym, standing for Findable, Accessible, Interoperable; Reusable. The concept was developed by the team of Barend Mons and Marco Roos at LUMC, and it has gained traction globally: Organisations that endorse FAIR data principles include ELIXIR, BBMRI, the European Open Science Cloud, FORCE11, NIH through its ‘commons’ program, and the G20. The FAIR principles acknowledge that actually sharing data between centres and certainly between jurisdictions is challenging, legally. Instead, it promotes making data queryable, which is an efficient -and far more achievable- goal. A key publication is <http://www.nature.com/articles/sdata201618> and there is a useful introduction to using FAIR concepts <https://www.slideshare.net/MarcoRoos/rare-disease-data-linkage-plan-2017-irdirc-2017-presentation>.

Joint Research Centre – European Platform for Rare Disease Registration - In December 2013, the Institute for Health and Consumer Protection (IHCP) at the Joint Research Centre (a research ‘arm’ of the European Commission, based in Ispra Italy) signed an Administrative Agreement to provide a European platform for RD registries. This platform would theoretically be a permanent structure and seems to have two main functions/goals: interoperability and sustainability. The EU RD Platform aims to address the fragmentation of rare disease patient data contained in >600 registries across Europe. To reach this objective, the Platform will support and promote interoperability between RD patient registries by setting European-level solutions for data collection and data sharing. The ultimate goal is to provide a source of information on RD patient data with a large transnational coverage, for all rare diseases. Thus, the Platform will be a knowledge generation centre for rare diseases bringing together providers of information (the

different types of RD patient registries existing at national, regional, local level) and users of information (healthcare providers, researchers, patients, industry, policy makers, etc.).

On the sustainability side: the goal is to provide a central data repository for two long-established surveillance networks, EUROCAT (congenital anomalies) and SCPE (cerebral palsy in children and young people). In total, the team has brought together at least 40 registries for EUROCAT and 20 for SCPE, which has been a complex legal and organisational process. Concerning Interoperability: it is not yet clear what the focus of this platform will be, and precisely what tools and resources it will provide. What does seem clear is that ISPRA will not become a hub for data/CDEs from RD registries in Europe, as once posited, nor a data 'repository' for registries poised on the brink of expiration. No data is expected to travel to and be stored at the JRC for RD registries, besides those associated with the EUROCAT and SCPE surveillance networks, as above. It remains therefore to clarify what exactly constitutes the interoperability aspect of this platform.

PARENT Joint Action - The PARENT Joint Action (Cross-border Patient Registries Initiative) was funded through the Second Public Health Programme from May 2012 until November 2015. The main objective of PARENT was to support European Member States in setting-up, developing and governing patient registries in areas of strategic importance such as chronic diseases and medical devices - rare diseases became an important focus of this work. PARENT was Coordinated by the *National Institute of Public Health of the Republic of Slovenia (NIPH)*, and sought to make registries comparable and interoperable to facilitate the re-use of data for public health and research purposes, thus maximising the potential of patient data in Europe. Example outputs include the [Methodological Guidelines and Recommendations for Efficient and Rational Governance of Patient Registries](#): provides a comprehensive overview of registry design, operation and utility. It explains the various types of registries and provides practical, detailed advice on how to set-up and manage patient registries, covering all aspects of the process. The Guidelines define essential quality components of registries (including but not limited to considerations around data quality). There are specific sections dedicated to the concept of interoperability and how to achieve this, on how to enable secondary use of data for public health policy and research, on sharing data across borders, and more. [Report on the sustainability of cross-border collaboration on secondary use of registry data](#): The consortium explored the use of business models to better understand of the trends and options available for achieving sustainability of registries with a cross-border scope, to support re-use of valuable data. A full list of deliverables is available [here](#)

RD-ACTION - the current Joint Action for rare diseases (2015-18, coordinator Ana Rath) incorporates the topic of RD registration in various ways. For instance:

- It has a WP dedicated to policy and Integration (WP6) which seeks to explore how ERNs might establish/integrate/link registries, and in so doing has attempted to highlight the points of commonality and, most importantly, the *difference* between clinical data and data collected as part of a registry; plus a Taskforce on interoperable data sharing within the operations of ERNs, which is open to the topic of registries (as one of four priorities identified by the eHealth network;

- The Orphanet team is directly responsible for maintaining the OrphaCode – the European agreed nomenclature for coding rare diseases – in an ontology (i.e. computer readable) format, which has particular relevance to registries. According to Orphanet' central database, and a published in the forthcoming mining report on the state of the art of RD activities in Europe, there are 690 disease registries in Europe (59 European, 74 Global, 482 National and 75 Regional). <http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf>

RD-Connect - RD-Connect <http://rd-connect.eu/> is a 6 year initiative, funded under FP7, mandated to establish a platform to support RD research by linking data from biobanks, registries, databases and bioinformatics. It is coordinated by Hans Lochmuller from Newcastle University. The value of RD data is exponentially greater if it can be linked: as an example, it would be very valuable for researchers if data from a single patient, patient X, held in more than one registry or repository, could nonetheless be 'identified' as belonging to one and the same person (anonymised, of course). Similarly, under the data-linkage principles explored in RD-CONNECT, a researcher could also ascertain whether a biobank somewhere contains a biosample from this same patient X (the ability to obtain a biosample from a patient with a complex condition is extremely important). The platform, hosted by the CNAG in Spain, is now functional, and is able to connect genomic data generated in a clinic through NextGen Sequencing with an in-depth phenotypic description of the patients. Regarding registries, specifically, RD-Connect is seeking to improve the accessibility and usability of existing RD **registries** by providing each with an ID card. RD-Connect [ID-Cards](http://rd-connect.eu/platform/registries/id-cards-linking-up-rare-disease-research-across-the-world) display important information about databases, registries and biobanks – Find out more here - <http://rd-connect.eu/platform/registries/id-cards-linking-up-rare-disease-research-across-the-world>

