



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

2018 Version

RD-ACTION WP6 Output



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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 or adapted 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:

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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 is complemented by Member State-specific webpages under the main RD-ACTION site, detailing activities at the national level.

The electronic version of this document -along with related materials- is available via the homepage of the 'Resource on the State of the Art of Rare Disease Activities in Europe' <http://www.rd-action.eu/rare-disease-policies-in-europe/>

In the absence of dedicated European Commission funding post RD-ACTION (i.e. after 31st July 2018), the team at Newcastle University will continue to sustain at least the *national* data collection for European Member States and EEA countries. This will enable an updating of the aforementioned country pages and country reports and -crucially- the elaboration of up-to-date transversal topic summaries (e.g. an overview of the current status of national plans and strategies, an overview of newborn screening practice) in the Autumn of 2018.

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1. Political frameworks for rare diseases in Europe

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 subsequent 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. In the decade since the passage of these watershed policies, the European rare disease scene has changed significantly, with many notable successes. However, alongside these successes, the rare disease community in mid-2018 is facing a number of challenges which have the potential to halt the rate of progress and threaten the continued advancement of diagnostics, treatment and care for people with rare diseases in Europe.

1.1. The EU rare disease field in 2018 - opportunities and challenges of the status quo

From the vantage point of mid-2018, there are many reasons to celebrate the progress of Europe's rare disease community:

- ✓ **25 EU MS have now adopted a national plan or strategy for rare diseases,² compared to only 4 in 2008, and the focus has shifted somewhat from 'adopting' to actually implementing and evaluating the success of these first (and in some cases second) 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, and opportunities for these Networks to add value in the rare disease field continue to emerge (see section 5).**
- ✓ **Collaboration between the 'healthcare' and 'research' domains is increasing, and will continue to grow (bolstered by the imminent European Joint Programme Co-Fund for Rare Disease research³).**

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

³ See section 8

- ✓ **Patient organisations such as EURORDIS (see 10.1) continue to grow and play leading roles in initiatives such as Joint Actions, Tender and Projects driving forwards progress.**
- ✓ **Orphanet (the global database for rare diseases, see section 11) celebrated its 20th anniversary in 2017 and the European Commission continues to provide financial support on the path towards sustainability of this important resource.**

However, despite these successes, there is still much to be done to ensure that people suffering from a rare disease can obtain the right diagnosis and best possible treatment throughout the EU: there are concerns in some quarters that ‘rare diseases’ as a policy area have reached a plateau of sorts:

- After 3 years of the EUCERD (European Union Committee of Experts in Rare Diseases) and 3 years of the Commission Expert Group on Rare Diseases (CEGRD), there is no replacement body to fulfil this role, nor are there plans to establish any such an entity from the EC side. This reflects the wider trend to disband all former Expert Groups, in view of a major reconsideration of the EC’s role in the health sphere.
- In place of these Expert Groups a ‘Steering Group on Health Promotion, Disease Prevention and Management of Non-Communicable Diseases’ (or *Steering Group on Prevention and Promotion*) has been established. This body will, it is foreseen, seek to involve experts in particular disease areas -such as rare diseases- as and when required. However, there is a major risk here that for rare conditions, a ‘one-size-fits-all’ approach simply will not work and the specificities of rare diseases will not be catered for by this new Group, given its very broad agenda. (See further Section 1.4)
- A further concern is that there are no plans for any future joint actions in the field of rare diseases (although Joint Actions in other areas -such as health inequalities and eHealth- have recently commenced operations). It is important to emphasise that Member States, apparently, have not asked for another Joint Action or similar entity for the rare disease field, and the EC establishes such Actions based upon requests from the Member States. This has resulted in a situation where, for the first time in 6 years, there is no Joint Action for rare diseases in Europe.
- A number of Recommendations exist, adopted by the EUCERD and CEGRD, which MS pledged to honour. These Recommendations pertain to specific topics, and in each case represent the consensus of leading European experts in their field; however, 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 for all 28 EU MS, a focus on regional cooperation or shared approaches based upon a country’s size, situation, wealth, language etc. is the wisest approach to identifying and embedding good practices. **But as above, there is no longer a dedicated Group to unite the MS representatives most closely concerned with rare disease issues, and integrate other key stakeholder groups (e.g. academics, patients, Industry, etc) to monitor the status quo at European level or examine the realities of what is happening in the rare diseases sphere at national level.**

There is a growing sense -in some quarters- that now the ERNs are active, all rare disease issues are somehow 'in-hand'. **Despite the significant potential for ERNs to add value to diagnostics, care and research for rare disease in Europe, there are a number of reasons why ERNs cannot, by themselves, address all challenges posed by rare and highly specialised conditions:**

- The Executive Body governing the ERNs cannot simply become a substitute Expert Group for all rare-disease related issues. The Board of Member States of ERNs (BoMS) dedicated specifically and solely to ERNs and they do not have a mandate to address 'rare diseases' *per se*.
- ERNs will not impact on all aspects of European policies for rare diseases, and it is difficult to see at present how they can, alone, be the future for national rare disease activities. Even if one could attempt to give this role to, for instance, the coordinating HealthCare Providers (HCPs), these are clustered in 7 countries, making it difficult to see how they could oversee and influence RD policy in the other 21 MS. Furthermore, the Networks are not logically connected to national plans and strategies: although they should be fully integrated to national pathways and networks of care for rare disease patients, ERNs do not sit at the *centre* of national rare disease activities, in the sense that they do not control issues such as NBS portfolios, national registries, coding, social integration of rare diseases, OMP access, etc. They have the power to positively impact some of these things, but the ERNs themselves, given their core duties, cannot reasonably be expected to consolidate and maintain momentum for all national activities relating to rare diseases.

1.1.1. Rare Disease Joint Action (RD-ACTION) call for renewed and comprehensive European focus on rare diseases

The current 'vacuum' for rare disease policy-making and policy-implementation has been highlighted by RD-ACTION, the Joint Action for Rare Diseases, which formally ends its funding period in Summer 2018. The partners of RD-ACTION addressed a letter detailing concerns to the Director General of DG Sante, Mr Xavier Prats-Monné. This letter, co-signed by 32 RD-ACTION Partners, asked the European Commission to reaffirm its exemplary leadership -in an area where it is unanimously recognised that EU added value is very high- by ensuring the following:

- A dedicated policy for rare diseases which, while creating synergies with other policy areas, effectively addresses the specificities of rare diseases;
- An overarching approach that integrates rare disease policies within a successful, harmonious and consistent framework;
- A multi-stakeholder approach and collaborative strategies that have proved key to the success of the actions of Europe in the fight for rare diseases;
- A rare disease community equipped with the most appropriate tools for exchange and policymaking for the years to come.

In terms of initial concrete steps, the EC was requested to:

1. Support at least the ***informal dialogue between national representatives in charge of rare disease policy at national level*** and relevant stakeholders representatives, by enabling meetings adjacent to meetings of the ERN BoMS, which the RD-ACTION community of stakeholders would commit to organising, content-wise, to constitute a 'Rare Disease Think Tank'

2. Maintain a **dedicated policy officer** who supervises all European Commission initiatives with a particular impact on rare disease policy.

1.2 Key Rare Disease Policy Documents and Legislation

1.2.1 Regulation on Orphan Medicinal Products

In December 1999, a landmark piece of legislation for the cause of rare diseases in Europe was adopted. *Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on Orphan Medicinal Products* highlighted the challenges hampering the development of medicinal products for rare diseases, and acknowledged the inherent inequality in patients being denied the same quality of treatment as other citizens because of the rarity of their condition. The Regulation established a Community procedure for the designation of potential medicinal products as 'Orphan Medicinal Products' (OMPs), which it defined as follows:

“A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or

that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment.

In thus defining an OMP, the Regulation defined what constitutes a rare disease in the European framework i.e. a condition affecting no more than 5 per 10,000 people.

This far-reaching Regulation established several key components of Europe's OMP framework, amongst them the following: it created the COMP (Committee for OMPs at the European Medicines Agency) and established its mandate; defined procedures for the designation of OMPs (and their removal from the register); made stipulations regarding Protocol assistance for the sponsor of an OMP; stipulated provisions for community marketing authorisation and market exclusivity; etc. (See further section 9.1.)

1.2.2 Commission Communication 'Rare Diseases: Europe's Challenges' (2008) and the Council Recommendation on an Action in the field of Rare Diseases (2009)

The key 'foundation' documents which have typically credited with inspiring significant activity and progress in the European rare disease policy sphere are

- The **Commission Communication on Rare Diseases: Europe's challenges [COM(2008) 679 final]**⁴; and
- The **Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02)**.⁵ Recommendations were made to the Member States around 7 distinct though inter-related topics:

⁴ https://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf

- Plans and Strategies in the field of rare diseases
- Adequate definition codification and inventorying of rare diseases
- Research on rare diseases
- Centres of expertise and European Reference Networks
- Gathering the expertise on rare diseases at European Level
- Empowerment of patient organisations
- Sustainability

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**⁶ 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 MS, 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 concluded 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 (IRDiRC) 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
- 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.

⁵ <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF>

⁶ http://ec.europa.eu/health/sites/health/files/rare_diseases/docs/2014_rarediseases_implementationreport_en.pdf

- Continue playing a global role in the rare diseases initiative and collaborating with important international stakeholders.⁷

1.2.3 The 'Cross-Border Healthcare Directive' of 2011

The **Directive on the Application of Patients' Rights in Cross-Border Healthcare (Directive 2011/24/EU)**⁸ has played a key role in the development of European Reference Networks, or ERNs, which have a 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. It is particularly important for the European rare disease community, as Article 12 provided the basis for the ERNs. This so-called 'Cross-Border Healthcare Directive' also established the eHealth Network. The impact of the Directive is monitored through a series of reports.⁹

⁷ <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52014DC0548&from=GA> (p16)

⁸ <http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A32011L0024>

⁹ See for instance:

- the *Member State Data on Cross-border healthcare* reports (the latest is available here - https://ec.europa.eu/health/sites/health/files/cross_border_care/docs/2016_msdata_en.pdf);
- the 2016 Report From The Commission To The European Parliament And The Council: Commission report on the operation of Directive 2011/24/EU on the application of patients' rights in cross-border healthcare - https://ec.europa.eu/health/sites/health/files/cross_border_care/docs/2015_operation_report_dir201124eu_en.pdf

1.3 Former European Expert Groups/Committees for Rare Diseases

1.3.1. 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)¹⁰ (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. Many 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:

- ***The Recommendation on ways to improve codification for rare disease in health information systems***¹¹ adopted at the 3rd meeting on 12-13th November 2014
- ***Rare Disease European Reference Networks: An Addendum to the EUCERD Recommendations of January 2013***¹² adopted during the 5th meeting 10-11th June 2015
- ***Recommendations on cross-border genetic testing of rare diseases in the European Union***¹³ adopted at the 6th meeting on 12th November 2015
- ***Recommendations to Support the Incorporation Of Rare Diseases Into Social Services,***¹⁴ 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 IRDiRC¹⁵ (International Rare Disease Research Consortium) initiative, RD-Connect,¹⁶ 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, topic such as Structural

¹⁰ http://ec.europa.eu/health/rare_diseases/docs/dec_expert_group_2013_en.pdf

¹¹ http://ec.europa.eu/health/sites/health/files/rare_diseases/docs/recommendation_coding_cegrd_en.pdf

¹² http://ec.europa.eu/health/sites/health/files/rare_diseases/docs/20150610_erns_eucerdaddendum_en.pdf

¹³ http://ec.europa.eu/health/sites/health/files/rare_diseases/docs/2015_recommendation_crossbordergeneticstesting_en.pdf

¹⁴ http://ec.europa.eu/health/sites/health/files/rare_diseases/docs/recommendations_socialservices_policies_en.pdf

¹⁵ <http://www.irdirc.org/>

¹⁶ <http://rd-connect.eu/>

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.

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

The EUCERD¹⁷ 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
- 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***,¹⁸ adopted 6th June 2013
- ***EUCERD CORE Recommendations on Rare Disease Patient Registration and Data Collection***,¹⁹ adopted 5th June 2013
- ***EUCERD Recommendations on European Reference Networks for Rare Diseases***,²⁰ adopted on 31st Jan 2013

¹⁷ http://ec.europa.eu/health/rare_diseases/expert_group/index_en.htm

¹⁸ http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_Indicators_adopted.pdf

¹⁹ http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_RDRegistryDataCollection_adopted.pdf

²⁰ http://www.eucerd.eu/?post_type=document&p=2207

- **EUCERD Recommendations on the Clinical Added Value of Orphan Medicinal Products (CAVOMP) Information Flow**,²¹ adopted September 2012
- **EUCERD Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases in Member States**,²² 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>

1.4 The Steering Group on Health Promotion, Disease Prevention and Management of Non-Communicable Diseases

This ‘Steering Group on Prevention and Promotion’ (SGPP), as it is often called, was formally established in July 2018 via Commission Decision C(2018) 4492.²³ The SGPP is chaired by the European Commission, and is composed entirely of Member State representatives. The main goal of this new Group is to facilitate the implementation of evidence-based best practices by EU countries, in order to ensure that the most up-to-date research findings and knowledge are put into practice. The SGPP will advise the Commission on the selection of best practices, to be transferred and scaled-up at the national and European level via suitable financial instruments (e.g. the EU Public Health Programme/future European Social Fund Plus (see below, Section 1.7)) For example, outputs and resources developed through past projects in particular domains could be assessed in terms of applicability for real-world/wider-world deployment, where MS express interest. Recommendations, reports or Opinions may be adopted by consensus or majority votes. Although widely viewed as a successor to the myriad Expert Groups previously supported by the EC, the suitability of the SGPP for a field such as rare diseases is not yet clear.

1.5 Consensus European Recommendations on Rare Disease Issues

Recommendation Title	Date Adopted	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 Diseases	January 2013	http://www.eucerd.eu/?post_type=document&p=2207

²¹ http://www.eucerd.eu/?post_type=document&p=2207

²² http://www.eucerd.eu/?post_type=document&p=1224

²³ https://ec.europa.eu/health/sites/health/files/major_chronic_diseases/docs/c2018_4492_en.pdf

Addendum to EUCERD Recommendations on Rare Disease ERNs	June 2015	https://ec.europa.eu/health/sites/health/files/rare_diseases/docs/20150610_erns_eucerdaddendum_en.pdf
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_crossbordergeneticstesting_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/CEGRD Recommendations and Opinions

1.6 Joint Actions in the field of Rare Diseases

1.6.1 RD-ACTION

RD-ACTION, 'Data and Policies for Rare Diseases' combined the foci of two previous Joint Actions in the rare disease field: the EUCERD JA and the Orphanet JA. RD-ACTION was coordinated overall by Ana Rath in INSERM, and the Policy & Integration workstream (WP6) was led by Kate Bushby from Newcastle University (Victoria Hedley from 2016 onwards). RD-ACTION united 34 beneficiaries and 30 collaborating partners from 40 countries, with a total budget of 8.3 million Euros.

The general objectives of RD-Action were 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 had 6 workpackages which covered 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)
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 and Victoria Hedley (UNEW)

Achievements of RD-ACTION

The latest Joint Action for Rare Diseases generated significant added-value, in many areas: key achievements include the following:

- WP2 delivered 19 new-format [EUROPLAN national conferences](#) during this Joint Action, co-organised by National Alliances, in order to address pressing policy priorities and needs at national level
- WP2 also explored issues around resilient and sustainable health systems for rare diseases and generated a number of policy briefs, whilst seeking to incorporate rare diseases to the focus of the [TO-REACH²⁴](#) coordination and support action (CSA)
- WP4 implemented a major overhaul of the Orphanet IT infrastructure, evolving the database from a relational to a graph database and initiating the move to a more distributed organisational model. The Consortium was expanded (one notable recent addition being Japan) and the accessibility of resources increased through the addition of new languages (the Orphanet site is now available in [Polish](#), and the nomenclature in Czech). The Orphanet team also improved the traceability and transparency of curation procedures, created tutorials to explain resources to users, and updated and expanded scientific annotations and the expert resources catalogue (including a map of ERNs).
- Concrete steps have been taken towards securing the sustainability of Orphanet over the past three years, steered by research and the evaluation activities under WP3 (see Section 11).
- WP5 delivered many outputs, including the following: a set of guidelines for coding rare diseases; the specification and implementation manual for the Master file; specifications for an adapted coding tool for rare diseases; and recommendations for routine

²⁴ TO-REACH is seeking to generate evidence to help healthcare services and systems become more resilient, effective, equitable, accessible, sustainable and comprehensive

maintenance. The achievements of this WP in supporting MS to adopt the OrphaCode in health information systems will form the basis of a subsequent 'OrphaCodes Project' under the Public Health Programme²⁵, to enable continued progress in this essential area.

- WP6 adapted the Resource on the [State of the Art of Rare Diseases Activities in Europe](#), to encompass 3 parts: the Overview Report, the national data resources, and transversal topic summaries. Two versions of the Overview Report were produced. All the countries which provided data on their rare disease activities received dedicated webpages bearing brief summaries and more detailed reports.
- WP6 inherited a key goal of the EUCERD Joint Action, namely to provide support for the conceptualisation and implementation of ERNs. The Team supported the generation of robust, collaborative and non-competitive ERN proposals, through its Matchmaker resource. In the grant preparation/evaluation period and the early days of the Networks' approval, the WP6 team canvassed perspectives and presented the views of all ERNs around important topics such as research strategies and registries. The main manifestation of the support to ERNs, however, was the planning and delivery of 6 major workshop for the ERN community, (usually co-organised with DG Sante) to allow the networks to find common solutions to shared challenges (see section 5.4)
- Under RD-ACTION WP6, the creation of ePAGs (European Patient Advocacy Groups) for ERNs received a stimulus – partners ensured the active involvement of ePAGs in all workshops

Once the RD-ACTION project formally ends (summer 2018) a brochure will be created, to summarise the achievements and added value of the Initiative for a lay-person audience.²⁶

1.6.2 EUCERD Joint Action

The creation of the EUCERD Joint Action (EJA) stemmed primarily from 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). 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.

²⁵ https://ec.europa.eu/health/sites/health/files/programme/docs/wp2018_annex_en.pdf (Call 2.1.3)

²⁶ This brochure will be available via the project home-page- <http://www.rd-action.eu/>

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 and delivered 25 national Europlan conferences with over 3000 participants. The final meeting of the EUCERD Joint Action, presenting the outcomes and future perspectives, took place on 15th September 2015 in Luxembourg.²⁷ 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).

1.7 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**²⁸. 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.

The Second and Third Public Health programmes financed and co-funded numerous projects dedicated to advancing diagnosis, treatment and care for rare diseases and rare cancers – a good summary, covering the most relevant projects funded between 2008-2016, is available here: http://ec.europa.eu/chafea/documents/health/rare-diseases-2018_en.pdf

Post 2020: The future of Health within the European Commission has been a matter of some debate, largely due to the political upheaval caused by developments such as Brexit. Post 2020, the Health Programme will no longer exist as a standalone Programme, but will instead be part of the European Social Fund Plus (ESF+), running from 2020-2027. This new ESF+ will encompass the existing European Social Fund, the Youth Employment Initiative (YEI), the Fund for Aid to the Most Deprived (FEAD), the EU Programme for Employment and Social Innovation (EaSI) and the EU Health programme. The combined ESF+ will have a total of ca. €101 billion across these seven

²⁷ For more on the EUCERD JA, see <http://www.sciencedirect.com/science/article/pii/S1769721216302439>

²⁸ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:271:0001:0011:EN:PDF>

years. Of this, the Health strand is expected to receive €413 million which will be implemented in direct management by the Commission.²⁹

At European level, research³⁰ 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 2007-2013³¹) the Health Theme of the "Cooperation" Specific Programme, was designed to support multinational collaborative research in different forms. FP7 was succeeded by Horizon 2020³² the Framework Programme covering the period 2014-2020.