In addition, a task within RD-Connect sought to create a set of Common Data Elements (CDEs) for rare diseases (accessible here <http://rd-connect.eu/platform/registries/ontologies/registry-common-data-elements/>) RD-Connect is also leading important work on the ELSI aspects of data sharing with some relevance to registration: <https://www.ncbi.nlm.nih.gov/pubmed/27049302>

3.2 Research Highlights

For a comprehensive summary of the state of the art of rare disease research, see the dedicated Support IRDiRC publications here – <http://www.irdirc.org/reports-guidelines/state-of-play-reports/>

Selected Facts and Figures:

- Over € 620 million was invested in over 120 projects during FP7FP6 gave way to Horizon 2020, covering the years 2014-2020: the 2014-15 Horizon2020 workplan provided ca. € 200 million funding for rare disease research, across 40 projects.
- Most of the H2020 funding for health and RD is concentrated in the SC1 (Societal Challenge Collaborative Health research) pillar. The 2016-17 workplan included two specific topics for RD:
 - Diagnostic characterisation of rare diseases (SC1PM-03–2017)
 - New therapies for rare diseases (SC1-PM-08–2017)

FP7 Funded several key 'Omics'⁷⁹ projects for rare diseases: EURENomics, dedicated to the molecular characterisation of rare kidney diseases; NeurOmics, dedicated to the molecular characterisation of rare neuromuscular and neurodegenerative disease; and RD-Connect, which set out to create a platform to integrate –omics data, clinical (phenotypic) data, registry data, biobanks, and clinical bioinformatics.

IRDiRC – Established in 2011, and designed to unite researchers with research funders, IRDiRC has two major goals: to create 200 new therapies for rare diseases and the means to diagnose most rare disease, both by 2020. IRDiRC involves over 40 members from 17 countries, with a financial commitment to-date of over 1 Billion USD. To achieve the two key goals, the consortium has undertaken dedicated actions to increase access to harmonized data and samples, enhance the molecular and clinical characterization of Rare Diseases, support translational, preclinical and clinical research, and streamline ethical and regulatory procedures. IRDiRC organised itself into:

- 3 constituent committees (funders, companies, patient advocates); and
- 3 scientific committees (Therapeutics, Diagnostics, and Interdisciplinary).

Under each of these sits a number of expert dedicated Task Forces:

- Under the Diagnostics Scientific Committee, there are Task Forces for Matchmaker Exchange (joint effort with GA4GH); Clinical Data Sharing; Solving the Unsolved.
- Under the Interdisciplinary Scientific Committee there are Task Forces for Automatable Access and Discovery (joint effort with GA4GH); Participant Unique Identifiers (joint effort with GA4GH).
- Under the Therapeutics Scientific Committee there are Task Forces for Patient Centred Outcome Measures; Small Population Clinical Trials; Data Mining/Repurposing; Patient Engagement

For more information on the broad range of IRDiRC activities, see the official website -

<http://www.irdirc.org/>

E-RARE: E-RARE-3 is the third ERA-NET for rare diseases, covering the period from 2015-2019. It involves 25 partners (public bodies, ministries and research funding organizations) in 17 countries:

⁷⁹ See www.eurenomics.eu; www.rd-neuromics.eu; www.rd-connect.eu

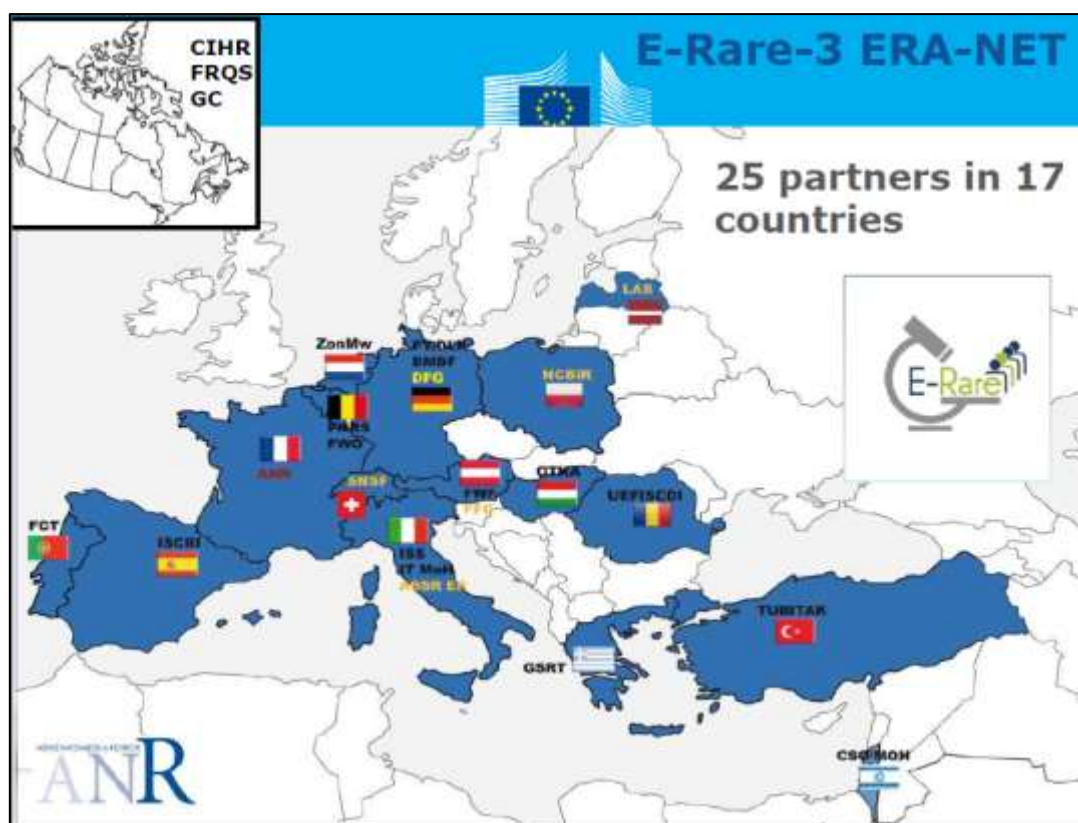


Fig 6 – E-RARE 3 countries, as per official E-RARE site (<http://www.erare.eu/project>)

E-RARE has two main areas of focus: coordination & support activities; and the transnational calls (in which each Country funds the participation of its own RD researchers). In this latest incarnation of the ERA-NET for rare disease, IRDiRC guidelines and policies are being implemented via the Joint Transnational Calls and representatives of the IRDiRC Scientific Committees have been invited to join the Advisory Board of E-Rare-3. E-Rare3 follows two very successful ERA-NETs - E-Rare-1 (2006-2010) and E-Rare-2 (2010-2014): in seven years, 56.4 Million Euros were invested to fund 79 research projects involving 347 research teams. For more information on the achievements of ERA-NETs for rare diseases, see <http://www.erare.eu/project>

European Joint Programme Co-Fund for Rare Diseases – in late 2016 a drafting committee was assembled to prepare documents to support a potential EU Joint Programme (EJP) Co-Fund in the field of Rare Diseases. (An EJP is an instrument allowing high-level strategic organization and performance of research activities in an organized and transversal manner. It is operated by Programme Owners (ministries) and Programme Managers (Research Funding and Research Performing organizations) in conjunction with other relevant stakeholders (e.g. patients' organizations, regulatory bodies and private sector).) The goal is to support translational research in the rare disease arena, from bench to bedside and back again: in other words, to develop a sustainable ecosystem allowing a virtuous circle between rare disease care, research and medical innovation. Efforts are being led by France, and are expected to progress to maturity in 2017.

4. Orphan Medicinal Products

The Regulation on Orphan Medicinal Products (Regulation (EC) No 141/2000)⁸⁰ was adopted in December 1999 and came into force in the European Union in 2000. The Regulation addresses the need to offer incentives for the development and marketing of drugs to treat, prevent, or diagnose rare conditions; without such incentives, it is unlikely that products would be developed for rare diseases as the cost of developing and marketing products for these disorders would not be recovered by sales. The Regulation delineates the designation criteria, outlines the procedure for designation, and provides incentives for products receiving an orphan designation (e.g. protocol assistance, market exclusivity, centralised procedure). The incentives contained in the legislation aim to assist sponsors receiving orphan medicinal product designations in the development of medicinal products with the ultimate goal of providing medicinal products for rare diseases to patients.

Since 2000, there has been a Committee for Orphan Medicinal Products (COMP) at the European Medicines Agency (EMA). The Commission adopts decisions on designation based on an opinion from the COMP. The COMP is also responsible for advising the European Commission on the establishment and development of a policy on orphan medicinal products in the EU and assists the Commission in drawing up detailed guidelines and liaising internationally on matters relating to orphan medicinal products.

The EMA is the most logical source of valuable information on OMP applications, Opinions and Marketing Authorizations.⁸¹

In summary however, 128 Orphan Marketing Authorisation Applications have been granted up to the end of 2016. This figure includes 12 authorized extensions of the indication; 13 withdrawals from the register of OMPs; 4 withdrawals from the register of medicinal products for human use; and 26 Authorisations which have expired, having reached the end of their marketing exclusivity. The vast majority of these MAAs(42 %) are for oncology: the full breakdown is as below:

⁸⁰ This section reproduces information from http://ec.europa.eu/health/rare_diseases/orphan_drugs/strategy/index_en.htm

⁸¹ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp . A useful summary is available here: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/04/WC500185766.pdf