Horizon 2020 will, in turn, be succeeded by Horizon-Europe. Horizon Europe will run between 2021 and 2027, and has a provisional budget of €100 billion (€97.6 billion in reality), which represents an increase from H2020's budget of ca. €77 billion.³³

2. Political framework at European 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:

- 25 countries have adopted a NP/NS for rare diseases at some stage.
- 19 of these countries adopted NP/NS which were time-bound (i.e. they were approved covering certain years of activity).
 - The following 13 countries have time-bound NP/NS which were still apparently active in July 2018: **Austria; Croatia; Czech Republic; Estonia; France; Hungary; Ireland; Luxembourg; Netherlands; Portugal; Romania; Slovak Republic; Slovenia**
 - The following 6 countries adopted time-bound NP/NS which had expired by July of 2018 and appear³⁴ not to have been replaced/renewed: **Bulgaria, Finland, Greece, Italy, Latvia, Lithuania**
- 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**

²⁹ See for instance <http://ec.europa.eu/esf/main.jsp?catId=62&langId=en> and https://ec.europa.eu/commission/sites/beta-political/files/budget-may2018-european-social-fund-plus-regulation_en.pdf

³⁰ For more on rare disease research, see section 8

³¹ http://cordis.europa.eu/fp7/home_en.html

³² http://ec.europa.eu/research/participants/data/ref/h2020/legal_basis/fp/h2020-eu-establact_en.pdf

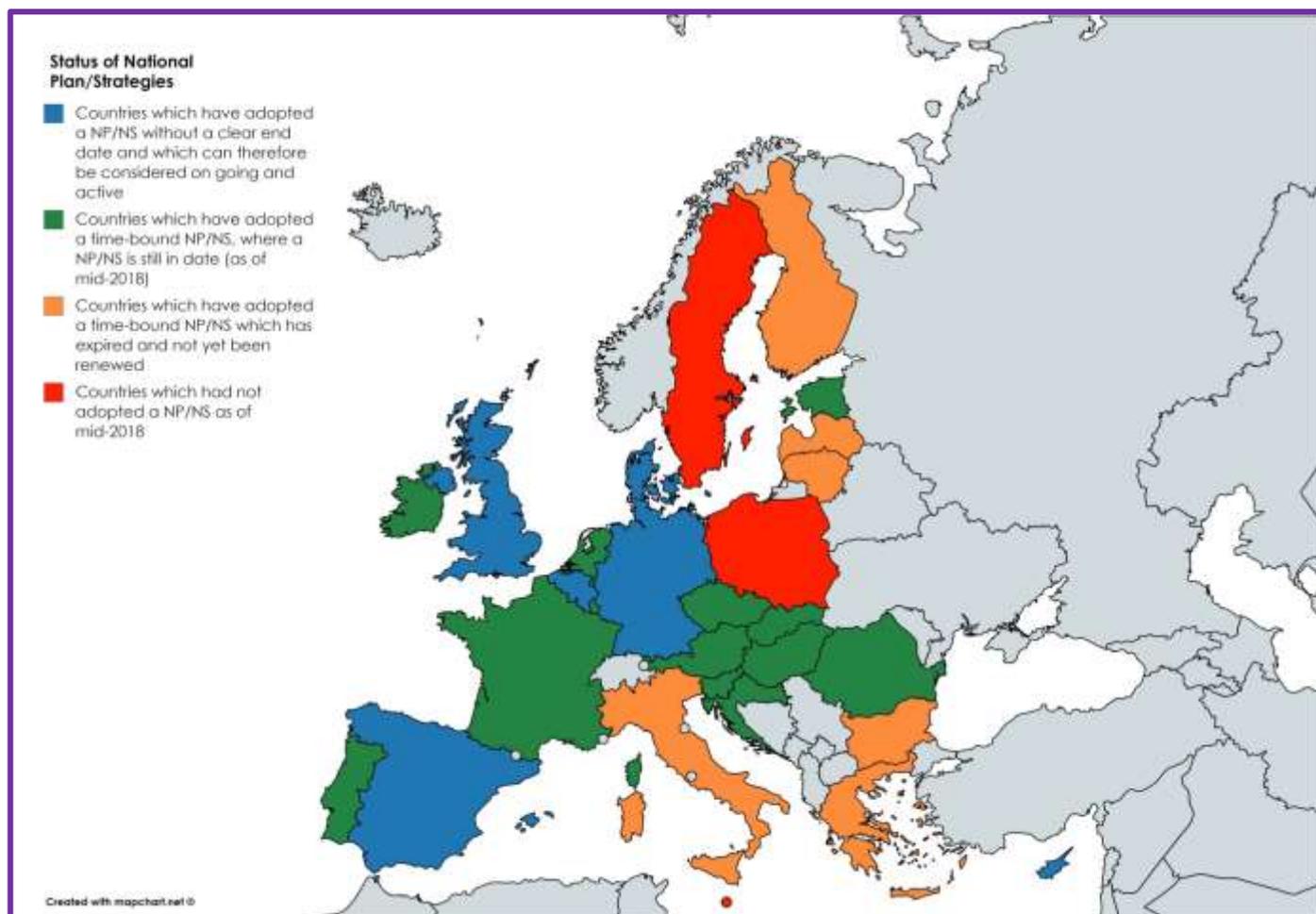
³³ http://europa.eu/rapid/press-release_IP-18-4041_en.htm

³⁴ Based upon the latest information received via the State of the Art country data collection procedures

- Three EU MS appear not to have adopted a NP/NS by the end of 2016: **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 July 2018



In July 2018, France became the first country to adopt a Third National Plan for Rare Diseases. This should represent an important example to other European countries, as many initial NP/NS are currently either out of date or else are nearing their ‘expiration’ date (often with limited evidence of the realistic impact and concrete levels of implementation). As above, it appears that the NP/NS of 6 countries are technically no longer ‘active’: in some cases, these NP/NS expired several years ago, whereas others expired more recently (Italy’s Plan covered the period to the end of 2016, whilst the National Plans adopted by Finland and Lithuania had a terminus of 2017). More worryingly, of the 13 time-bound NP/NS which are still ‘in date’, many are also approaching the end of their terms: Austria’s NP is active until the end of 2018, as is that of the Netherlands. The NP/NS of Croatia, Hungary, Portugal, Romania, Slovak Republic and Slovenia all technically come to an end

in 2020, as does the current Action Plan for Czech Republic. **At this crucial juncture, it is imperative that a renewed focus is placed on the National Plans and Strategies for Rare Diseases in Europe,** in order to:

- a) evaluate the extent to which existing NP/NS have actually been implemented in European countries;
- b) encourage countries to adopt their 2nd and 3rd NP/NS, to maintain the much-needed national focus and momentum on rare diseases; and
- c) define the key objectives and content for this next generation of NP/NS, by identifying good practices which have yielded results in particular countries/regions, assessing their transferability to other countries/situations, and agreeing *new* issues and topics which should be addressed via robust Plans and Strategies for the coming years.

More detailed and updated information on the status of European NP/NS will be available via the dedicated output 'state of the art of national plans and strategies for rare diseases in Europe' (Autumn 2018)

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 (OMPs). Policies for OMPs 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 OMPs 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 diseases, designed to guide and structure rare disease 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 MS, the number of European countries having adopted a NP or NS for rare diseases at some stage now sits at 25. 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.

NB – 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 Act³⁵ of 2002**.

Research: A flagship of the US rare disease policy framework is the Office of Rare Diseases Research³⁶ (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 Networks³⁷.

The Undiagnosed Diseases Network³⁸ was launched in 2008 and is funded by the NIH Common Fund. Coordinated by the Department of Biomedical Informatics at Harvard Medical School, it

³⁵ <http://history.nih.gov/research/downloads/PL107-280.pdf>

³⁶ <http://www.ncats.nih.gov/research/rare-diseases/ordr/ordr.html>

³⁷ <http://rarediseases.info.nih.gov/research/pages/41/rare-diseases-clinical-research-network>

operates via a shared cloud portal through which patients can apply and researchers and clinicians can collaborate.³⁹ 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.⁴⁰ These new grants were awarded through the Orphan Products Clinical Trials Grants Program, to principal investigators from academia and industry working on both national and multinational trials.

In early 2016, the NIH National Human Genome Research Institute (NHGRI) announced⁴¹ 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.

In October 2017, the FDA⁴² announced it had awarded 15 new clinical trial research grants totalling over \$22 million across the next four years, to boost the development of products (drugs, biologics, medical devices, or medical foods) for patients with rare diseases. These new grants were awarded to principal investigators from academia and industry across the United States

Orphan Drug Legislation

The US was the first country world-wide to pass legislation on 'orphan drugs' – the 1983 'Orphan Drug Act'⁴³ 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

³⁸ <https://undiagnosed.hms.harvard.edu/> .

³⁹ A recent of the protocol and progress of the UDN can be found here - [https://www.cell.com/ajhg/fulltext/S0002-9297\(17\)30006-X](https://www.cell.com/ajhg/fulltext/S0002-9297(17)30006-X)
⁴⁰ <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm525468.htm>

⁴¹ <https://www.nih.gov/news-events/news-releases/nih-genome-sequencing-program-targets-genomic-bases-common-rare-disease>

⁴² <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm579366.htm>

⁴³ <http://history.nih.gov/research/downloads/PL97-414.pdf>

OOPD⁴⁴ (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);
- 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"*⁴⁵

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 revisions⁴⁶ 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

⁴⁴ <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm>

⁴⁵ <http://www.orpha.net/actor/EuropaNews/2012/120901.html>

⁴⁶ <http://www.gpo.gov/fdsys/pkg/FR-2013-06-12/pdf/2013-13930.pdf>

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”.

In 2017, the Centre for Drug Evaluation and Research (CDER) at the FDA -which oversees the approval of small molecules and antibodies - reported the approval of 46 novel drugs (either as new molecular entities under New Drug Applications or as new therapeutic biologics under Biologics License Applications). 18 were approved to treat rare diseases, including Brineura (cerliponase alfa), a treatment for a specific form of Batten disease, and Hemlibra (emicizumab), for the prevention of bleeding (or to reduce the frequency of bleeding episodes) in patients with haemophilia.⁴⁷

Patient Alliance

June 2018 marked the 35th anniversary of the patient organisation NORD (the National Organization for Rare Disorders), which began as a grassroots coalition of rare disease advocates who played a key role in the passage of the Orphan Drug Act. NORD later evolved into a leading American charity helping to support orphan drug programmes throughout the world, working closely with health related industries, rare disease consumer groups, the research community and the government.

Rare Disease Registration: The ORDR launched a pilot project in 2012 to establish the Global Rare Diseases Patient Registry and Data Repository (GRDR)⁴⁸. 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.

⁴⁷<https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ReportsBudgets/UCM591976.pdf>

⁴⁸<http://www.ncats.nih.gov/grdr>

In 2017, the GRDR changed its name to the Rare Disease Registry (RaDaR) Program.⁴⁹ The old GRDR website will be revised to form the RaDaR website, and will include up-to-date information on the status of the RaDaR. This next phase of activity will focus on:

- Identifying, validating, and developing data standards, data collections and data sharing practices that can be broadly accepted and used across the rare disease registry community.
- Developing best practices and advice to build high-quality registries able to support therapeutics development; and
- Ensuring that advice and standards are made broadly available to -and are easily accessible by- the rare disease community.

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.⁵⁰ 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.

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. PhenomeCentral⁵¹ 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

⁴⁹ <https://rarediseases.info.nih.gov/radar>

⁵⁰ http://www.raredisorders.ca//content/uploads/CORD_Canada_RD_Strategy_22May15.pdf

⁵¹ <https://www.ncbi.nlm.nih.gov/pubmed/26251998> and <https://www.phenomecentral.org/About>

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 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.

Genome Canada initiated a 10.4 million CAD initiative known as the ‘Silent Genome’⁵² project in 2017. Led by researchers at the University of British Columbia, the project aims to create a database of genetic variations among Indigenous populations living in Canada and globally, to enable more accurate diagnosis and treatment of Indigenous patients.

The Canadian Organization for Rare Disorders (CORD) 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.⁵³

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.

In recent 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.**

⁵² <https://www.genomecanada.ca/en/silent-genomes-reducing-health-care-disparities-and-improving-diagnostic-success-indigenous-children>

⁵³ F1000 Research published a review 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 <https://f1000research.com/articles/4-57/v1>

26.689⁵⁴ -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**⁵⁵ 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 meetings.⁵⁶ Moreover, Argentina is promoting the use of telemedicine within its health system more broadly, through the National Cybersalud Plan adopted in 2014:⁵⁷ rare diseases may be a particular beneficiary of such approaches.

ii. Peru

Peru established its first national law concerning patients with rare diseases in the Summer of 2011. **Law 29698**⁵⁸ 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’.⁵⁹

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.⁶⁰

⁵⁴ <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>

⁵⁵ <http://www.alua.org.ar/DISPOSICION%20%204622-2012%20ANMAT.pdf>

⁵⁶ See <http://www.cybersalud.gob.ar/>

⁵⁷ https://www.paho.org/arg/index.php?option=com_content&view=article&id=9789:cibersalud-mejor-conectividad-que-aporta-al-acceso-universal-en-salud-de-los-argentinos&Itemid=270

⁵⁸ <http://www.orpha.net/actor/EuropaNews/2011/doc/PeruLaw.pdf>

⁵⁹ <http://www.minsa.gob.pe/erh/index.html>

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 29698.⁶¹

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 established⁶² 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.⁶³ 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.⁶⁴

Colombia recently established its first rare disease registry, following the passage of laws promoting the development of clinical guidelines for diagnosis, management, census and registry of patients suffering from rare conditions. In total, 13,215 patients have been recorded in the Colombian registry, covering 653 rare diseases.⁶⁵

⁶⁰ <http://lainfo.es/en/2014/02/23/published-list-of-399-rare-diseases-in-peru/#more-3953>

⁶¹ : <http://www.rarediseaseday.org/country/pe/peru>

⁶² <http://www.fecoer.org/>

⁶³ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4367080/> and <https://cuentadealtocosto.org/site/index.php/patologias/9-patologias/24-enfermedades-huerfanas/?template=cuentadealtocostocontenido>

⁶⁴ <https://decisionresourcesgroup.com/drg-blog/rare-diseases-a-colombian-perspective/>

⁶⁵ <https://link.springer.com/content/pdf/10.1186%2Fs13104-017-2840-1.pdf>

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 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**,⁶⁶ 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 2015⁶⁷.

⁶⁶ http://bvsm.sau.de.gov.br/bvs/sau.delegis/gm/2014/prt0199_30_01_2014.html

⁶⁷ <https://www.ihs.com/country-industry-forecasting.html?ID=1065999046>

C. Asia

Asia gave the world its first programme for rare disease research and care back in 1972, when Japan established the Medical Care Programme for Specific Diseases. Today, more countries are joining the call to elaborate and adopt specific legislation and national frameworks to support people living with a rare disease. Recent years have seen the emergence of geographically broad grass-roots movements in the rare disease patient community:

- Rainbow Across Borders (RAB)⁶⁸ was the first regional patient support group alliance in Asia. Founded in Singapore in 2015, RAB works closely with many stakeholders from countries in the region and all across the world. In November 2016, RAB organised the Second Asia Rare Diseases Conference entitled ‘Working in Once Voice’ which took place in Kuala Lumpur
- RAB served as a catalyst towards the creation of the first ASEAN+ Rare Disease Network in 2017.⁶⁹ This Network unites patient support groups from across Southeast Asia and Hong Kong, and seeks to better understand the needs of rare disease patients and their caregivers in the region, in order to identify areas of improvement and mobilise community involvement and humanitarian solutions.

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)⁷⁰. 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 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

⁶⁸ <http://www.rabasia.org/>

⁶⁹ See for instance <https://www.asiabiotech.com/21/2106/21060014x.html>

⁷⁰ <http://www.nanbyou.or.jp/english/index.htm>

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 emphasis 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 UK. A major goal is the establishment of a genome database of people with rare diseases.⁷¹

In 2017, the IRUD moved into its second phase, entitled 'IRUD Beyond', composed of three AMED-supported activity clusters:

1. Beyond diagnosis: Innovative medical drug candidates will be sought by targeting novel, single pathological mutations discovered in IRUD research.
2. Beyond genotyping: Innovative technologies will be applied to cases which remain unsolved following next generation sequencing (NGS)-based genome analysis.
3. Beyond borders: International data sharing will be enhanced, to integrate currently inaccessible but medically valuable databases to globally compatible systems.

In 2018, Japan became the first country in Asia to officially join the Orphanet Consortium as the 41st member.

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 license 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 drug 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

⁷¹ <http://www.amed.go.jp/en/program/IRUD/>

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.

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.⁷² 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 2000⁷³. 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.

⁷² <https://www.singhealth.com.sg/DoctorsAndHealthcareProfessionals/Medical-News/2007/Pages/Expanded-Newborn-Screening-Using-Tandem-Mass-Spectrometry.aspx>

⁷³ http://www.tfrd.org.tw/english/laws/upload/20080328098114_01.html

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 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 helpline⁷⁴ 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)⁷⁵ 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 currently 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. Since then, several attempts were made to create a list of diseases recognised as 'rare' in China. In May 2018, an important step was taken: China published its first official *National List of Rare Diseases*. This list was issued jointly by five national bodies, including the National Health Commission, the Ministry of Science and Technology, the Ministry of Industry and Information Technology, the State Drug Administration, and the State Administration of Traditional Chinese Medicine. 121 rare diseases were identified. In creating the list, priority was given to rare diseases with a relatively high prevalence which pose a significant burden, and are

⁷⁴ <http://helpline.nih.go.kr/cdhelp/index.gst>

⁷⁵ <http://www.snubi.org/software/raredisease/>

highly treatable. It is hoped that this will facilitate treatment and raise awareness of these conditions, and of the concept of rare diseases in China.⁷⁶

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 diseases⁷⁷.

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 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 were summarised as follows:⁷⁸

- 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
 - 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.

- 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.

Related to the Second Goal - in December 2016, a 'Rare Diseases Clinical Cohort Study' was launched, seeking to create a unified national rare disease registry system in China. The study will last until 2020 and will include an investigation and analysis of more than 50 rare conditions.⁷⁹

⁷⁶ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5982625/>

⁷⁷ *Intractable and rare diseases research in Asia*, P Song et al, *BioScience Trends*, 2012 ; 6(2):48-51

⁷⁸ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3937133/>

⁷⁹ <https://www.liebertpub.com/doi/pdf/10.1089/hum.2017.215>

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) had imposed regulatory constraints on the provision of clinical genetic tests.⁸⁰ The scope of the ban is unclear: there was a blanket ban on prenatal DNA testing, for instance, but the exact scope of what falls inside the ban is ambiguous (e.g. the status of cancer screening).

In 2016, several articles were published regarding rare disease policies in China,⁸¹ which expressed concern over the availability of OMPs. These articles emphasise that even when drugs *are* available, many are not reimbursed: one publication claims that 22 orphan drugs available in China (for 14 diseases) are unaffordable for most of the Chinese population.⁸²

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 diseases, designed to help them cope with their illnesses and at the same time build a support system around them.⁸³

ICORD (the International Conference on Rare Diseases and Orphan Drugs) was held in 2017 in Beijing, back to back with the 6th China Rare Disease Summit organised by the Chinese Organization for Rare Disorders.⁸⁴

⁸⁰ <http://www.phgfoundation.org/blog/15702/> and <http://www.forbes.com/sites/shuchingjeanchen/2014/03/03/china-cracks-down-on-dna-testing-2/#3e52d5d17407>

⁸¹ <http://ojrd.biomedcentral.com/articles/10.1186/s13023-015-0361-3>; <http://ojrd.biomedcentral.com/articles/10.1186/s13023-015-0333-7>

⁸² <http://ojrd.biomedcentral.com/articles/10.1186/s13023-016-0392-4>

⁸³ <http://www.orpha.net/actor/EuropaNews/2015/150117.html>

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

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;

⁸⁴ <http://icord.se/past-events/icord-2017-in-beijing-china>

- 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 2011⁸⁵. 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

⁸⁵ <http://www.ojrd.com/content/7/1/50/abstract>

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 report⁸⁶ 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 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)⁸⁷ 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.)

⁸⁶ <https://mckellinstitute.org.au/app/uploads/McKell-Institute-Funding-Rare-Disease-Therapies-in-Australia-Nov-2014.pdf>

⁸⁷ http://www.nzord.org.nz/_data/assets/pdf_file/0004/56695/NZORD-2016-Annual-Report.pdf

New Zealand's pharmaceutical management agency [PHARMAC](#), established a rare disease pilot⁸⁸ 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 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

At present, Russia's Ministry of Health maintains a list of 215 rare diseases. In June 2018, the Russian Federation Council emphasised the need for an increased focus on ensuring that people with rare diseases receive appropriate medication, wherever they live. This Council announced that a new law would be created, to improve the situation: it is expected that the medicines will be purchased by central government authorities using national funds, and subsequently made available to people living in the regions.⁸⁹

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;

⁸⁸ <https://www.pharmac.govt.nz/medicines/how-medicines-are-funded/medicines-for-rare-disorders/>

⁸⁹ <http://www.bearr.org/new-law-to-give-russians-access-to-medication-for-rare-diseases>

- 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.⁹⁰

⁹⁰ <https://www.mzsr.gov.kz/en/node/334964>

4. Expert services in Europe: 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 2006⁹¹ 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***⁹².

The Council Recommendation on an action in the field of rare diseases (2009) asked MS 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 drive for countries to endorse centres to formally join ERNs has, in some ways, reignited the topic of Centre of Expertise designation. Each country was responsible for defining its own criteria and procedure by which to endorse a Centre (HCP in the ERN vernacular) to participate, and naturally these criteria varied. For some countries, the logical approach –given the particular relevance of ERNs to rare disease– was to only endorse national centres which had formally been designated as a centre of expertise (or similar) for rare diseases. And indeed, for some countries this was a proviso. Other countries, including those which did not have a formal process in place for designating CEs for rare diseases, found other ways to endorse applicants. This has led to at least two issues:

- 1.) There is concern in some countries about the robustness of the criteria others have used to endorse their HCPs to participate formally in the ERNs: it is likely that some HCPs are indeed functioning as ‘true’ CEs in the sense that they fulfil the criteria (or most of the criteria) for excellence established by the EUCERD. However, it is also likely that some centres have been granted the accolade of HCPs but were *not* assessed against the EUCERD criteria or a similarly robust national criteria system, and thus are not perhaps commensurate with the concept of a rare disease CE in Europe. Thus there is the risk that

⁹¹ <http://www.eucerd.eu/upload/file/Publication/RDTFECD2006.pdf>

⁹² <http://www.eucerd.eu/upload/file/EUCERDRecommendationCE.pdf>

the ERNs encompass a certain degree of heterogeneity in terms of the excellence of their constituent member HCPs. One consequence of this, potentially, could be a lack of mutual trust and confidence in the quality of care and advice stemming from HCPs in other countries (which could in turn impact on national authorities' willingness to actually implement advice from that ERN).

- 2.) There is a concern that in the countries without a formal process to designate CEs in rare diseases, or in countries which have begun this work but have far still to go, this essential process of mapping and officially acknowledging particular types of rare disease expertise will stall or will not take place. Countries might feel that endorsement of a handful of HCPs to participate in ERNs is sufficient, whereas in reality it is essential to nonetheless establish a clear internal perspective on the sort of expertise available in-country for particular diseases, and to make that information publically available. Indeed, a well-mapped and well-organised national approach to rare disease diagnosis, treatment and care is essential for the efficient operations of ERNs (which should complement but never unnecessarily *replace* national pathways for patients).

It is important to note that the topic of 'centre of expertise for rare diseases' emerged as one of the key priorities for European countries during the 19 Europlan national conferences/roundtables organised between 2015 and 2018 under the framework of RD-ACTION.⁹³

The dedicated supplement on centres of expertise for rare disease will be available in Autumn 2018, and will present the latest information of the respective designation procedures for Centres of Expertise in Europe.

⁹³ <http://www.rd-action.eu/europlan-rd-national-plans-conferences-reports/>

5. Expert services in Europe: European Reference Networks

5.1 The Concept

Following their formal approval at the end of 2016⁹⁴, the 24 European Reference Networks (ERNs) have taken significant strides over the last eighteen months to evolve from conceptual entities to functional Networks establishing concrete systems to impact positively on the diagnosis, treatment and care of rare diseases/other domains requiring a particular concentration of expertise and resources.

Under the terms of Directive 2011/24/EU (the so-called Cross-Border Healthcare Directive) Europeans are entitled to seek healthcare in a country besides the country of residence, under specific circumstances and by following pre-determined procedures. ERNs (based upon Article 12 of the aforementioned Directive) 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.

There are now 24 ERNs, involving over 900 specialist units in over 300 hospitals across 26 countries (25 EU MS –all except Greece, Malta, and the Slovak Republic- plus Norway).

Information about the 24 Networks, their scope and their priorities, is available here - http://ec.europa.eu/health/ern/policy_en, where one can find:

- the downloadable brochure, summarising all 24 Networks (see screenshot above)
- a myriad of communication materials, including videos and leaflets
- Summaries of each country's participation in ERNs (i.e. lists showing which HCPs are members of which ERNs)
- Summaries of each ERN, listing the member HCPs per country
- Links to the individual websites of the ERNs.

Further information was compiled during the ERN application process by the RD-ACTION team and is available [here](#))



⁹⁴ In the case of ERN EuroGEN, the beginning of 2017

5.2 The Road to ERNs

5.2.1 The 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.)

5.2.2 The 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 rare disease 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 Commission Expert Group on Rare Diseases (CEGRD) 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.**

5.2.3 Addendum to the Original Recommendations

At the November 2014 meeting of the CEGRD, it was agreed that although the Recommendations on Rare Disease ERNs overall remained highly relevant and comprehensive, **two topics should be revisited and elaborated at this stage:** the grouping of rare diseases into thematic networks and the necessity of a patient-centred approach to ERNs. Accordingly, the Addendum was drafted by the Joint Action for Rare Disease and was adopted by the CEGRD in June 2015. **This Addendum had a fundamental impact on the development of ERNs, in two key ways:**

- 1) It stipulated that meaningful patient participation and engagement in ERNs meant the following:
 - 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 built the framework to ensure that all rare disease patients could find a 'home' within a logical, manageable number of broad ERNs, by proposing a disease-grouping model:

- 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

5.2.4 The Application process and launch of ERNs

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.

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 ERNs. This was a major event, involving approximately 600 delegates.



Fig. 3: The official launch of the ERNs in Vilnius, March 2017

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**.

5.3 The Status Quo of ERN Operations: 2018

Once established, ERNs commenced work very rapidly in 2017, seeking to address their multiple responsibilities as Networks spanning the domains of care *and* research for rare diseases/conditions requiring a concentration of expertise. By mid-2018, the Networks and their Coordinators have already managed to make important strides, in various domains.⁹⁵

5.3.1 Virtual Patient Care

The ERNs now all have access to a dedicated Clinical Patient Management System ([CPMS](#)), through which to provide virtual, cross-expert and cross-border consultations for real patients whose cases warrant the pooling of knowledge across the ERN community. Virtual case review was always [acknowledged as the heart of the ERNs](#) and a way to bring advice to professionals both inside and outside of the Network's member centres (Health Care Providers, or HCPs) and support them by recommending routes to diagnosis, advising on optimal care and treatment regimes, assessing suitability for surgery, etc. The CPMS was delivered via a Tendering process, in which the successful bid was led by [OpenApp](#) (a software company based in Dublin, specialising in innovative healthcare solutions). The System went 'live' in November 2017, and as of May 2018, over 100 patients had

⁹⁵ Much of this material stems from the Editorial for the of 9th February 2018 edition of OrphaNews, which was written by the SoA Team

been referred via the CPMS. Adaptations and improvements are foreseen to the CPMS over the next year, in-line with the expressed needs of the community (for instance, there should hopefully be opportunities to implement the sorts of tools and resources highlighted in the [Recommended Practices for Data Standardisation in the Context of the Operations of ERNs.](#)) It is already possible to involve experts from across different ERNs in the virtual consultations. Important next steps, as the volume of data entered to this system increases, will be strategic decisions on how to link such data with valuable data housed in other -currently separate- resources, such as registries of value to the ERNs' sphere of expertise, electronic health records, biobanks, and more.

5.3.2 Data Integration and Interoperability

This question of data interoperability and 'linkability' will foreseeably be an important focus of 5 ERN-specific grants awarded in 2017 through the Public Health Programme. A Call was launched, to provide 'support for new registries' based upon ERNs. This was a competitive call, attracting 21 proposals. 5 ERNs were ultimately successful, and details of their proposals are available via the links below:

- EndoERN ([European Registries for Rare Endocrine Conditions \(EuRECa\)](#))
- ERK-NET ([ERKNet Registry for Rare Kidney Diseases \(ERK-REG\)](#))
- ERN-LUNG ([RD REGISTRY DATA WAREHOUSE \[REGISTRY WAREHOUSE\]](#))
- MetabERN ([Unified European Registry for Inherited Metabolic Disorders \[U-IMD\]](#))
- PAEDCAN ([ERN-PAEDCAN Partner: Paediatric Rare Tumours Network - European Registry \[PARTNER\]](#))

There are fundamental questions concerning how ERNs can make best use of the (often fragmented and *not* interoperable) disease-focused registries that exist under the broad Thematic Groups around which the ERNs are arranged:

- How can existing collections 'speak' to each other and enable the pooling of this data (or at least the querying of these collections at a metadata level, to see what *sort* of data is there)?
- Where are the gaps/where might new registries be desirable?
- How should these new registries be built, to optimise the value and usability of prospective -and ideally legacy- data?

Several initiatives are exploring how to integrate data pertaining to rare disease registries (see below 7.3). In the meantime, it is anticipated that the experiences and achievements of these 5 funded ERNs will help to shape advice and recommendations for the remaining 19 Networks, regarding how best to approach this crucial but challenging topic.

5.3.3 Financial Support for ERNs

The European Commission has provided non-competitive funding opportunities to all of the Networks, for general coordination purposes, which is essential to the operations of the ERNs. The Networks applied for 5-year Framework Partnership Agreements, and as of July 2018 are about to

submit the 3rd applications for Coordination funding (under the Single Grant Agreement mechanism): the 2018 Public Health Programme dedicates 13.8 Million Euros to the Networks (cumulatively) in ‘Multiannual specific grant agreements for European Reference Networks’ for years 3-5. Furthermore, a Call was launched in 2017 via the Connecting Europe Facility (CEF), to support the ERNs in engaging with and using the CPMS. This [Call](#) offered a maximum of 9 Million Euros, cumulatively, and is enabling each ERN to appoint help-desk staff/ IT experts to support engagement with the CPMS. A subsequent call will open in summer 2018, with a budget of 5 million Euros cumulatively, designed to sustain these posts for the year 2019-2020.

5.3.4 Governance Structures of the ERN Coordinators

ERNs are excellent example of pan-European collaboration, uniting many different stakeholder groups: as such, they are a very attractive resource for future collaborations with many actors, as they touch-upon many topics under the rare disease ‘umbrella’ and indeed are ‘ripe’ for expansion beyond, into fields such as data-stewardship and interoperability, eHealth and mHealth, paediatrics, and patient empowerment. It is therefore important for these wider communities to understand the governance model of the 24 ERNs, which was developed in mid-2017, to ensure collaboration and avoid duplication of efforts in many key areas of activity. Recognising the sheer number of ERNs, and the need to strategically oversee representation at meetings and events with a relevance to *all* Networks, the ERN Coordinators Group (ECG) was formed, headed by a rotating Chair. Maurizio Scarpa, Coordinator of the MetabERN, severed as Chair of the ECG for the first year, from June 2017. Franz Schafer (ERK-NET) is currently the Chair of the ECG, as of the June 2018 ECG meeting. The Coordinators organised themselves into dedicated Working Groups on the following topics:

IT and Data-Sharing	Chair: Ruth Ladenstein, ERNPaedcan
Research	Chair: Eduardo López Granados, ERN TransplantChild
Legal Aspects, Data Protection and Ethics	Chair: Nicoline Hoogerbrugge, GENTURIS
Cross-Border Healthcare and Business Continuity	Chairs: Holm Graessner (ERN-RND) and Kate Bushby (EURO-NMD)
Monitoring and Assessment	Chair: Chris Chapple, EUROGEN
Guidelines, Education and Training	Chair: Paolo Casali, ERN EURACAN
Special projects; NHS Integration; Sustainability	Chair: Maurizio Scarpa, MetabERN

Fig. 4: Working Groups of the ERN Coordinators' Group, as of May 2018

5.3.5 Collaboration with the Board of Member States of ERNs

The ERN Coordinators' Group meets several times per year, typically back-to-back with the meetings of the ERN Board of Member States. (The Minutes of the latter are published and available [here](#).)

5.3.6 Patient Involvement in ERNs

The EUCERD ERN Recommendations⁹⁶ and Addendum⁹⁷ formally recognised the critical and integral role that patient representatives play as formal members of the decision and opinion making structures of ERNs. As experts by experience, rare disease patients draw on their knowledge of living with a rare disease, enhancing the expertise in clinical services and research networks, building a critical mass of knowledge to tackle the EU rare disease public health priority. ERNs provide a unique opportunity for patients and clinicians to collaborate across Europe, to drive forward improvements in access and quality of diagnosis, care and treatment for people living with a rare disease. The success of the Networks depends on the degree and effectiveness of this collaboration. ERNs are created on the founding principle of patient centeredness and empowerment, with patients being central to the governance and decision making of the networks.



In 2016 EURORDIS, in collaboration with the European rare disease community, established 24 **European Patient Advocacy Groups (ePAGs)** as forums to optimise the involvement of patient representatives of the rare disease community in the 24 ERNs. Each ePAG corresponds to the scope of one of the 24 ERNs, aligning patient organisations and clinicians, experts and researchers working on the same rare or complex disease or highly specialised intervention. Today there are over 300 ePAG patient advocates participating in the different groups. The ePAG advocates have been involved in the development of ERNs' applications and are currently members of the ERNs Boards, Steering Committees and task forces.

5.3.7 Future Expansion of ERNs

An important issue in 2018 is how to manage the expansion of the 24 ERNs, both in terms of

- a) launching a call for new Member HCPs; and
- b) agreeing how to bestow the status of 'affiliated' partners, as outlined in the Legal Acts governing ERN operations.

Regarding the former, it will be important for the ERNs to accrue new members in a logical, strategic way, to meet the goal of ensuring -through stepwise development- a comprehensive coverage of all rare conditions, and also to maximise geographical coverage by encouraging all

⁹⁶ http://www.eucerd.eu/?post_type=document&p=2207

⁹⁷ https://ec.europa.eu/health/sites/health/files/rare_diseases/docs/20150610_erns_eucerdaddendum_en.pdf

eligible countries to participate (ideally via a limited number of HCPs to activate a ‘hub and spoke’ model, engaging all national experts via these select member HCPs). The timing of the next call for membership is not confirmed, as the Board of Member States, DG Sante, and the ERN Coordinators, are in discussion to agree the best way forwards.

Recently, the BoMS published several official documents on the topic of the so-called ‘Affiliated Partners’:

- *Statement adopted by the Board of Member States on the definition and minimum recommended criteria for Associated National Centres and Coordination Hubs designated by Member States and their link to European Reference Networks* (November 2017) ⁹⁸
- *Statement on the Timeline for the designation of Associated National Centres and Coordination Hubs (Affiliated Partners) by the Member States* (June 2018) ⁹⁹
- *Rules for Termination of Affiliated Partners* (June 2018) ¹⁰⁰

5.3.8 Fourth Official ERN Conference

The 4th official ERN Conference will take place from 21st -22nd November in Brussels, with the theme of ‘ERNs in Action’. The conference will highlight key successes in the ERN story to-date, whilst analysing the challenges that ERNs are facing in terms of deployment, and seeking ways to overcome these challenges. The conference will combine plenary sessions with parallel sessions each addressing particular topic, for instance clinical practice guidelines, clinical research, patient engagement, etc. News of the conference (e.g. the final agenda) will be published here - https://ec.europa.eu/health/ern_en in due course.

5.4 RD-ACTION Support for ERNs

RD-ACTION (2015-2018) inherited the mandate of the previous Joint Action for Rare Diseases (the EUCERD Joint Action) – i.e. supporting the rare disease field in adding depth and clarity to the concept of an ERN and preparing the way for implementation of the Networks. Through its Policy and Integration WP (WP6 - led by Newcastle University) in particular, RD-ACTION has supported the ERNs by organising meetings and workshops and seeking to create policies and guidance *with* the Networks, *for* the Networks.

HANDS-ON SUPPORT TO ENSURE COLLABORATIVE AND NON-COMPETITIVE ERN PROPOSALS

- In preparation for the first Call for ERNs, RD-ACTION organised a major workshop (Summer 2015) to build capacity amongst field leaders and assist the RD community in organising itself around the 21 broad thematic groupings identified by this same team and adopted by the CEGRD as the backbone for ERN structure and scope.
- As many experts expressed a desire for a means of identifying Healthcare Providers (HCPs) interested in setting –up/joining an ERN within the same disease area, the RD-ACTION team designed a ‘**Matchmaker tool**’. Launched in December 2015, the Matchmaker ran

⁹⁸ https://ec.europa.eu/health/sites/health/files/ern/docs/boms_affiliated_partners_en.pdf

⁹⁹ https://ec.europa.eu/health/sites/health/files/ern/docs/2018_statementtimeline_ap_en.pdf

¹⁰⁰ https://ec.europa.eu/health/sites/health/files/ern/docs/2018_rulestermination_ap_en.pdf

until May 2016. This tool allowed the specialists to make contact and align intentions. In total, the Matchmaker had received **801** responses across the **21** thematic groups.

POLICY SUPPORT FOR ERNs

The ERNs represent a great opportunity to embed good practices and disseminate these into broader healthcare systems. RD-ACTION's vision was that, as ERNs were established & evolved, dedicated guidance would be important to support but also to ensure a baseline compatibility and interoperability (at many levels) *between* the ERNs. RD-ACTION partners thus developed a workplan for the years 2016-2018, designed to capitalise on the lessons learned in the broader RD field and 'pilot' Networks and bring these to the ERN stakeholder community, to agree together how to address shared challenges. By the end of the project, 6 major workshops have been delivered (many co-organised with DG Sante) each addressing a particular policy area in which consensus building was deemed important.

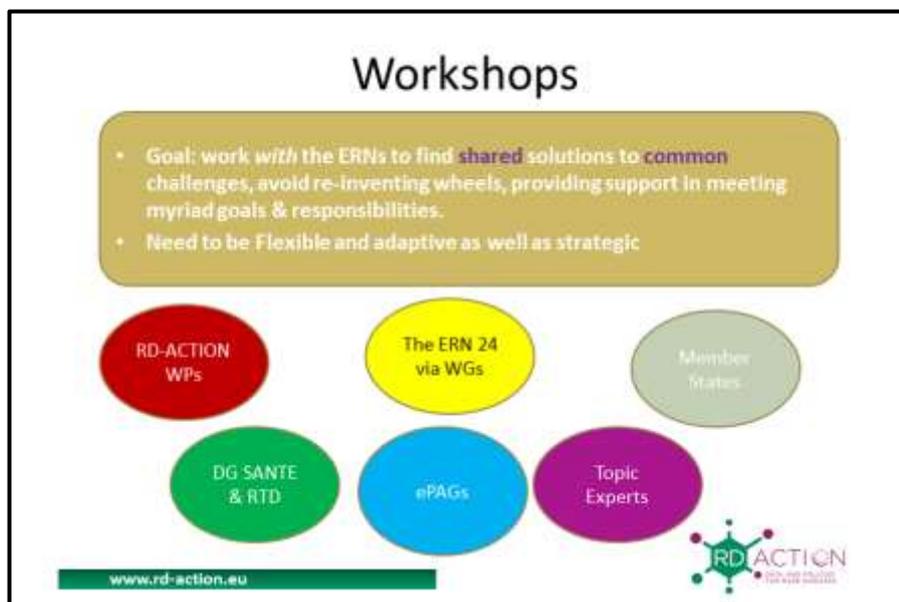


Fig. 5: Stakeholders involved in RD-ACTION ERN-focused workshops

5.4.1 Workshops

Exchanging data for virtual care in the ERN framework – 27-28 September 2016, Brussels: With over 55 participants, this workshop:

- ✓ Agreed practical advice to enhance the efficiency and utility of virtual consultations;
- ✓ Clarified the legal issues around data protection -especially in view of the new General Data Protection Regulation- and the legal, ethical and social issues relating to consent for the sharing of data in the ERN framework;
- ✓ Brainstormed how patients will enter/ be 'referred' to the ERN for virtual care
- ✓ Shared experiences on the standardisation of data in the RD field, to identify good practices which should be embedded in the ERNs

Using standards and embedding good practices to promote interoperable data sharing in ERNs – 26-27th April 2017, Brussels: 68 participants (a mixture of ERN Coordinators, EURORDIS and Orphanet partners, data/eHealth specialists, Coding experts, Phenotype ontology experts, data linkage experts, and DG Sante representatives) met to agree how best to capture data collected in the ERNs for care purposes.

- ✓ After previously identifying the value of using the ORDO and the HPO -deemed most sensitive and appropriate ontologies for RD- participants had expressed a desire to learn more about how to use these sorts of tools practically, to optimise the use and re-use of data collection in the ERN context.
- ✓ This was followed by a session on linking data, especially through the concepts of FAIR data and the 'PPRL'.
- ✓ The workshop generated a list of recommended good practices, to enhance the use and reusability of data collected in the operations of ERNs, and created 'tool-kits' on how to practically use the most relevant of these data resources/practices.