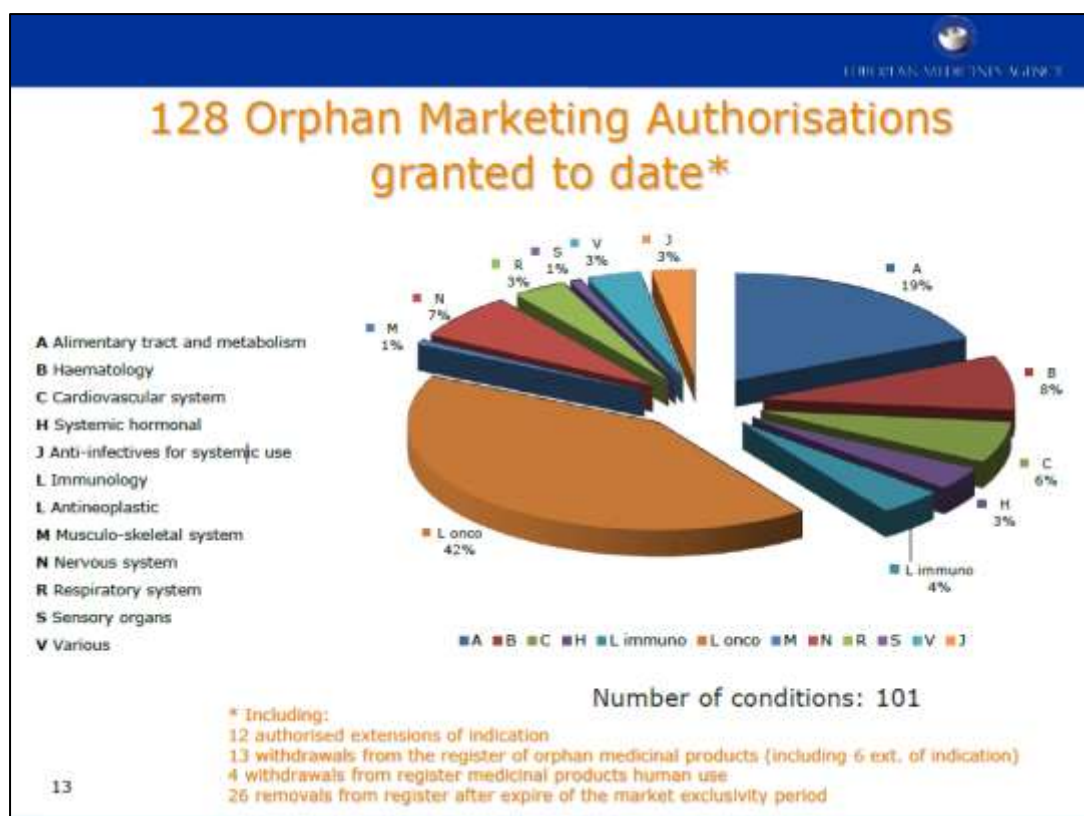


Fig 7 – Breakdown of 128 European Orphan Marketing Authorisations (Source is http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/04/WC500185766.pdf)

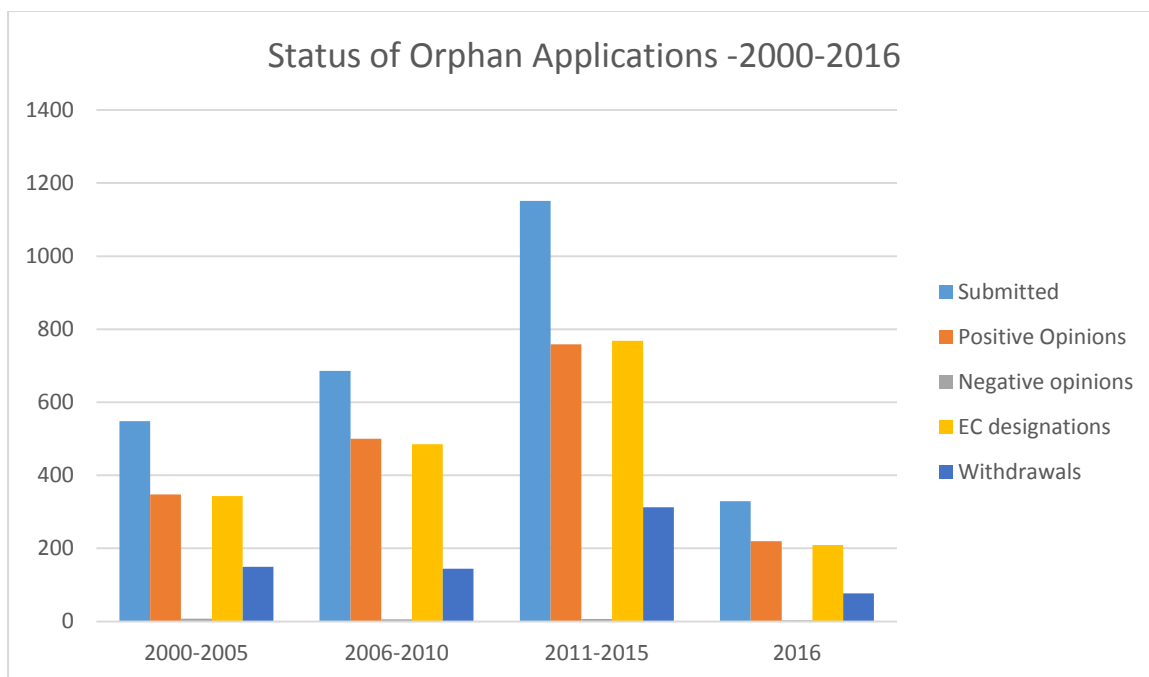


Fig. 8 Status of Orphan Applications between the years of 2000 and 2016, based upon EMA data:
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/04/WC500185766.pdf