Indicators and Outcomes for ERNs - 1-2 June 2017, Newcastle: This workshop united 40 participants to work closely on issues related to the impact and monitoring of ERNs. It allowed the ERN community to:

- ✓ better understand terminology around indicators and become acquainted with the different types of indicators (structure, process, outcome) and their use in health systems
- ✓ to discuss an initial set of indicators, common to all ERNs, for the purposes of monitoring impact, and isolate the definitions needed to advance this selection
- ✓ to identify key issues and challenges on data collection and reporting
- ✓ to elucidate the challenges in selecting clinically-oriented indicators in the rare disease/highly specialised healthcare field

How can ERNs generate, appraise and utilise clinical practice guidelines, to enhance the impact of consensus guidelines in national health systems? 6-7 Dec 2017, Rome: This workshop united 63 participants to discuss for the first time the various ways in which ERNs might add value to a host of activities concerning Clinical Practice Guidelines (CPGs). The group sought to identify good practices which could be shaped into 'recommendations' concerning several aspects of this vast and complex topic, including:

- ✓ methodological approaches to the generation and appraisal of CPGs;
- ✓ strategies for engaging with key stakeholder groups, such as patients and learned societies to partner in all CPG activities
- ✓ highlighting financial issues and time-commitments of guideline activity, proposing strategies to address the need for ethical engagement with stakeholders such as Industry
- ✓ options to engage national authorities, to ensure that CPGs emerging from ERNs can actually be used 'on the ground' in countries
- ✓ outlining concrete future activities needed to support the ERNs in their CPG-related tasks

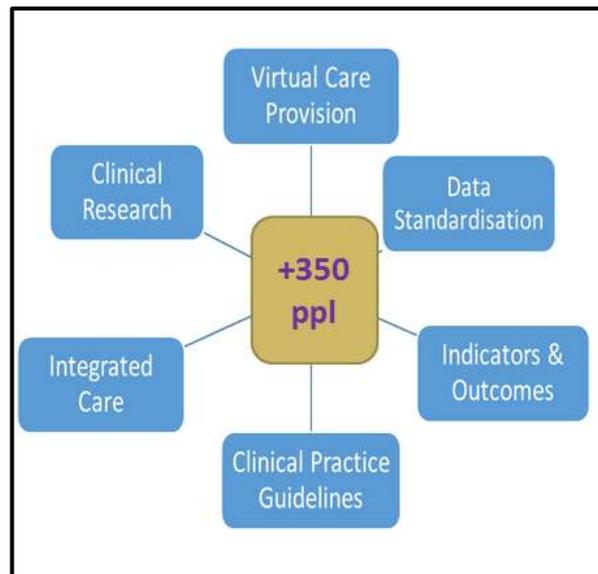


Fig. 6: Overview of the key topics of RD-ACTION's ERN-focused workshops

Creating a Sustainable Environment for Holistic & Innovative Care for Rare Diseases & Complex Conditions - 12-13 April 2018., Frambu, Norway: This workshop, hosted at Frambu Resource Centre, was organised jointly with the [INNOVCare initiative](#). The event united 67 participants from 22 countries, with diverse backgrounds. The workshop addressed many issues, including the following:

- ✓ The state of the art in terms of integrated, holistic approaches to care for people with rare diseases
- ✓ How best to enhance and expand identified good practices to support integrated and holistic care
- ✓ How ERNs -or, sometimes more appropriately, the Healthcare Providers of which they are composed) might add value in this arena

The workshop participants proposed practical actions which could be feasible for ERNs and their constituent HCPs (essentially centres of expertise), for instance concerning patient empowerment and involvement; identifying the full medical and societal burden of rare diseases; creating high quality information resources and 'setting the standard' for the types of multidisciplinary, holistic care that patients with a given conditions should receive; etc.

How ERNs can add value to clinical research in rare diseases and highly specialised domains - 29th -30th May 2018, London: This workshop was hosted by the European Medicines Agency: the EMA was a co-organiser this time, along with DG SANTE (and RD-ACTION of course). The workshop united 64 participants, and had several ambitious goals:

- ✓ To share the state of the art of tools and resources which exist in 2018 to streamline and optimise each 'point' in the clinical research pipeline

- ✓ To better understand the priorities and needs of the ERN community specific to clinical research, and explore case studies
- ✓ To elucidate the services and opportunities offered by the EMA which are of relevance to clinical research in rare and highly specialised domains
- ✓ To identify concretely how and where ERNs could make a positive difference to each 'timepoint' in the clinical trial pathway, including points of engagement specifically with the EMA, to agree a roadmap to a more strategic and streamlined collaboration in future.

In addition to these large, ERN-focused workshops, RD-ACTION Policy & Integration Work-Package organised several meetings and workshops in 2015 and 2016, designed to build synergies between the ERN and rare disease community on the one hand, and the eHealth field on the other (see <http://www.rd-action.eu/ehealth-and-european-reference-networks/>)

5.4.2 Sample Outputs

The workshops were a key part of the project's activities in the ERN sphere, but WP6 has been active in uniting and supporting the Networks in other ways, as evidenced from the following sample of outputs:

- [Concept paper on convergence of eHealth and Rare Disease initiatives \(2016\)](#)
- Report on [1st meeting between the ERN Board of MS and the future Coordinators \(Sept '16\)](#)
- [Highlights and conclusions from Workshop on Exchanging data for Virtual Care](#) (Sept '16)
- [Identifying ERN requirements for an IT platform](#) (Aug '16 exploration of IT needs and correlation to published CPMS Tender)
- Canvassing of ERN plans and perspectives re. Registries (Nov '16) and [Analysis of the key issues concerning ERNs & Registries](#)
- [Report on Activities of the JA Task-Force on Interoperable Data-sharing in the framework of the operations of ERNs](#)
- [Canvassing perspectives on ERNs and Research](#) for Maltese Presidency event (March '17)
- [Draft Annotated Table](#) of core indicators for ERNs (Summer '17) (built upon DG Sante draft and subsequently refined by a dedicated ERN Working Group)
- [Tool-Kits on resources for standardising data](#) (Summer '17)
- [Recommended Practices for Data Standardisation in the Context of the operation of ERNs](#) (Sept '17)
- [Recap of Breakout Discussions from the workshop on Integrated and Holistic Care](#) (April '18)

The home page for all these pages/document is:
<http://www.rd-action.eu/european-reference-networks-erns/>

6. Expert services in Europe: Expert Clinical Laboratories

Expert clinical laboratories and diagnostic tests are an essential part of quality healthcare in the field of rare diseases. Major progress in gene identification has 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 from just 1 country back in 1997, rising to 15 in 2003, 26 in 2006, and now totalling 31 countries (thanks to resources from the EC). In collaboration with EuroGentest, a Network of Excellence (financed by DG Research and Innovation), information on quality management has been added to the Orphanet database in recent years.

Users can search for information on genetic testing in Orphanet by disease name or by gene (symbol or name in English) as well as by laboratory or by professional. The information provided on laboratories includes data on quality management. Information is freely accessible online and access to all data can be granted upon request. For instance, Orphanet data 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 area (see below).

It is important to emphasise that 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.

6.1 The genetic testing capacity of laboratories in European countries – a summary

Over time, the number of laboratories registering their activities with Orphanet has increased, to reach **1301 at the beginning of 2018**. The Orphadata extractions enable a comparison of genetic testing capacity over time, both for single gene tests and also for panels (as panel testing becomes more commonplace)¹⁰¹:

¹⁰¹ 'Next generation sequencing' is the term applied to a broad range of genetic testing approaches which are able to examine a number of genes at the same time. If there is some indication of the diagnosis, laboratories may offer Targeted Gene Panel Testing or Untargeted Disease Panel Testing. The former tests a number of genes simultaneously which are associated with a particular genetic condition (e.g. a specific condition present in the family). The latter is broader, and examines the exons (coding areas) of all genes known to be disease-causing. (Where there is even less clarity on the potential diagnosis, broader explorations may be conducted, for instance Whole Exome Sequencing or Whole Genome Sequencing - for a layperson summary, see for instance https://www.eshg.org/fileadmin/eshg/documents/ESHG_Patient_leaflet_on_NGS.pdf)

	No. of Laboratories registered in Orphanet	No. of genes these laboratories test for (excluding panels)	No of diseases these laboratories test for (excluding panels)	No. of genes these laboratories test for (with panels)	No of diseases these laboratories test for (with panels)
Jan 2017	1301	2897	3658	4017	4421
Jan 2018	1388	3018	3737	4303	4421

6.2: Country Variations in Genetic Testing Capabilities

The tests offered differs greatly from one country to another: a breakdown is provided in Figures 7 and 8 below.

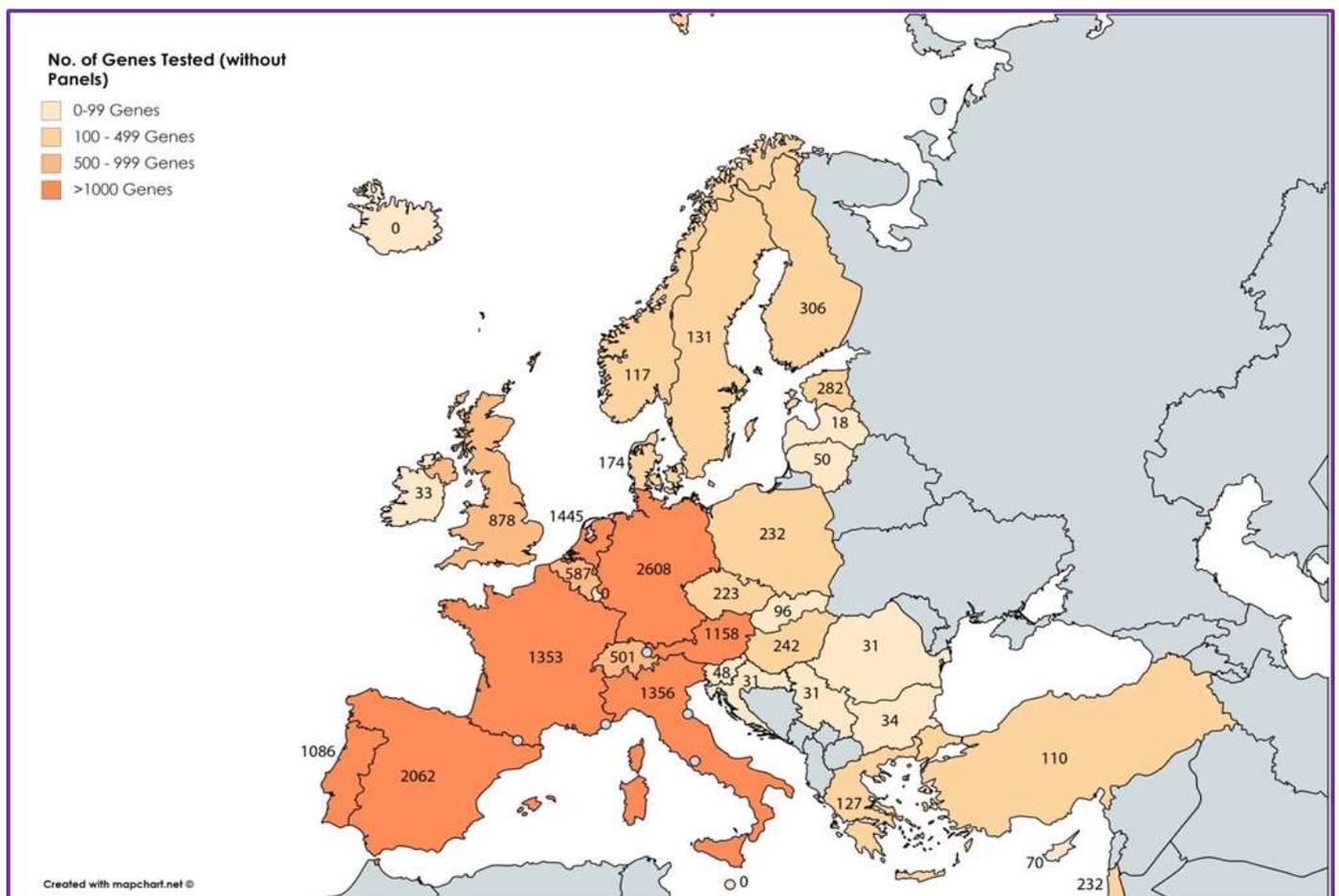


Fig. 7: Number of genes tested in each European Country (excluding panels), as of January 2018 (source Orphanet Data)

Country	Diseases Tested (with Panels)	Diseases Tested (without panels)	Genes Tested (with panels)	Genes Tested (without panels)
AT	1396	1396	1158	1158
BE	514	514	587	587
BG	40	40	34	34
CH	598	527	607	501
CY	96	96	70	70
CZ	233	233	223	223
DE	3003	2772	2747	2608
DK	237	237	174	174
EE	233	114	367	282
ES	2788	2338	2505	2062
FI	243	243	306	306
FR	3199	1336	3963	1353
GB	899	899	878	878
GR	188	188	127	127
HR	50	50	31	31
HU	252	252	242	242
IE	36	36	33	33
IL	239	239	232	232
IS	-	-	-	-
IT	1333	1333	1360	1356
LT	29	29	50	50
LU	-	-	-	-
LV	18	18	18	18
MT	-	-	-	-
NL	1601	1303	1739	1445
NO	123	123	117	117
PL	320	320	232	232
PT	1150	1150	1086	1086

RO	31	31	31	31
RS	28	28	31	31
SE	189	189	131	131
SI	53	53	48	48
SK	113	113	96	96
TR	149	149	110	110

Fig. 8: Table illustrating no. of genes and no. of diseases each country is able to test for (as of January 2018 – source Orphanet Data)¹⁰²

It is important to note that the option for laboratories to submit their panel tests to Orphanet is still quite new (Orphanet expanded its dataset to enable the capture of this data in 2016), and only a few countries are providing this detailed breakdown at present. In Figure 8 above, the countries highlighted in blue are those which provided data on testing capacity *with* and *without* panels: where countries did not provide this data, the same values are recorded in both the ‘with panel’ and ‘without panel’ columns.

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 2772 diseases and 2608 genes (Germany) without panels.

These figures alone demonstrate the need for a substantial cross-border exchange of specimens, as concluded by the EUCERD JA study mentioned above¹⁰³. The Orphanet data provides further evidence of the heterogeneity in genetic testing capacity across Europe:

Significant numbers of Genes are only tested in 10 or fewer countries:

Excluding Panels:

- 578 genes are tested in just one country;
- 1879 genes are tested only in 5 countries or fewer
- 2721 genes are tested in 10 countries or fewer

With Panels:

- 1267 genes are tested in just one country;
- 2946 genes are tested only in 5 countries or fewer
- 3982 genes are tested in 10 countries or fewer

¹⁰² The countries highlighted in blue are those which provided data on testing capacity *with* and *without* panels: where countries did not provide this data, the same values are recorded in both the ‘with panel’ and ‘without panel’ columns

¹⁰³ <http://www.nature.com/ejhg/journal/v24/n11/full/ejhg201670a.html>

Significant numbers of genetic Diseases are only tested in 10 or fewer countries:

Excluding Panels:

- 986 diseases are tested for in just one country;
- 2689 diseases are tested for in only in 5 countries or fewer
- 3458 diseases are tested for in 10 countries or fewer

With Panels:

- 733 diseases are tested for in just one country;
- 2888 diseases are tested for only in 5 countries or fewer
- 3850 diseases are tested for in 10 countries or fewer

This table illustrates the 5 most widely-tested diseases (i.e. the diseases which are tested in the largest number of countries):

Disease	Number of countries testing for this Disease
Cystic fibrosis	30
Huntington disease	28
Hemochromatosis type 1	28
Duchenne and Becker muscular dystrophy	27
Hereditary breast and ovarian cancer syndrome	27

This table illustrates the 6 most widely-tested genes (i.e. the genes which are tested in the largest number of countries)

Gene	Number of countries
CFTR	30
HTT	28
HFE	28
DMD	27
BRCA1	27
BRCA2	27

6.3 Quality Assurance of European laboratories

In accordance with the *2015 Recommendations on Cross-Border Genetic Testing of Rare Diseases*¹⁰⁴ Orphanet now annotates laboratory entries which have provided evidence of their Quality Assurance accreditation. As of January 2018, **345 laboratories from 20 countries have demonstrable quality assurance accreditations**. (This is a significant increase from January 2017, when only **263** laboratories (again from **20** countries) had demonstrated possession of quality assurance accreditation to Orphanet).

¹⁰⁴ http://ec.europa.eu/health/sites/health/files/rare_diseases/docs/2015_recommendation_crossbordergenetictesting_en.pdf

7. Rare Disease Registries

7.1 Rare Disease Registration – an Introduction

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 exist 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.¹⁰⁵ 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;
- 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 way¹⁰⁶- 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

¹⁰⁵ 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.

¹⁰⁶ 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]

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).¹⁰⁷

- 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.

7.2 European Rare Disease Registry Status Quo

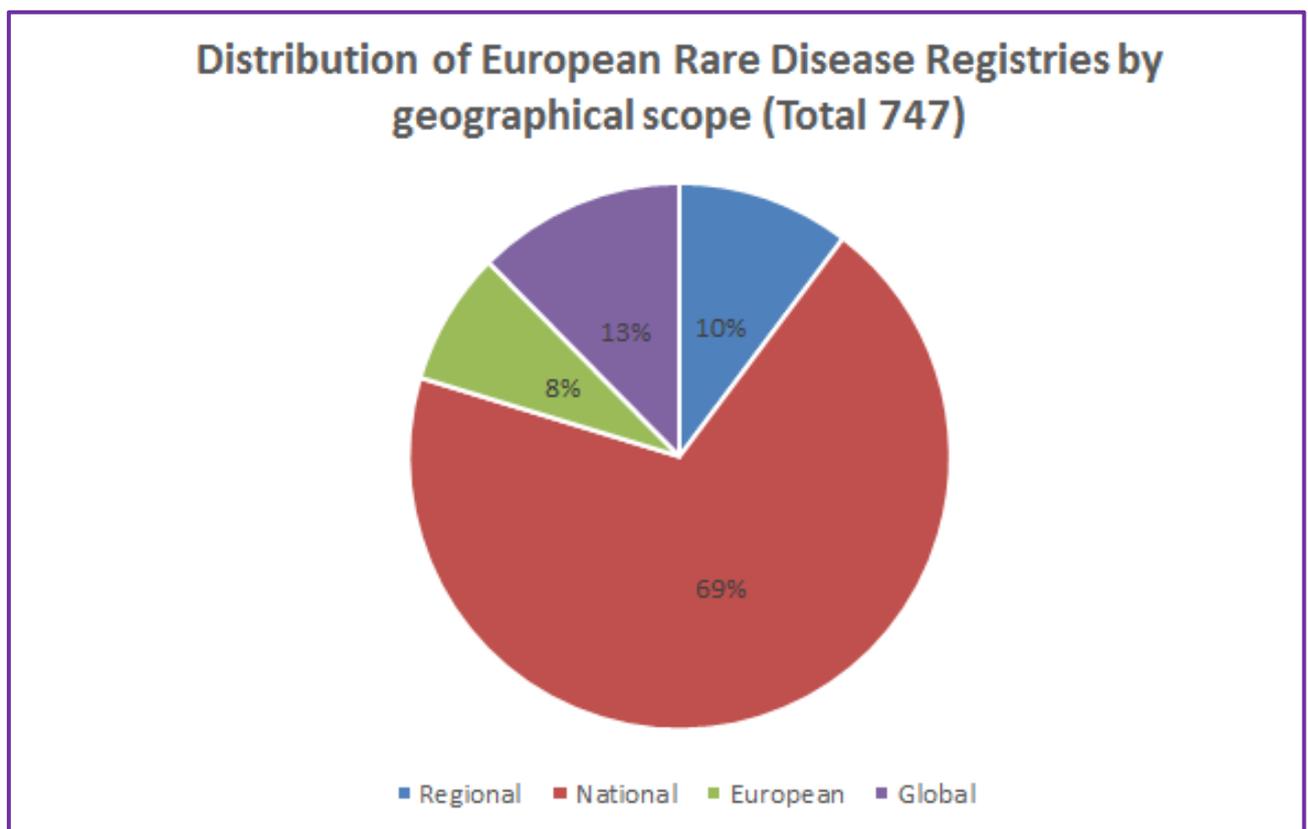


Fig. 9 Distribution of European Rare Disease Registries by geographical 'scope' (Source: Orphanet Report Series 'Rare Disease Registries in Europe' May 2018)

¹⁰⁷ Brookes, A., and Robinson, P. (2015) 'Human genotype-phenotype databases: aims, challenges and opportunities', *Nature Reviews Genetics* 16 [doi:10.1038/nrg3932]

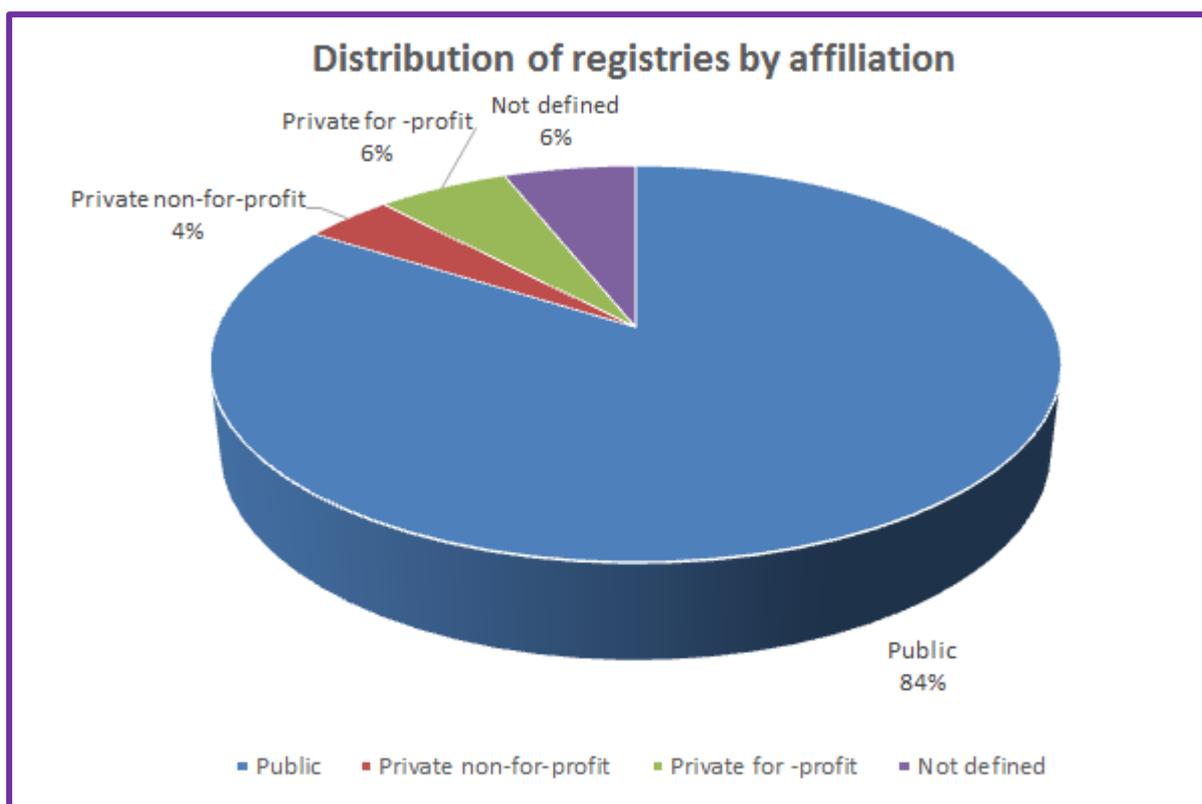


Fig. 10: Distribution of Registries by affiliation (Source: Orphanet Report Series ‘Rare Disease Registries in Europe’, May 2018)

According to the May 2018 Orphanet Report Series report ‘Rare Disease Registries in Europe’⁷⁷, there are 747 disease registries in Europe: 51 operate at the European level; 93 Global; 518 National and 77 Regional.

Most of the registries are established in academic institutions. A minority 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>

7.3 Summary of sample initiatives with particular relevance to Rare Disease Registration¹⁰⁸

7.3.1 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 explores ways of expanding the utility of patient registries helping them to contribute more strategically and systematically to the benefit-risk evaluation of medicines within the European Economic Area. Issues such as quality requirements for safety and efficacy data are also of central importance. Though not specifically designed for rare disease registries, there are clear points of intersection and mutual relevance. Regulators often request companies use registries in the context of risk management and other regulatory requirements, e.g. for OMP, advanced therapies, and medicinal products for use in paediatric populations (a recent study calculated that a registry is requested by Regulators for 9% of authorised products¹⁰⁹).

Key achievements over the first 3 years include the following:

- Organisation of a Workshop in October 2016 involving multiple stakeholder groups, to identify possible challenges and barriers to collaboration around registry data, and seek solutions to overcome these. The report is available here: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2016/08/event_detail_001315.jsp&mid=WC0b01ac058004d5c3.
- Subsequent workshops were organised in 2017, focusing on stakeholders in particular diseases, namely cystic fibrosis and multiple sclerosis. In each case, recommendations were proposed, concerning registry data elements, consent, governance, data sharing and interoperability. These reports are now available:
 - [cystic fibrosis workshop](#) (see also the [European CF Registry qualification Opinion](#))
 - [multiple sclerosis workshop](#)
- In 2018, two further workshops were organised, on Registries for CAR T cell therapies, and Haemophilia (Factor VIII) registries
- The creation of a registries' inventory through ENCePP (the European Network of Centres for pharmacoepidemiology and pharmacovigilance) - <http://www.encepp.eu/encepp/resourcesDatabase.jsp>: registry owners whose registries are not yet listed are encouraged to **add their registries** to the database

The 'home page' for the Patient Registries Initiative is:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000658.jsp

¹⁰⁸ 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

¹⁰⁹ <https://www.ncbi.nlm.nih.gov/pubmed/28345151>

7.3.2 European Platform on Rare Diseases Registration

In December 2013, the European Commission's Joint Research Centre, in collaboration with DG SANTE, initiated development of the European Platform on Rare Diseases Registration (EU RD Platform) to address the serious fragmentation of rare disease patient data contained in hundreds of registries across Europe. The ultimate objective is to provide a source of information on rare disease patient data with a large transnational coverage, for all rare diseases. **Over the last year, considerable progress was made on the development of the Platform**, the major feature and achievement of which is to make rare disease patient data searchable, queryable and findable across rare disease patient registries.

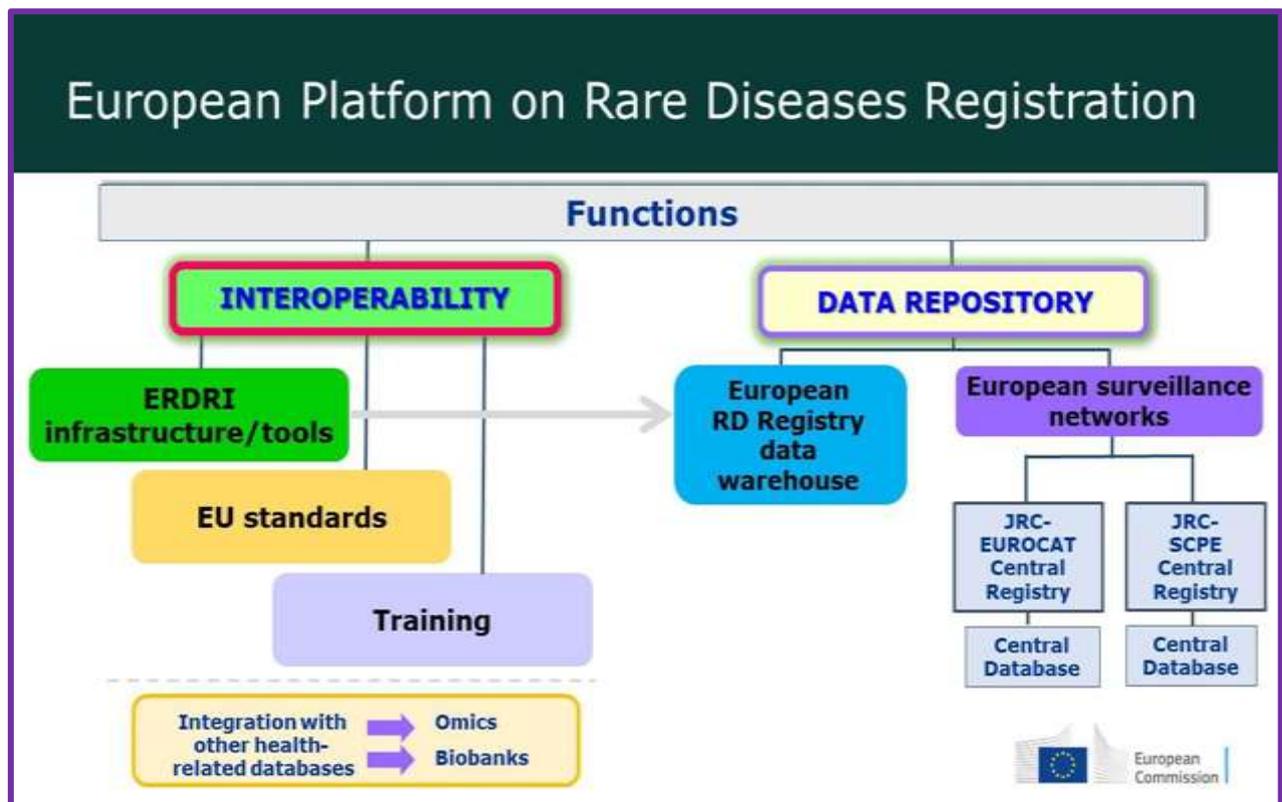


Fig. 11 The EU RD Platform (image courtesy of the JRC)

The Platform has two main functions, as above: Interoperability and Data Repository

1. Searchable, queryable and findable RD patient data across RD patient registries (Interoperability)

This achievement, requested for many years by the RD community, is based on the development of the European RD Registry Infrastructure (ERDRI), which contains the following main components:

- the European Directory of Registries (ERDRI.dor) which gives an overview of the RD registries joining the Platform, with their main characteristics and description;

- the Central Metadata Repository (ERDRI.mdr) which ensures semantic interoperability between RD registries;
- the Pseudonymisation Tool (EUPID) providing pseudonyms to participating registries;
- a Search broker helping to retrieve data of interest;

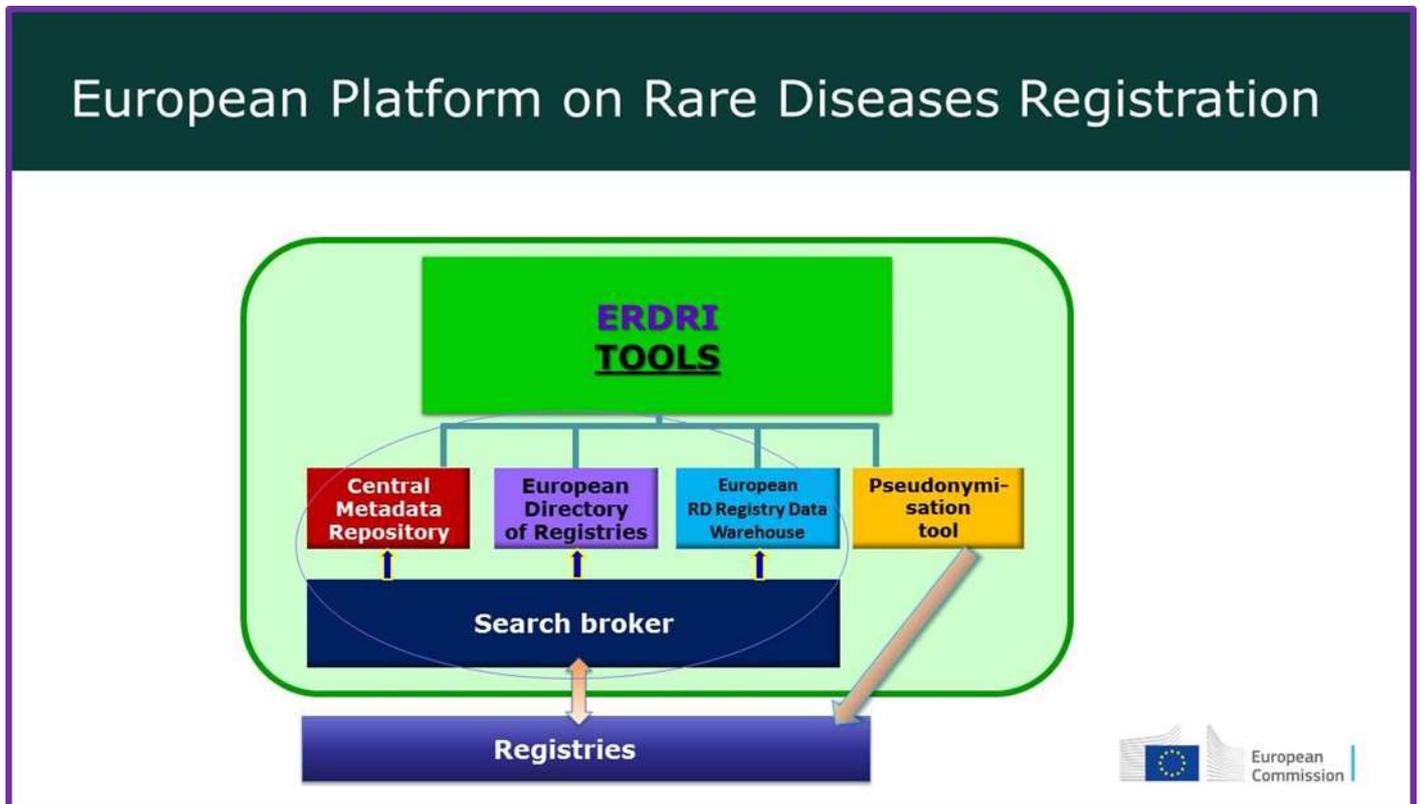


Fig. 12: The ERDRI Tools (image courtesy of the JRC)

These ERDRI tools will be provided free of charge to all interested rare disease registries willing to join the EU RD Platform. Details of the ERDRI will soon be available on the website of the JRC, to explain how registries can in fact ‘join’ the EU RD Platform, i.e. what they are required to contribute, what users will receive in return, etc. The Platform has also begun to collaborate with the ERNs to provide ERDRI support to any registries they plan to sustain/create anew.

In addition to ERDRI, the EU RD Platform provides EU-level standards for data collection and data sharing – notable amongst these is the Set of Common Data Elements for rare disease registries, released in 2017. This resource was agreed by a dedicated Working Group, and took into consideration work conducted under previous EU-funded initiatives most notably the EUCERD Joint Action, RD-CONNECT, and EPIRARE:

SET OF COMMON DATA ELEMENTS FOR RARE DISEASES REGISTRATION

GROUP	ELEMENT N°	ELEMENT NAME	ELEMENT DESCRIPTION	CODING	COMMENT
1. Pseudonym	1.1.	Pseudonym	Patient's pseudonym	<ul style="list-style-type: none"> String 	The JRC is working on providing a pseudonymisation tool to the registries
2. Personal information	2.1.	Date of birth	Patient's date of birth	<ul style="list-style-type: none"> Date (dd/mm/yyyy) 	
	2.2.	Sex	Patient's sex at birth	<ul style="list-style-type: none"> Female Male Undetermined Foetus (Unknown) 	
3. Patient Status	3.1.	Patient's status	Patient alive or dead	<ul style="list-style-type: none"> Alive Dead Lost in follow-up Opted-out 	If dead then answer question 3.2
	3.2.	Date of death	Patient's date of death	<ul style="list-style-type: none"> Date (dd/mm/yyyy) 	
4. Care pathway	4.1.	First contact with specialised centre	Date of first contact with specialised centre	<ul style="list-style-type: none"> Date (dd/mm/yyyy) 	

5. Disease history	5.1.	Age at onset	Age at which symptoms/signs first appeared	<ul style="list-style-type: none"> • Antenatal • At birth • Date (dd/mm/yyyy) • Undetermined 	
	5.2.	Age at diagnosis	Age at which diagnosis was made	<ul style="list-style-type: none"> • Antenatal • At birth • Date (dd/mm/yyyy) • Undetermined 	
6 Diagnosis	6.1.	Diagnosis of the rare disease	Diagnosis retained by the specialised centre	Orpha code (strongly recommended – see link) / Alpha code/ ICD-9 code/ ICD-9-CM code / ICD-10 code	http://www.orphadata.org/cgi-bin/inc/product1.inc.php
	6.2.	Genetic diagnosis	Genetic diagnosis retained by the specialised centre	International classification of mutations (HGVS) (strongly recommended – see link) / HGNC / OMIM code	http://www.hgvs.org
	6.3	Undiagnosed case	How the undiagnosed case is defined	<ul style="list-style-type: none"> • Phenotype (HPO) • Genotype (HGVS) 	
7. Research	7.1.	Agreement to be contacted for research purposes	Patient's permission exists for being contacted for research purposes	<ul style="list-style-type: none"> • YES • NO 	
	7.2.	Consent to the reuse of data	Patient's consent exists for his/her data to be reused for other research purposes	<ul style="list-style-type: none"> • YES • NO 	
	7.3.	Biological sample	Patient's biological sample available for research	<ul style="list-style-type: none"> • YES • NO 	If YES answer question 7.4
	7.4.	Link to a biobank	Biological sample stored in a biobank	<ul style="list-style-type: none"> • YES (if appropriate use link) • NO 	https://directory.bbmri-eric.eu
8.Disability	8.1.	Classification of functioning/disability	Patient's disability profile according to International Classification of Functioning and Disability (ICF)	<ul style="list-style-type: none"> • Disability profile / Score 	http://www.who.int/classifications/icf/whodasii/en/

Fig 13: the EU RD Platform Set of Common Data Elements for Rare Disease registries

The European Commission's JRC is also offering training on the tools and functions provided. Once all components are in place, the EU RD Platform has huge potential to optimise the utility and reusability of precious rare disease data in Europe; for the first time, the Platform will enable the interoperability of rare disease registries through the tools mentioned above, and will also support the creation of new registries.

The second function of the EU RD Platform (see above, Fig 11) is:

2. Data Repository

The EU RD Platform provides:

- the European RD Registry Data Warehouse (data repository), which will contain aggregated data from the RD registries;

- the central data repositories (and function of Central Registries) for two long-established surveillance networks: EUROCAT (congenital anomalies) and SCPE (cerebral palsy in children and young people). This activity involves more than 40 registries for EUROCAT and more than 20 for SCPE; therefore, establishing these repositories and central registries was a complex legal and organisational process.

7.3.3 GO-FAIR Implementation Network for Rare Diseases

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 at LUMC, and it has gained traction globally: organisations which 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 *exchanging* data between centres and certainly between jurisdictions is challenging. Instead, 'FAIR' promotes the concept of 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 [here](#).

Registries are by no means the only source of rare disease data which could benefit from adherence to the FAIR principles; however, given the fragmentation and lack of harmonisation observed in the registry field, this is an important focus for any attempt to render rare disease data 'FAIR'.

In 2017, a number of fields established GO-FAIR Implementation Networks, designed to unite stakeholders interested in promoting the spread of FAIR principles in their particular domain, working towards an ecosystem of FAIR data services. A number of stakeholders from the LUMC, RD-ACTION, Orphanet, RD-Connect, ELIXIR and EURORDIS teams, amongst others, establish a 'seed group' to advance discussions on how to FAIRify legacy data in the rare disease field and promote the FAIRification of new data resources.

Particular emphasis is placed upon supporting the ERN community to make their data FAIR, given the unique opportunities and economies of scale offered by these new Networks. For instance, the GO-FAIR Network is an opportunity to advance the actions espoused by the '[RD-ACTION Recommended Practices on Standardising Data in the context of the operation of ERNs](#)' relating to FAIR data in the ERN framework.