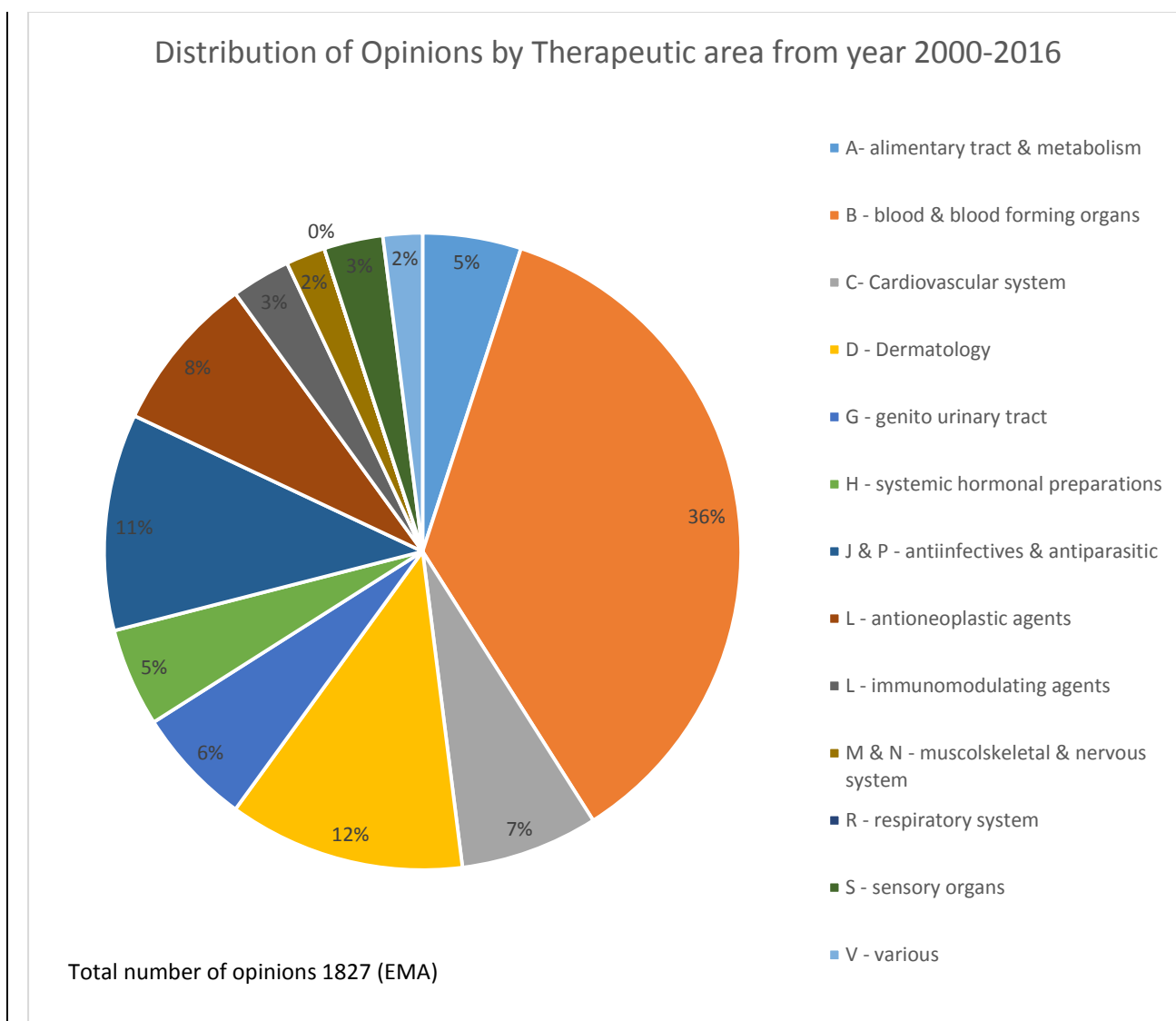


Fig.9: Distribution of Opinions Years 2000-2016. Source =
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/04/WC500185766.pdf

For more information on developments concerning Orphan Medicinal Products and their availability and accessibility in Member States, please see the forthcoming 2017 summary report under the main State of the Art webpages

5. EURORDIS and Patient Organisations for Rare Diseases in Europe

5.1 EURORDIS

EURORDIS seeks to improve the quality of life of people living with rare diseases in Europe through advocacy at the European level, support for research and medicines development, facilitating

networking amongst patient groups, raising awareness, and many other actions designed to reduce the impact of rare diseases on the lives of patients and family. (<http://www.eurordis.org/what-we-do>).

EURORDIS is not only supported by its members but by the French Muscular Dystrophy Association (AFM-Telethon), the European Commission, and European and international corporate foundations and health industry. EURORDIS represents over 738 rare disease organisations in 65 countries (of which 28 are EU Member States), covering more than 5,000 different rare diseases. (<http://www.eurordis.org/about-eurordis>)

EURORDIS' achievements are numerous –a comprehensive list of these successes has been compiled for its 20th anniversary in 2017⁸², but these include:

- Contribution to the adoption of the EU Regulation on Orphan Medicinal Products in 1999
- Contribution to the adoption of the EU Regulation on Paediatric Drugs in 2006
- Contribution to the adoption of the EU Regulation on Advanced Therapy Medicinal Products in 2007
- Contribution to the adoption of the EU Commission Communication Rare Diseases: Europe's Challenges in 2008
- Contribution to the adoption of the EU Council Recommendation on a European action in the field of rare diseases in 2009
- Contribution to the adoption of the EU Directive on Patients' Right to Cross-Border Healthcare in 2011
- Contribution to the promotion and maintenance of rare diseases as:
 - EU Public Health Policy priority
 - EU Research Framework Programme priority
- Promotion of National Plans and Strategies on Rare Diseases in all 28 EU Member States and other European countries
- Contribution to the designation of over 1100 orphan drugs
- Organisation of the European Conferences on Rare Diseases (ECRD)
- Organisation of the International Rare Disease Day

The mission of EURORDIS is to build a strong pan-European community of patient organisations and people living with rare diseases, to be their voice at the European level, and – directly or indirectly – to fight against the impact of rare diseases on their lives. (<http://www.eurordis.org/what-we-do>). With this in mind the activities of EURORDIS focus on empowering rare disease patient groups, advocating rare diseases as public health issue, raising public rare disease awareness, and also that of national and international institutions, improving access to information, treatment, care and support for people living with rare diseases, encouraging good practices in relation to these, promoting scientific and clinical research, developing rare disease treatments and orphan drugs and improving quality of life through patient support, social, welfare and educational services. (<http://www.eurordis.org/content/our-mission>)

Sample EURORDIS Initiatives:

Rare Diseases International

⁸²http://download.eurordis.org.s3.amazonaws.com/20yrs/20years_AchievementsofRDCommunity_0117.pdf

- Rare Diseases International (RDI) is the global alliance of people living with a rare disease of all nationalities across all rare diseases.
- RDI brings together national and regional rare disease patient organisations from around the world as well as international rare disease-specific federations to create the global alliance of rare disease patients and families.
- RDI is an international network currently embedded in EURORDIS, which supports its development. An RDI Council was elected in April 2016. It is made up of seven rare disease patient advocates representing international, national and regional patient member organisations.

Rare Disease Day

- Held each year on the last day of February, Rare Disease Day is an annual awareness-raising event coordinated by EURORDIS. The main objective of Rare Disease Day is to raise awareness amongst the general public and decision-makers about rare diseases and their impact on patients' lives. The campaign targets the general public and also seeks to raise awareness amongst policy makers, public authorities, industry representatives, researchers, health professionals and everyone with an interest in rare diseases.
- Since Rare Disease Day was first launched by EURORDIS and its Council of National Alliances in 2008, thousands of events have taken place throughout the world, reaching hundreds of thousands of people and resulting in a great deal of media coverage.
- The political momentum resulting from Rare Disease Day also serves advocacy purposes. It has notably contributed to the advancement of national plans and policies for rare diseases in a number of countries.
- Even though the campaign started as a European event, Rare Disease Day has progressively become a worldwide phenomenon, with the USA joining in 2009, and patient organisations in 85 countries around the world participating in 2015. 2016 saw organisations in Andorra, Indonesia, Tanzania, Tunisia and Uganda participate for the first time.

NGO Committee on Rare Diseases

- The NGO Committee for Rare Diseases is a multi-stakeholder, inclusive, global ecosystem focused on rare diseases, which aims:
 - To increase visibility of rare diseases at the global level
 - To extend and share knowledge about rare diseases and their unmet needs
 - To connect NGOs interested in rare diseases and their partners within a global platform
 - To promote international, multi-stakeholder collaboration and actions for rare diseases
 - To align rare diseases as a global priority in public health, research and medical and social care policies.
- The NGO Committee for Rare Diseases (United Nations, New York) is a substantive committee established under the umbrella of the Conference of NGOs in Consultative Relationship with the United Nations (CoNGO).

- CoNGO has been the primary support and platform for a civil society since 1948, represented by a global community of informed, empowered and committed NGOs that fully participate with the UN in decision-making and programs leading to a better world, a world of economic and social justice.
- The NGO Committee for Rare Diseases was initiated by the Ågrenska Foundation and EURORDIS – Rare Diseases Europe with a view to bringing greater political recognition of the challenges of rare diseases at the global level. Its formation was approved by a vote of 27 CoNGO member organisations in April 2014, and its inception meeting as a Substantive Committee within CoNGO took place in October 2015 in New York.
- The formal inauguration of the Committee took place on the 11 November 2016 at the UN headquarters in New York.