For further details, see <https://www.go-fair.org/implementation-networks/overview/go-fair-rare-disease/>

7.3.4 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 MS 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](#)' which 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. In the [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 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](#)

7.3.5 RD-ACTION

The Joint Action for rare diseases (2015-18, coordinator Ana Rath) addressed the topic of rare disease registration in various ways. For instance:

- The Orphanet team is directly responsible for maintaining the OrphaCode – the consensus European nomenclature for coding rare diseases – in an ontology (i.e. computer readable) format, which has particular relevance to registries.
- Orphanet is the source of information on standalone rare disease registries in Europe, as above (section 7.2)
- The WP dedicated to policy and Integration (WP6) sought to explore how *ERNs* might establish/integrate/link registries, and in so doing attempted to highlight the points of commonality and, most importantly, the *differences* between clinical data and data collected as part of a registry. Furthermore, a Taskforce was established on interoperable data sharing within the operations of ERNs, later reconstituted as the *Task-Force on Interoperable Data-Sharing between the Rare Disease and eHealth Fields*, which continues after the RD-ACTION funding period ended. This Task-Force will place more emphasis in the future on the topic of rare disease registration (as one of four priorities identified by the eHealth network;

7.3.6 RD-Connect

RD-Connect <http://rd-connect.eu/> is a 6 year initiative, funded under FP7, mandated to establish a platform to support rare disease research by linking data from biobanks, registries, databases and bioinformatics (see below 7.3.6). Regarding registries, specifically, RD-Connect has sought to improve the accessibility and usability of existing rare disease registries by providing each with an ID card. RD-Connect [ID-Cards](#) display important information about databases, registries and biobanks: more information is available here - <http://rd-connect.eu/platform/registries/id-cards-linking-up-rare-disease-research-across-the-world>

RD-Connect has also led important work on the ELSI aspects of data sharing, which have particular relevance to registration: <https://www.ncbi.nlm.nih.gov/pubmed/27049302>

7.3.7 EUCERD Joint Action

The EJA was funded from 2012 to 2015 by DG SANTE (SANCO as was) and was coordinated by Kate Bushby from 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_RDRRegistryDataCollection_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);
- A Thesaurus of Registry Terminology (http://www.eucerd.eu/wp-content/uploads/2015/03/WP8_Registries_Thesaurus.pdf)

7.3.8 EPIRARE

EPIRARE¹¹⁰ <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 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.

¹¹⁰ See http://ec.europa.eu/chafea/documents/health/rare-diseases-2018_en.pdf Page 90

8. Rare Disease 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/>



8.1 Overview of EU Rare Disease Research Funding:

At European level, research 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 2007-2013¹¹¹) the Health Theme of the "Cooperation" Specific Programme, was designed to support multinational collaborative research in different forms. FP7 was succeeded by Horizon 2020¹¹² the Framework Programme covering the period 2014-2020. Horizon 2020 will, in turn, be succeeded by Horizon-Europe. Horizon Europe will run between 2021 and 2027, and has a provisional budget of €100 billion (€97.6 billion in reality), which represents an increase from H2020's budget of ca. €77 billion.¹¹³

- Over €1 billion (across 200+ projects) has been invested for rare disease-related research, across FP7 and H2020. This has funded research in pathophysiology, natural history, and the development of new diagnostics and therapies.
- Most of the H2020 funding for health and RD is concentrated in the SC1 (Societal Challenge Collaborative Health research) pillar.

FP7 Funded several key 'Omics'¹¹⁴ 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 (see below).¹¹⁵

8.1.1 Recently-funded H2020 projects

Recent rare disease-focused projects funded under H2020 include the following:

¹¹¹ http://cordis.europa.eu/fp7/home_en.html

¹¹² http://ec.europa.eu/research/participants/data/ref/h2020/legal_basis/fp/h2020-eu-estabact_en.pdf

¹¹³ http://europa.eu/rapid/press-release_IP-18-4041_en.htm

¹¹⁴ See www.eurenomics.eu; www.rd-neuromics.eu; www.rd-connect.eu

¹¹⁵ For an overview of the achievements of these 3 complementary projects, see Lochmuller et. al (2018) 'RD-Connect, NeurOmics and EUREnomics: collaborative European initiative for rare diseases, EJHG 26 (DOI <http://dx.doi.org/10.1038/s41431-018-0115-5>)

Solve-RD: ‘Solving the Unsolved rare diseases’¹¹⁶

- This is a ca. €15million project, funded under the call ‘Disease characterisation of rare disease (SC1-PM-03-2017)
- The project will run from 2018-2022
- It is coordinated by Eberhard Karls Universitaet Tuebingen, Germany, with over 20 partners (including several ERNs, namely ERN-RND; ERN-ITHACA; ERN-EURO-NMD, and ERN GENTURIS)
- Solve-RD contributes towards the IRDiRC goal of delivering diagnostic tests for most rare diseases by 2020. The partners seek to solve undiagnosed cases with unknown molecular causes, via sophisticated combined ‘omics’ approaches.

ImmunAID: ‘Immunome project consortium for AutoInflammatory Disorders’

- This is a ca. €15million project, also funded under the call ‘Disease characterisation of rare disease (SC1-PM-03-2017)
- It is coordinated by the Institut National de la Sante et de la recherché Medicale (INSERM) and has over 20 partners
- ImmunAID dedicated to comprehensive ‘omics’ studies in Systemic auto-inflammatory diseases (SAID). The project will involve over 700 individuals (patients with monogenic SAID, patients with undiagnosed SAID, and healthy controls)

Numerous projects were funded under SC1-PM-08- 2017 (‘New therapies for rare diseases’), focusing on conditions including Cystic Fibrosis, skeletal dysplasia, Usher Syndrome, and Severe Combined Immunodeficiency.¹¹⁷

8.1.2 Upcoming Grants of relevance to rare disease research

The Societal Challenges 1 (SC1) Work Programme for the remainder of H2020 (2018-2020) includes the calls of relevance for rare disease research:

- Rare Disease European Joint Programme Cofund (SC1-BHC-04-2018) (see below)
- HTA research to support evidence-based healthcare (SC1-BHC-26-2018)
- Innovation Procurement: Next Generation sequencing (NGS) or routine diagnosis (SC1-BHC-10-2019)

8.2 The International Rare Disease Research Consortium (IRDiRC)

Established in 2011, and designed to unite researchers with research funders, IRDiRC initially had two major goals: to create 200 new therapies for rare diseases and enable diagnostics for most rare disease, both by 2020. However, given the early success in meeting these goals (the target



¹¹⁶ See www.solve-rd.eu for more information

¹¹⁷ Details of all funded projects are available here - see http://cordis.europa.eu/projects/home_en.html

of 200 new therapies was met in early 2017) the consortium revised its objectives 2017 during the 3rd IRDiRC conference which took place in Paris in February 2017.

A new overarching vision was agreed, for the period 2017-2027: **‘Enable all people living with a rare disease to receive an accurate diagnosis, care, and available therapy within one year of coming to medical attention’.**

To make this vision a reality, 3 new goals were agreed:

- **Goal 1:** All patients coming to medical attention with a suspected rare disease will be diagnosed within one year if their disorder is known in the medical literature; all currently undiagnosable individuals will enter a globally-coordinated diagnostic and research pipeline
- **Goal 2:** 1000 new therapies for rare diseases will be approved, the majority of which will focus on diseases without approved options
- **Goal 3:** Methodologies will be developed to assess the impact of diagnoses and therapies on rare disease patients

In 2018, IRDiRC involves over 50 members from 22 countries, with a combined financial commitment to-date of over 1 Billion USD. These member organisations are either Funding Organisations (which must pledge to invest over 10 Million USD specifically to rare disease research across 5 years) or umbrella patient advocacy organisations.

To achieve its goals, IRDiRC has undertaken numerous 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 (dedicated to funders, companies, and patient advocates respectively); and
- 3 scientific committees (Therapeutics, Diagnostics, and Interdisciplinary).

Under each of these sits a number of dedicated Task Forces¹¹⁸:

- Automatable Discovery and Access
- Data Mining and Repurposing
- International Consortium of Human Phenotype Terminologies
- Matchmaker Exchange
- Model Consent Clauses for Rare Disease Research
- Patient Centred Outcome Measures
- Privacy-Preserving Record Linkage
- Small Population Clinical Trials
- Solving the Unsolved

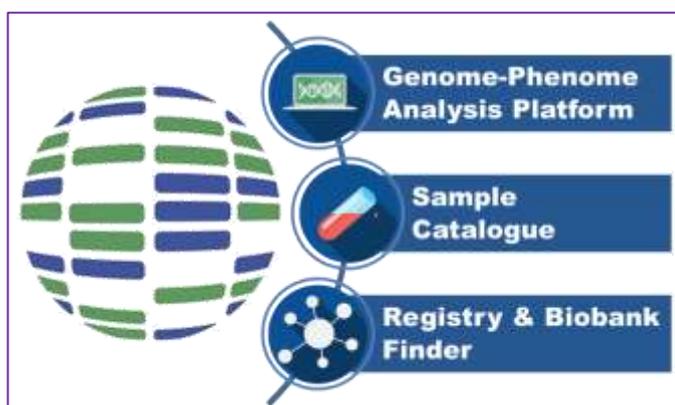
For more information on the broad range of IRDiRC activities, see the official website - <http://www.irdirc.org/>

¹¹⁸ <http://www.irdirc.org/activities/task-forces/>

8.3 RD-Connect

RD-Connect <http://rd-connect.eu/> is a €12 million, 6 year initiative (2012-2018) funded under FP7. Its mandate was to establish a platform to support rare disease research by linking data from biobanks, registries, databases and bioinformatics. Coordinated by Newcastle University (UK), RD-Connect set out to address the fragmentation and lack of interoperability between precious rare disease data sources, principally -omics data (especially genomic data from next generation sequencing), detailed clinical descriptions (i.e. phenotypic data), data contained in registries, and biosamples. Each of these types of data can, in theory, be pooled to relate human phenotypes to a particular gene or pathway of interest, create larger cohorts, find confirmatory cases, and access samples for further study: but to realise this potential, the research community required suitable infrastructure. RD-Connect addressed this gap by creating a global rare disease research platform, to link data from disparate sources and combine it using state of the art bioinformatics and interoperability expertise.

The RD-Connect platform consists of three systems: Genome-Phenome Analysis Platform; Registry & Biobank Finder; and Sample Catalogue, which are open to any rare disease.



- The **Genome-Phenome Analysis Platform** is not only a data repository but also a full-featured genomic analysis interface with a particular focus on diagnosis and gene discovery. It enables researchers and clinicians (even without bioinformatics training) to easily identify disease-causing genes and find matching cases across databases.
- The **Registry & Biobank Finder** is a global directory of RD patient registries and biobanks. It is unique in the sense that for each database, it provides regularly-updated numbers of registered patients/samples per disease, including genetic diagnosis, which could facilitate the organisation of clinical trials.
- The **Sample Catalogue** allows researchers to browse sample collections and find detailed information about *individual* rare biosamples available in rare disease biobanks. The tool facilitates the reuse of scarce and valuable biosamples for research.

The platform currently contains over 3000 cases, enabling complete clinical profiles to be linked with -omics data and information on biosamples for the same patient: it plays a major role in achieving the research goals of the International RD Research Consortium (IRDiRC).

To complement the main platform, RD-Connect has developed a number of clinical bioinformatics tools which facilitate data analysis and interpretation. RD-Connect ethical and legal experts developed guidelines for researchers and optimal models for data sharing, while the engagement of patients and patient representatives at every level of the project's work ensured patient-centred approach.

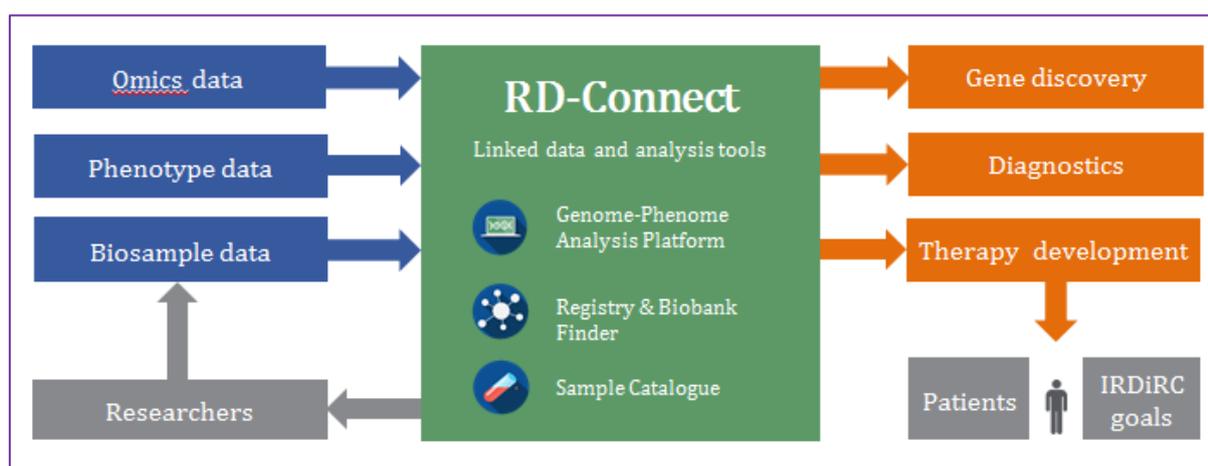


Fig. 14: Overview of RD-Connect Tools and Resources

For further information on the achievements of RD-Connect, see <http://rd-connect.eu/>.¹¹⁹

¹¹⁹ A good overview may be found in Lochmuller et. al (2018) 'RD-Connect, NeurOmics and EURenOmics: collaborative European initiative for rare diseases, EJHG 26 (DOI <http://dx.doi.org/10.1038/s41431-018-0115-5>)

8.4 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:

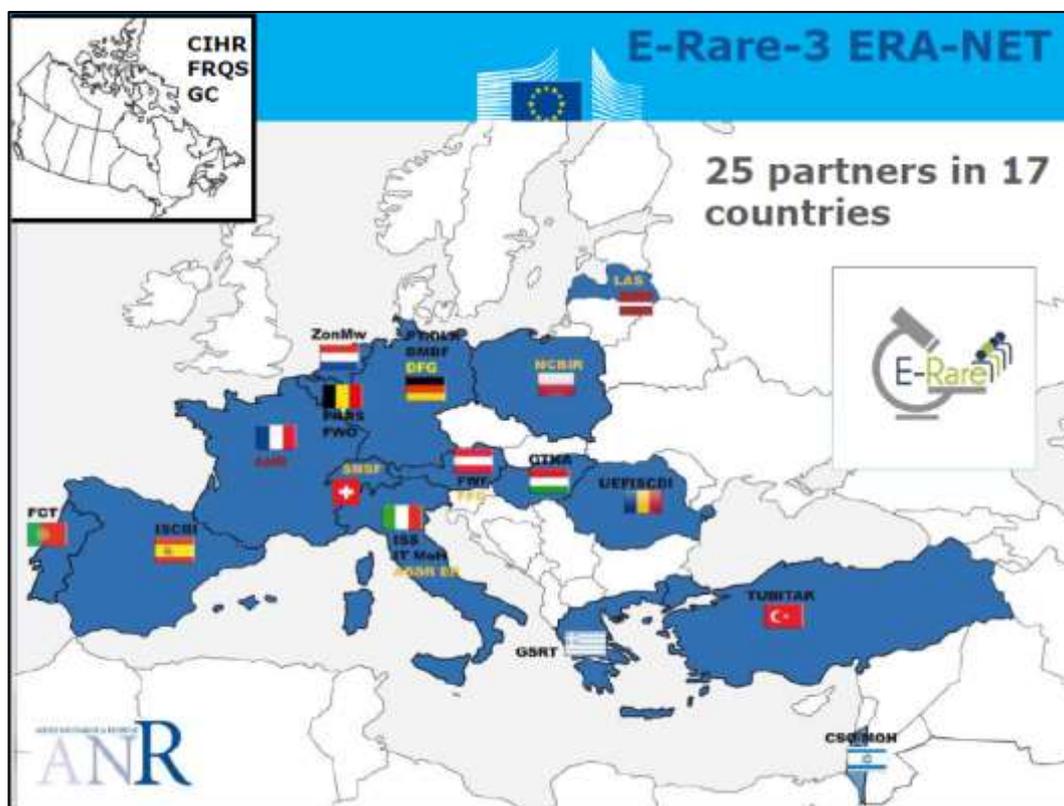


Fig. 15 – E-RARE 3 countries, as per official E-RARE site (<http://www.erare.eu/project>)

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. The latest E-Rare call for proposals was launched in December 2017, entitled ‘Transnational research projects on hypothesis-driven use of multi-omic integrated approaches for discovery of disease causes and/or functional validation in the context of rare diseases’.

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.

An ex-post analysis of E-Rare projects financed between 2007 and 2011 demonstrated that all were able to achieve the critical mass of resources necessary to complete their goals. Many joint publications resulted from these projects: 525 peer review articles were published by 37 consortia with a mean impact factor of 7.32 (range from 0.5 to 59).¹²⁰ For more information on the achievements of ERA-NETs for rare diseases, see <http://www.erare.eu/project>

¹²⁰ This data was taken from the EJP RD proposal, submitted in April 2018.

8.5 European Joint Programme Co-Fund for Rare Diseases

A European Joint Programme (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 (typically ministries) and Programme Managers (Research Funding and Research Performing organizations) in conjunction with other relevant stakeholders (e.g. patients' organisations, regulatory bodies and the private sector).

The 2018 Work Programme of H2020 included a very important call, to establish an EJP in the field of rare disease research (SC1-BHC-04-2018) with an EC budget of €55 million for 5 years (2019-2023). In preparation for this call, an expert drafting committee was assembled in late 2016, to outline the contents of an EJP for RD. The basic goal was 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.

The proposal was further developed during the course of 2017 and 2018, and the drafting group expanded to a vast consortium of 85 partners, led by the INSERM (Coordinator Daria Julkowska). The proposal was submitted in April 2018 and approved in July, with an anticipated start date of January 2019.

The total budget of the entire EJP is expected to exceed €110 million (€55 million directly from the EC, supplemented with substantial national and in-kind contributions).

33 countries will participate in total, from 25 EU Members States,¹²¹ 8 Associated Countries,¹²² and one Third Country (Canada).

The 85 partners represent many diverse organisations:

- 29 research funding bodies/ministries
- 12 research institutes
- 22 universities/hospital universities
- 11 hospitals
- 5 EU infrastructures (BBMRI, EATRIS, ECRIN, ELIXIR, INFRAFRONTIER) + EORTC
- EURORDIS & ePAGs
- 5 charities/foundations (FTELE, AFM, FFRD, FGB, BSF)

¹²¹ AT, BE, BG, CZ, DE, ES, EE, FI, FR, HU, IE, IT, NL, LT, LV, LU, MT, PL, PT, RO, SE, SK, SL, SV, UK

¹²² AM, CH, GE, HR, IL, NO, RS, TK

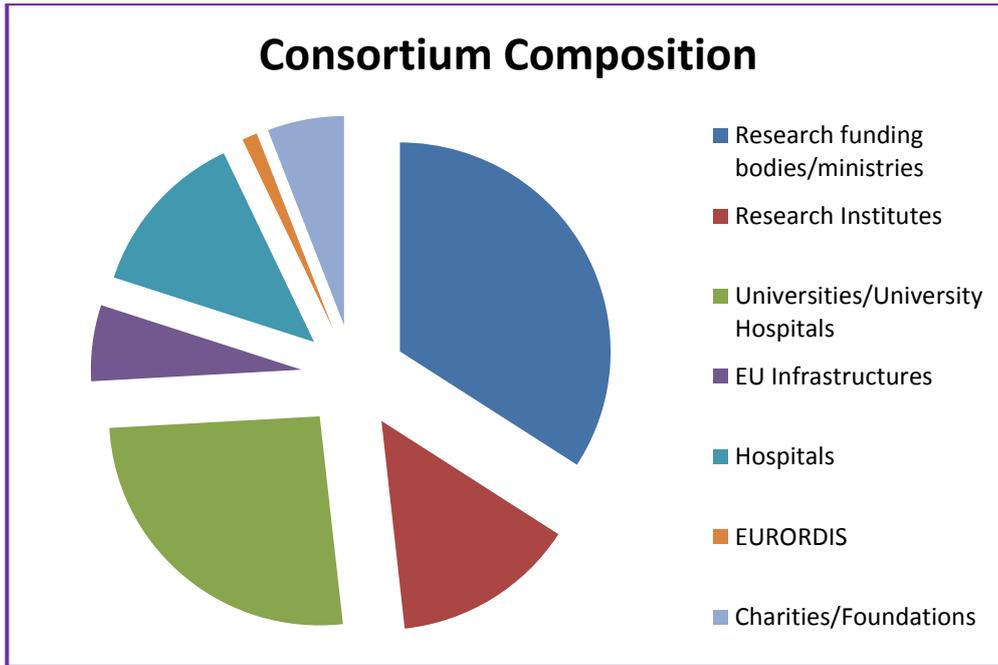


Fig. 16: Composition of the EJP RD Consortium

The main goals of the EJP RD are as follows:

- To improve the integration, the efficacy, the production and the social impact of research on RD through the development, demonstration and promotion of Europe/ world-wide sharing of research and clinical data, materials, processes, knowledge and know-how;
- To implement and further develop an efficient model of financial support for all types of research on RD (fundamental, clinical, epidemiological, social, economic, health service) coupled with accelerated exploitation of research results for benefit of patients.

The activities of the EJP are concentrated in assigned to 4 distinct (though inter-connected) pillars, assisted by the central coordination:

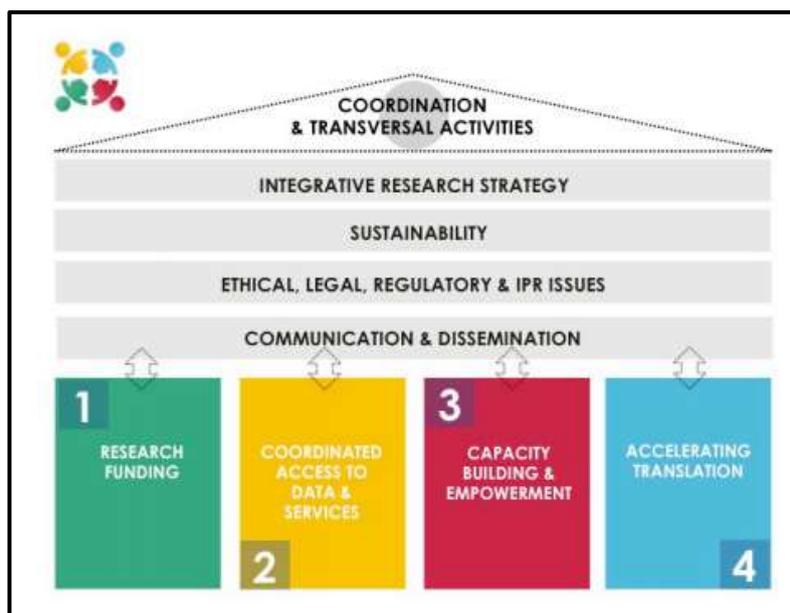


Fig. 17: EJP RD Structure (source – submitted EJP Proposal)

Pillar 1: Collaborative Research Funding¹²³

Pillar 1 will be based on the strengths and reputation of the E-Rare ERA-Nets (see above, section 7.4), whilst seeking to address identified areas for improvement (such as insufficient level of interactions between different types of stakeholders and an observed lack of commitment from private investors and industry). Pillar 1 will engage 29 funding bodies from 22 countries and will be open for further integration of new partners. The first two joint transnational calls have provisionally been allocated a combined budget of €37 M. Further engagement of at least €20 M for calls 2021-22 is also planned. Importantly, the proposed funding support will be extended beyond the mechanism of joint transnational calls and will encompass the Networking scheme (2 M€) and the Rare Diseases Research Challenges (1.5 M€ of public funding), the latter targeting public-private partnerships.

Pillar 2: Innovative coordinated access to data and services for transformative rare disease research

Pillar 2 will create a sustainable and interoperable ecosystem of resources -the 'EJP RD virtual platform'- coupled to robust standards, tools and procedures that will infuse 'FAIR' (see above, 6.3.3) principles into advanced and secure forms of data discovery, linkage and sharing. It will allow flexible, real-time access to data (under suitably controlled conditions), with supporting tools and services which serve the ultimate goal of increasing the efficiency and efficacy of rare disease research.

- ✓ Driven by concrete use-cases and needs arising from the rare disease clinical and research community, P2 will provide the means to **harmonise and standardise the way in which relevant data, samples and tools are made findable, accessible, interoperable and re-usable**
- ✓ It will ensure the 'queryability' of an increasing number of resources and repositories connected to the EJP RD virtual platform, through a central facility.
- ✓ Stronger collaborations will be forged, between the rare disease community and European Research Infrastructures and global consortia.

Pillar 2 will develop three parallel and complementary axes of work, each governed by consistent quality, regulations and compliance with agreed standards requirements. The axes are:

- **A Centralized metadata repository** describing pre-existing resources (including catalogues, data repositories, tools and infrastructures) with rare disease-specific semantic standards and metadata which conforms to an ontological, machine-readable model.
- **A federated ecosystem of FAIR-at-the-source resources**, in order to enable data discovery, sharing and analysis down to the record level. This axis of work entails partnering with target resources to make them FAIR compliant, as well as the required interdisciplinary collaboration between rare disease domain experts and data experts. Beyond achieving FAIRification of resources in the virtual platform, Pillar 2 will support the broader rare disease community to enlarge the scope of the federated ecosystem, by building a sustainable FAIRification service.

¹²³ The Pillar summaries which follow are taken largely from the submitted EJP proposal

- Extension of the virtual platform with workflows which allow holistic research based on rare disease data and biological knowledge, by **filling gaps in data** on disease modifiers. This axis will be based on important collaboration between ERNs and top-level research teams excelling in data mining and interpretation.

Pillar 3: Capacity-Building and Empowerment

Pillar 3 will work with 45 partners to integrate rare disease activities under a common joint education & training programme, to raise the level of knowledge and build capacity within the rare disease community. By pooling and centralising existing resources, training initiatives, and relevant expertise and experience from the different partners, Pillar 3 should facilitate the engagement of the rare disease community with regulatory bodies, the private sector and the biomedical industry, in order to fast-track access and bring diagnoses to unsolved cases whilst facilitating clinical trials and boosting therapy development.

Investment in capacity-building for all stakeholders groups, and especially for patients, is crucial for sustainable research and the translation of new knowledge into health systems: significant opportunities will therefore be created, to enhance the research and innovation capability among all stakeholders, enabling effective, patient-centred outcomes which address rare disease patient needs and can be readily adopted within healthcare systems. Pillar 3 will ultimately develop and deliver a seamless flow of training programmes on key aspects of relevance for the rare disease community, expanding existing training courses and developing new ones as required.

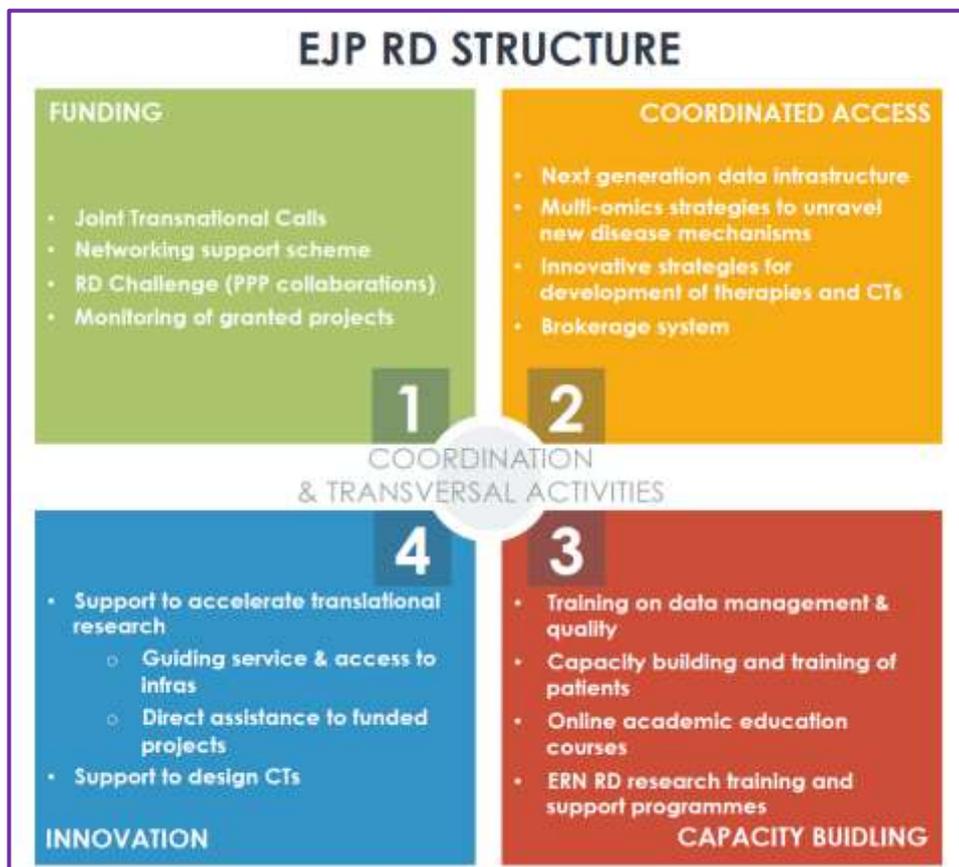


Fig. 18: Overview of the 4 EJP RD Pillars (Source – submitted EJP Proposal)

Pillar 4: Accelerating the translation of high potential projects and improving outcomes of clinical studies in small populations

Pillar 4 will create a long-term sustainable strategy to improve the productivity of pipelines for rare disease therapies and optimise translational research capacities, working closely with ERNs and other actors in the rare disease community. It will address the many barriers to successful translation of research results, by focusing on mindset, professional management, and mentoring.

An active mentoring programme (coordinated by an Innovation Manager assigned to project teams, investigators and funders of Pillar 1) will provide hands-on guidance and input into the design, development and (where possible) execution of cutting-edge translational and clinical studies.

In addition, Pillar 4 will support projects with high potential to find and utilise the resources and expertise of private and for-profit funders and developers, in order to complete the development pathway to the patient.

Pillar 4 will create a roadmap for innovation funding in rare diseases, utilizing blended investment modes to feed the sustainability strategy. It will harness the capacity and expertise of the ERNs, strengthened by the know-how of ECRIN and high-level methodologists from the IDEAl project. The partners will:

- identify optimal existing methodological standards for clinical trials in the rare disease field, and promote their use via the ERNs and other relevant EJP RD partners;
- enable 'demonstrator' projects focusing on the validation of recently-developed methodologies for the design and analysis of clinical trials;
- design innovative methodologies for aspects of clinical design which are hitherto lacking or not sufficient (e.g. strive towards more appropriate endpoints allowing better assessment of clinically meaningful responses as PCOMs; validation of composite endpoints and surrogates; capture efficacy and important safety information through life span, via natural history studies; etc).

9. Orphan Medicinal Products

9.1 Overview of Regulation EC 141/2000 and the approval process for an OMP

The Regulation on Orphan Medicinal Products (Regulation (EC) No 141/2000)¹²⁴ 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. The process by which a medicinal product enters the market as an orphan medicinal product (OMP) involves several stages:

- A sponsor submits an application to the European Medicines Agency (EMA), seeking orphan designation for their medicinal product
- The application is evaluated by the Committee for Orphan Medicinal Products (COMP) at the EMA (the COMP was established in 2000 via the aforementioned Regulation, and is also responsible for advising the European Commission on the establishment and development of a policy on OMPs in the EU. It assists the Commission in drawing up detailed guidelines and liaising internationally on matters relating to OMPs
- The COMP provides an Opinion on the application, which could be positive or negative: this Opinion is then conveyed to the European Commission
- The European Commission decides whether or not to bestow Orphan Designation

There are specific criteria which a medicinal product needs to fulfil, in order to qualify for this orphan designation:

- ✓ it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating;
- ✓ the prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development;
- ✓ no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

Once orphan designation has been granted, the product attracts a range of incentives. For example:

¹²⁴ This section reproduces information from http://ec.europa.eu/health/rare_diseases/orphan_drugs/strategy/index_en.htm. A useful summary of OMP activity over the years 2000-2017 is available here: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/04/WC500185766.pdf

- The sponsor is eligible to receive **protocol assistance** -a particular form of scientific advice for OMPs- at a reduced cost. Sponsors can pose questions on the most appropriate tests and studies to bring the product to market, seek advice on how to demonstrate ‘significant benefit’, discuss similarity with other products/ clinical superiority of their product compared to others (given the implications for market exclusivity), etc.
- Market exclusivity: no similar medicines for the same indication can enter the market for 10 years
- Depending upon the status of the company, the sponsor might qualify for a reduction in the fees paid to bring the product to the market. SMEs are also eligible in some cases for administrative and procedural support from the EMA
- If the sponsor chooses to add an indication for paediatric use (and accordingly follows a paediatric investigation plan, or PIP), the medicinal product is eligible for a 2-year extension of the supplementary protection certificate (i.e. they receive an extra 2 years of market exclusivity)

Once a sponsor is ready to submit an application for **marketing authorisation (MA)**, they are able to use a centralised procedure (i.e. a single MA will apply across all EU territory). Sponsors may need to submit a ‘Similarity Report’ as part of this MAA, if other OMPs have been authorised for the same therapeutic indication. They also submit a ‘report on the maintenance of the orphan designation’, to ensure the product still warrants that designation (e.g. the prevalence still meets the criteria, the condition is sufficiently debilitation or is life-threatening, etc.).

The MAA itself will be assessed by the Committee for Medicinal Products for Human Use (CHMP), which will issue an opinion and convey this to the European Commission.

It is possible for patients to access OMPs which have not yet received a MA (i.e. have received orphan designation but are still working their way through the research and development stage) – an example is ‘compassionate-use’.

A set of FAQs has been issued by the EMA on the subject of orphan medicinal products and rare diseases:

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2018/02/WC500244578.pdf

A major issue in the European rare disease field is that OMPs which receive a central European Marketing Authorization are often *not* in fact available in all EU countries: each country determines for itself whether to make an authorised OMP available within the national territory, and whether to reimburse patients for using it.

9.2 EMA data regarding OMP Designations and Authorisations

The EMA is naturally the most comprehensive source of valuable information on OMP applications, Opinions and Marketing Authorizations.¹²⁵ The table below summarises OMP activity at the EMA across the period 2000-2017:

¹²⁵ 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

	2000 2005	2006 2010	2011 2015	2016	2017	Total
Applications submitted	548	686	1151	329	260	2974
Positive COMP Opinions	348	500	759	220	144	1971
Negative COMP Opinions	8	6	7	2	2	25
EC Designations	343	485	768	209	147	1952
Withdrawals during assessment	150	144	313	77	100	784

Fig. 19: Applications of OMP designation (screenshot from EMA presentation http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/04/WC500185766.pdf)

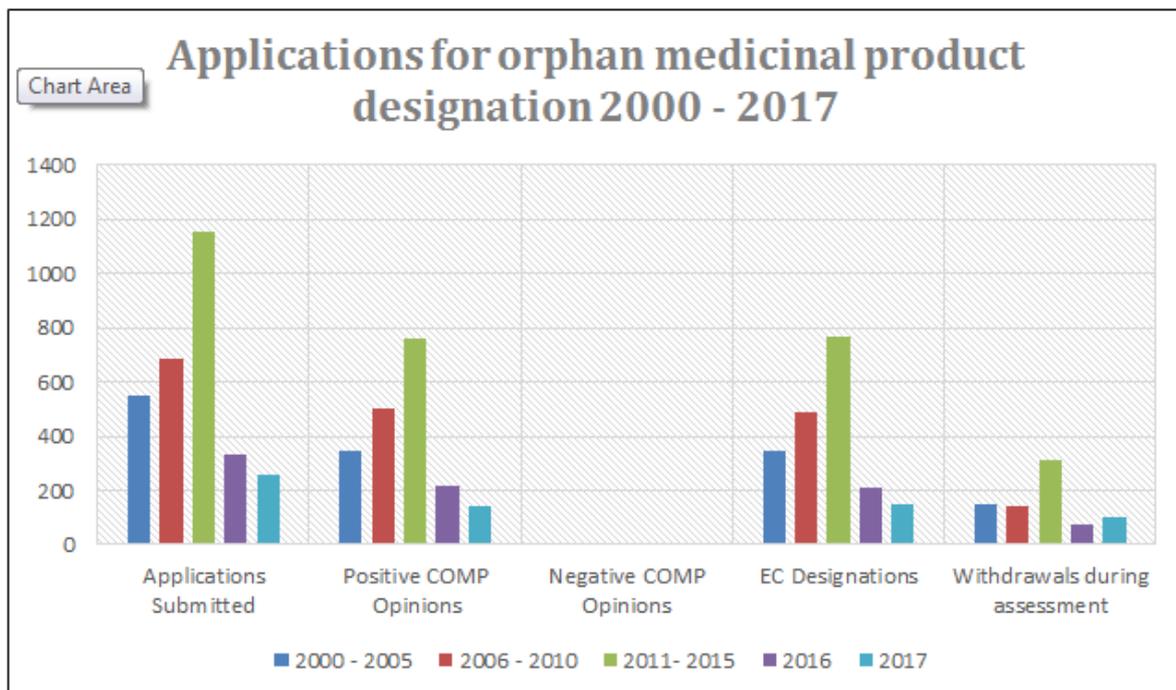


Fig. 20: Status of Orphan Applications between the years 2000 and 2017, based upon EMA data: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/04/WC500185766.pdf

DISTRIBUTION OF OPINIONS ON ORPHAN DESIGNATION BY THERAPEUTIC AREA: 2000 - 2017

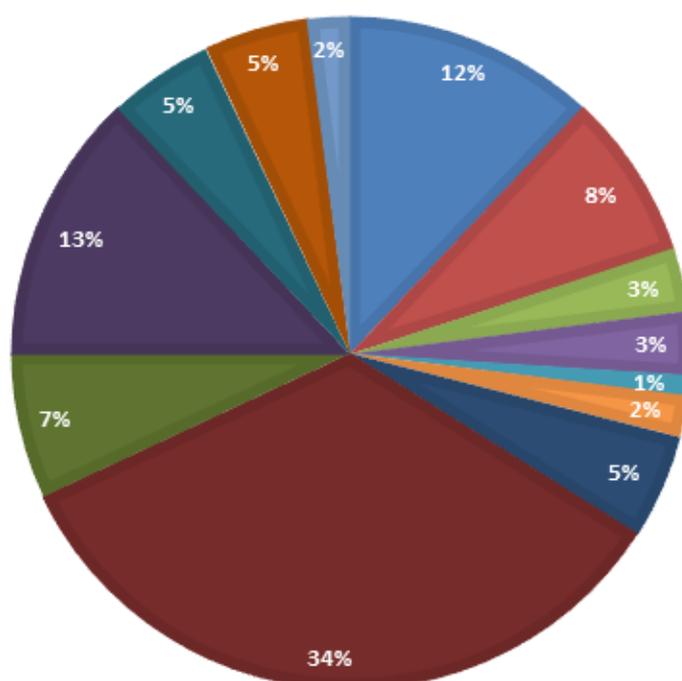
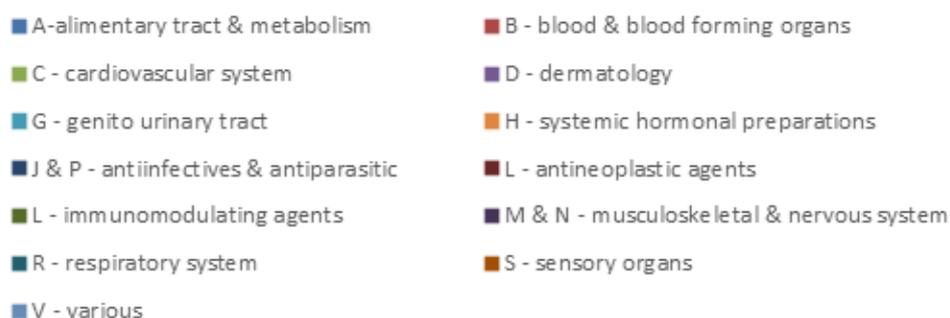


Fig. 21: Distribution of Opinions on Orphan Designation by Therapeutic Area, during the period 2000 – 2017. Source:

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/04/WC500185766.pdf

Designations and Prevalence ¹²⁶

Of the 1952 medicinal products granted orphan designations up to the end of 2017:

- 49% were for diseases with a prevalence of between 1 and 3 per 10,000;
- 40% were for diseases with a prevalence of *fewer* than 1 per 10,000;
- 11% were for diseases with a prevalence of *more* than 3 per 10,000

¹²⁶ Source is http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/04/WC500185766.pdf

Designations and Adult/Paediatric Use

Of the 1952 medicinal products granted orphan designations up to the end of 2017:

- 32% were for adult patients
- 13% were for paediatric patients
- 55% were designated for both paediatric and adult use

According to EMA figures (accurate up to the end of 2017) 142 initial Marketing Authorisations have been granted for OMPs. 36 of these have now reached the end of the market exclusivity period. 20 'extensions of indication' have been granted (for 1 of these 20 the extended market exclusivity has already expired). Marketing Authorisation Applications are not always successful: up until the end of 2017 there had been 14 negative outcomes. Products are sometimes withdrawn during the evaluation phase, and occasionally after approval (at the end of 2017, 13 had been withdrawn from the register of OMPs).

The majority of OMPs receiving a Marketing Authorisation address rare cancers (42% are antineoplastic products) and diseases of the alimentary tract/metabolism (19%).