RareConnect

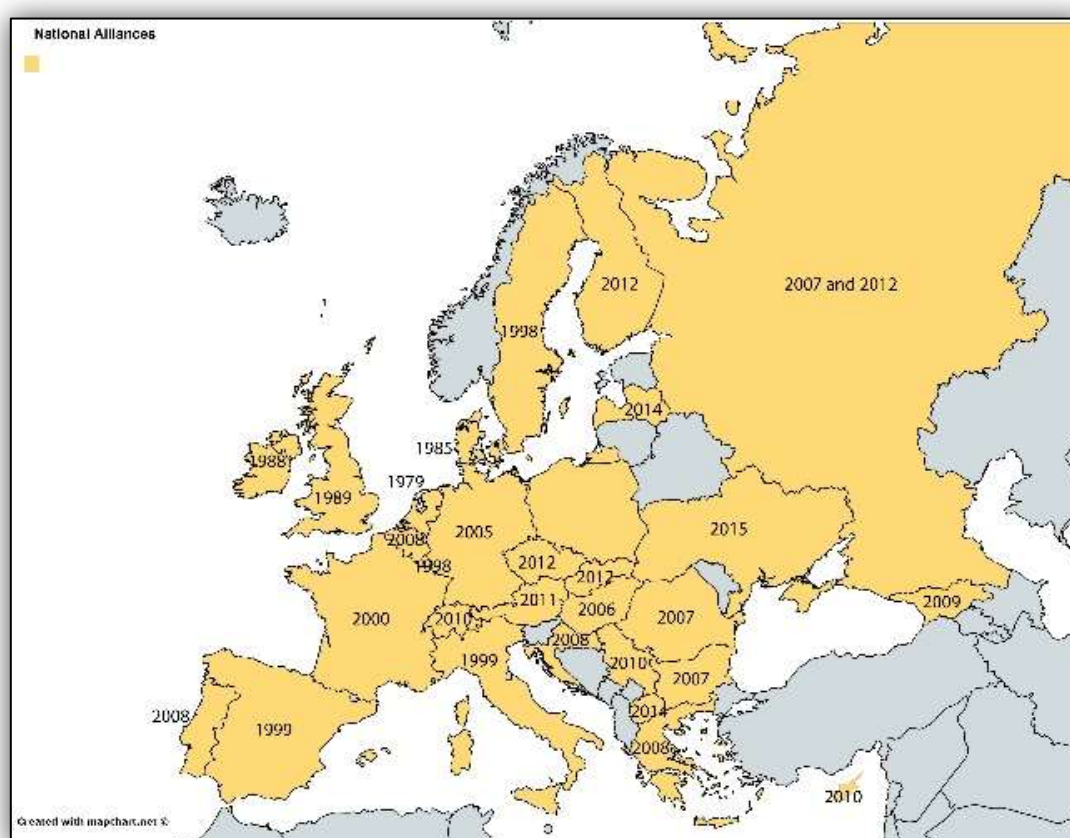
- RareConnect a EURORDIS initiative, is the growing online network of rare disease communities that brings together thousands of patients, families and groups who might otherwise be isolated. Through RareConnect, patients and those who care for them can communicate, sharing experiences and information in a safe, moderated online forum. With human translation available at no cost to participants, RareConnect allows patients from different countries to interact in English, French, German, Italian, Portuguese or Spanish languages.
- Each of the rare disease-specific communities is supported by the full-time community managers who animate and promote the communities and support volunteer moderators from the member group. If a community has not yet been created for a specific rare disease, the discussion groups provide a platform to ask questions and participate in discussions about more transversal issues related to living with a rare disease. It is an invaluable tool for sharing experiences and solutions to common problems based on the experiences of the wider rare disease community.

5.2 National alliances of rare disease patient organisations

National alliances of rare diseases patient organisations are important structures for this key group of stakeholders at Member State level, serving to provide patients with a common voice and the presence needed to have an impact on national policy. Indeed, many of these national alliances have played (or are playing) key roles in elaborating the national plans or strategies for rare diseases under development or already in place. Many also have a plan on official committees treating issues directly related to the needs of rare disease patients.

An increasing number of National Alliances of rare disease patient organisations have been created in Europe. Currently, there are 38 National Alliances who are members of EURORDIS, of which 29 form the European Network of National Alliances for Rare Diseases. The latter are all organisations recognised as “National Alliances of Rare Disease Patient Organisations” by the EURORDIS Board of Directors. The European Network of National Alliances for Rare Diseases is governed by the Council of National Alliances. The Member States where National Alliances have been established include: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Luxembourg, Netherlands, Poland, Portugal, Romania, Slovak Republic, Spain, Sweden, and the United Kingdom. In addition Alliances have been established in the following countries: Georgia (2009), Macedonia (2014), Romania (2007), the Russian Federation (2 alliances 2007 and 2012), Serbia (2010), Switzerland (2010) and in the Ukraine (2015).

Figure 10: National Alliances and year of foundation



EURORDIS runs the Council of National Alliances for rare disease patient organisations (CNA) bringing together the majority of Alliances in Europe as well as Alliances in the USA and Canada. The Council allows national representatives of rare diseases to work together on common European and international actions, for instance Rare Disease Day.

EURORDIS and the National Alliances also work together to help translate European directives or recommendations into national policies such as adopting a national plan for rare diseases and implementing the EU Directive on Patients' Rights in Cross-Border Healthcare.

5.3 Disease specific patient organisations in the field of rare diseases

As of January 2017, 2,613 disease specific patient organisations were registered in the Orphanet Database. Of these:

- 2218 were national disease specific-organisations
- 244 were regional disease-specific organisations
- 86 were European disease-specific patient organisations
- 65 were international (global) disease-specific patient organisations.

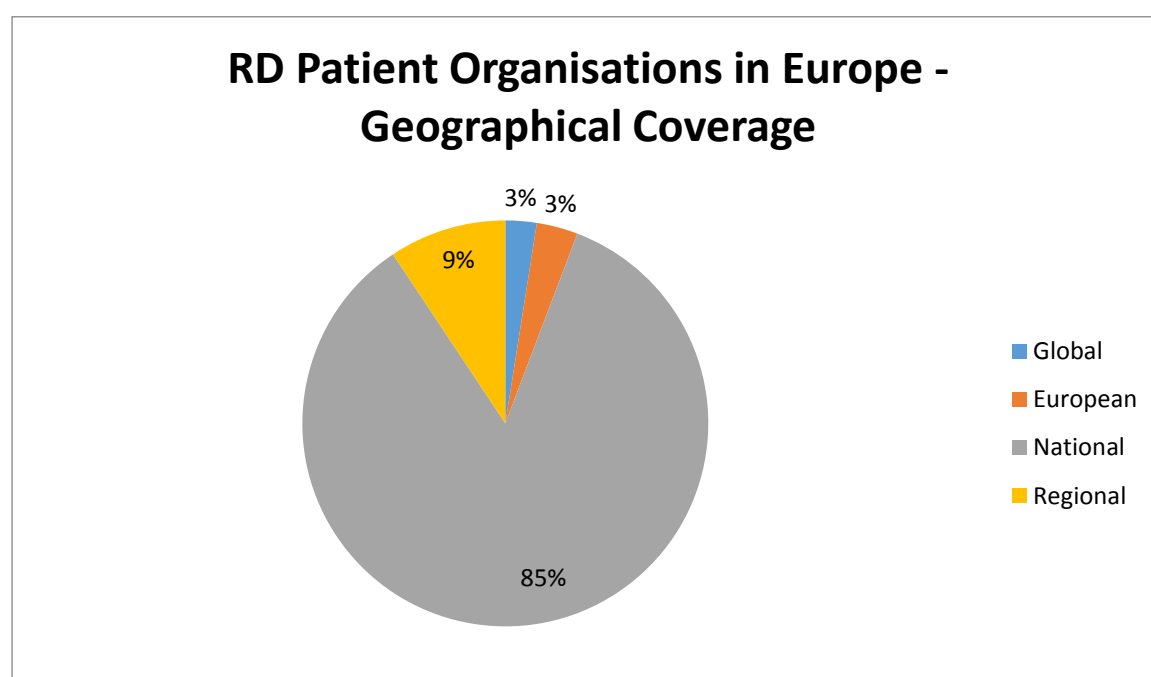


Fig. 11: RD Patient Organisations and Geographical Coverage

6. Orphanet

Orphanet is the largest repository of information about Rare Diseases globally. It was established in 1997 –celebrating its 20th anniversary in 2017- and quickly evolved to become a user-friendly internet-based portal providing high quality information to support the diagnosis, treatment and care of people with rare diseases world-wide. The new-look Orphanet database and tool-suite will be launched in early 2017, as part of the continued development under RD-ACTION.

The three main goals of Orphanet are as follows:

- Improve the visibility of rare diseases in the fields of healthcare and research by maintaining the Orphanet rare disease nomenclature (ORPHANumbers): providing a common language to understand each other across the rare disease field
- Provide high-quality information on rare diseases and expertise, ensuring equal access to knowledge for all stakeholders: orientating users and actors in the field in the mass of information online.
- Contribute to generating knowledge on rare diseases: piecing together the parts of the puzzle to better understand rare diseases.

The heart of Orphanet is the system of nomenclature it created: each disease is given a unique and stable number, known as the ORPHA Number. Each of these numbers is given a preferred term and all known synonyms and are mapped to OMIM, to ICD10, UMLS, SNOMED-CT, MeSH and MedDRA (where corresponding codes exist) and are also translated to numerous languages. The OrphaCode has been approved on both the European⁸³ and global⁸⁴ levels as the most appropriate nomenclature for the clinical coding of rare diseases, in view of its granularity and ability to distinguish between specific rare diseases, which makes it preferable to all alternatives.

The Orphanet site encompasses many resources, however, to support the global rare disease community, including the following⁸⁵:

- The [inventory of rare diseases](#) and a [classification](#) of diseases elaborated using existing published expert classifications.
- The [encyclopaedia of rare diseases](#) in English, also available in the other languages of the website.
- An [inventory of orphan drugs](#) at all stages of development.
- A directory of expert resources, providing information on [expert clinics](#), [medical laboratories](#), [ongoing research projects](#), [clinical trials](#), [registries](#), networks, technological platforms and [patient organisations](#), in the field of rare diseases, in each of the countries in Orphanet's consortium.
- An [assistance-to-diagnosis tool](#) allowing users to search by signs and symptoms.
- An encyclopaedia of recommendations and [guidelines for emergency medical care and anaesthesia](#).
- A fortnightly newsletter, [OrphaNews](#), newsletter for RD-ACTION, which provides an overview of scientific and political current affairs in the field of rare diseases and orphan drugs
- The [Orphanet Reports Series](#), which focuses on overarching themes
- The Orphadata platform, providing high-quality datasets related to rare diseases and [Orphan Drugs](#), in a reusable and computable format.

⁸³ The OrphaCode is the subject of dedicated recommendations issued by the Commission Expert Group on Rare Diseases: *Recommendation on Ways to Improve Codification for Rare Diseases in Health Information Systems* (2014) http://ec.europa.eu/health/sites/health/files/rare_diseases/docs/recommendation_coding_cegrd_en.pdf

⁸⁴ The OrphaCode has received 'IRDiRC Recommended Resources' label, reserved for resources which "if used more broadly, would accelerate the pace of discoveries and translation to clinical services": <http://www.irdirc.org/activities/irdirc-recognized-resources/>

⁸⁵ See the official Orphanet site for full details: <http://www.orpha.net/consor/cgi-bin/index.php?lng=EN>