10. Patient Advocacy for Rare Diseases

10.1 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 represents over 810 rare disease organisations in 70 countries (including all 28 EU Member States), covering more than 5000 different rare diseases. (<http://www.eurordis.org/about-eurordis>)

EURORDIS' achievements are numerous – a comprehensive list was compiled for the 20th anniversary in 2017¹²⁷, but key highlights include the following:

- 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 (ECDR)
- 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 reduce the burden of rare diseases. (<http://www.eurordis.org/what-we-do>). Consequently, the activities of EURORDIS focus on empowering rare disease patient groups, advocating rare diseases as a public health issue, raising public rare disease awareness, improving access to information, treatment, care and support for people living with rare diseases, encouraging good practices, 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>)

¹²⁷http://download.eurordis.org.s3.amazonaws.com/20yrs/20years_AchievementsofRDCommunity_0117.pdf

In 2017, EURORDIS published the results of a major survey -conducted through its [Rare Barometer Voices](#) tool- to which 3000 people from 42 countries responded. This [survey](#) provided concrete data on the burden of rare diseases for patients and carers, across many aspects of daily life:

- More than 70% of patients have difficulties with daily activities and tasks such as preparing meals and handling household chores, with motor and sensorial functioning such as visual, hearing and body positioning issues, and with social life such as maintaining relations with others.
- 30% of carers spend over 6 hours a day on disease-related tasks, with over 60% of these carers being women.
- Having to reduce or stop professional activity due to the illness occurs to 70% of rare disease patients and carers.
- Feelings of depression and unhappiness are three times more common amongst rare disease patients and carers compared with the general population.



Fig. 22: Infographic of EURORDIS survey results (courtesy of EURORDIS presentations)

Full details of the survey are available via the EURORDIS website.¹²⁸

(EURORDIS plays a prominent role in the following initiatives, and indeed often instigated the activities outlined)

¹²⁸ <https://www.eurordis.org/news/3000-rare-disease-patients-carers-voice-difficulties-balancing-care-life> . See also infographic at http://download2.eurordis.org/rbv/juggling_care_and_daily_life.infographic_final.pdf

10.2 Rare Diseases International



Rare Diseases International (RDI)¹²⁹ is the global alliance for rare diseases.

- The mission of RDI is to provide a strong common voice on behalf of all people living with a rare disease around the world.
- RDI's objectives are as follows:
 - ✓ To promote rare diseases as an international public health and research priority through public awareness and policy-making
 - ✓ To represent its members and people living with a rare disease at large, in international institutions and forums
 - ✓ To enhance the capacities of its members through information, exchange, networking, mutual support and joint actions
- RDI unites national and regional rare disease patient organisations from around the world, as well as international rare disease-specific federations, to create a global alliance of rare disease patients and families.
- RDI is 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.
- As of May 2018, RDI was composed of 53 member organisations in 34 countries

10.3 Rare Disease Day

- Held each year on the last day of February, Rare Disease Day is an annual awareness-raising event coordinated by EURORDIS. 2018 saw the 10th anniversary of Rare Disease Day, the main objective of which is to raise awareness 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.
- Although the campaign started as a European event, Rare Disease Day has truly become a worldwide phenomenon. The USA joined in 2009, and new additions since 2016 include



¹²⁹ <https://www.rarediseasesinternational.org/>

Andorra, Cape Verde, Ghana, Indonesia, Syrian Arab Republic, Tanzania, Togo, Trinidad & Tobago, Tunisia and Uganda. **In 2018, Rare Disease Day was celebrated in 90 countries**

10.4 NGO Committee for Rare Diseases

The NGO (Non-Governmental Organisation) 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
- Extend and share knowledge about rare diseases and their unmet needs
- Connect NGOs interested in rare diseases and their partners within a global platform
- Promote international, multi-stakeholder collaboration and actions for rare diseases
- Align rare diseases as a global priority in public health, research and medical and social care policies.

The NGO Committee for Rare Diseases¹³⁰ (United Nations, New York) was 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 programmes 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, 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.

10.5 RareConnect

- RareConnect¹³¹ is maintained by Care4Rare Canada in partnership with EURORDIS. It is an online network of rare disease communities which seeks to reduce isolation by bringing together patients, families and organisations in the rare disease field. Stakeholders can communicate and share experiences and information in a safe, moderated online forum. Translation services enable patients from different countries to interact in English, French, German, Italian, Portuguese, Spanish, Russian, Serbo-Croatian, Ukrainian, and Japanese.
- Communities are set-up for specific diseases, supported by full-time community managers. 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

¹³⁰ <https://www.ngocommitteerarediseases.org/>

¹³¹ <https://www.rareconnect.org/en/communities>

for sharing experiences and solutions to common problems based on the experiences of the wider rare disease community.

10.6 National alliances of rare disease patient organisations

National alliances of rare diseases patient organisations play a key role in advocacy and governance: they provide patients with a common ‘home’ (essential for very rare conditions, which may not otherwise be able to set-up dedicated patient organisations) and enable stakeholders to impact national policies by speaking with a single cohesive ‘voice’. Many 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.

Europe has many national alliances for rare diseases. 29 of these are members of the European Network of National Alliances for Rare Diseases.¹³² This network is governed by a EURORDIS-established Council of National Alliances for rare disease patient organisations, which unites the majority of Alliances in Europe with 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.

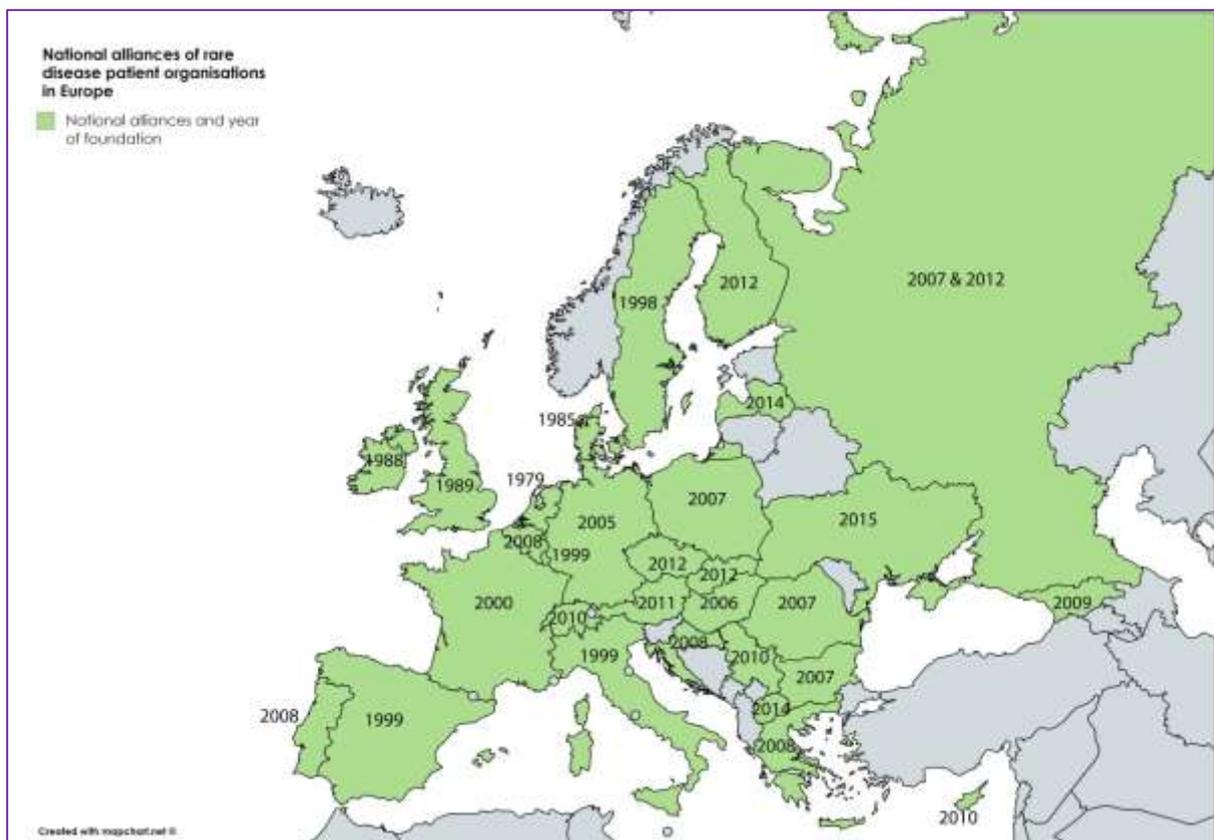


Fig. 23: European National Alliances and their year of foundation

¹³² See <https://www.eurordis.org/content/national-alliances-rare-diseases> for a list of participating National Alliances

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.

10.7 Disease-specific patient organisations in the field of rare diseases

As of January 2018, 2,395 disease specific patient organisations were registered in the Orphanet Database. Of these:

- 2405 were national disease specific-organisations
- 181 were regional disease-specific organisations
- 83 were European disease-specific patient organisations
- 63 were international (global) disease-specific patient organisations

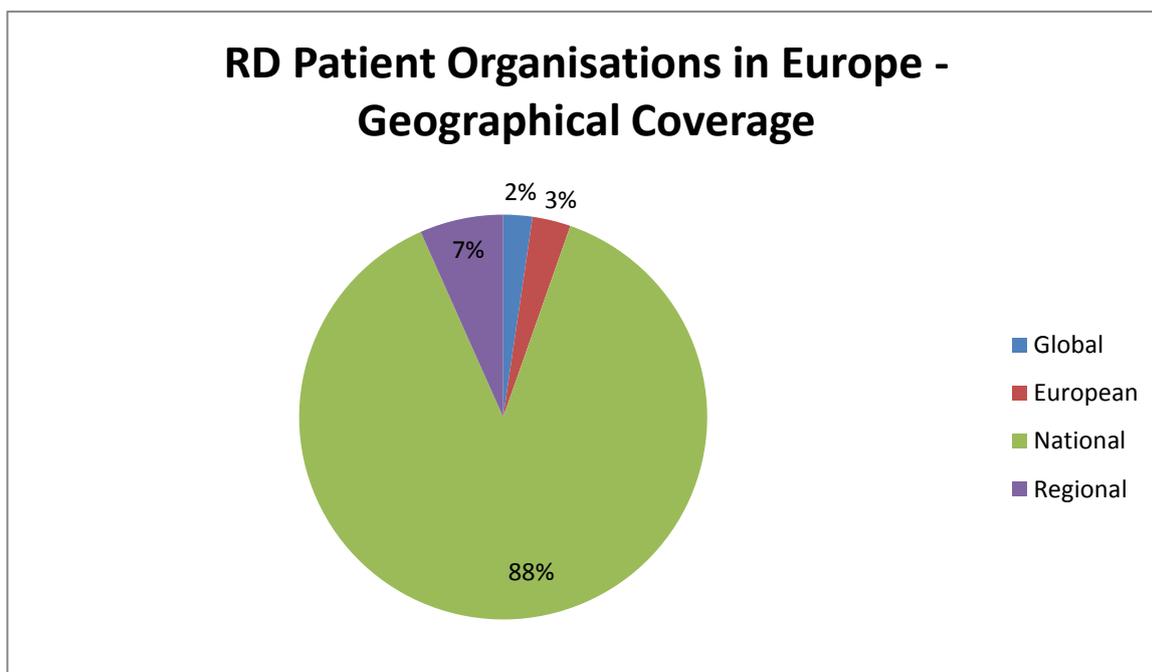


Fig. 24: Rare Disease Patient Organisations and Geographical Coverage (Source: Orphanet database)

11. Orphanet

Orphanet is the largest repository of information about Rare Diseases globally. It was established in 1997 –thus 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 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.

At the beginning of 2018 the Orphanet consortium encompassed 40 countries from all across the globe.

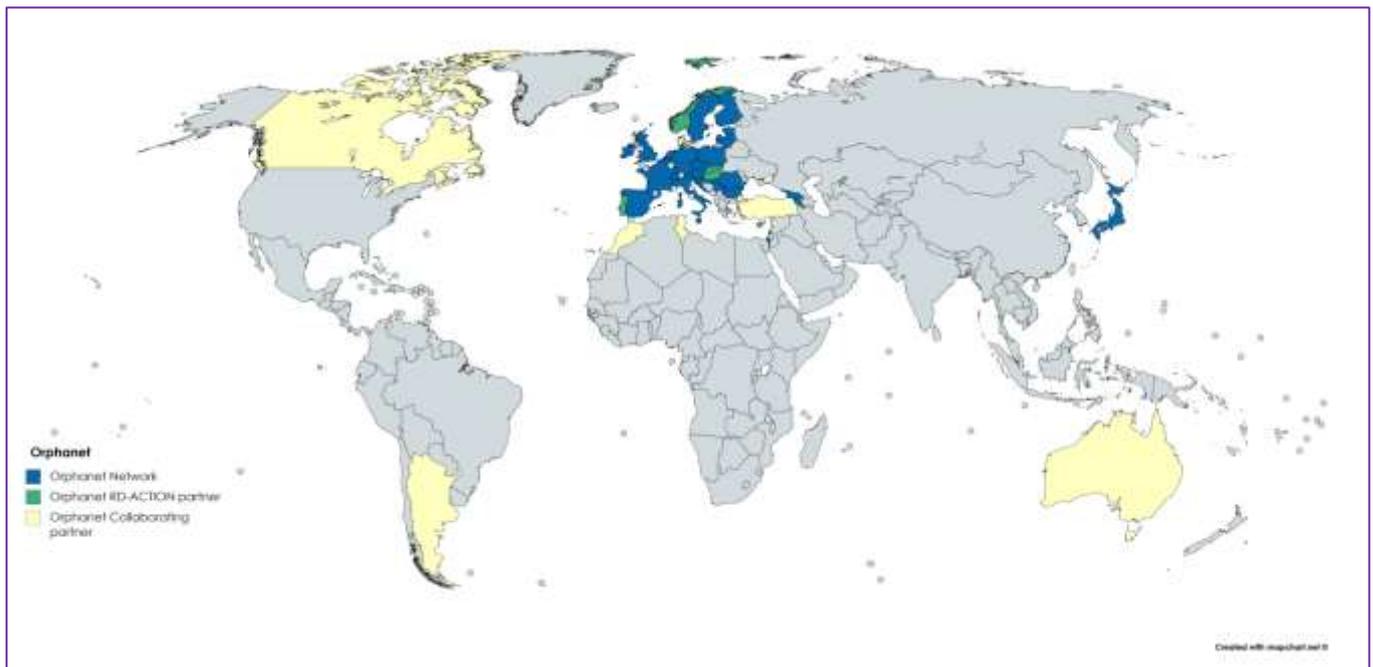


Fig. 25: The Orphanet consortium in January 2018 (image courtesy of Orphanet)

A key component 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 European¹³³ and global¹³⁴ 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 following¹³⁵:

- The [inventory of rare diseases](#) and a [classification](#) of diseases elaborated using existing published expert classifications and expert curation
- 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](#), 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
- Tutorials on the tools and resources Orphanet provides

Under RD-ACTION (the European Joint Action for Rare Diseases, 2015-2018), the Orphanet website and portal underwent a major transformation, in order to become more user-friendly and effective.

¹³³ 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

¹³⁴ 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/>

¹³⁵ See the official Orphanet site for full details: <http://www.orpha.net/consor/cgi-bin/index.php?lng=EN>



Fig. 25: Revamped Orphanet catalogue of services (home page)

Curation of the resources of the Orphanet portal is now simpler and more efficient, and procedures have been published to ensure transparency and traceability. Partnerships have been formed with SNOMED CT and the NIH in the US.

In summary, through RD-ACTION and other key projects (e.g. HIPBI) Orphanet has made a major contribution in recent years, to the greater availability and interoperability of data in the field of rare diseases. In recognition of this, Orphanet was named an 'IRDIRC Recommended Resource' (see section 8.2).

The legacy of Orphanet following RD-Action is three-fold:

- ✓ delivery of a standard common language for health and research (the Orphanet nomenclature)
- ✓ the provision of a comprehensive, reliable database for decision-making (for both Member States and ERNs)
- ✓ and a site providing information for professionals and patients

Post-RD-ACTION, the maintenance and evolution of the Orphanet database will be supported for 3 more years (on a co-funding basis) via an EU Health Programme Direct Grant. In parallel, discussions are underway at INSERM level and with the EC Steering Group on Prevention and Promotion (see section 1.4) regarding the long-term sustainability of Orphanet.

12. Parliamentary Advocates for Rare Diseases Network

On 17th October 2017 a new *Parliamentary Advocates for Rare Diseases network* was launched at the European Parliament in Brussels. This was the fruit of ongoing efforts spearheaded by EURORDIS to ensure that European stakeholders continue to unite to tackle the deep-seated challenges -and often also inequalities- which rare diseases create. The network was launched during an event entitled 'Juggling Care and Daily Life: The Balancing Act of the Rare Diseases Community' and included the presentation of highlights of the results of the survey conducted by EURORDIS via its Rare Barometer initiative (see above, section 10.1). The goal of the network is essentially to unite Members of the European Parliament as well as Members of National Parliaments, who are dedicated to:

- exploring and discussing specific challenges faced by people living with a rare disease and ensuring stronger EU-wide action through targeted support; and
- shaping political input for future legislation and programmes, ensuring that rare diseases are made an integral part of EU, national and regional programmes in health, research, social affairs and other relevant policies.

Through this network, EURORDIS aims to bring together Members of Parliament to ensure strong international and local action, shape political input for current and future legislation, and integrate rare diseases into all relevant policies at all levels.

A core group of Parliamentary Advocates for Rare Diseases was identified, comprising Members of the European Parliament (MEPs) who have been long-standing advocates of the rare disease cause, alongside MEPs who –thanks to the essential contribution of EURORDIS' National Alliances- showed interest and committed to implement concrete actions in support of people living with rare diseases within the political agenda. In 2018, a brainstorming meeting of the Network was organised, to identify priority actions and initiatives that the Network could carry out before the end of the legislative term (mid-2019). On Rare Diseases Day 2018, policy events at the European Parliament were supported by parliamentarian members of the Network.

13. Rare 2030 – Participatory Foresight in Rare Disease Policy

In 2018, as a result of a Pilot Project adopted by the European Parliament, the European Commission (DG SANTE) issued a call for a 'Foresight Study' dedicated to rare disease policy. A consortium was created, led by EURORDIS, and in July 2018 the proposal was approved.

The project is expected to run from 1st January 2019 until 31st December 2020, and has a total budget of over €2.1 million. The goal of the project is to employ innovative research-based methods to best support future policy decisions in the field of rare diseases. Drivers of change and determinants of health for people with rare diseases -both 'traditional' i.e. well-known determinants and 'wild card' factors) will be identified and ranked, to develop policy scenarios for the years leading up to 2030.

The partners will then use these scenarios to prepare **recommendations** to guide future policy by using the participatory foresight approach and additional innovative consensus-building methods, encouraging broad and sustainable uptake by patients, all relevant stakeholders, (in particular policy makers) and society at large.

List of Common Acronyms

BoMS	Board of Member States of ERNs
CEGRD	Commission Expert Group on Rare Diseases
CHMP	Committee for Medicinal Products for Human Use at EMA
COMP	Committee on Orphan Medicinal Products at EMA
CPMS	Clinical Patient Management System (of the ERNs)
DG	Directorate General
DG EMPL	DG for Employment, Social Affairs & Inclusion
DG RTD	European Commission Directorate General Research and Innovation
DG SANTE	European Commission Directorate General Health and Consumers
EC	European Commission
ECG	ERN Coordinators' Group
ECRD	European Conference on Rare Diseases (and Orphan Drugs)
EEA	European Economic Area
EJA	EUCERD Joint Action
EJP	European Joint Programme Co-Fund
EMA	European Medicines Agency
ERN	European Reference Network
ESF(+)	European Social Fund (Plus)
EU	European Union
EUCERD	European Union Committee of Experts on Rare Diseases
EUROCAT	European surveillance of congenital anomalies
EUROPLAN	European Project for Rare Diseases National Plans Development
EURORDIS	European Organisation for Rare Diseases
FDA	US Food and Drug Administration
FP	Framework Programme
HCP	HealthCare Provider
HTA	Health Technology Assessment
INSERM	Institut National de la Santé et de la Recherche Médicale

IRDiRC	International Rare Diseases Research Consortium
JA	Joint Action
JRC	Joint Research Centre
MA	Marketing Authorisation
MoH	Ministry of Health
MS	Member State
NBS	New born screening
NCA	National Competent Authorities
NHS	National Health System
NP/NS	National Plan/National Strategy
OMP	Orphan Medicinal Product
RDTF	Rare Disease TaskForce
SGPP	Steering Group on Prevention and Promotion of Health
WG	Working Group
WHO	World Health Organization